IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Plaintiffs, v. MODERNA, INC. and MODERNATX, INC., Defendants.	)	C.A. No. 22-252-MSG **HIGHLY CONFIDENTIAL – OUTSIDE COUNSELS EYES ONLY** **FILED UNDER SEAL**

LETTER TO THE HONORABLE MITCHELL S. GOLDBERG FROM NATHAN R. HOESCHEN REGARDING DISCOVERY DISPUTE

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HIGHLY CONFIDENTIAL - OUTSIDE COUNSEL EYES ONLY
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Re: *Arbutus Biopharma Corporation, et. al. v. Moderna, Inc., et. al.* C.A. No. 22-252-MSG

Dear Judge Goldberg:

Plaintiffs move for the production of three limited, relevant categories of documents. Plaintiffs first seek a narrow set of regulatory documents for products that use LNPs with the lipid molar ratios in Plaintiffs' asserted patent claims—specifically, the chemistry, manufacturing, and controls sections (typically contained in Module 3) of Moderna's "Investigational New Drug" applications ("INDs") and related correspondence with the FDA. These documents, which are relevant to non-obviousness, willful infringement, and damages, can be produced from a centralized repository with minimal burden. Second, Plaintiffs seek documents concerning the marketing, negotiation, and contracting for batches of Moderna's COVID-19 vaccine that Moderna unilaterally declares are "not accused of infringement" because they were allegedly ***manufactured*** and ***used*** abroad. However, such batches, which are accused of infringement, could have been ***sold*** in the U.S. under black-letter law, and are thus subject to damages in this action. Moderna cannot prevent discovery about the locus of sale for these batches based on its untested say-so. Third, Plaintiffs seek minutes from meetings of, and materials provided to, Moderna's Board of Directors discussing the accused product. This is a narrow category of documents that are squarely relevant to damages, and Moderna has not asserted any undue burden.

INDs (RFPs 163–67, Ex. 1 at 9–10). Despite criticizing Plaintiffs' LNP technology both publicly and in this case, Moderna repeatedly sought FDA approval to perform human testing using LNPs within the scope of Plaintiffs' asserted patent claims. Moderna publicly has admitted to performing such studies using LNPs within Plaintiffs' claimed ratios, Ex. 2 at 1322–24; Ex. 3 at 3327–28. The INDs seeking approval to perform these human studies contain detailed, non-public statements that discuss the patented technology, report on studies with the technology, and provide scientific justifications for use of Plaintiffs' claimed lipid molar ratios and components.

There is no genuine dispute that Moderna's INDs are relevant. [redacted] Exs. 4, 5; Ex. 6 at 28–29. [redacted] Ex. 7 at *767. And Moderna repeatedly has demanded that Plaintiffs also produce INDs sponsored by Plaintiffs' predecessors. While Plaintiffs agreed to produce such documents, Ex. 8 at 1, Moderna has steadfastly refused to produce the requested IND excerpts, despite admitting that it maintains them in a centralized repository, minimizing any production burden on Moderna.

Any such minimal burden is vastly outweighed by the documents' substantial relevance. For example, by reflecting Moderna's widespread copying of the patented inventions, Moderna's

INDs provide "compelling evidence" nullifying its obviousness defenses, to the extent Moderna is not estopped from raising them in light of its failed IPRs. *Adv. Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000). Moderna's INDs are also relevant to willful infringement by demonstrating its knowledge of, and history with, the patents and patented technology. *Georgetown Rail Equip. Co. v. Holland L.P.*, 867 F.3d 1229, 1245 (Fed. Cir. 2017). Even divorced from these legal theories, Moderna's INDs likely contain statements directly commenting on the technology at issue in this case, and are plainly relevant for that reason as well.

Moderna offers no valid reason the requested IND sections should not be produced. First, Moderna asserts that certain INDs (from 2017) are irrelevant to copying and willfulness because Moderna's work was conducted pursuant to an unauthorized sublicense from Acuitas, D.I. 1 ¶¶ 32–34, or based on publicly available information. Setting aside that this argument does not address the full scope of non-public INDs that Plaintiffs seek, Moderna's attorney argument does not render its INDs non-discoverable. Nor does the fact that certain IND studies may have been conducted pursuant to a license change their relevance to willful infringement here, which concerns activities beyond the scope of the license. *Georgetown Rail*, 867 F.3d at 1245. And none of this addresses the fact that the requested documents contain Moderna's indisputably relevant statements regarding the patented technology.

Moderna also objects that the INDs concern non-accused products. But the requested INDs include information about [redacted] Exs. 2–6. Regardless, there is no rule limiting discovery to the accused product only. *See, e.g.*, *Eli Lilly & Co. v. Wockhardt Ltd.*, 2010 WL 2605855, at *5 (S.D. Ind. June 22, 2010) (compelling production of IND for another formulation). "[C]ourts have allowed discovery to include non-accused products where a party either demonstrates the relevance of the non-accused products to the allegations and or their reasonable similarity to the accused product," as Plaintiffs have done here, and "Delaware federal district courts . . . have concluded that discovery into non-accused products, particularly prior to the filing of final contentions, is permissible as long as it is narrowly tailored." *LKQ Corp. v. Kia Motors Am., Inc.*, 2023 WL 3455315, at *3 (N.D. Ill. May 15, 2023); *Invensas Corp. v. Renesas Elecs. Corp.*, 287 F.R.D. 273, 283 (D. Del. 2012); *Elm 3DS Innovations, LLC v. Samsung Elecs. Co., Ltd.*, 2015 WL 13902870, at *1–2 (D. Del. June 30, 2015). Moderna's INDs for products using Plaintiffs' lipid ratios are precisely the sort of "narrowly tailored," highly relevant discovery that poses minimal burden, and should be compelled.

Sales Discovery (RFPs 60, 64, 69, 74, 75, 81, 83, Ex. 9 at 14–18; Interrog. 11, Ex. 10). Moderna also refuses to produce discovery concerning sales of the batches that it unilaterally deems non-infringing under 35 U.S.C. § 271(a) because they were not manufactured or used in the U.S. Ex. 11 at 1. Moderna disregards Plaintiffs' allegations that Moderna's ***sales*** of these batches occurred in the U.S., *e.g.*, D.I. 1 ¶¶ 50–54, 70, and defies binding precedent stating that such U.S. sales are infringing acts. *E.g.*, *Caltech v. Broadcom Ltd.*, 25 F.4th 976, 993 (Fed. Cir. 2022); *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1310 (Fed. Cir. 2015). Sales "for products manufactured, delivered, and used ***entirely abroad***," may "be found to have occurred in the United States"—and thus infringing under § 271(a)—"where a substantial level of sales activity occur[ed]" in the U.S. Ex. 12 at Appx184, *aff'd in relevant part Caltech*, 25 F.4th at 992. And products "not made or used in, or imported into, the United States" may infringe if there is a "domestic location of sale." *CMU*, 807 F.3d at 1310. Determining where a sale occurred is a fact-specific inquiry, in which courts have considered (1) where a contract or sale was negotiated; (2) where purchase orders and payments issue or are received; (4) where a contract was executed; (5)

where contingent actions under a contract occur; (6) where specific orders are negotiated or finalized; (7) where marketing activities occur or are directed; and/or (8) where testing or design work underlying the sale occurred. *See, e.g.*, *Caltech*, 25 F.4th at 976; *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 831 F.3d 1369, 1378 (Fed. Cir. 2016); *CMU*, 807 F.3d at 1308; Ex. 13.

Moderna ignores this precedent, and refuses discovery, by baldly declaring its sales occurred abroad. Ex. 14 at 1. Moderna improperly confuses its unilateral view of the merits of infringement with discoverability. Plaintiffs are not obligated to accept Moderna's untested assertions, but are "entitled to discover the extent to which [Moderna] has engaged in foreign sales activities" to determine if sales of products made and used abroad in fact "occurred within the U.S." *McGinley v. Luv N'Care, Ltd.*, 2018 WL 9814589, at *5 (W.D. La. Sept. 10, 2018). Plaintiffs are "not required to prove [their] case" for infringing sales "before being entitled to such discovery." *Apeldyn Corp. v. AU Optronics Corp.*, 2010 WL 11470585, at *1 (D. Del. Apr. 12, 2010) (compelling "worldwide sales data"); *Pos. Techs., Inc. v. Sony Elecs., Inc.*, 2013 WL 707914, at *6 (N.D. Cal. Feb. 26, 2013) ("It would be improper under Rule 26 to expect Plaintiff to show that the discovery it seeks is admissible when it has not yet obtained the discovery."). Moderna cannot dispute that significant sales activities occurred at its U.S. headquarters, key testing and design work occurred in the U.S., and employees executed contracts in the U.S. Moderna should be compelled to produce documents and information concerning the sales of its COVID-19 vaccine that it contends were for batches manufactured and used abroad, and not to limit discovery to batches manufactured or used in the U.S, as it has in response to each of Plaintiffs' requests.[1]

Board Materials (RFP 130, Ex. 1 at 2). Moderna refuses to produce minutes of meetings of, and materials provided to, its Board of Directors discussing the accused product. Moderna has acknowledged that this request "is narrowly circumscribed," Ex. 15 at 7, and has not disputed relevance. Nor could it. Such materials are directly relevant to damages, as planning and strategy around the accused product are evidence about the hypothetical negotiation. Indeed, Moderna's CEO testified before Congress that its Board made strategic sales decisions, including agreeing to give an unsolicited ***$2.9 billion*** discount to the U.S. Government. Ex. 16, 54:5-22, 83:9. Moderna also has not asserted burden, as such materials generally are centrally stored. Ex. 15 at 10.

Moderna's sole basis to resist production has been shifting counter-demands. Plaintiffs agreed to produce the same scope of Board materials requested from Moderna, plus more. Ex. 15 at 4. So Moderna demanded yet more: first that Plaintiffs produce their and their predecessors' board materials concerning not just the accused product, but effectively every LNP made in their two-decade-plus history. Then, Moderna demanded that Plaintiffs ***and*** non-party Roivant produce documents discussing lipid molar ratios and the asserted patents. Ex. 15 at 2. This conditioning is improper. *Genentech, Inc. v. Trustees of Univ. of Pa.*, 2011 WL 7074208, at *1 (N.D. Cal. June 10, 2011). The documents Plaintiffs seek are targeted and plainly relevant to damages. Courts routinely compel defendants in patent litigation to produce board materials regarding the accused product, and Plaintiffs respectfully request the Court follow suit here. *E.g.*, *Vasudevan Software, Inc. v. MicroStrategy Inc.*, 2013 WL 597655, at *1 (N.D. Cal. Feb. 15, 2013) (ordering production of board minutes); *Unilin Beheer B.V. v. NSL Trading Corp.*, 2015 WL 12698382, at *9 (C.D. Cal. Feb. 27, 2015) (ordering investigation into board minutes and other financial documents).

[1] Plaintiffs have also sought samples of such batches. D.I. 161.

Respectfully submitted,

/s/ Nathan R. Hoeschen

Nathan R. Hoeschen (No. 6232)

cc: Clerk of the Court (by CM/ECF)
All counsel of record (by CM/ECF & e-mail)

EXHIBIT 1

HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL EYES ONLY

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Plaintiffs, v. MODERNA, INC. and MODERNATX, INC., Defendants.	)	C.A. No. 22-252-MSG **CONTAINS INFORMATION MODERNA DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL EYES ONLY**

PLAINTIFFS' THIRD SET OF REQUESTS FOR PRODUCTION TO DEFENDANTS (NOS. 128–173)

Pursuant to Federal Rules of Civil Procedure 26 and 34, Plaintiffs Arbutus Biopharma Corporation ("Arbutus") and Genevant Sciences GmbH ("Genevant") direct the following requests for production to Defendants Moderna, Inc. and ModernaTX Inc. (collectively, "Moderna" or "Defendants"). Responses to these requests shall be served upon Plaintiffs' undersigned counsel within 30 days of service of these requests, or at such time and location as may be mutually agreed upon by the parties. Copies shall be produced as they are kept in the ordinary course of business, including their labeling as to the source of the documents. Pursuant to Fed. R. Civ. P. 26(e), these requests are continuing and require supplemental answers.

DEFINITIONS & INSTRUCTIONS

Plaintiffs incorporate herein by reference as though fully set forth herein the Definitions and Instructions of Plaintiffs' First Set of Requests for Production to Defendants (Nos. 1–98) served December 20, 2022.

1. The "2013 Moderna-AstraZeneca Agreement" refers to the 2013 agreement between Moderna and AstraZeneca related to the development of "mRNA therapeutics." *See, e.g.*, https://news.modernatx.com/news/news-details/2013/AstraZeneca-and-Moderna-Therapeutics-Announce-Exclusive-Agreement-to-Develop-Pioneering-Messenger-RNA-Therapeutics-in-Cardiometabolic-Diseases-and-Cancer/default.aspx; https://www.astrazeneca.com/media-centre/press-releases/2013/astrazeneca-moderna-therapeutics-cardiometabolic-diseases-cancer-treatment-21032013.html#!; https://www.sec.gov/Archives/edgar/data/1682852/000095012318009738/filename5.htm.

REQUESTS FOR PRODUCTION

REQUEST FOR PRODUCTION NO. 128

All documents that estimate, define, describe, assess, study, or summarize the market for the Accused Product, including but not limited to company reports or studies, third-party research, or other information related to the market for the Accused Product.

REQUEST FOR PRODUCTION NO. 129

All documents and other information relating to the pricing strategies for the Accused Product, including, but not limited to, the factors, information, and/or data that Moderna considered in developing pricing strategies for the Accused Product.

REQUEST FOR PRODUCTION NO. 130

All documents and communications created, prepared, and/or reviewed for or by Moderna's Board of Directors, or any committee of such Board, related to the Accused Product, including, but not limited to, meeting minutes of Moderna's Board of Directors, presentations prepared for or provided to Moderna's Board of Directors, or financial analyses or projections about sales of the Accused Product provided to Moderna's Board of Directors.

REQUEST FOR PRODUCTION NO. 160

All documents and communications relating to the conception, reduction to practice, research, or development of the subject matter disclosed and/or claimed in WO 2023/019181 and any priority application thereto (including U.S. Provisional Application No. 63/232,128 listed on the cover of WO 2023/019181), including but not limited to laboratory notebooks, notes, records, logs, files, invention disclosures, or other documents generated by or at the direction of any named inventors, and all laboratory notebooks, notes, records, logs, files, invention disclosures, or other documents in which any named inventors made any entries.

REQUEST FOR PRODUCTION NO. 161

All documents and communications regarding the disclosure in WO 2023/019181 concerning the effect of adding steric stabilizers, such as polyethylene glycol (PEG)

REQUEST FOR PRODUCTION NO. 162

All documents and communications regarding the disclosure in WO 2023/019181 of "turbulent mixing ('T-mix')," "vortex mixing ("V-mix")," or "microfluidic mixing."

REQUEST FOR PRODUCTION NO. 163

Documents sufficient to show the lipid composition and/or lipid molar ratio for all Investigational New Drug Applications submitted by Moderna to the U.S. Food & Drug Administration and Moderna's reasons for selecting the lipid composition and lipid molar ratio.

REQUEST FOR PRODUCTION NO. 164

Documents sufficient to show the lipid composition and/or lipid molar ratio for all Investigational New Drug Applications submitted by Moderna to the U.S. Food & Drug Administration using (1) 50 mol % to 65 mol % cationic lipid; (2) 4 mol % to 10 mol % of phospholipid; (3) 30 mol % to 40 mol % cholesterol or derivative thereof; and (4) 0.5 mol % to 2 mol % PEG-lipid or conjugated lipid that inhibits aggregation of particles, and Moderna's reasons for selecting the lipid composition and lipid molar ratio.

REQUEST FOR PRODUCTION NO. 165

Documents sufficient to show the lipid composition and/or lipid molar ratio for all Investigational New Drug Applications submitted by Moderna to the U.S. Food & Drug Administration using (1) 50 mol % to 65 mol % cationic lipid; (2) 3 mol % to 15 mol % of phospholipid; (3) 30 mol % to 40 mol % cholesterol or derivative thereof; and (4) 0.5 mol % to 2 mol % PEG-lipid or conjugated lipid that inhibits aggregation of particles, and Moderna's reasons for selecting the lipid composition and lipid molar ratio.

REQUEST FOR PRODUCTION NO. 166

Documents sufficient to show the LNP manufacturing process for all Investigational New Drug Applications submitted by Moderna to the U.S. Food & Drug Administration wherein the proposed product comprised LNPs.

REQUEST FOR PRODUCTION NO. 167

Documents sufficient to show the lipid composition and lipid molar ratio for all Investigational New Drug Applications submitted by Moderna to the U.S. Food & Drug Administration wherein the proposed product comprised LNPs.

Respectfully submitted,

/s/ Emily S. DiBenedetto

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Dated: August 3, 2023

CERTIFICATE OF SERVICE

I, Emily S. DiBenedetto, hereby certify that on August 3, 2023, this document was served on the persons listed below in the manner indicated:

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EXHIBIT 2

Molecular Therapy
Original Article

Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

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Recently, the World Health Organization confirmed 120 new human cases of avian H7N9 influenza in China resulting in 37 deaths, highlighting the concern for a potential pandemic and the need for an effective, safe, and high-speed vaccine production platform. Production speed and scale of mRNA-based vaccines make them ideally suited to impede potential pandemic threats. Here we show that lipid nanoparticle (LNP)-formulated, modified mRNA vaccines, encoding hemagglutinin (HA) proteins of H10N8 (A/Jiangxi-Donghu/346/2013) or H7N9 (A/Anhui/1/2013), generated rapid and robust immune responses in mice, ferrets, and nonhuman primates, as measured by hemagglutination inhibition (HAI) and microneutralization (MN) assays. A single dose of H7N9 mRNA protected mice from a lethal challenge and reduced lung viral titers in ferrets. Interim results from a first-in-human, escalating-dose, phase 1 H10N8 study show very high seroconversion rates, demonstrating robust prophylactic immunity in humans. Adverse events (AEs) were mild or moderate with only a few severe and no serious events. These data show that LNP-formulated, modified mRNA vaccines can induce protective immunogenicity with acceptable tolerability profiles.

INTRODUCTION

Several avian influenza A viruses (H5N1, H10N8, H7N9, and H1N1) have crossed the species barrier, causing severe and often fatal respiratory disease in humans. Fortunately, most of these strains are not able to sustain person to person transmission.[1] However, lessons learned from these outbreaks demonstrated that new approaches are needed to address potential future pandemic influenza outbreaks.[2]

Two major glycoproteins, crucial for influenza infection, are hemagglutinin (HA) and neuraminidase (NA); both are expressed on the surface of the influenza A virion.[3] HA mediates viral entry into host cells by binding to sialic acid containing receptors on the cell mucosal surface and the fusion of viral and host endosomal membranes.[4]

The segmented influenza A genome permits reassortment and exchange of HA (or NA) segments between different influenza strain subtypes during concomitant host cell infection. Generation of novel antigenic proteins (antigenic shift) and sustainable person to person transmission are hallmarks of pandemic influenza strains.[5] Such strains can spread quickly and cause widespread morbidity and mortality in humans due to high pathogenicity and little to no pre existing immunity. Recent cases (2013) of avian to human transmission of avian influenza A virus subtypes included H7N9, H6N1, and H10N8.[6–8] The case fatality rate in over 600 cases of H7N9 infections was ~30%.[1,9] Most recently, the World Health Organization reported another 120 cases since September 2016 resulting in 37 deaths.[10] To date, H10N8 infection in man has been limited; yet, of the three reported cases, two were fatal.[11]

The limited efficacy of existing antiviral therapeutics (i.e., oseltamivir and zanamivir) makes vaccination the most effective means of protection against influenza.[12] Conventional influenza vaccines induce protection by generating HA specific neutralizing antibodies, the major correlate of protection, against the globular head domain.[13–15] Such vaccines utilize the HA protein, administered as a subunit, split virion, inactivated whole virus, or live attenuated virus. A majority of approved influenza vaccines are produced in embryonated chicken eggs or cell substrates. This process takes several months and relies on the availability of sufficient supplies of pathogen free eggs and adaptation of the virus to grow within its substrate.[16,17] The 5–6 months required to produce enough vaccine to protect a substantial proportion of the population consumes much of the duration of the often devastating first wave of a pandemic.[18] This mismatch between the speeds of vaccine production and epidemic spread drives the search for vaccine platforms that can respond faster.[19]

Using mRNA complexed with protamine (RNActive, Curevac), Petsch et al.[20] demonstrated that intradermal (ID) vaccination of mice with RNActive encoding full length HA from influenza virus H1N1 (A/Puerto Rico/8/1934) induced effective seroconversion and

Received 23 January 2017; accepted 24 March 2017;
http://dx.doi.org/10.1016/j.ymthe.2017.03.035.

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virus neutralizing antibodies in all vaccinated animals. Immunity was long lasting and protected both young and old animals from lethal challenge with the H1N1, H3N2, and H5N1 strains of the influenza A virus.[20] Efficacy of these RNActive vaccines was also shown in ferrets and pigs.[21]

The use of a delivery system can dramatically reduce the doses needed to generate potent immune responses, without an additional conventional adjuvant. Lipid nanoparticles (LNPs) have been used extensively for the delivery of small interfering RNA (siRNA), and they are currently being evaluated in late stage clinical trials via intravenous administration.[22]

Exogenous mRNA can stimulate innate immunity through Toll like receptors (TLRs) 3, 7, and 8 and cytoplasmic signal recognition proteins RIG I and MDA5.[23,24] The adjuvant effect of stimulating innate immunity may be advantageous for purified protein vaccines, but indiscriminate immune activation can inhibit mRNA translation, reducing antigen expression and subsequent immunogenicity.[25,26] This can be overcome by replacing uridine nucleosides with naturally occurring base modifications, such as pseudouridine and 5 methylcytidine.[27–29] Recently, we[30] and others[31] have shown how LNP encapsulated modified mRNA vaccines can induce extraordinary levels of neutralizing immune responses against the Zika virus in mice and nonhuman primates, respectively.

In this study, we evaluated the immunogenicity of two LNP formulated, modified mRNA based influenza A vaccines encoding the HA of H10N8 (A/Jiangxi Donghu/346/2013) and H7N9 (A/Anhui/1/2013) in animals and H10N8 HA mRNA in humans from an ongoing trial. In the animal studies, we show that both vaccines generated potent neutralizing antibody titers in mice, ferrets, and cynomolgus monkeys (cynos) after a single dose. Additionally, a single dose of H7N9 HA mRNA protected mice from an autologous lethal challenge and reduced lung viral titers in ferrets. Encouraged by these findings, a first in human, dose escalating, phase 1 trial is ongoing, with interim results reported here that confirm the observed, preclinical immunogenicity data with a safety profile consistent with other non live vaccines.

RESULTS

H10N8 and H7N9 HA mRNA Immunogenicity in Mice

In vitro protein expression for both H10N8 HA (H10) and H7N9 HA (H7) mRNA vaccines were confirmed by transfection of HeLa cells. Western blot of resulting cell lysates demonstrated a 75 kDa band for both constructs using the corresponding HA specific antibodies (Figure S1), consistent with previous reports for other HAs.[22] Due to a lack of glycosylation, both H10 HA and H7 HA protein controls had a molecular weight of 62 kDa.

Hemagglutination inhibition (HAI), IgG1, and IgG2a titers were measured after a single 10 μg dose of either formulated H10 or H7 mRNA in BALB/c mice immunized ID. HAI titers were below the limit of detection (<10) at day 7 but increased well above baseline by day 21 (Figure 1A). Unlike HAI, both anti H10 and anti H7 IgG1 and IgG2a titers were detected on day 7 (Figures 1B and 1C). For H10, IgG1 and IgG2a titers continued to increase until day 21 and were maintained at day 84. For H7, both IgG1 and IgG2a antibody titers increased 10 fold between day 21 and day 84 (Figure 1C). IgG2a titers were greater than IgG1 titers at all time points following formulated H10 or H7 mRNA immunization, suggesting a TH1 skewed immune response. For H10, these differences were significant at day 84 ($p = 0.0070$) and for H7 at day 7 ($p = 0.0017$) and day 21 ($p = 0.0185$). A 10 μg H10 mRNA boosting immunization (21 days post prime) resulted in a 2 to 5 fold increase in HAI titers, compared to a single dose at all time points tested ($p < 0.05$) (Figure 1D). Titers remained stable for more than a year, regardless of the number of doses.

While most vaccines are delivered via an intramuscular (IM) or subcutaneous administration,[32] the ID route of administration has the potential to be dose sparing. Therefore, to examine the effect of administration route on immunogenicity, BALB/c mice were immunized ID or IM with formulated H10 or H7 mRNA at four different dose levels. All animals received a boosting immunization on day 21, and serum was collected 28 days post boost (day 49). Immune responses were observed for both vaccines at all dose levels tested (Figures S2A and S2B). Titers were slightly higher following IM administration at 2 and 0.4 μg for H10, but this difference was only significant at the 2 μg dose ($p = 0.0038$) (Figure S2A). The differences in H10 HAI titers were significant between some of the dose levels following IM administration: 10 versus 0.4 μg, $p = 0.0247$; 10 versus 0.08 μg, $p = 0.0002$; 2 versus 0.08 μg, $p = 0.0013$; and 0.4 versus 0.08 μg, $p = 0.0279$. HAI titers following H7 immunization trended higher as the dose increased although no significance was detected. In addition, there was no significant difference between IM and ID immunization (Figure S2B). T cell responses, as measured by IFNɣ ELISpot, were observed for both H10 and H7 at all doses tested (Figures S2C and S2D). Similar to H7 HAI titers, T cell responses trended higher following IM administration, especially for H7. However, significance could not be established due to pooling of the samples by group. Overall, after two doses, immunization with either H10 or H7 mRNA elicited an immune response at all doses tested with both ID and IM administration.

Given this innovative vaccine platform, we examined the biodistribution of the mRNA vaccines for both routes of administration. Male CD 1 mice received 6 μg formulated H10 mRNA either IM or ID. Following IM administration, the maximum concentration (C_{max}) of the injection site muscle was 5,680 ng/mL, and the level declined with an estimated $t_{1/2}$ of 18.8 hr (Table 1). Proximal lymph nodes had the second highest concentration at 2,120 ng/mL (t_{max} of 8 hr with a relatively long $t_{1/2}$ of 25.4 hr), suggesting that H10 mRNA distributes from the injection site to systemic circulation through the lymphatic system. The spleen and liver had a mean C_{max} of 86.9 ng/mL (area under the curve $[AUC]_{0-264}$ of 2,270 ng.hr/mL) and 47.2 ng/mL (AUC_{0-264} of 276 ng.hr/mL), respectively. In the remaining tissues and plasma, H10 mRNA was found at 100 to 1,000 fold lower levels.

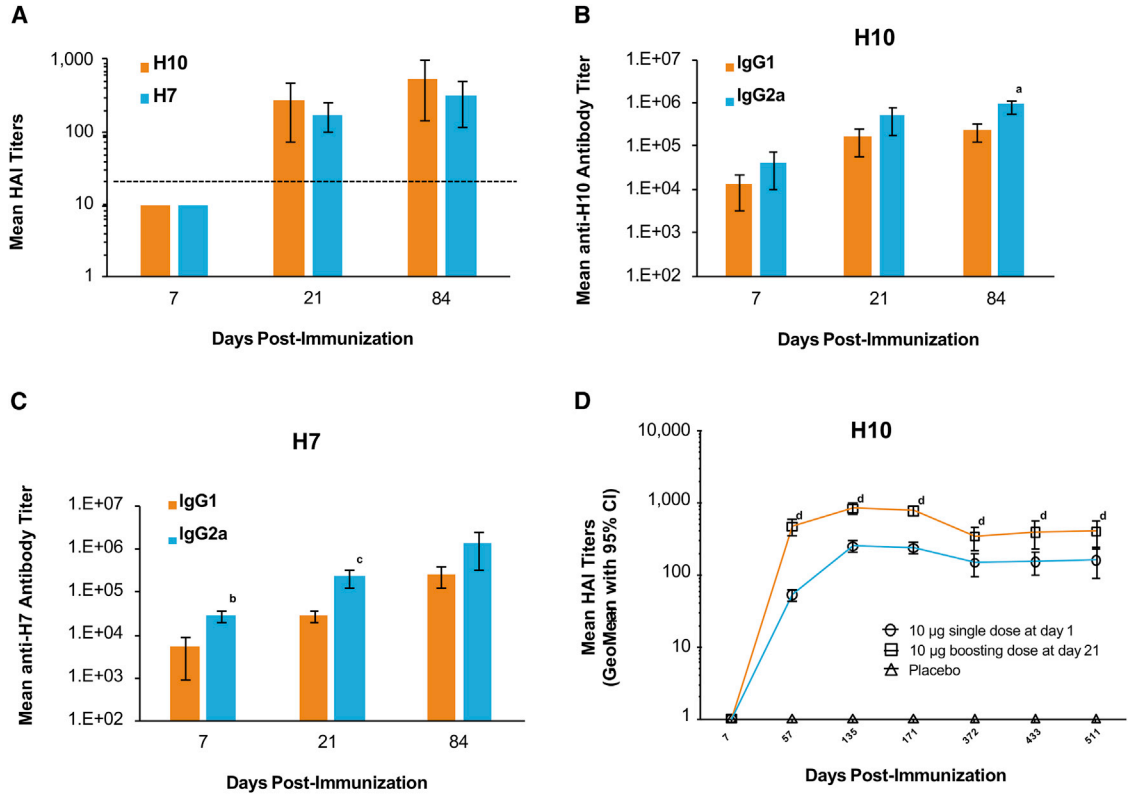

Figure 1. Mice Immunized with H10 or H7 mRNA Generate Robust and Stable Antibody Responses Consistent with a TH1 Profile

BALB/c mice were vaccinated ID with a single 10 µg dose of formulated H10 or H7 mRNA. (A) H10 and H7 indicate mean HAI titers (limit of detection is 1:10). Dotted line indicates the correlate of protection in humans (1:40). (B and C) IgG1 and IgG2a titers were measured for both H10 (B) and H7 (C) via ELISA (n = 5/group). [a]p = 0.0070, [b]p = 0.0017, and [c]p = 0.0185 versus IgG2a at the same time point. (D) BALB/c mice were immunized ID with a single 10 µg dose of formulated H10 mRNA. A subset of these mice received a 10 µg boost on day 21. Serum was collected at the indicated time points, and neutralizing antibody titers were determined by HAI (n = 15/group). Placebo controls were also included. [d]p < 0.05 single dose versus boosting dose at the same time point. Error bars indicate standard mean error.

Following ID administration, C_{max} within the skin at the injection site was 18.2 µg/mL. Levels declined by 24 hr with an estimated $t_{1/2}$ of 23.4 hr, suggesting that the H10 mRNA likely dissipated to systemic circulation via the proximal draining lymph node, as seen for the IM dosing. Consistent with this, the spleen, with a C_{max} of 1.66 ng/mL (1,663.52 pg/mL; AUC_{0-96} of 114.25 ng.hr/mL), had the highest levels among distal tissues. Only trace amounts of H10 mRNA were found in the heart, kidney, liver, and lung. Overall, whether administered ID or IM, the biodistribution of this vaccine was consistent with that observed for other vaccines,[33] where a local deposition effect was observed followed by draining to the local lymph nodes and subsequent circulation in the lymphatic system (Table 1; Table S1).

To understand the expression profile of mRNA after IM and ID administration, BALB/c mice were injected on day 0 with formulated luciferase mRNA at four different dose levels (10, 2, 0.4, and 0.08 µg). Expression was found to be dose dependent. As the dose increased, expression was found in distal tissues, with peak expression observed 6 hr after dosing. There were no significant differences when comparing maximum expression and time of maximal expression across IM and ID routes (Figure S3A). The time course of expression was also similar with both routes (Figures S3B and S3C). However, the distribution of expression changed slightly when the two routes were compared. Expression outside of the site of administration was observed across all dose levels, but it was more pronounced following IM administration, which is consistent with the biodistribution data (Figures S4A–S4E; Table 1; Table S1).[34]

H7 mRNA Vaccine Provides Protection against Lethal Influenza H7N9, A/Anhui/1/2013, in Mice and Ferrets

To determine the time to onset and duration of immunity to influenza H7N9 (A/Anhui/1/2013) lethal challenge, BALB/c mice were immunized ID with 10, 2, or 0.4 µg formulated H7 mRNA. For negative controls, placebo and 10 µg formulated H7 mRNA deficient in expression, due to the removal of a methyl group on the 2′ O position of the first nucleotide adjacent to the cap 1 structure at the 5′ end of the mRNA (15 Da cap), were included. Serum was collected on days 6, 20, and 83, and mice were challenged via intranasal (IN) instillation with a target dose of 2.5×10^5 tissue culture infectious dose ($TCID_{50}$) on days 7, 21, and 84. Changes in body weight and clinical signs of disease were monitored for 14 days post challenge. A single vaccination was found to be protective against H7N9 challenge (2.5×10^5

Table 1. Biodistribution of H10 mRNA in Plasma and Tissue after IM Administration in Mice

		C_{max} (ng/mL)		$AUC_{0\ 264\ h}$ (ng.hr/mL)		
Matrix	t_{max} (hr)	Mean	SE	Mean	SE	$t_{1/2}$ (h)
Bone marrow	2.0	3.35	1.87	NA		NC
Brain	8.0	0.429	0.0447	13.9	1.61	NR
Cecum	8.0	0.886	0.464	11.1	5.120	NC
Colon	8.0	1.11	0.501	13.5	5.51	NC
Distal lymph nodes	8.0	177.0	170.0	4,050	2,060	28.0
Heart	2.0	0.799	0.225	6.76	1.98	3.50
Ileum	2.0	3.54	2.60	22.6	10.8	5.42
Jejunum	2.0	0.330	0.120	5.24	0.931	8.24
Kidney	2.0	1.31	0.273	9.72	1.44	11.4
Liver	2.0	47.2	8.56	276	37.4	NC
Lung	2.0	1.82	0.555	12.7	2.92	16.0
Muscle (injection site)	2.0	5,680	2,870	95,100	20,000	18.8
Plasma	2.0	5.47	0.829	35.5	5.41	9.67
Proximal lymph nodes	8.0	2,120	1,970	38,600	22,000	25.4
Rectum	2.0	1.03	0.423	14.7	3.67	NR
Spleen	2.0	86.9	29.1	2,270	585	25.4
Stomach	2.0	0.626	0.121	11.6	1.32	12.7
Testes	8.0	2.37	1.03	36.6	11.8	NR

Male CD-1 mice received 300 μg/kg (6 μg) formulated H10 mRNA via IM immunization. Two replicates of bone marrow, lung, liver, heart, right kidney, inguinal- and popliteal-draining lymph nodes, axillary distal lymph nodes, spleen, brain, stomach, ileum, jejunum, cecum, colon, rectum, testes (bilateral), and injection site muscle were collected for bDNA analysis at 0, 2, 8, 24, 48, 72, 120, 168, and 264 hr after dosing (n = 3 mice/time point). NA, not applicable AUC with less than three quantifiable concentrations; NC, not calculated; NR, not reported because extrapolation exceeds 20% or R-squared is less than 0.80.

$TCID_{50}$; Figures 2A 2C). There was a significant increase in survival for animals in the three vaccine dose groups compared to the animals from the two control groups ($p < 0.0001$). Clinical observations in influenza infected mice included rough coat, hunched posture, orbital tightening, and, in some cases, labored breathing. Weight loss (incidence and duration) was more prevalent for animals in the control groups and seen to a lesser extent in the low dose vaccine group (Figures 2D 2F). HAI titers were below the limit of detection until day 20 for both the 10 and 2 μg dose groups (Figure S5). There was a 5 to 7 fold increase in HAI titers from day 20 to day 83 at all doses tested ($p < 0.0001$). Day 83 titers were dose dependent with mean titers of 224, 112, and 53 for the 10 μg dose, 2 μg dose, and 0.4 μg dose groups, respectively ($p < 0.0001$). Interestingly, despite complete protection to challenge at the 0.4 μg dose at day 21 (Figure 2B), a protective HAI titer (≥ 40) was not detected until day 83 at this dose, suggesting additional mechanism(s) of protection.

The negative mRNA control unexpectedly showed some delayed efficacy by day 21. However, this group of animals appeared to have received a dose lower than the day 7 and day 84 groups, based on back titer calculation (6.2×10^3 $TCID_{50}$ versus 3.8×10^5 and 6.1×10^5, respectively.), which was only ~3 fold higher than the LD_{50} of 1.88×10^3 (95% confidence interval [CI] = 8.02×10^2 5.51×10^3). Nonetheless, this group had comparable weight loss to the placebo group, and it was just above the threshold for euthanasia (30%) for some of the animals, thus confirming the significant protection observed in the positive vaccine groups. Additionally, it is not possible to rule out a low level of protein expression from the de methylated cap of the negative mRNA control.[35]

Unlike mice, ferrets are naturally susceptible to human influenza virus isolates. Human and avian influenza viruses both replicate efficiently in the respiratory tract of ferrets, and numerous clinical signs found in humans following seasonal or avian influenza virus infection are also present in the ferrets.[36,37] Ferrets (n = 8/group) were vaccinated ID on day 0 with 200 , 50 , or 10 μg doses of formulated H7 mRNA. Formulated H7 mRNA with a 15 Da cap and placebo were included as negative controls. A subset of ferrets received a second ID vaccination on day 21. All groups were exposed to influenza H7N9 via IN challenge (1×10^6 $TCID_{50}$). The primary endpoint for this study was viral burden determined by $TCID_{50}$ in the lung at 3 days post challenge, which is when the peak viral load is seen in control animals (data not shown). A reduction in lung viral titers was observed when ferrets were challenged 7 days post immunization at all doses tested (Figures S6A S6C). Ferrets immunized with 200 μg and challenged on day 49 had viral loads below the level of detection (Figure S6C). Antibody titers, as measured by HAI, increased significantly by day 21 for all dose groups ($p < 0.05$); as measured by microneutralization (MN), significant increases were observed by day 49 for all dose groups ($p < 0.05$) (Figures S7A and S7B). A second immunization increased titers but showed no statistical benefit compared to a single immunization, likely due to the two to four log reduction in viral lung titers seen in both the single and double immunization groups (Figures S7A S7D). Two immunizations with 50 μg doses significantly increased HAI and MN titers compared to placebo ($p < 0.05$), and two immunizations with 200 μg doses generated significant HAI and MN titers versus placebo and all other doses ($p < 0.0001$) (Figures S7C and S7D).

In the absence of an H10N8 (A/Jiangxi Donghu/346/2013) challenge model, the onset and duration of immunity to formulated H10 mRNA in ferrets was tested by HAI. Groups of ferrets were immunized ID once, twice, or three times with 50 or 100 μg H10 mRNA. Immunization with a single dose of 50 or 100 μg resulted in significant and comparable increases in HAI titers at days 21, 35, and 49 ($p < 0.0001$; Figure 3). Immunization with a 100 μg dose resulted in only slightly elevated antibody responses on day 7 compared to day 0 ($p < 0.0001$), with minimal differences observed with the 50 μg dose on day 7 compared to day 0 ($p < 0.3251$). Subsequent boosts with either a 50 or 100 μg dose (delivered on day 21 or on both days 21 and 35) resulted in significant and comparable increases in HAI titers on days 35 and 49 ($p < 0.0001$). Overall, the H10 mRNA administered at a 50 or 100 μg dose yielded significant increases in HAI antibody titers as compared with prevaccination baseline values

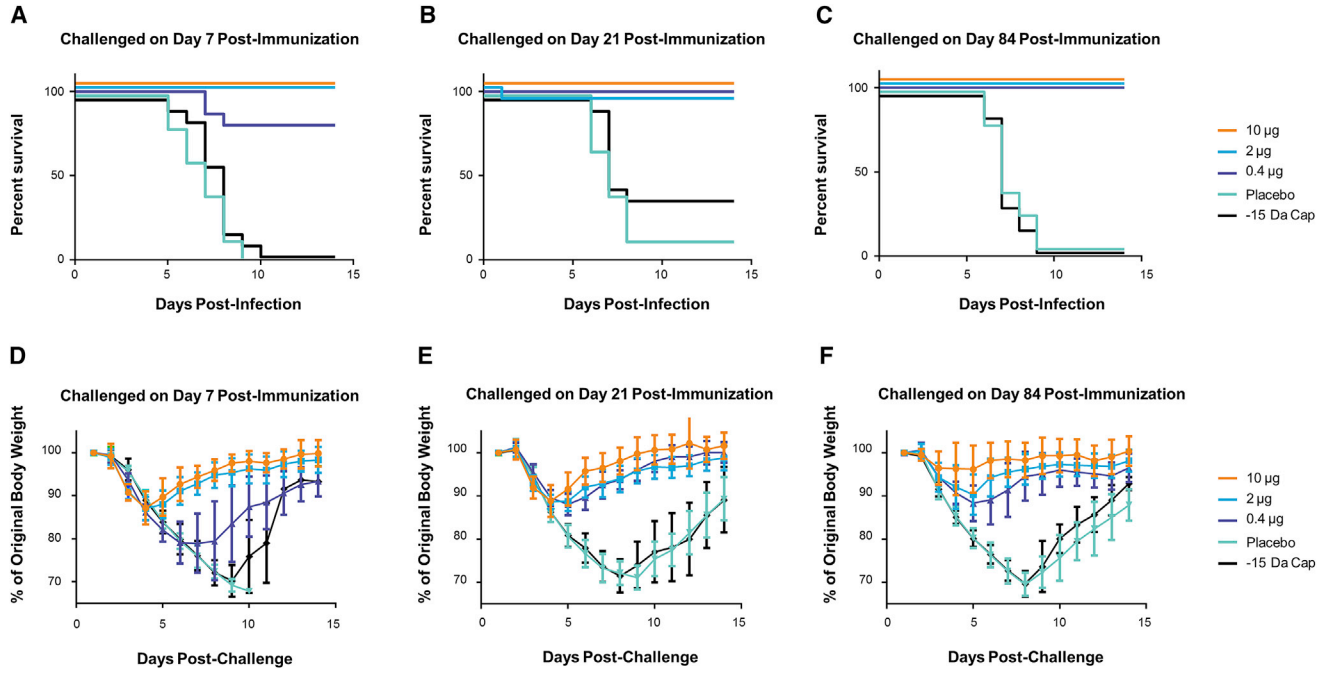

Figure 2. A Single Injection of an H7 mRNA Vaccine Achieves Rapid and Sustained Protection in Mice

BALB/c mice were vaccinated ID with 10, 2, or 0.4 µg formulated H7 mRNA. Placebo and 10 µg formulated H7 mRNA with a reduced 5′ cap structure (15 Da cap) were included as negative controls. On day 7, 21, or 84 post immunization, mice were challenged via intranasal (IN) instillation with a target dose of 2.5×10^5 $TCID_{50}$ of influenza A/Anhui/1/2013 (H7N9). Serum was collected prior to challenge (days 6, 20, and 83). (A C) Survival curves of mice challenged on day 7 (A), day 21 (B), or day 84 (C) post immunization at the indicated doses. $p < 0.0001$ 10 , 2 , and 0.4 µg dose groups versus placebo or 15 Da cap at days 7, 21, and 84 post immunization. (D F) Weight curves of mice challenged on day 7 (D), day 21 (E), or day 84 (F) post immunization at the indicated doses (n = 15/group). Error bars indicate standard mean error.

and controls ($p < 0.0001$). A single booster vaccination provided a sig nificant increase in titers, but a second booster dose did not yield an additional increase (Figure 3).

H10 HA and H7 HA mRNA Immunogenicity in Nonhuman Primates

One of the major limitations with other nucleic acid based technolo gies, such as plasmid DNA, has been translation to higher order spe cies, such as nonhuman primates. To evaluate the immune responses elicited in nonhuman primates, HAI titers were measured in cynos af ter two immunizations (days 1 and 22) at two dose levels (0.2 and 0.4 mg) of formulated H7 mRNA administered IM and ID (Figures 4A and 4B). Formulated H10 mRNA was tested with only the 0.4 mg dose delivered ID and IM with the same immunization schedule (days 1 and 22) (Figure 4C). Both H10 and H7 mRNA vac cines generated HAI titers between 100 and 1,000 after a single immu nization (day 15). HAI titers of 10,000 were generated for both H10 and H7 at 3 weeks following the second immunization (day 43), regardless of dose or route of administration. At 0.4 mg, the cynos experienced some systemic symptoms, such as warm to touch pain at the injection site, minor injection site irritation, and, in some cases, decreased food consumption following either H10 or H7 immuniza tion. All symptoms resolved within 48 72 hr. Overall, both ID and IM administration elicited similar HAI titers regardless of dose, suggest ing that lower doses may generate a similar HAI titer.

H10 mRNA Immunogenicity and Safety in Humans

To evaluate the safety and immunogenicity of H10 mRNA in humans, a randomized, double blind, placebo controlled, dose escalating phase 1 trial is ongoing (Clinical Trials Identifier NCT03076385). We report here interim results, obtained 43 days post vaccination of 31 subjects (23 of whom received active H10 at 100 µg IM and eight of whom received placebo). Immunogenicity data show that 100% (n = 23) and 87% (n = 20) of subjects who received the H10 vaccine had an HAI $\geq$ 40 and MN $\geq$ 20 at day 43, respectively, compared to 0% of placebo subjects (Figures 5A and 5B). A total of 78% (n = 18) and 87% (n = 20) who received the H10 vaccine had an HAI baseline <10 and post vaccination HAI $\geq$ 40 or HAI four or more times baseline, respectively, compared to 0% for placebo (Figures 5A and 5B). HAI geometric mean antibody titers of subjects given the H10 vaccine were 68.8 compared to 6.5 for placebo, and the MN geometric mean ti ters were 38.3 versus 5.0, respectively (Figures 5C and 5D).

The majority of adverse events (AEs) were mild (107/163 events; 66%) or moderate (52/163 events; 32%), using the Center for Biologics Eval uation and Research (CBER) severity scale.[38] AEs were comparable in frequency, nature, and severity to unadjuvanted and adjuvanted H1N1 influenza vaccines.[39] Twenty three subjects who received 100 µg H10 IM reported 163 reactogenicity events with no idiosyncratic or persis tent AEs observed. The majority of events were injection site pain, myalgia, headache, fatigue, and chills/common cold like symptoms

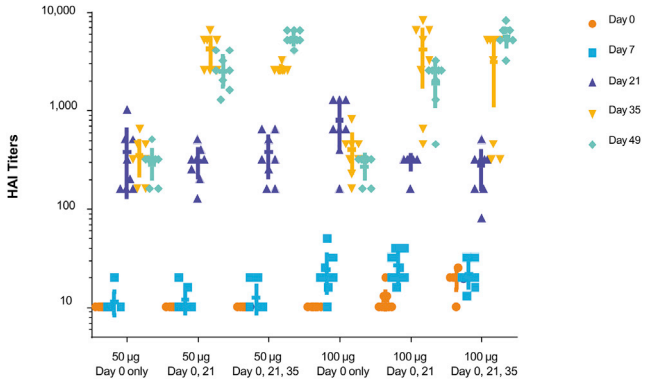

Figure 3. A Single Dose of H10 mRNA in Ferrets Generates Robust HAI Titers, Which Are Significant and Comparable at All Time Points

Ferrets were vaccinated ID with 50 or 100 µg formulated H10 mRNA. $p < 0.0001$, days 21, 35, and 49 versus day 0 with single doses of 50 or 100 µg; $p < 0.0001$ 100 µg single dose, day 7 versus day 0. A subset of immunized ferrets received a boost on day 21 and an additional subset received a second boost on day 35. HAI titers were measured on days 0, 7, 21, 35, and 49 (n = 8/group). $p < 0.0001$ 50 or 100 µg boosting dose(s), days 35 and 49 versus day 0.

(Table S2). Only four events (2.5%), reported by three subjects (13% of exposed subjects), were categorized as severe and included injection site erythema (1.2%), injection site induration (0.6%), and chills/common cold (0.6%) (Table 2; Table S2). No serious AE occurred and all events were expected and reversible. Overall, this reactogenicity profile is similar to that of a monovalent AS03 adjuvanted H1N1 vaccine, and it is comparable to that of meningococcal conjugate vaccine in healthy adults (19 55 years).[40,41]

DISCUSSION

Nucleic acid vaccines (NAVs) offer the potential to accurately express any protein antigen, whether intracellular, membrane bound, or secreted. Although first identified in the early 1990s, mRNA vaccines were not advanced into the clinic until recently due to concerns around stability and production.[42,43] The mRNA vaccines are produced by a well controlled, enzymatic, and well characterized scalable process that is agnostic to the antigen being produced. Additionally, host cell production and presentation of the antigen more closely resemble viral antigen expression and presentation than compared to an exogenously produced, purified, and formulated protein antigen. They offer advantages in speed, precision, adaptability of antigen design and production control that cannot be replicated with conventional platforms. This may be especially valuable for emerging infections, such as potential pandemic influenza.[44] The mRNA vaccine platform described here allows for rapid mRNA production and formulation, within a few weeks, at sufficient quantities to support typical sized clinical trials. Moreover, this mRNA based vaccine technology overcomes the challenges other nucleotide approaches pose, such as pre existing antivector immunity for viral vectors, and concern for genome integration, or the high doses and devices needed (e.g., electroporation), for DNA based vaccines.

Other mRNA vaccine approaches have previously been reported for influenza.[20,45–47] Unmodified, sequence optimized mRNA was used to generate H1 specific responses in mice, ferrets, and pigs at dose levels ~4 to 8 fold higher than tested by us.[20] Brazzoli et al.[45] evaluated a self amplifying mRNA that expressed H1 HA from the 2009 pandemic formulated with a cationic nanoemulsion in ferrets. HAI titers were low but measurable for the 15 µg dose (two of six responders) and at the 45 µg dose (three of six responders) after a single immunization. Following a boost, titers were measurable in all animals and provided protection to a homologous challenge strain.[45] In another study, mice singly immunized against H1N1 (A/WSN/33), receiving a self amplifying mRNA, showed no IgG responses after 7 days. After a second immunization, responses were boosted and animals were protected against a homologous challenge.[46] Immunization in mice against either H1 or H7, with a self amplifying mRNA, induced HAI and IgG titers that were comparable to those achieved in our study at similar doses (Figure 1).[47] Our platform, therefore, is surprisingly efficacious when compared to existing self replicating RNA approaches. It also offers potential additional advantages in terms of rapid onset of immunity, as shown by the protection from challenge achieved after one immunization at low doses (Figure 2), and manufacturability, since it obviates the need to produce very large sized mRNAs to accommodate the self replicating portions of the vectors (typically 7 9 kb).

Modified mRNA has been shown to express more efficiently than unmodified mRNA, likely due to its reduced indiscriminate activation of innate immunity.[29] When included in a vaccine formulation, our modified mRNA technology balances immune stimulation and antigen expression, leading to very potent immune responses that are superior to unmodified mRNA approaches. The very high, transient levels of protein, expressed shortly after administration, are similar to what is seen during a viral infection. Indeed, the biodistribution we observed (Table 1; Table S1) is similar to an influenza virus, where virus could be measured outside the primary site of inoculation after 5 days.[48] Importantly, there was no way for our vaccine to revert to a virulent form because key parts of the virus were missing, including any nonstructural elements or capsid structures.

We selected LNPs for delivery of the mRNA as they have been validated in the clinic for siRNA and are well tolerated compared to other nonviral delivery systems.[22,49] Other groups have relied on either exogenous RNA as an adjuvant or on the adjuvant properties generated during self amplification of the mRNA. Using an LNP, we generate very high levels of transient expression without the need for additional immunostimulatory compounds.

In the studies summarized here, we demonstrated that the LNP based, modified mRNA vaccine technology is able to generate robust and protective immune responses in mice, ferrets, and cynomolgus monkeys. In animals, we showed that a range of doses of formulated mRNA encoding the HA protein of either H7N9 or H10N8 is able to stimulate rapid, robust, and long lasting, immune responses, as measured by HAI, MN assay, and protection from viral challenge. A

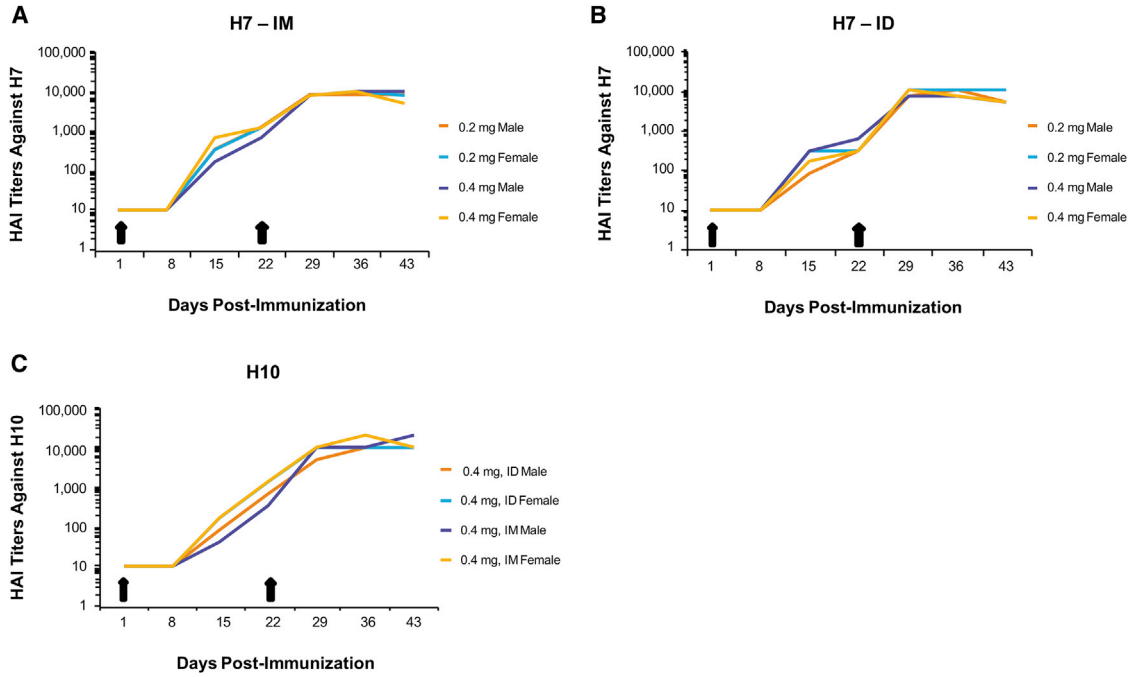

Figure 4. Vaccination with Either H10 or H7 mRNA Generates Strong HAI Titers in Nonhuman Primates following ID and IM Immunizations

(A and B) Male or female cynomolgus monkeys (cynos) were immunized on day 1 with 0.2 or 0.4 mg formulated H7 mRNA, both IM and ID, and received a boosting immunization on day 22. Serum was collected on days 1, 8, 15, 22, 29, 36, and 43 to determine HAI titers. (C) Male and female cynos were immunized with 0.4 mg formulated H10 mRNA via an IM or ID route and received a boosting immunization on day 22. Serum was collected on days 1, 8, 15, 22, 29, 36, and 43 to determine HAI titers (n = 1/group).

single vaccination on day 0 with as little as 0.4 μg was shown to protect mice against challenge with H7N9 on days 7, 21, and 84 (Figure 2), despite the fact that H7 HA has demonstrated relatively poor immunogenicity.[50,51] Increased survival of mice vaccinated with H7 HA and challenged with H7N9 (A/Anhui/1/2013) at early time points (Figure 2) suggests additional mechanism(s) of protection, since HAI titers were below the level of detection (Figure S5). T cells have been shown to elicit protection against pandemic influenza strains.[52,53] We detected T cell responses to both H10 and H7 vaccines at multiple doses (Figures S2C and S2D). Additional follow up studies are ongoing, to determine whether T cell responses alone offer protective benefits, to lend insight into the specific mechanism of vaccine protection.

These interim results of H10 mRNA vaccination in humans are the first published example of a nucleic acid vaccine against an infectious disease working in man without the use of electroporation. Although strategies, such as electroporation, have been developed to increase the efficacy of DNA based vaccines, they continue to have relatively poor immunogenicity compared to protein vaccines.[54] Initial data from the first in human trial appear to confirm a robust immune response with a safe and well tolerated profile. However, the full data set from the trial will need to be evaluated in order to confirm this interim analysis. Nonetheless, these results are encouraging in that microgram dose levels provided immunogenicity with a safety profile comparable to traditional vaccines.[40,41]

The completion of these and additional clinical trials is needed to confirm whether mRNA vaccines will become an effective vaccine platform that can overcome many of the shortcomings of conventional vaccines. Our initial findings are nonetheless encouraging and provide support for further clinical exploration.

MATERIALS AND METHODS

mRNA Synthesis and Formulation

Our mRNA was synthesized in vitro by T7 polymerase mediated transcription from a linearized DNA template, which incorporates 5′ and 3′ UTRs, including a poly A tail.[55] The mRNA is purified and resuspended in a citrate buffer at the desired concentration. A donor methyl group S adenosylmethionine (SAM) is added to methylated capped RNA (cap 0), resulting in a cap 1 to increase mRNA translation efficiency.[56]

LNP formulations were prepared using a modified procedure of a method previously described for siRNA.[57] Briefly, lipids were dissolved in ethanol at molar ratios of 50:10:38.5:1.5 (ionizable lipid: 1,2 distearoyl sn glycero 3 phosphocholine (DSPC): cholesterol: PEG lipid). The lipid mixture was combined with a 50 mM citrate buffer (pH 4.0) containing mRNA at a ratio of 3:1 (aqueous:ethanol) using a microfluidic mixer (Precision Nanosystems). Formulations were dialyzed against PBS (pH 7.4) in dialysis cassettes for at least 18 hr. Formulations were concentrated using Amicon ultra centrifugal filters (EMD Millipore),

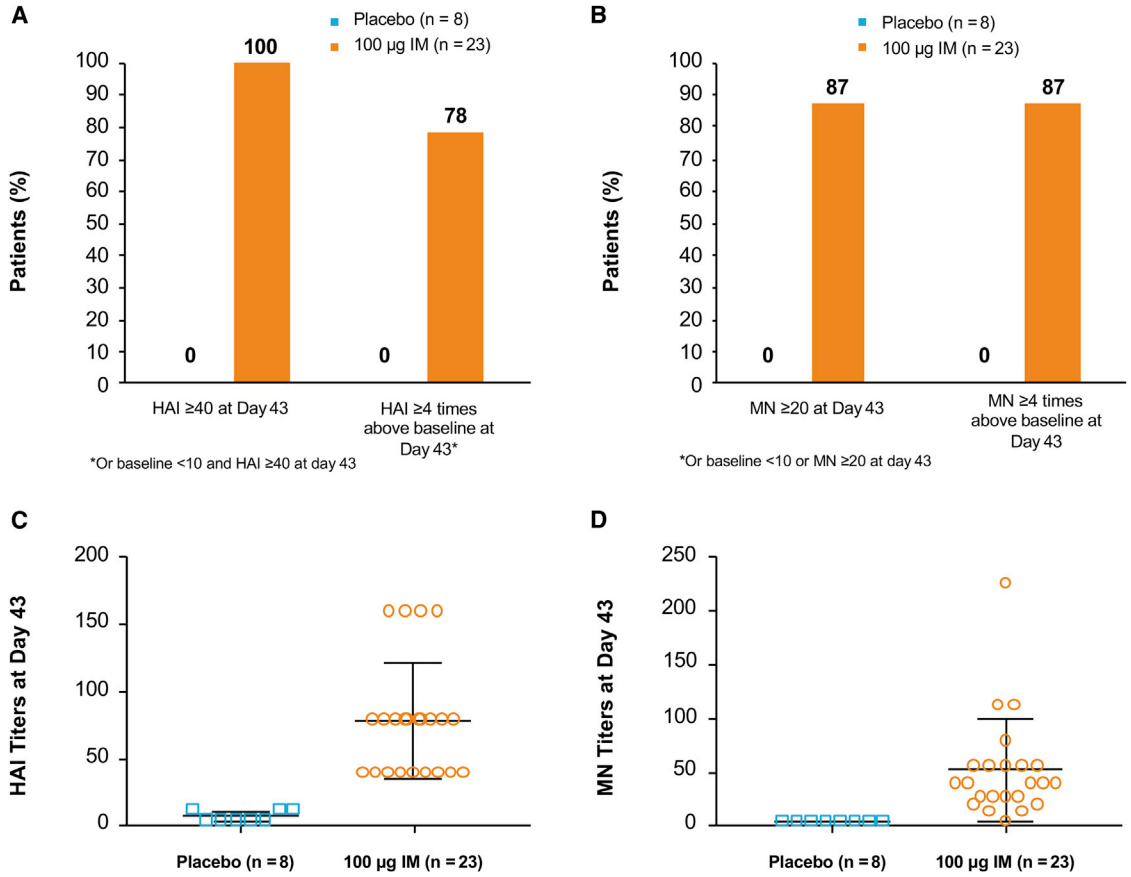

Figure 5. H10 mRNA Immunogenicity in Humans

(A and B) A greater percentage of subjects who received active vaccine had an HAI ≥ 40 (A) and MN ≥ 20 (B) compared to placebo. (C and D) HAI (C) and MN (D) titers of individual subjects were substantially more pronounced in those who received active vaccine compared to placebo. Error bars indicate SEM (100 µg IM, n = 23; placebo, n = 8).

passed through a 0.22 µm filter, and stored at 4°C until use. All formu lations were tested for particle size, RNA encapsulation, and endotoxin, and they were found to be between 80 and 100 nm in size, with >90% encapsulation and <1 EU/mL endotoxin.

In Vitro Expression

The day before transfection, 400,000 HeLa cells (ATCC) were seeded in a six well cell culture plate, and 2.5 µg of either H10 or H7 HA mRNA was transfected using the Transit mRNA transfection kit (Mi rus Bio). Recovered protein lysate, 30 µg, was resolved on a NuPage Novex 4% 12% Bis Tris Protein Gel and transferred onto nitrocellu lose using an iBlot 2 (7 min transfer). Blots were incubated with either anti H10 HA polyclonal antibody (rabbit, 11693; Sino Biological) or anti H7 HA monoclonal antibody (mouse, 11082 MM04; Sino Bio logical) overnight at 4°C. Included as positive controls were 0 5 µg recombinant H10 HA protein (1505 001; IBT) and recombinant H7 HA protein (1502 001; IBT). A polyclonal antibody against actin was also included as a loading control (rabbit, A2066; Sigma Aldrich). Blots were scanned and analyzed on an Odyssey CLx (LI COR Biosciences).

Animal Studies

Female BALB/c mice 5 8 weeks old were purchased from Charles River Laboratories and housed at the study site (Noble Life Sciences or Moderna Therapeutics,). For mouse H7N9 challenge studies, fe male BALB/c mice 7 8 weeks old were purchased from Harlan Lab oratories and housed at MRIGlobal's ABSL 3 facility.

Male ferrets 13 15 weeks old (Triple F Farms) with a baseline HAI titer of ≤20 to influenza virus, A/California/07/2009 (H1N1), A/Wiscon sin/15/2009 (H3N2), and B/Massachusetts/2/2012, were used for studies at MRIGlobal's ABSL 3 facility.

Nonhuman primate studies were conducted at Charles River Labora tories using naive cynomolgus monkeys (cynos), 2 4 years old, weigh ing 2 6 kg. Animals were housed in stainless steel, perforated floor cages, in a temperature and humidity controlled environment (21° 26°C and 30% 70%, respectively), with an automatic 12 hr dark/light cycle. Animals were fed PMI Nutrition Certified Primate Chow No. 5048 twice daily. Tuberculin tests were carried out on arrival at the test facility. The study plan and procedures were approved by

Table 2. Number and Percentage of Subjects Who Experienced a Solicited Reactogenicity Event after Receiving 100 μg H10N8 mRNA IM or Placebo

Parameter	100 μg IM H10N8 mRNA n (%)	Placebo n (%)
Total number of subjects	23 (100)	8 (100)
Any reactogenicity event	23 (100)	5 (62.5)
Mild	23 (100)	3 (37.5)
Moderate	12 (52.2)	1 (12.5)
Severe	3 (13.0)	1 (12.5)
Any local reactogenicity event	12 (91.3)	2 (25.0)
Mild	20 (87.0)	2 (25.0)
Moderate	9 (39.1)	0
Severe	2 (8.7)	0
Any systemic reactogenicity event	21 (91.3)	5 (62.5)
Mild	21 (91.3)	3 (37.5)
Moderate	11 (47.8)	1 (12.5)
Severe	1 (4.3)	1 (12.5)

Reactogenicity was defined as selected AE signs and symptoms occurring after dose administration that were reported by the subject using diary cards during the day of and 6 days after each dose administration. Events were categorized according to the toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials (CBER 2007). AEs were defined as any unfavorable and unintended medical occurrence. Mild AEs were defined as those having no limitations in normal daily activities, moderate AEs as causing some limitations, and severe AEs were defined as events causing inability to perform normal daily activities. The total number of patients are those who received at least one dose of treatment. Percentages are based on the number of patients who reported at least one solicited reactogenicity event after treatment.

PCS SHB Institutional Animal Care and Use Committee (IACUC). Animal experiments and husbandry followed the NIH (NIH Publications No. 8023, eighth edition) and the USA National Research Council and the Canadian Council on Animal Care (CCAC) guidelines. No treatment randomization or blinding methods were used for any of the animal studies. Sample sizes were determined by the resource equation method.

First-in-Human Phase 1 Study

A single center, randomized, double blind, placebo controlled, dose ranging study is ongoing to evaluate the safety and immunogenicity of H10N8 antigen mRNA in humans between the ages of 18 and 64 (Clinical Trials Identifier NCT03076385). Subjects are being followed for up to 1 year post vaccination for safety and immunogenicity. Only interim analysis (day 43) of one dose group cohort (100 μg IM) in healthy adults is reported (all other analyses are ongoing).

Briefly, males and females were eligible for this study if they had a body mass index between 18.0 and 30.0 kg/m^2, were considered in general good health with no ongoing acute or chronic illness, did not have any asymptomatic (e.g., mild hypertension) or any suspected immunosuppressive condition, or and did not have a history of serious reactions to influenza vaccinations or Guillain Barre Syndrome. Eligible adults were randomized at a ratio of 3:1 to receive either H10N8 mRNA 100 μg IM or placebo. All study personnel who conducted assessments were blinded to treatment. Immunogenicity was determined by HAI and MN assays.

Safety was assessed from solicited (local and systemic reactogenicity events) and unsolicited AEs via scheduled clinic visit (vital signs, laboratory assessments, and physical examinations), subject diaries, and follow up telephone calls at specific intervals. AEs were defined as any problematic medical occurrence even if seemingly unrelated to treatment and graded by the Toxicity Grading Scale and defined as mild (transient with no normal daily activity limitations), moderate (some normal daily limitations), and severe (unable to perform normal daily activities).[38] Serious AEs were defined as any occurrence of death, a life threatening situation, hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or any medical event that jeopardizes the subject or requires medical intervention. A safety review committee reviewed safety data at key intervals throughout the study before allowing dose expansion or dose escalation. Prior to study enrollment, all subjects completed a written informed consent in accordance with all applicable local and country specific regulations. This study was conducted by PAREXEL International and was reviewed and approved by an Independent Ethics Committee. This study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki.

Immunizations

For mouse IM immunizations, 50 μL was injected in either the left or right quadriceps. For ferret and mouse ID immunizations, the needle was inserted bevel up with the point visualized through the skin. The vaccine (50 μL) was administered slowly, creating a blister like formation.

For ID delivery to cynos, the material was injected into the lumbar region in a 100 μL vol for the 0.2 mg dose and delivered at two sites for the 0.4 mg dose (0.2 mg in 100 μL per site). For IM delivery to cynos, the material was injected into the left thigh in a 100 μL vol for the 0.2 mg dose or a 200 μL vol for the 0.4 mg dose.

In the human study, each subject in the 100 μg IM cohort received two treatment doses on day 1 and day 22. Each subject received their vaccine via IM administration according to standard procedures in their deltoid muscle, with the second dose administered in the same arm.

Viral Challenges

Influenza strain A/Anhui/1/2013 (H7N9) was grown and characterized at MRIGlobal to a concentration of 3.3×10^8 $TCID_{50}$/mL. BALB/c mice were challenged via IN instillation (2.5×10^5 $TCID_{50}$ in 50 μl Dulbecco's phosphate buffered saline [DPBS]). Anesthetized ferrets were inoculated IN with 1×10^6 $TCID_{50}$ with 2×250 μL per nostril.

Serum Collection

Approximately 200 μL blood was collected from mice via tail vein or retro orbital bleed (1 mL for terminal bleeds) and centrifuged at 1,200 × *g* for serum isolation (10 min at 4°C). Collected blood

(1 3 mL) from the ferrets' cranial vena cava was processed to serum us ing a serum separator tube (SST). Blood collected from the peripheral vein of cynos (0.5 mL) was centrifuged at 1,200 × *g* (10 min at 4°C). All serum was frozen immediately and stored at 80°C.

In the human study, blood samples for immunogenicity analysis were collected via intravenous cannula or by direct venipuncture of the forearm. Serum samples were stored and transported under controlled conditions to Synexa Life Sciences for HAI analysis and to Southern Research Institute for MN testing.

Lung Homogenate

Ferrets were then euthanized by intraperitoneal injection of Euthasol, and lungs (1 cm^3 of the lower part of each of the three right lung lobes), nasal turbinates, and a portion of the trachea were collected. The lung portions were weighed and immediately homogenized and tested in the $TCID_{50}$ assay.

$TCID_{50}$ Assay

Influenza virus levels in nasal washes and lung homogenates were determined by $TCID_{50}$ assay. Madin Darby canine kidney (MDCK) cells were seeded in 96 well plates in serum free media and incubated at 37°C with 5% CO_2. Nasal washes and lung homogenates (four to eight replicates) were serially diluted in serum free media and added to plates that were ≥95% confluent after a single wash. Cytopathic effects (CPEs) were determined after 3 5 days at 37°C with 5% CO_2. The $TCID_{50}$/mL was calculated using the lowest dilution at which CPE was observed. Lung homogenate results were reported as $TCID_{50}$/g lung tissue.

Biodistribution Studies

Male CD 1 mice received 300 μg/kg (6 μg) H10 HA mRNA (50 uL vol) via ID or IM (left side) administration. Blood, heart, lung, spleen, kidney, liver, and skin injection sites were collected pre dose and 2, 4, 8, 24, 48, 72, and 96 hr post ID dosing (n = 4 mice/time point). Two replicates each of bone marrow (left and right femur), lung, liver, heart, right kidney, inguinal and popliteal draining lymph nodes, axillary distal lymph nodes, spleen, brain, stomach, ileum, jejunum, cecum, colon, rectum, testes (bilateral), and injection site muscle were collected pre dose and 2, 8, 24, 48, 72, 120, 168, and 264 hr post IM dosing (n = 3 mice/time point). Blood samples were collected from jugular venipuncture at study termination.

H10 HA mRNA quantification for both serum and tissues was performed by AxoLabs using the Quantigene 2.0 branched DNA (bDNA) Assay (Panomics/Affymetrix).[57] A standard curve on each plate of known amounts of mRNA (added to untreated tissue sam ples) was used to quantitate the mRNA in treated tissues. The calcu lated amount in picograms (pg) was normalized to the amount of weighed tissue in the lysate applied to the plate.

Luciferase Studies

Female BALB/c mice 6 8 weeks old were dosed with formulated lucif erase mRNA via IM or ID administration at four dose levels as follows: 10, 2, 0.4, and 0.08 μg (n = 6 per group). At 6, 24, 48, 72, and 96 hr post dosing, animals were injected with 3 mg luciferin and imaged on an in vivo imaging system (IVIS Spectrum, PerkinElmer). At 6 hr post dosing, three animals were sacrificed and dissected, and the muscle, skin, draining lymph nodes, liver, and spleen were imaged ex vivo.

MN Assay

Heat inactivated serum was serially diluted on 96 well plates, and ~2 × 10^3 $TCID_{50}$/mL H7N9 (A/Anhui/1/2013) was added to each dilution. Following a 1 hr incubation at room temperature, the serum/ virus mixtures from each well were transferred to plates containing MDCK cells and incubated at 37°C (5% CO_2). After 3 5 days, the CPE titer was determined based on the most dilute sample at which no CPE was observed. Each sample was tested three times, and the geo metric mean of the three replicates was reported as the overall titer.

HAI Assay

The HAI titers of serum samples in both the animal and human studies were determined using a protocol adapted from the World Health Organization protocol.[18] Sera were first treated with recep tor destroying enzyme (RDE) to inactivate nonspecific inhibitors. RDE was inactivated by incubation at 56°C for 30 min. Treated sera were serially diluted in 96 well plates, mixed with a standardized amount of recombinant HA (eight HA units of H10N8 or H7N9 rHA; Medigen), and incubated for 30 min at room temperature. Turkey red blood cells (RBCs) (Lampire Biological Laboratories) were then added to the wells of the 96 well plates, mixed, and incubated at room tem perature for 45 min. The most dilute serum sample that completely inhibited hemagglutination was the reported titer for that replicate. Each serum sample was analyzed in triplicate and the results are re ported as the geometric mean of the three results.

IFNγ ELISpot

Mouse IFNγ ELISpot assays were performed using the IFNγ pre coated ELISpot kit catalog 3321 4APW (MabTech), according to the manufacturer's protocol. Briefly, the plates were blocked using complete RPMI (R10) and incubated for 30 min prior to plating cells. Peptide libraries for H7 or H10 were diluted to a final concentration of 10 μg/mL. Mouse splenocytes were pooled by group and plated at 600,000 cells/well, with peptide, phorbol myristate acetate (PMA) + Ionomycin or R10 media alone. Cells were stimulated in a total vol ume of 125 μL/well. Plates were then incubated at 37°C, 5% CO_2 for 18 24 hr. Assay plates were developed and counted using the automated ELISpot reader CTL ImmunoSpot/FluoroSpot. Overlap ping peptide libraries (15mers with ten amino acid overlaps) for H10 HA (A/Jiangxi Donghu/346/2013) and H7 HA (A/Anhui/1/ 2013) were ordered from Genscript.

Statistical Analysis and Data Collection

In general, two datasets were compared by two sample t test and more than two groups were compared by ANOVA proc mixed model. Two way ANOVA was used to analyze titers in lung tissue. Survival curves were compared via log rank (Mantel Cox) test. Statistical an alyses for the animal studies were performed with GraphPad Prism 6.

The phase 1 human clinical trial is being conducted by PAREXEL International, and data were collected utilizing their electronic records ClinBase system. All statistical analyses for the human trial are performed using SAS (SAS Institute, version 9.1 or higher).

SUPPLEMENTAL INFORMATION

Supplemental Information includes seven figures and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.ymthe.2017.03.035.

AUTHOR CONTRIBUTIONS

G.C. led and planned the studies. K.B. and G.C. contributed to the experimental design and analysis of all in vivo studies. O.Y. contributed to the HAI analysis. J.J.S. and A.B. contributed to the toxicology and biodistribution studies, respectively. L.A.B., K.J.H., and O.A. contributed to formulation design and expression optimization. M.E.L. and M.S. contributed to mRNA synthesis and process optimization. A.R., T.Z., and M.W. supervised the conduct of the human study. All authors drafted and revised the manuscript for critical intellectual content and have reviewed and approved the final paper.

CONFLICTS OF INTEREST

This study was funded by Valera Therapeutics, a Moderna Therapeutics venture. Authors K.B., O.Y., K.J.H., A.R., M.W., and G.C. are employees of Valera Therapeutics. Authors J.J.S., A.B., L.A.B., M.E.L, M.S., O.A., J.T., and T.Z. are employees of Moderna Therapeutics.

ACKNOWLEDGMENTS

Statistical analyses were conducted by Georges Carlettis of Strategiestat and Katherine Kacena of BioBridges. Editorial support was provided by Stephanie Eide of BioBridges.

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YMTHE, Volume *25*

Supplemental Information

Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

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SUPPLEMENTAL MATERIALS

Figure S1

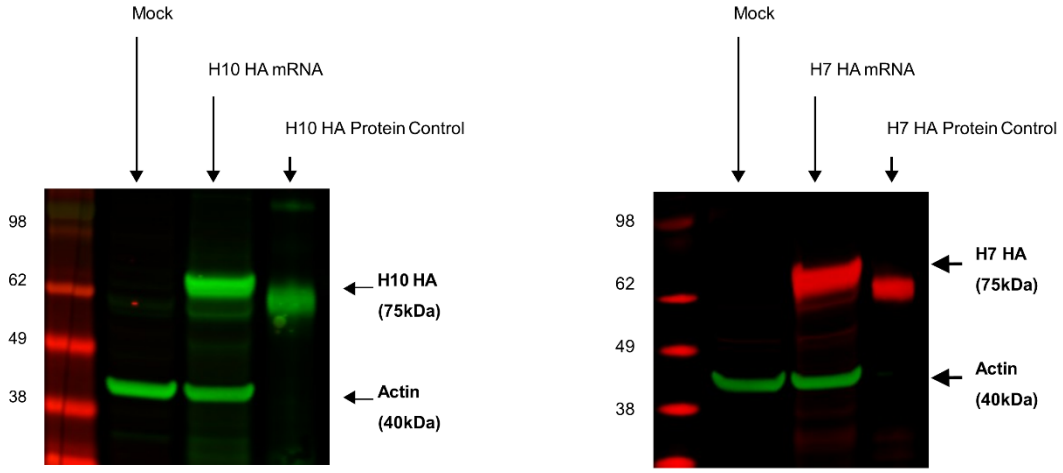

Figure S1. Western blot of resulting cell lysates demonstrated a 75 kDa band for both constructs using the H10 and H7 HA-specific antibodies. H10 and H7 HA protein expression following transfection *in vitro.* HeLa cells were transfected with 2.5 ug of H10 or H7 mRNA for 18–20 h. Lysates were collected and analyzed via Western blot using the corresponding antibodies for detection. H7 and H10 HA protein, along with actin, were included as positive controls.

Figure S2

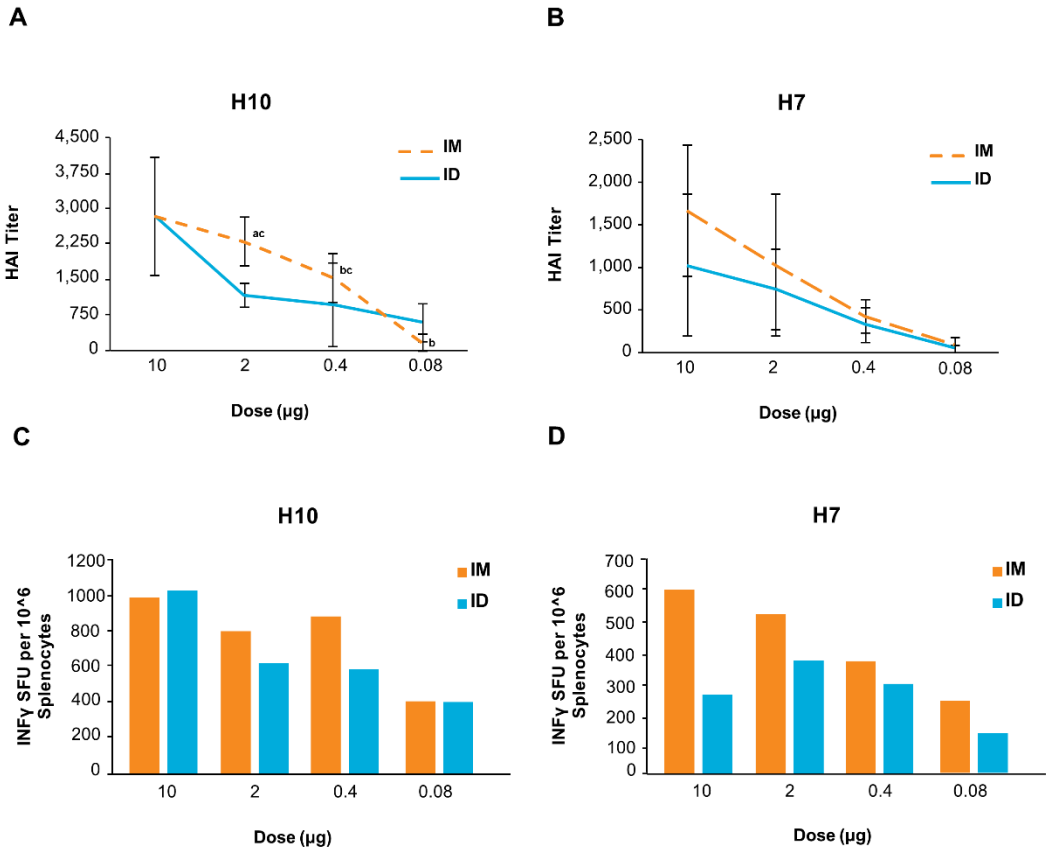

Figure S2. Mice immunized with H10 or H7 mRNA have comparable immune responses following ID and IM immunization at multiple dose levels. BALB/c mice were immunized either ID or IM with doses of 10, 2, 0.4, or 0.08 µg of formulated H10 mRNA or formulated H7 mRNA on days 0 and 21. Serum (individual) and spleens (pooled by group) were collected 28 days post-boost (day 49) to determine HAI titers and T cell responses (IFNγ ELISpot) for H10 (A, C) and H7 (B, D), respectively. [a]$p = 0.0038$ IM versus ID administration; [b]$p < 0.05$ versus 10 µg IM administration and [c]$p < 0.05$ versus 0.08 µg IM administration. (n = 5/group). Error bars indicate standard mean error.

Figure S3

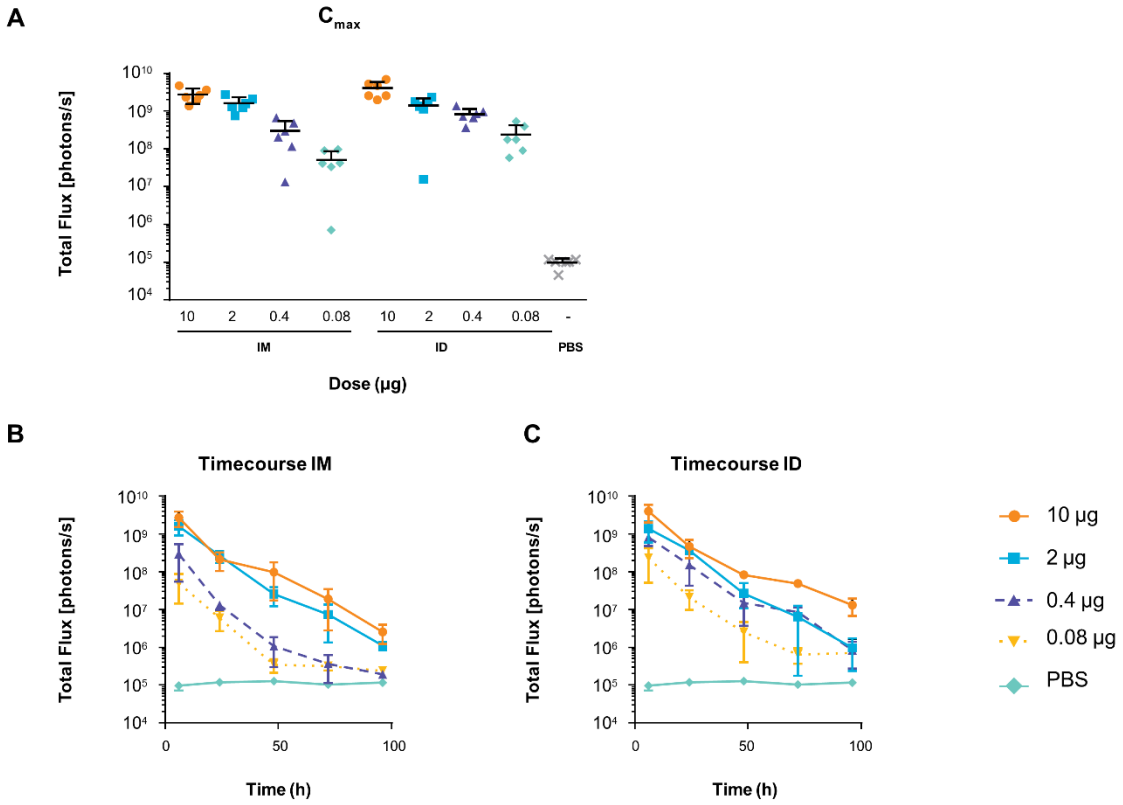

Figure S3. Luciferase expression following IM and ID administration of formulated mRNA. BALB/c mice (*n* = 6/group) were immunized IM or ID with formulated luciferase mRNA with the following doses on day 0: 10 µg, 2 µg, 0.4 µg, or 0.08 µg. At the time of imaging, all mice were injected with 3 mg of luciferin and imaged on an *in vivo* imaging system (IVIS Spectrum, Perkin Elmer). (A) Peak flux (photons/s) after IM and ID administration. (B) Time course of expression following IM administration measured at 6, 24, 48, 72, and 96 hours. (C) Time course of expression following ID administration measured at 6, 24, 48, 72, and 96 hours. Error bars indicate standard mean error.

Figure S4

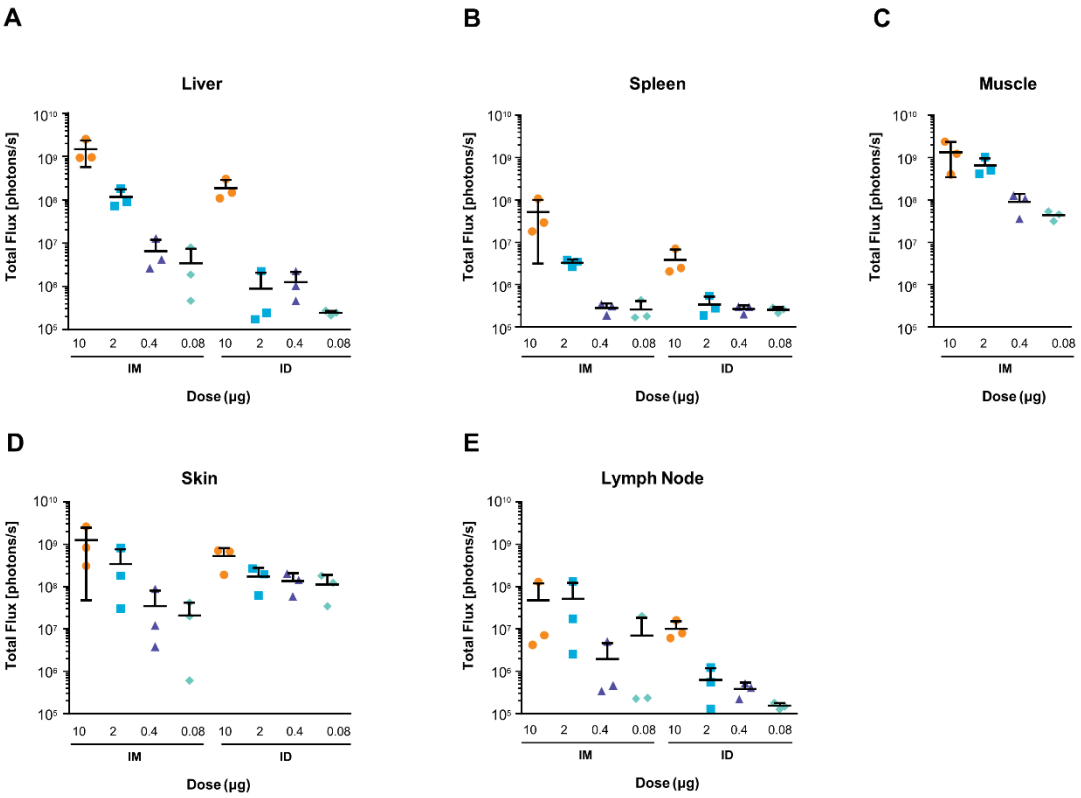

Figure S4. Luciferase expression following IM and ID administration of formulated mRNA. BALB/c mice (*n* = 6/group) were immunized IM or ID with formulated luciferase mRNA with the following doses on day 0: 10 µg, 2 µg, 0.4 µg, or 0.08 µg. At the time of imaging, all mice were injected with 3 mg of luciferin and imaged on an *in vivo* imaging system (IVIS Spectrum, Perkin Elmer). At 6 hours, 3 mice from each group were sacrificed and autopsied, and organs were imaged *ex vivo*. (A) *Ex vivo* liver flux after IM and ID administration. (B) *Ex vivo* spleen flux after IM and ID administration. (C) *Ex vivo* muscle flux after IM administration. (D) *Ex vivo* skin flux after IM and ID administration. (E) *Ex vivo* draining lymph-node flux after IM and ID administration. Error bars indicate standard mean error.

Figure S5

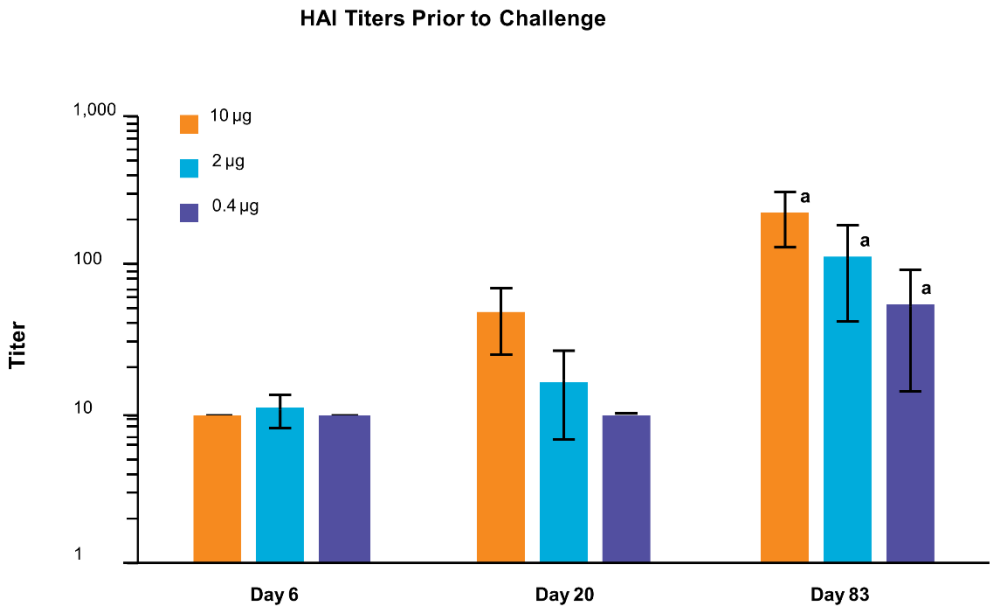

Figure S5. A single injection of an H7 mRNA vaccine achieves high HAI titers in mice. BALB/c mice were vaccinated ID with 10 µg, 2 µg, or 0.4 µg of formulated H7 mRNA. Serum was collected prior to challenge (days 6, 20, and 83) to determine H7 HAI titers. [a]$P < 0.0001$ versus day 6 and day 20 between equivalent dose groups. Error bars indicate standard mean error (n = 15/group).

Figure S6

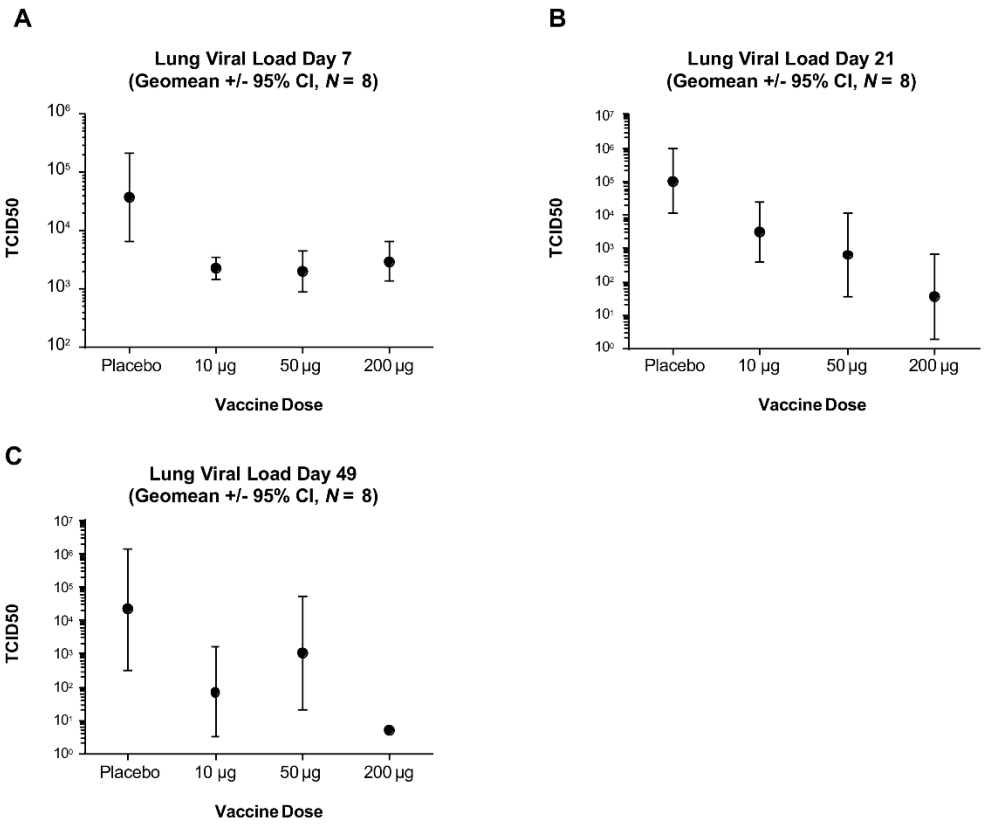

Figure S6. A single dose of H7 mRNA vaccine reduces H7N9 viral loads by 2 logs in ferrets. Ferrets were vaccinated ID with 200 µg, 50 µg, or 10 µg of formulated H7 mRNA. Placebo and 200 µg of formulated H7 mRNA with a reduced 5' cap structure (-15 Da cap) were included as negative controls. A subset of immunized ferrets received a boosting ID vaccination on Day 21 with the indicated doses. (A,B,C) On Day 7 (A), 21 (B), or 49 (C) post-immunization, ferrets were challenged ID with a target dose of 1×10^6 $TCID_{50}$ of influenza A/Anhui/1/2013 (H7N9). Viral burden in the lung was determined by $TCID_{50}$ 3 days post-challenge at the indicated doses. Error bars indicate standard mean error.

Figure S7

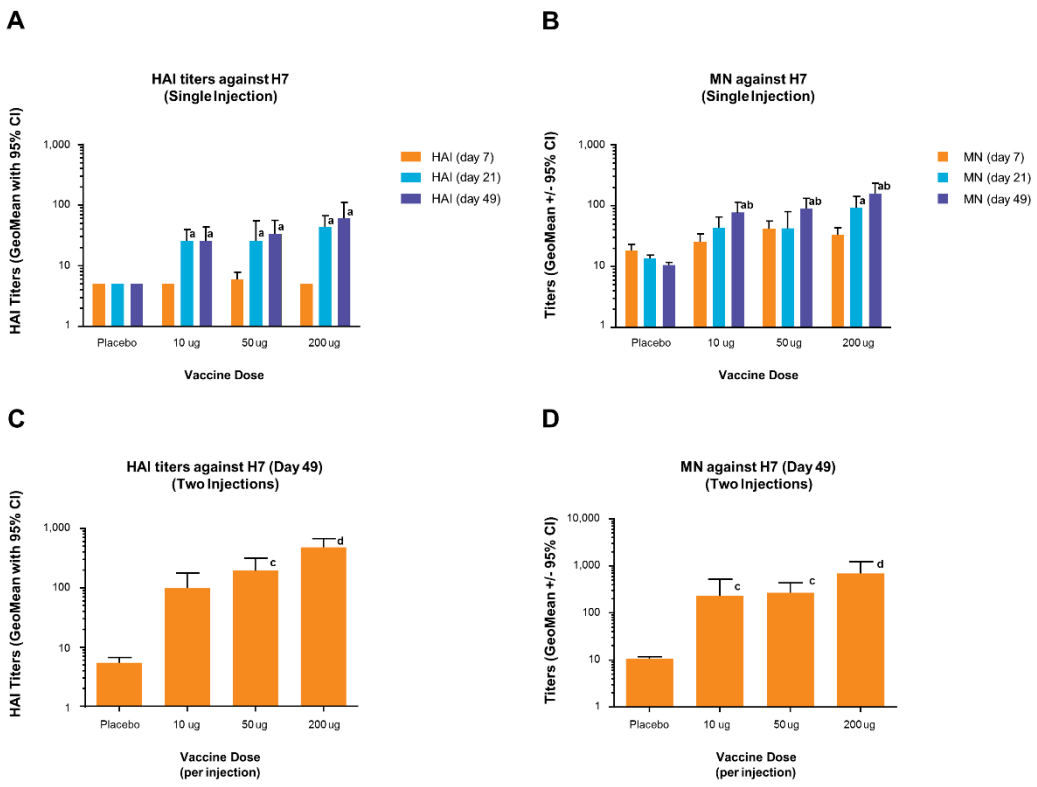

Figure S7. A single dose of H7 mRNA vaccine generates robust HAI titers in ferrets. Ferrets were vaccinated ID with 200 µg, 50 µg, or 10 µg of formulated H7 mRNA. Placebo and 200 µg of formulated H7 mRNA with a reduced 5' cap structure (-15 Da cap) were included as negative controls. A subset of ferrets received a bosting ID vaccination on Day 21 with the indicated doses. Serum was collected from all groups immediately prior to challenge to measure antibody titers via HAI (A) and MN (B) for ferrets that received a single immunization; $^{a}p < 0.05$ versus day 7 and $^{b}p < 0.05$ versus day 21 between equivalent dose groups. Day 49 (28 days post-boost) antibody titers were also measured by HAI (C) and MN (D) for ferrets that received a boosting immunization (n = 8/group). $^{c}P < 0.05$ versus placebo; $^{d}p < 0.05$ versus all others. Error bars indicate standard mean error.

Table S1

Biodistribution of H10 mRNA in plasma and tissue after ID administration in mice. Male CD-1 mice received 300 μg/kg (6 μg) of formulated H10 mRNA via ID immunization. Blood and tissue samples, including heart, lung, spleen, kidney, liver, and skin-injection site, were collected at predose and 2, 4, 8, 24, 48, 72, and 96 hours following dosing. Plasma and tissue sample mRNA levels were quantified using a branched DNA (bDNA) assay (*n* = 4 mice/time point).

	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (pg/mL)	$AUC_{(0-96)}$ (h.pg/g or mL)	$AUC_{(0-inf)}$ (h.pg/g or mL)	T/P
Heart	38.81	24	5.19	226.19	270.16	0.022
Kidney	22.98	24	23.75	612.84	624.76	0.059
Liver	17.98	24	108.62	2957.06	3024.73	0.284
Lung	13.49	24	41.85	1405.46	1433.05	0.134
Spleen	65.74	24	1663.52	114252.46	195225.6	18.3
Skin	23.4	4	18248000	520046043	551134018	50190
Plasma	18.31	24	360.44	10361.63	10660.86	

Table S2

Solicited local and systemic reactogenicity events by severity in subjects who received 100 µg H10N8 mRNA IM or placebo following the toxicity grading scale for heathy adult and adolescent volunteers enrolled in preventative vaccine clinical trials; Tables for laboratory abnormalities (CBER 2007). Adverse events were defined as any unfavorable and unintended medical occurrence. Mild adverse events were defined as those having no limitations in normal daily activities, moderate adverse events as causing some limitations, and severe adverse events were defined as events causing inability to perform normal daily activities. AE = adverse event. [a]Based on the total number of patients who received at least one dose of treatment. [b]Percentages based total number of adverse events after treatment.

	100 µg IM H10N8 mRNA (*N* = 23)					**Placebo (*N* = 8)**				
		Number of Adverse Events[b]					Number of Adverse Events[b]			
	Number of Subjects[a] *n* (%)	Total *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)	Number of Subjects[a] *n* (%)	Total *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)
Any solicited adverse events	23 (100)	163 (100)	107 (65.6)	52 (31.9)	4 (2.5)	5 (62.5)	18 (100)	12 (66.7)	3 (16.7)	3 (16.7)
Any solicited local adverse events	21 (91.3)	52 (31.9)	33 (20.2)	16 (9.8)	3 (1.8)	2 (25.0)	2 (11.1)	2 (11.1)	0	0
Injection site ecchymosis	0	0	0	0	0	0	0	0	0	0
Injection site erythema	5 (21.7)	7 (4.3)	2 (1.2)	3 (1.8)	2 (1.2)	0	0	0	0	0
Injection site induration	5 (21.7)	6 (3.7)	2 (1.2)	3 (1.8)	1 (0.6)	0	0	0	0	0
Injection site pain	21 (91.3)	39 (23.9)	29 (17.8)	10 (6.1)	0	2 (25.0)	2 (11.1)	2 (11.1)	0	0
Any solicited systemic adverse events	21 (91.3)	111 (68.1)	74 (45.4)	36 (22.1)	1 (0.6)	5 (62.5)	16 (88.9)	10 (55.6)	3 (16.7)	3 (16.7)
Appetite loss/decrease	4 (17.4)	4 (2.5)	3 (1.8)	1 (0.6)	0	0	0	0	0	0
Arthralgia, generalized	0	0	0	0	0	0	0	0	0	0
Arthralgia, others	7 (30.4)	8 (4.9)	6 (3.7)	2 (1.2)	0	1 (12.5)	1 (5.6)	1 (5.6)	0	0
Chills, common cold, feeling cold	11 (47.8)	11 (6.7)	4 (2.5)	6 (3.7)	1 (0.6)	1 (12.5)	1 (5.6)	0	1 (5.6)	0
Diarrhea	1 (4.3)	1 (0.6)	1 (0.6)	0	0	1 (12.5)	1 (5.6)	1 (5.6)	0	0
Fatigue	12 (52.2)	20 (12.3)	16 (9.8)	4 (2.5)	0	5 (50.0)	4 (22.2)	3 (16.7)	0	1 (5.6)
Fever	4 (17.4)	4 (2.5)	2 (1.2)	2 (1.2)	0	1 (12.5)	1 (5.6)	1 (5.6)	0	0
Headache	18 (78.3)	21 (12.9)	14 (8.6)	7 (4.3)	0	3 (37.5)	3 (16.7)	2 (11.1)	0	1 (5.6)

Malaise	10 (43.5)	14 (8.6)	9 (5.5)	5 (3.1)	0	2 (25.0)	2 (11.1)	1 (5.6)	0	1 (5.6)
Myalgia, generalized	0	0	0	0	0	0	0	0	0	0
Myalgia, others	12 (52.2)	23 (14.1)	17 (10.4)	6 (3.7)	0	2 (25.0)	2 (11.1)	1 (5.6)	1 (5.6)	0
Nausea, vomiting	3 (13.0)	3 (1.8)	2 (1.2)	1 (0.6)	0	0	0	0	0	0
Systemic others (palpitation, night sweats, throat pain)	2 (8.7)	2 (1.2)	0	2 (1.2)	0	1 (2.5)	1 (5.6)	0	1 (5.6)	0

EXHIBIT 3

Vaccine 37 (2019) 3326–3334

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials

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ARTICLE INFO

Article history:
Received 8 November 2018
Received in revised form 16 April 2019
Accepted 24 April 2019
Available online 10 May 2019

Keywords:
mRNA
Vaccines
Pandemic influenza
Safety
Immunogenicity

ABSTRACT

Background: We evaluated safety and immunogenicity of the first mRNA vaccines against potentially pandemic avian H10N8 and H7N9 influenza viruses.

Methods: Two randomized, placebo controlled, double blind, phase 1 clinical trials enrolled participants between December 2015 and August 2017 at single centers in Germany (H10N8) and USA (H7N9). Healthy adults (ages 18 64 years for H10N8 study; 18 49 years for H7N9 study) participated. Participants received vaccine or placebo in a 2 dose vaccination series 3 weeks apart. H10N8 intramus cular (IM) dose levels of 25, 50, 75, 100, and 400 μg and intradermal dose levels of 25 and 50 μg were evaluated. H7N9 IM 10 , 25 , and 50 μg dose levels were evaluated; 2 dose series 6 months apart was also evaluated. Primary endpoints were safety (adverse events) and tolerability. Secondary immuno genicity outcomes included humoral (hemagglutination inhibition [HAI], microneutralization [MN] assays) and cell mediated responses (ELISPOT assay).

Results: H10N8 and H7N9 mRNA IM vaccines demonstrated favorable safety and reactogenicity profiles. No vaccine related serious adverse event was reported. For H10N8 (N 201), 100 μg IM dose induced HAI titers ≥ 1:40 in 100% and MN titers ≥ 1:20 in 87.0% of participants. The 25 μg intradermal dose induced HAI titers > 1:40 in 64.7% of participants compared to 34.5% of participants receiving the IM dose. For H7N9 (N 156), IM doses of 10, 25, and 50 μg achieved HAI titers ≥ 1:40 in 36.0%, 96.3%, and 89.7% of participants, respectively. MN titers ≥ 1:20 were achieved by 100% in the 10 and 25 μg groups and 96.6% in the 50 μg group. Seroconversion rates were 78.3% (HAI) and 87.0% (MN) for H10N8 (100 μg IM) and 96.3% (HAI) and 100% (MN) in H7N9 (50 μg). Significant cell mediated responses were not detected in either study.

Conclusions: The first mRNA vaccines against H10N8 and H7N9 influenza viruses were well tolerated and elicited robust humoral immune responses.

ClinicalTrials.gov NCT03076385 and NCT03345043.

1. Introduction

H10N8 avian influenza first breached the avian human species barrier in 2013, and was fatal in 2 of the 3 three persons infected [1]. No additional H10N8 human infections have been reported, but the virus has a high affinity for the human receptor, and mutated strains with increased virulence are a significant concern [2]. Also in 2013, the first human H7N9 infections were reported in China, with a fatality rate of 37% [3]. Since 2013, five waves of H7N9 outbreaks have caused over 1500 documented infections

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https://doi.org/10.1016/j.vaccine.2019.04.074
0264-410X/

and more than 600 deaths [4]. In February 2017, the pandemic threat was further highlighted by a death due to a highly pathogenic H7N9 strain with a R292K amino acid mutation associated with neuraminidase inhibitor resistance [5].

Emerging influenza strains reinforce the urgent need for vaccine technologies with precise yet flexible antigen design that generate potent and well tolerated immune responses with rapidly scalable, high volume manufacturing [6]. Egg based technologies do not fulfil these requirements. During the 2009 H1N1 pandemic, 6 months elapsed from the start of the epidemic until the first vaccine doses became available, and an additional 2 months were needed to produce the tens of millions of doses required for the epidemic [6]. The vaccine itself was effective [7,8], suggesting that earlier deployment could have had greater impact. Stockpiling strategies are expensive and lack the flexibility to continuously adapt the vaccine to mutating threats [9]. For example, currently stockpiled vaccines against H7N9 are expected to offer reduced protection against the emerging "wave five" Yangtze River Delta Lineage virus [10].

mRNA vaccines have the potential for rapid, high volume manufacturing with the precision and flexibility of antigen design necessary to provide both timely and effective responses to emerging threats from influenza and other pathogens. They also offer the opportunity for a more flexible stockpiling approach, with the potential to store low volume libraries of frozen plasmid and/or unformulated mRNA for many decades, which can be rapidly formulated and distributed as threat levels rise. mRNA vaccines can direct expression of virtually any membrane bound, soluble, or polyprotein antigens, mimicking antigen expression during natural infection [11]. For influenza, mRNA vaccines could also avoid antigenic drift associated with egg based vaccine production [12]. Additional advantages are economies in time, cost, and scale that derive from using a single development and manufacturing platform. Production of mRNA vaccines does not require pathogen growth: only identification, optimization, and mRNA expression of protective antigen(s) are required.

To assess the safety and immunogenicity of mRNA influenza vaccines, we have developed two avian influenza strains of pandemic potential [13] in our lipid nanoparticle (LNP) formulated mRNA vaccine platform. We present safety and immunogenicity data from two phase 1, randomized, double blind, placebo controlled studies of H10N8 and H7N9 mRNA vaccines in healthy adults. The tolerability and immunogenicity of different dose levels and routes of administration were explored.

2. Methods

2.1. Study design and participants

Two phase 1, randomized, double blind, placebo controlled, dose ranging studies evaluated mRNA H10N8 and mRNA H7N9 vaccines at single centers in Berlin, Germany (PAREXEL International) and South Miami, Florida, USA (Miami Research Associates), respectively. Eligible participants were healthy adults who provided written consent and had no prior history of adverse reactions to influenza vaccinations, diagnosis of Guillain Barré syndrome, receipt of licensed vaccines within 2 4 weeks, receipt of H10N8 or H7N9 vaccine at any time, or history of poultry or wild bird handling.

In the H10N8 study, participants aged 18 64 years were randomized to receive two doses of vaccine or placebo 3 weeks apart at intramuscular (IM) dose levels of 25, 50, 75, 100, and 400 μg or intradermal (ID) dose levels of 25 and 50 μg. In the H7N9 study, adults aged 18 49 years received two doses of vaccine or placebo 3 weeks apart at IM dose levels of 10, 25, and 50 μg. A protocol amendment allowed participants in the 25 and 50 μg IM dose groups to receive a booster dose at 6 months.

The H10N8 trial was approved by the Ethics Committee of the Land Berlin, State Office for Health and Social Affairs, Berlin, Germany. The H7N9 trial was approved by the Chesapeake International Review Board, Columbia, Maryland. The studies were designed in accordance with the Guidance on Clinical Evaluation of New Vaccines [14] and were conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. All participants provided written, informed consent before initiation of any study related procedures.

2.2. Vaccines

The H10N8 and H7N9 mRNA vaccines consisted of chemically modified mRNAs encoding the full length, membrane bound form of the hemagglutinin (HA) glycoprotein from the H10N8 influenza strain (A/Jiangxi Donghu/346/2013) or the H7N9 influenza strain (A/Anhui/1/2013). An LNP delivery system was used as previously described [15]. The H10N8 and H7N9 vaccines were manufactured in compliance with current Good Manufacturing Processes. Each vaccine vial contained 2 mg/mL H10N8 or H7N9 mRNA and 40 mg/mL of LNP excipients formulated in isotonic 8.0% sucrose/20 mM buffer. Study vaccine was diluted with 0.9% saline and administered at a final injection volume of 200 μL. Placebo doses were 200 μL of 0.9% sodium chloride. The initial vaccine doses were selected according to the Guidance for Industry based on the preclinical animal models [13,16].

2.3. Procedures

All participants and study personnel responsible for any clinical evaluations were masked to treatment arm assignment except for 3 sentinel participants in each dose group receiving active vaccine. Vaccines were prepared and administered by unmasked study personnel with no other study involvement. A third party biostatistician performed interim analyses. Randomization codes were generated centrally and stored at study sites with access restricted to designated personnel.

At each dose level, 3 sentinel participants receiving active vaccine were sequentially enrolled 48 h apart for safety evaluation. After review of safety data through 14 days after last sentinel vaccination, additional participants were randomized 3:1 to vaccine or placebo. The study advanced similarly for each subsequent dose level. No sentinel participants were enrolled in the H10N8 vaccine 50 and 75 μg IM dose groups as they were added after enrollment of the 100 μg dose group. IM doses were delivered in the deltoid following standard procedures; ID doses were delivered over the deltoid area. All H7N9 vaccines were administered IM in the deltoid muscle.

2.4. Safety monitoring

In both studies, physical examinations, vital signs, and clinical laboratory assessments were conducted at screening and at days 1 (prior to first vaccination), 8, 22 (prior to second vaccination), 30, and 43. Participants were observed for 60 min after vaccination and followed for 1 year after last vaccination. Safety blood testing was performed at specific timepoints through 21 days after each vaccination (eAppendix 1). Participant diary cards captured solicited local adverse events (AEs; injection site pain, tenderness, erythema, ecchymosis, and injection site swelling) and solicited systemic AEs (headache, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhea, chills, loss of appetite, malaise, and fever) from the day of each vaccination through the following 6 days, and

unsolicited AEs through 21 days after each vaccination. Participants were instructed to call or return to the study site within 24 h if any AE was severe or life threatening during the first 7 days following vaccination.

The intensity of AEs and laboratory abnormalities was graded by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or potentially life threatening (Grade 4) using the Center for Biologics Evaluation and Research toxicity grading scale [17]. AEs were determined by the investigator to be probably, possibly, or not related to study vaccine. Serious AEs (SAEs), severe AEs, medically attended AEs, events of special interest (AESI; a subset of potentially immune mediated medical conditions that are historically associated with a vaccination), new onset of chronic illness, and AEs leading to study withdrawal were collected throughout each study. All AEs were monitored until resolution, or if the event became chronic, until a cause was identified.

For each study, an independent safety monitoring committee performed a blinded safety data review at pre specified time points prior to proceeding to the next dose level. Rules to pause the study were in place to halt further dosing until a safety review was performed (eAppendix 1). For the H10N8 study, the study was paused for any vaccine related anaphylactic reaction, generalized urticarial event, severe unsolicited systemic event, or any SAE. In addition, for any H10N8 cohort (with or without sentinel), the study was paused for any severe solicited AE (systemic or local), any Grade 4 vaccine related AE, or 3 or more Grade 3 vaccine related AEs in any one treatment arm. For the H7N9 study, the study was paused for any vaccine related systemic hypersensitivity event, severe solicited AE (systemic or local), severe unsolicited AE, SAE, Grade 4 AE, or 3 or more severe AEs in any one treatment arm.

2.5. Immunogenicity assessments

Immunogenicity was determined by hemagglutination inhibition (HAI) using recombinant, full length HA proteins for H10N8 (A/Jiangxi Donghu/346/2013, Medigen) or the A/Shanghai/02/2013XPR8 virus for H7N9 and by microneutralization (MN) assays, using the A/quail/Italy/1117/1965 and the A/Shanghai/02/2013XPR8 viruses for H10N8 and H7N9, respectively, as previously described [18,19]. Testing for HAI was performed on blood samples collected at days 1, 8, 22, 30, 43, and 84, and testing for microneutralization (MN) assays was performed on blood samples collected at days 1, 22, and 43. Blood samples for HAI persistence testing were collected at approximately 6 and 12 months after the last vaccination. Peripheral blood mononuclear cells (PBMC) were collected at days 1, 6, 22, 30, 43, and 84 and were analyzed by enzyme linked immunospot (ELISPOT).

Serum antibodies to influenza virus HA proteins (HAI assay) were measured by serial dilution of heat inactivated sera incubated with the titer reported as the reciprocal of the highest dilution that effectively inhibited agglutination of red blood cells by a specific influenza strain. Serum neutralizing antibodies (MN assay) were measured by serial dilution of heat inactivated sera incubated with influenza virus and transferred to plates containing Madin Darby canine kidney (MDCK) cells, with the titer reported as the reciprocal of the highest dilution at which no cytopathic effect was observed. Influenza viruses A/quail/Italy/1117/1965 and A/Shanghai/02/2013XPR8 were used for H10N8 and H7N9 MN assays, respectively [18,19]. Cell mediated immune response was assessed by interferon γ ELISPOT assays of PBMC stimulated with H10N8 and N7N9 HA protein peptide libraries.

2.6. Outcomes

The primary endpoints were safety and reactogenicity as measured by frequency and severity of solicited AEs, unsolicited AEs, and SAEs. Secondary immunogenicity endpoints were HAI (percentage of participants with HAI titers $\geq$ 1:40) and MN (percentage of participants with MN titers $\geq$ 1:20) seroprotective rates and seroconversion rates at day 43. HAI seroconversion rates were defined as baseline HAI titer < 1:10 and post vaccination titer $\geq$ 1:40 or baseline titer $\geq$ 1:10 and $\geq$ 4 fold increase in post vaccination titer. MN seroconversion rates were defined as baseline MN titer < 1:10 and post vaccination titer $\geq$ 1:20 or baseline titer $\geq$ 1:10 and $\geq$ 4 fold increase in post vaccination titer. HAI and MN antibody responses were described as the anti log of the arithmetic mean of the log 10 transformed titers (GMTs) and geometric mean ratios (GMR, post vaccination titer to baseline titer). Endpoints were defined according to the international guidelines for vaccine evaluation [20].

2.7. Statistical analysis

Descriptive statistics were used to summarize demographic and baseline characteristics; there was no planned formal statistical testing. Sample size was not hypothesis driven. A sample size of 30 participants per dose level was planned in both studies; however, actual enrollment was determined by safety and reactogenicity data at each of the dose levels.

Safety and immunogenicity data were analyzed using summary statistics, and included all randomized participants who received $\geq$ 1 dose of vaccine or placebo. Solicited and unsolicited AEs and SAEs were reported as numbers and percentages. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

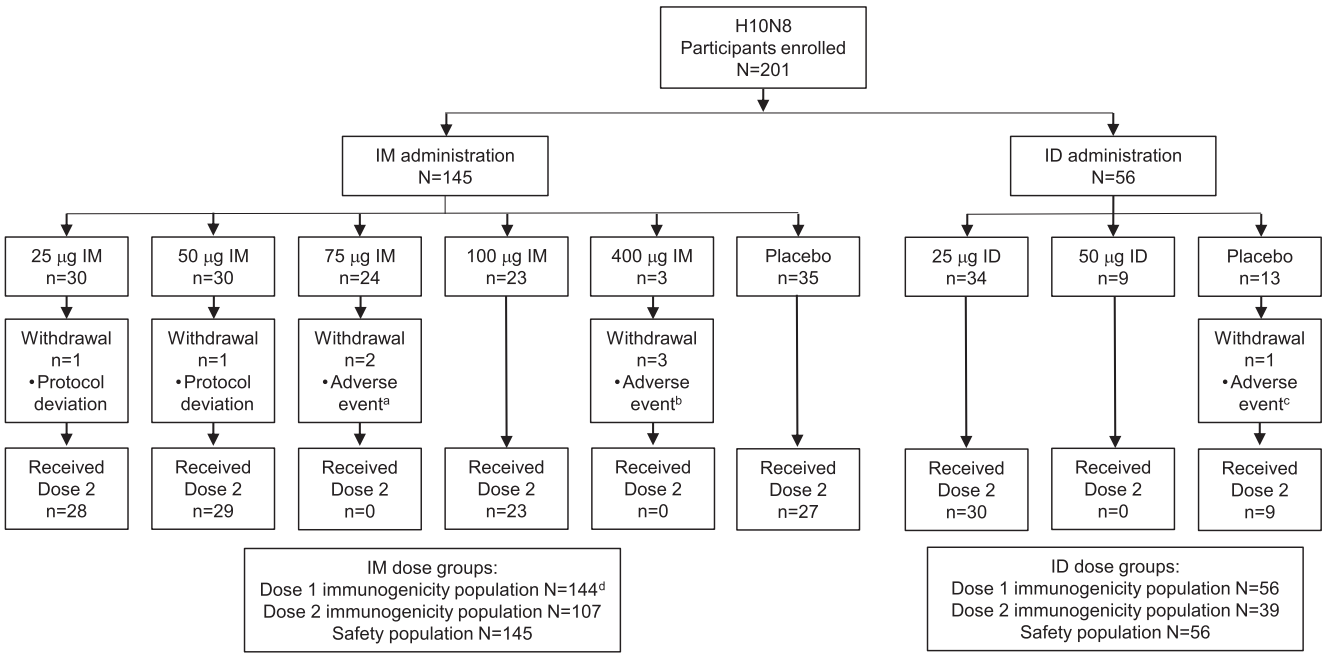
Day 43 analyses of HAI and MN GMT, GMR, seroconversion, and antibody response were conducted for participants who received both doses of vaccine and provided immunogenicity data at baseline and day 43. GMR was calculated as the ratio of GMT pre vaccination (day 1) to GMT at day 43. The fold increase in titer was calculated as a ratio of GMT at Day 43 (21 days after the second vaccination) to the pre vaccination GMT on Day 1 for each participant with both Day 1 and Day 43 results. For GMT calculations, values that were reported as below the lower limit of quantitation (LLOQ) were replaced by 0.5 $\times$ LLOQ. For calculations of fold rise, values < LLOQ were replaced by 0.5 $\times$ LLOQ for the numerator and by LLOQ for the denominator.

Antibody persistence analyses included all participants who received $\geq$ 1 dose and provided immunogenicity data at day 22, and all participants who received both doses of vaccine and provided immunogenicity data at any or all days 43, 84, or 183 (H10N8 study), and days 43, 84, or 205 (H7N9 study). HAI and MN GMTs and their associated 95% confidence intervals (CIs) were reported by study and dose level. Continuous variables were calculated as means with 95% CIs or means with standard deviations (SD). Statistical analyses were performed using SAS® version 9.1 or higher (SAS Institute Inc., Cary, North Carolina, United States).

3. Results

3.1. Participants

Participants were enrolled in the H10N8 study from December 2015 to December 2016 and in the H7N9 study from February 2016 to February 2017. There were 201 participants randomized in the H10N8 study; 145 received IM vaccination and 56 received ID vaccination (Fig. 1). In the IM dose groups, 144 participants received the first vaccination and provided immunogenicity samples at day 22, and 107 participants received both vaccinations and provided immunogenicity samples at baseline and day 43. The second vaccination in the 75 μg dose group was not initiated



Placebo participants were pooled from all treatment arms of similar administration (IM or ID). Immunogenicity population was based on participants who provided evaluable blood samples. All enrolled participants received Dose 1. Dose 2 was administered 21 days after Dose 1. Participant withdrawals are those who withdrew by day 18. [a]Events included severe fatigue on day of vaccination (n=1) and severe erythema on day of vaccination (n=1). [b]Events included injection site erythema on day of vaccination (n=1), severe headache 2 days after vaccination (n=1), and other (n=1). [c]Event was a moderate cold 3 days after vaccination (n=1). [d]1 participant did not provide an evaluable blood sample at day 22.

Fig. 1. Patient flow for the H10N8 Study.

after finding minimal safety concerns in the previously completed 100 μg dose group. Baseline characteristics were similar across all IM dose groups (Table 1). Of the 56 participants in the ID dose groups who received the first vaccination, 39 received the second vaccination. In the 50 μg ID dose group, enrollment was halted because of local reactogenicity, and the second vaccination was not administered. Baseline characteristics for the ID dose groups are shown in eTable 1 (supplemental materials).

There were 156 participants randomized in the H7N9 study (Fig. 2). Thirty participants in the day 1 and day 21 dose groups at the 10 , 25 , and 50 μg dose levels received both vaccinations. Overall, 122 participants provided immunogenicity data at 21 days after the first dose, and 117 participants received 2 doses, provided samples at day 43, and were included in day 43 immunogenicity evaluations. Baseline characteristics were similar across all dose groups (Table 1). Ten participants in the day 1, month 6 dose groups received the first vaccination, and 3, 0, and 2 participants received the second vaccination at the 10 , 25 , and 50 μg dose levels, respectively.

3.2. Safety

3.2.1. H10N8 study

Solicited local and systemic AEs are summarized Table 2. In the IM dose groups, injection site pain after either dose was the most common solicited local AE (78.6 93.1%), followed by erythema (0 17.4%), and injection site swelling (6.7 16.7%). There were 3 Grade 3 solicited local AEs, which all occurred in the 100 μg dose group. The most common solicited systemic AEs after either IM dose were myalgia (7.8 58.6%), fatigue (26.7 47.8%), and headache (14.3 69.6%). Most solicited systemic reactions were mild to mod erate in severity, of short duration (1 3 days), and resolved with out intervention. The incidence of fever was higher following the second dose in the 100 μg dose group and increased with increas ing dose for both first and second vaccinations. In the 400 μg IM dose group, 2 sentinel participants experienced grade 3 solicited AEs (1 injection site erythema, 1 headache) within 24 h of the first vaccination, which resolved spontaneously but met study pause rules (data not shown). After safety review, further 400 μg IM vac cinations were stopped. In the 75 μg IM dose group, 2 participants experienced grade 3 solicited AEs (1 severe swelling, 1 with severe fatigue, myalgia, and injection site pain) following the first vacci nation (data not shown).

Overall, 124 unsolicited AEs were reported in the IM dose groups. The most common unsolicited AEs were upper respiratory tract infection, back pain, pharyngitis, and oropharyngeal pain. Three severe unsolicited AEs (back pain, tonsillitis, ruptured ovar ian cyst) and 2 SAEs (cholecystitis, ruptured ovarian cyst) were reported and deemed unrelated to vaccination. No AESIs or cases of new onset of chronic illness were reported.

ID vaccination was associated with high rates of solicited AEs (eTable 2, supplemental materials), and the sponsor elected to dis continue enrollment of these cohorts.

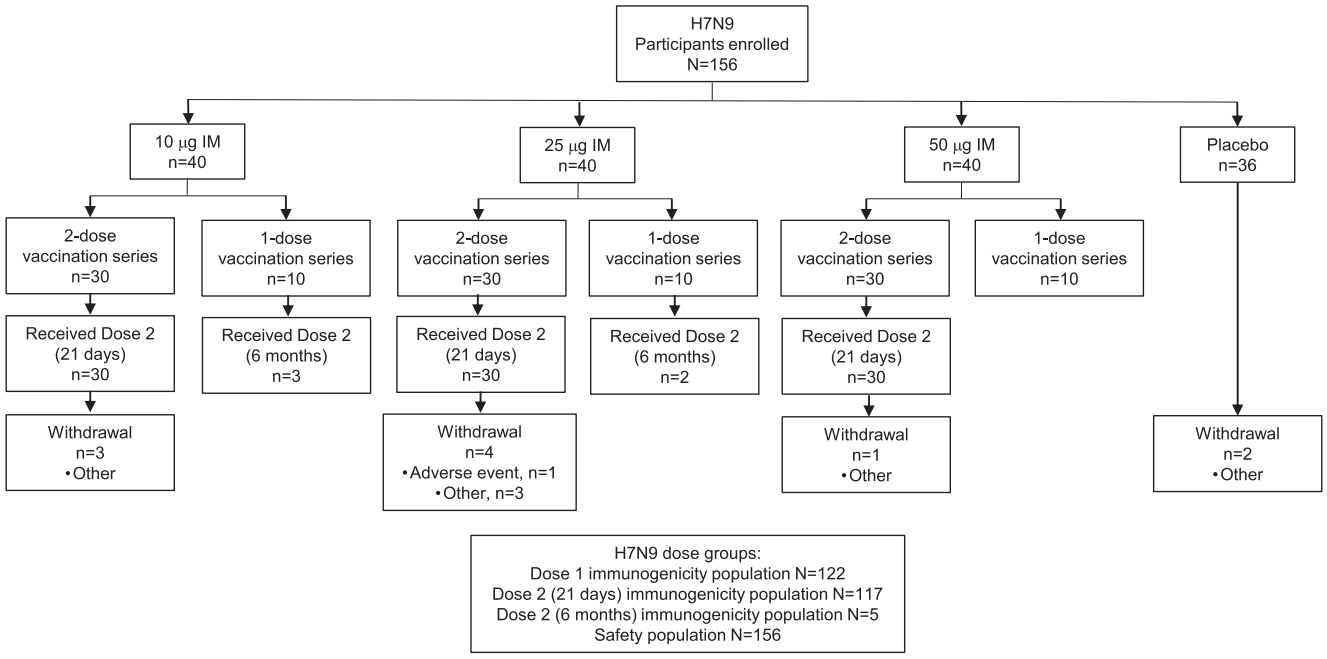
3.2.2. H7N9 study

For H7N9, injection site pain was the most common solicited local AE after either IM dose (43.3 80.0%), followed by swelling (16.7 30.0%) (Table 2); there was no injection site erythema above Grade 1. No severe local solicited AEs were reported after first vac cination; however, 3 participants in the 50 μg dose group experi enced severe injection site pain after the second vaccination. The most common solicited systemic AEs after either dose were head ache (10.0 26.7%), myalgia (10.0 26.7%), and arthralgia (6.7 20.0%). Eleven of the 12 severe solicited AEs occurred in the 50 μg dose group; none required intervention or caused early ter mination. Except for fever in 50 μg dose group, the frequency of solicited local or systemic AEs did not increase after the second vaccination (Table 2).

Table 1
Baseline characteristics of IM administration dose groups.

	H10N8 Study (IM administration)						H7N8 Study (IM administration)			
	25 μg (n = 30)	50 μg (n = 30)	75 μg (n = 24)	100 μg (n = 23)	400 μg (n = 3)	Placebo (n = 35)	10 μg (n = 30)	25 μg (n = 30)	50 μg (n = 30)	Placebo (n = 36)
Age, mean yrs (range)	43.1 (20–62)	42.8 (21–61)	43.3 (19–62)	52.5 (32–64)	45.3 (35–55)	41.4 (35–55)	35.3 (20–49)	39.3 (20–47)	34.6 (19–47)	37.7 (27–46)
Sex, n male (%)	17 (57)	15 (50)	10 (42)	11 (48)	2 (67)	22 (63)	18 (60)	18 (60)	15 (50)	16 (44)
Race, n white (%)	29 (97)	29 (97)	23 (96)	21 (91)	3 (100)	35 (100)	27 (90)	19 (63)	26 (87)	30 (83)
BMI, mean kg/m^2	24.3	25.5	24.6	24.9	22.3	24.7	24.9	28.8	27.3	25.5

All subjects received vaccinations at day 1 and day 21.
IM, intramuscular; BMI, body mass index.



Placebo participants were pooled from all treatment arms. Immunogenicity population was based on participants who provided evaluable blood samples. All enrolled participants received Dose 1. Dose 2 was administered 21 days after Dose 1. Participant withdrawals are those who withdrew by day 18.

Fig. 2. Patient flow for the H7N9 study.

Percentages of participants who reported ≥ 1 unsolicited AE were similar across groups (53.3 73.3% vaccine; 63.9% placebo). Rates of severe unsolicited AEs were 0 20% vaccine and 8.3% pla cebo. The majority of possibly and probably related unsolicited AEs were ≥ Grade 2 laboratory abnormalities and occurred at sim ilar rates in vaccine and placebo groups. Four severe unsolicited AEs were deemed possibly related to vaccination: 2 cases of increased alanine aminotransferase (1 50 μg, 1 placebo), 1 case of increased aspartate aminotransferase (50 μg), and 1 case of throm bocytopenia (placebo). All cases were asymptomatic and resolved without intervention. Five reported SAEs were deemed unrelated to vaccination: unintentional firearm related death, testicular can cer, pancreatitis, facial cellulitis, and exacerbated hypertension. No AESIs or cases of new onset of chronic illness were reported.

3.3. Immunogenicity

For H10N8, HAI and MN GMT increased with increasing dose (Fig. 3A and B) and the percentage of participants with HAI titers ≥ 1:40 or MN titers ≥ 1:20 at day 43 also increased with increasing dose (Fig. 3C and D). At the 25 μg dose level, ID dosing induced higher HAI titers than IM dosing (eFigure 1, supplemental materials). In the H10N8 study, there was a discrepancy between the day 43 seroprotection rate and seroconversion rate in HAI at the 100 μg IM dose, and in MN at the 25 μg IM dose. The number of participants for each dose level was identical in the calculation of seroprotection rate and seroconversion rate. Of the 23 partici pants in the 100 μg dose group, 9 had baseline HAI titers < 1:10, 10 had baseline HAI titers between ≥1:10 and <1:40, and 4 had baseline HAI titers > 1:40. Of the 30 participants in the 25 μg dose group, 25 had baseline MN titers < 1:10, 1 had a baseline MN titer between ≥1:10 and <1:20, and 4 had baseline MN titers > 1:20. Six months after the second 100 μg dose, HAI GMT was 13.9 (Fig. 4A), and 22 of 23 participants (95.6%) remained seropositive (HAI titer ≥ 1:10) (data not shown).

For H7N9 participants dosed on days 1 and 22, post vaccination HAI and MN GMTs were generally high across all doses (Fig. 5A and B). The rate of HAI titer ≥ 1:40 at day 43 was 96.3% in the 25 μg dose group (Fig. 5C). Across all dose levels, all but 1 participant achieved a post vaccination MN titer ≥ 1:20 (Fig. 5D). Six months after vaccination, the HAI GMT was 13.6 (Fig. 4B), and 13 of 25 par ticipants (52%) remained seropositive (HAI titer ≥ 1:10; data not shown).

Five participants (2 in the 25 μg dose level and 3 in the 10 μg dose level) received second doses at 6 months. HAI GMT increased from a baseline of 5 to 73 at the 10 μg dose, and 5 to 381 at the

Table 2
Solicited adverse events within 7 days after each IM vaccination on days 1 and 22.[a]

	H10N8 Study (IM administration)					H7N9 Study (IM administration)			
	25 μg	50 μg	75 μg[b]	100 μg	Placebo	10 μg	25 μg	50 μg	Placebo
Dose 1	n = 30	n = 30	n = 24	n = 23	n = 35	n = 30	n = 30	n = 30	n = 36
Injection site pain	23 (76.6) [0]	25 (83.3) [0]	21 (87.5) [4.2]	19 (82.6) [0]	2 (5.7) [0]	22 (73.3) [0]	17 (56.7) [0]	24 (80.0) [0]	5 (13.9) [0]
Erythema	1 (3.3) [0]	0	1 (3.3) [0]	3 (13.0) [0]	0	0	0	0	0
Injection site swelling	2 (6.7) [0]	5 (16.7) [0]	5 (16.7) [4.2]	3 (13.0) [0]	0	5 (16.7) [0]	5 (16.7) [0]	10 (30.0) [0]	2 (5.6) [0]
Headache	5 (16.7) [0]	12 (40.0) [0]	9 (37.5) [0]	7 (30.4) [0]	5 (14.3) [0]	5 (16.7) [0]	5 (16.7) [0]	7 (23.3) [6.7]	6 (16.7) [0]
Fatigue	8 (26.7) [0]	13 (43.3) [0]	14 (58.3) [4.2]	8 (34.8) [0]	7 (20.0) [0]	1 (3.3) [0]	4 (13.3) [0]	3 (10.0) [0]	2 (5.6) [0]
Myalgia	16 (53.3) [0]	17 (56.7) [0]	17 (70.9) [4.2]	12 (52.2) [0]	1 (2.9) [0]	3 (10.0) [0]	6 (20.0) [0]	8 (26.7) [0]	6 (16.7) [0]
Arthralgia	0	2 (6.7) [0]	4 (16.7) [0]	2 (8.7) [0]	1 (2.9) [0]	2 (6.7) [0]	3 (10.0) [0]	3 (10.0) [0]	4 (11.1) [0]
Nausea	0	1 (3.3) [0]	5 (20.8) [0]	1 (4.3) [0]	0	1 (3.3) [0]	1 (3.3) [0]	1 (3.3) [0]	1 (2.8) [0]
Fever	1 (3.3) [0]	1 (3.3) [0]	0	2 (8.7) [0]	0	0	1 (3.3) [0]	0	0
Dose 2	n = 28	n = 29	NA	n = 23	n = 27	n = 30	n = 30	n = 30	n = 36
Injection site pain	22 (78.6) [0]	27 (93.1) [0]	NA	20 (87.0) [0]	3 (11.1) [0]	14 (46.7) [0]	13 (43.3) [0]	22 (73.3) [10.0]	2 (5.6) [0]
Erythema	0	0	NA	4 (17.4) [8.7]	0	0	0	0	0
Injection site swelling	2 (7.1) [0]	4 (13.8) [0]	NA	3 (13.0) [4.3]	0	3 (10.0) [0]	6 (20.0) [0]	6 (20.0) [0]	1 (2.8) [0]
Headache	4 (14.3) [0]	14 (48.3) [0]	NA	16 (69.6) [0]	6 (22.2) [3.7]	3 (10.0) [0]	2 (6.7) [3.3]	8 (26.7) [6.7]	1 (2.8) [0]
Fatigue	8 (28.6) [0]	13 (44.8) [0]	NA	11 (47.8) [0]	4 (14.8) [0]	1 (3.3) [0]	3 10.0 [0]	4 (13.3) [0]	0
Myalgia	14 (50.0) [0]	17 (58.6) [0]	NA	11 (47.8) [0]	1 (3.7) [0]	3 (10.0) [0]	4 (13.3) [0]	8 (26.7) [3.3]	0
Arthralgia	0	2 (6.9) [0]	NA	7 (30.4) [0]	1 (3.7) [0]	2 (6.7) [0]	1 (3.3) [0]	6 (20.0) [3.3]	0
Nausea	1 (3.6) [0]	1 (3.4) [0]	NA	3 (13.0) [0]	0	0	0	1 (3.3) [0]	0
Fever	1 (3.6) [0]	2 (6.9) [0]	NA	4 (17.4) [0]	1 (3.7) [0]	0	0	6 (20.0) [6.7]	0

AE, adverse event; IM, intramuscular; NA, not applicable.
[a] Data represent n participants reporting any solicited AE (% of any solicited AEs) [% severe solicited AEs] in the safety population.
[b] Participants receiving 75 μg H10N8 vaccine did not receive a second dose.

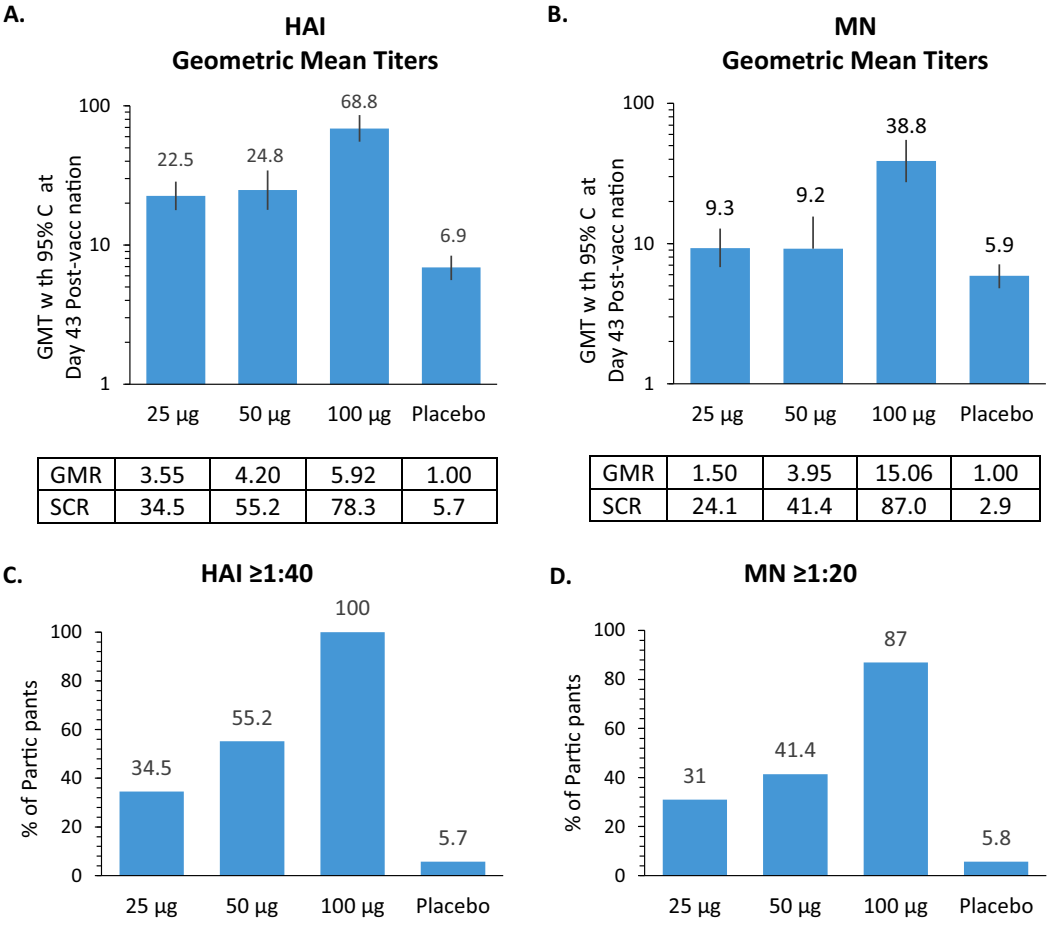


Fig. 3. H10N8 vaccine HAI and MN results at 3 weeks (day 43) after the second IM vaccination at day 21. (A) HAI GMTs, (B) MN GMTs, (C) HAI seroprotective rates (titer ≥ 1:40), and (D) MN seroconversion rates (titer ≥ 1:20) are shown. Error bars represent 95% confidence intervals. HAI, hemagglutination inhibition; MN, microneutralization; GMT, geometric mean titer, GMR, geometric mean ratio (day 43 post-vaccination titer/day 1 pre-vaccination titer); SCR, seroconversion rate (% of participants who achieved seroconversion).

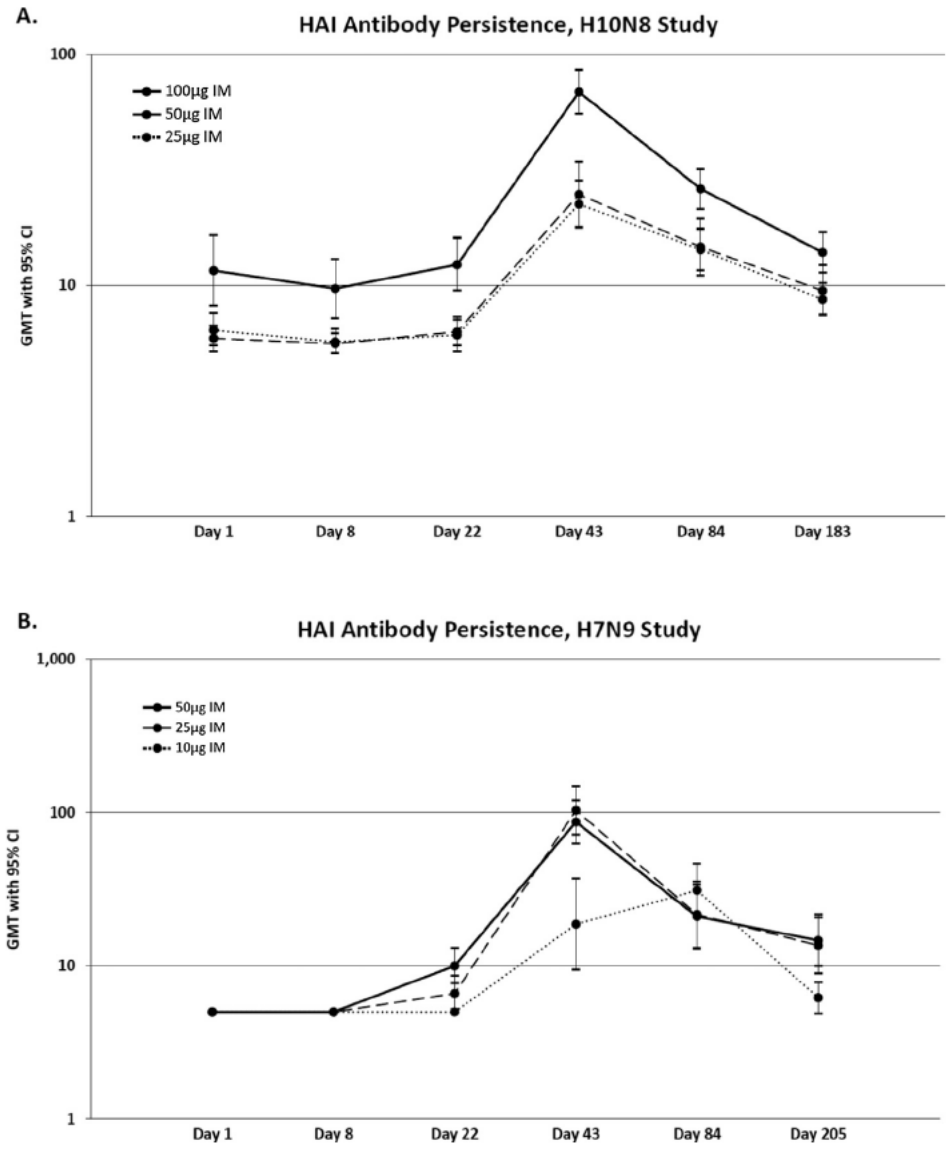


Fig. 4. H10N8 and H7N9 HAI antibody persistence up to 6 months after vaccine doses administered at day1 and day 22. HAI GMT for (A) H10N8 100 µg and (B) H7N9 25 µg dose groups are shown through day 183 (H10N8) or day 205 (H7N9). HAI, hemagglutination inhibition; GMT, geometric mean titers.

25 µg dose. MN GMT increased from 9 to 453 and 7 to 1280 at the 10 and 25 µg dose levels, respectively (eTable 2, supplemental materials).

Significant HA specific cell mediated responses were not detected by interferon γ ELISPOT in either study (data not shown).

4. Discussion

These findings demonstrate the ability of mRNA vaccines to eli cit robust humoral immune responses in healthy adults against H10N8 and H7N9 influenza viruses without adjuvantation [21]. Our studies demonstrate proof of concept that LNP formulated mRNA provides an effective vaccine platform.

Low immune responses observed with unadjuvanted vaccines and low HAI titers seen with natural infection suggest that the HA protein of H7N9 is poorly immunogenic [21,22]. Other H7N9 vaccine candidates have required adjuvantation to elicit acceptable seroconversion and seroprotection rates [23]. Without adjuvant, HAI GMTs and seroconversion rates for these candidates were low (40 47% seroconversion, GMTs 24.1 32.8) [23]. The highest seroconversion rates (96% HAI, 93% MN) were reported with an AS03 adjuvanted vaccine [24] and were comparable to our H7N9 mRNA vaccine seroconversion rates of 36.0 89.7%, and HAI GMTs of 18.7 87.0 (although intrinsic variability in HAI assays precludes direct comparisons). The HA protein, particularly H7N9 HA, is not predicted to be a robust T cell antigen [21], perhaps explaining the lack of significant HA specific cell mediated responses in our studies.

In addition, our H7N9 mRNA vaccine showed HAI titers that were detectable and persistent 6 months post vaccination, sug gesting the development of memory B cell responses. A rapid and high anamnestic like immune response was observed in par ticipants with undetectable HAI titers 43 days after the first 10 µg dose, suggesting robust antibody maturation [25]. Although based on results from only 5 participants, post vaccination titers at 6 months exceeded the level of immunity observed after 2 doses 3 weeks apart at the 10 and 25 µg dose levels, suggesting that a day 1, month 6 immunization schedule in pandemic settings could confer sufficient protective immunity.

To our knowledge, no other H10N8 vaccine has been evaluated; therefore, no immunological benchmark for vaccine response exists. High seroconversion rates observed in our study are consis

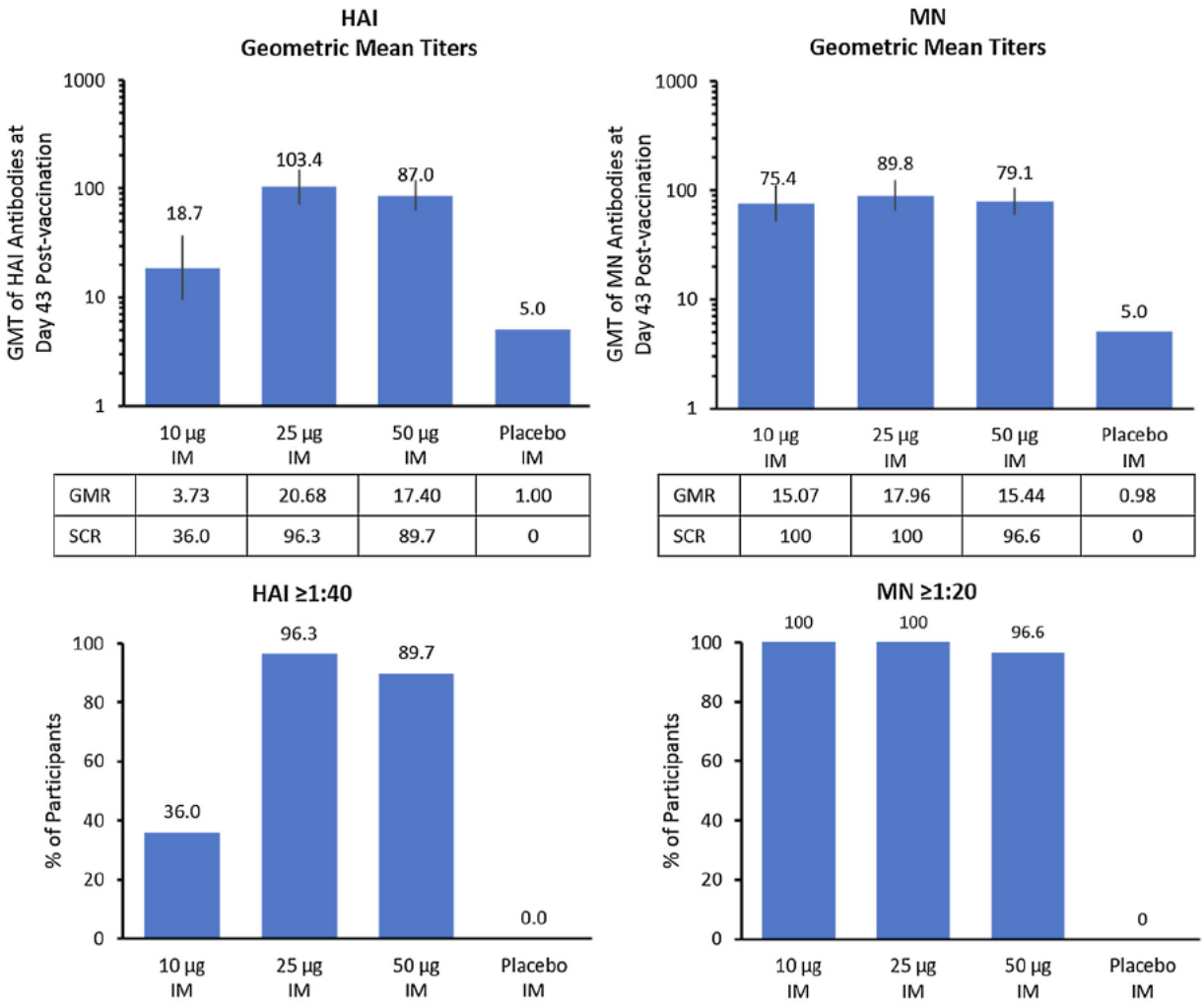


Fig. 5. H7N9 HAI and MN results at 3 weeks (day 43) after the second IM vaccination at day 21. (A) HAI GMTs, (B) MN GMTs, (C) HAI seroprotective rates (titer ≥ 1:40), and (D) MN seroconversion rates (titer ≥ 1:20) are shown. Error bars represent 95% confidence intervals. HAI, hemagglutination inhibition; MN, microneutralization; GMT, geometric mean titer, GMR, geometric mean ratio (day 43 post-vaccination titer/day 1 pre-vaccination titer); SCR, seroconversion rate (% of participants who achieved seroconversion).

tent with a similarly immunogenic vaccine to H7N9, albeit requir ing a higher dose. Overall, for doses up to 100 µg, safety and reac togenicity profiles for our H10N8 and H7N9 vaccines were comparable to licensed adjuvanted and unadjuvanted influenza vaccines [26 30]. The nature, severity, frequency, and patterns of AEs were consistent with those seen with other vaccinations [28 30].

A limitation in the H10N8 MN assay was the lack of availability of a live H10N8 strain; therefore, a surrogate quail virus (A/quail/1117/1965) with 91% homology for the HA protein was used for MN assays. This may have contributed to differences in dose levels required to elicit ~100% seroconversions. Although HAI and MN titers correlated with levels expected to provide protection with seasonal influenza vaccines, it is unknown if these titers are protec tive [23,31 34]. Though HAI and MN parameters are current stan dards for vaccine response, these tests may underestimate immunogenicity [35], and may not accurately estimate protective immunity for pandemic influenza strains [14,36]. However, based on these tests, our mRNA vaccines elicited some of the highest sero protective and seroconversion rates observed for influenza vaccines.

Both influenza strains A/H7N9 and A/H10N8 are serious poten tial threats to public health, which emphasizes the need for effec tive, rapidly deployable vaccines. Recent mechanistic studies with the mRNA vaccine platform [37,38] confirm translatability from preclinical studies, and safety data from a non LNP formulated vaccine [39] provide further support for this new class of vaccines. These phase 1 studies demonstrate both safety and robust immune responses to mRNA vaccines against H10N8 and H7N9 influenza viruses, and support the potential of mRNA to deliver a vaccine platform with precision, speed, adaptability, and scalability.

Acknowledgments

Formulation support was provided by Luis Brito and Kimberly Hassett. Statistical support was provided by Strategistat, SPRL, Bel gium. Medical writing support was provided by Stephanie Eide of BioBridges, Wellesley Hills, MA and Julia R. Gage of Gage Medical Writing, LLC, Moorpark, CA and was funded by Moderna.

Author disclosures

R. Feldman has nothing to disclose. R Fuhr is an employee of PAREXEL International, a contract research organization that was sponsored to conduct this study. I. Smolenov, A. Ribeiro, L. Panther, M. Watson, J.J. Senn, M. Smith, Ö. Almarsson, H.S. Pujar, M.E. Laska, J. Thompson, T. Zaks, and G. Ciaramella are employees of Moderna Therapeutics. G. Ciaramella also has a patent 9872900 licensed to Modera Therapeutics.

Author contributions

G. Ciaramella led the projects. G. Ciaramella and T. Zaks designed the studies. R.A. Feldman and R. Fuhr were the principal investigators for the H7N9 and the H10N8 studies, respectively, and contributed equally to this work. A. Ribeiro and L. Panther were responsible for the clinical operations of the studies. I. Smo lenov, M. Watson, and T. Zaks had overall supervision for the clin ical and safe conduct of the studies. Ö. Almarsson, M. Smith, J.S. Pujar, and M.E. Laska were responsible for mRNA process and for mulation development. J.J. Senn conducted GLP toxicology studies. J. Thompson and M.E. Laska were responsible for process develop ment for the vaccine manufacturing. I. Smolenov and G. Ciaramella reviewed and analyzed the data and wrote the manuscript. All authors reviewed and approved the final version of this manuscript for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.074.

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EXHIBIT 4

Molecular Therapy
Nucleic Acids
Original Article

Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines

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mRNA vaccines have the potential to tackle many unmet medical needs that are unable to be addressed with conventional vaccine technologies. A potent and well-tolerated delivery technology is integral to fully realizing the potential of mRNA vaccines. Pre-clinical and clinical studies have demonstrated that mRNA delivered intramuscularly (IM) with first-generation lipid nanoparticles (LNPs) generates robust immune responses. Despite progress made over the past several years, there remains significant opportunity for improvement, as the most advanced LNPs were designed for intravenous (IV) delivery of siRNA to the liver. Here, we screened a panel of proprietary biodegradable ionizable lipids for both expression and immunogenicity in a rodent model when administered IM. A subset of compounds was selected and further evaluated for tolerability, immunogenicity, and expression in rodents and non-human primates (NHPs). A lead formulation was identified that yielded a robust immune response with improved tolerability. More importantly for vaccines, increased innate immune stimulation driven by LNPs does not equate to increased immunogenicity, illustrating that mRNA vaccine tolerability can be improved without affecting potency.

INTRODUCTION

Since the first active immunization, vaccines have provided increased life expectancy and improved public health, saving countless lives.[1,2] Today, a variety of technologies exist for vaccine development, including live and attenuated viruses, recombinant proteins, synthetic peptides, glycoconjugates, and nucleic acids.[1] Nucleic acid (DNA and mRNA) based vaccines offer several advantages over other technologies. They can be rapidly produced with reduced development time and costs by using a common manufacturing platform and purification methods regardless of the antigen. Unlike manufacturing for other vaccines, these methods would not include propagation of viruses or purification of a recombinant protein. The antigen would be expressed *in situ*, allowing for transmembrane domains to be present, if needed, and multimeric complexes to be formed.[3] Additionally, nucleic acids do not suffer from anti vector immunity like viral vectored vaccines do. Lastly, proteins produced by nucleic acid based vaccines can provide a more natural presentation to the immune system, yielding better T cell responses.[4] Even so, more than two decades after the first proof of concept report,[5] no nucleic acid based vaccine has been approved for use in humans.

A key factor hampering both DNA and mRNA vaccine development is the lack of a potent, well tolerated delivery system. Because DNA requires delivery to the nucleus, an inherently inefficient process, high doses (1–2 mg) and an electroporation device are required to generate robust immune responses. Although recent advances in DNA electroporation have shown promise, the broad adoption of the technology will likely be limited due to the necessity of a specialized device and the pain associated with electroporation.[6–8] An advantage of mRNA over DNA is that mRNA only requires cytosolic delivery. In rodents, early studies showed that intramuscular administration of buffer formulated mRNA can lead to measurable levels of immunogenicity.[9] However, a recent phase I trial of a rabies mRNA vaccine administered in Ringer's buffer yielded no immunogenicity unless delivered with a high pressure intradermal injection device.[10]

Although promising, these results highlight the need for more potent intracellular delivery technologies for mRNA vaccines. One such technology is lipid nanoparticles (LNPs). LNPs are typically composed of an ionizable lipid, cholesterol, PEGylated lipid, and a helper lipid such as distearoylphosphatidylcholine (DSPC). Early work with small interfering RNA (siRNA) identified the ionizable lipid as the primary driver of potency.[11–13] The most clinically

Received 28 September 2018; accepted 26 January 2019;
https://doi.org/10.1016/j.omtn.2019.01.013.

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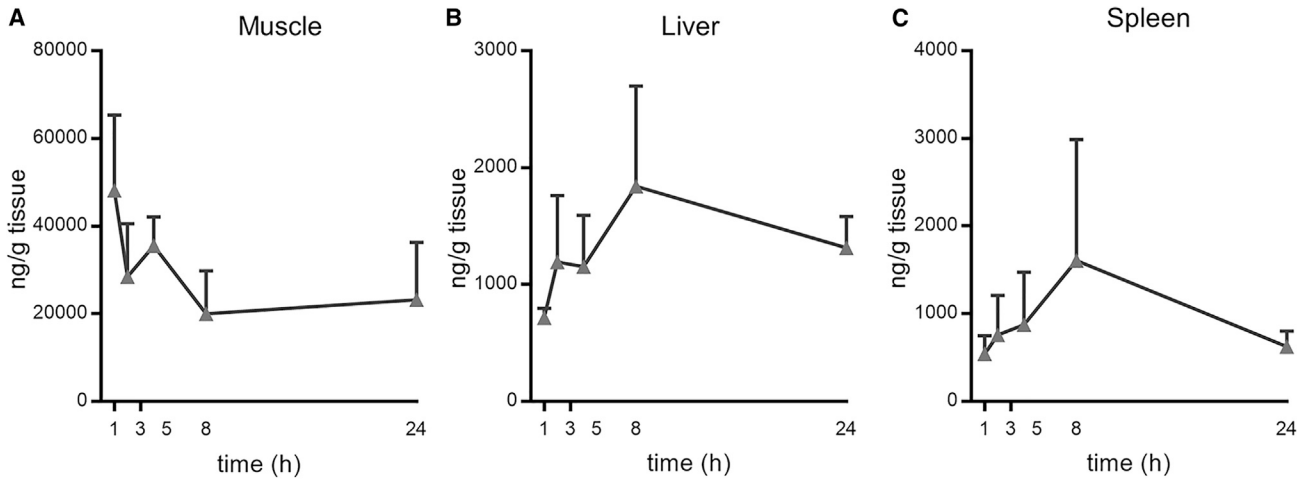

Figure 1. Pharmacokinetics of LNPs containing MC3 after IM administration in mice

Lipid concentration (nanograms per gram) after IM administration of modified mRNA encoding luciferase formulated in LNPs containing MC3 (gray triangles) in muscle, liver, and spleen up to 24 h post injection (n = 3 per group per time point).

advanced LNP contains the ionizable lipid MC3 and has been shown to be safe in humans after intravenous (IV) administration of siRNA.[14] Our own vaccine trials with MC3 based LNPs for influenza gave 100% seroconversion with a 100 μg dose of modified mRNA. However, consistent with other vaccines,[15,16] we did observe mild to moderate local and systemic adverse events.[17] As healthy individuals ranging from day old newborns to the elderly receive vaccines, critical features for broad vaccine adoption are minimal injection site reactivity and high tolerability. To date, the only LNPs evaluated for intramuscular (IM) mRNA vaccine delivery were originally optimized for IV delivery of siRNA to the liver.[18,19] Although there are preclinical reports of novel LNPs being evaluated for vaccines, no rationale has been provided regarding formulation composition or selection.[20–22]

Here, we describe rational evolution and selection of an improved formulation for IM administration of mRNA, focusing on the impact of the ionizable lipid component as the primary driver of expression and tolerability. Our previous experience with IV administration of the proprietary ionizable lipids showed rapid clearance compared to MC3,[23] resulting in improved systemic tolerability. Our work here illustrates that the ideal formulation for IV expression is not necessarily ideal for IM expression. Additionally, we also show that increased innate immune stimulation driven by the LNP is not necessary for increased immunogenicity, illustrating that we have an opportunity to improve vaccine tolerability without affecting vaccine potency.

RESULTS

Observations of mild to moderate adverse events in our clinical work with MC3[17] and data showing slow MC3 clearance after IV administration[23] fueled a hypothesis that the adverse events might be related to the extended presence of MC3 at the injection site. Mass spectrometry analysis of muscle tissue revealed that, 24 h after IM injection, the MC3 concentration only decreased by 50% compared to C_{max} (Figure 1A). Further, MC3 was also detectable in liver and spleen 24 h post IM injection (Figures 1B and 1C). Thus, IM administration of MC3 formulated mRNA LNPs resulted in extended local and systemic lipid exposure.

The goal of the work described here was to identify a new ionizable lipid with improved tolerability and a potency equal or better than that of MC3. To do so, we screened 30 novel LNPs, each containing a different ionizable lipid in place of MC3. Each LNP formulation maintained the same lipid nitrogen to phosphate ratio (N:P) and molar composition of lipid components (ionizable lipid, cholesterol, phospholipid, and polytheylene glycol [PEG] lipid). Co formulation of mRNAs encoding firefly luciferase and the H10N8 influenza hemagglutinin (HA) antigen allowed both protein expression and immunogenicity to be evaluated in the same study. Luciferase activity was measured by whole body imaging 6 h post IM injection of the first dose. Immunogenicity was evaluated by quantifying α H10 immunoglobulin (Ig)G titers 2 weeks after the second dose, which was administered 3 weeks after the first. The ionizable lipids screened here all contain a tertiary amine with ester containing lipid tails to enable rapid *in vivo* metabolism.[23] In addition, we also tested the quaternary ammonium containing lipid N [1 (2,3 Dioleoyloxy)propyl] N,N,N trimethylammonium (DOTAP).

Consistent with our previous publications, MC3 formulated mRNA yielded robust titers and protein expression at a low dose (0.001 mg per kg).[17,24] In contrast, we observed no detectable protein expression or immunogenicity for DOTAP containing LNPs (Figure 2A). Many of our novel biodegradable lipids proved superior to MC3 for both protein expression and immunogenicity upon IM administration. However, there was no strong relationship between protein

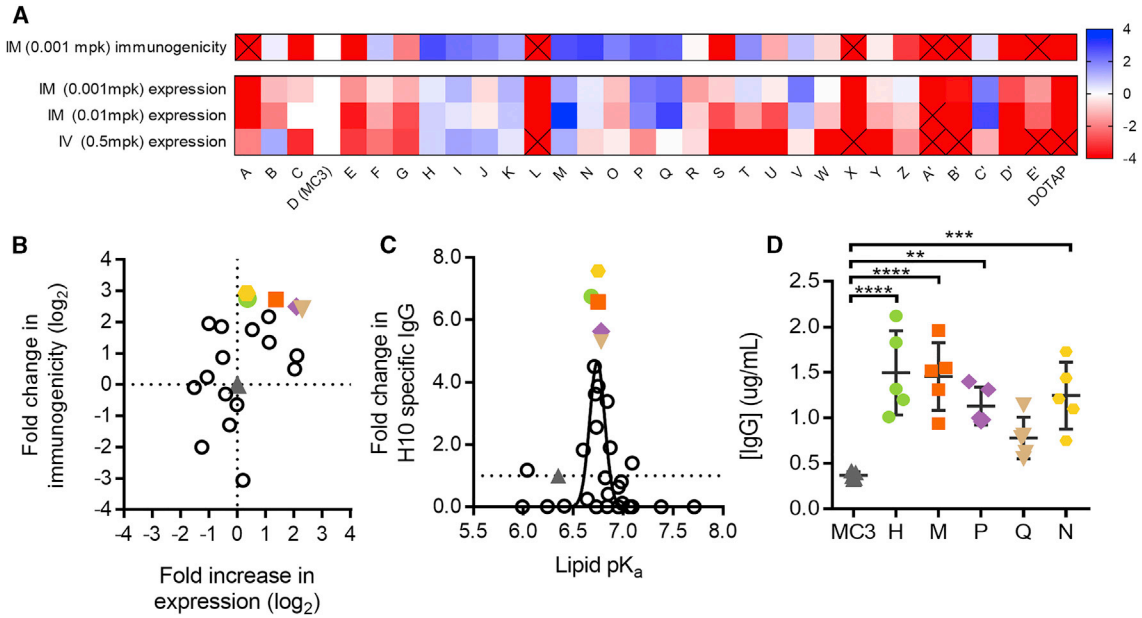

Figure 2. Expression and Immunogenicity from LNPs Containing Novel Ionizable Lipids in Mice

(A) Thirty novel lipid LNPs, A through E′ were compared to a D (MC3) LNP control for expression and immunogenicity. Lipids are arranged left to right in order of pKa from low (A) to high (DOTAP). Expression measured by luminescence in flux (photons per second) 6 h after administration of modified mRNA encoding luciferase delivered at 0.5 mg/kg IV in CD 1 mice, 0.01 mg/kg IM or 0.001 mg/kg IM in BALB/c mice (n = 5 per group). Immunogenicity measured by H10 specific IgG titers measured 2 weeks after two doses administered 3 weeks apart delivered IM at 0.001 mg/kg IM in BALB/c mice (n = 5 per group). Data are represented as $\log_2$ fold change compared to MC3. Squares containing an X indicate >4 fold change ($\log_2$) lower than for MC3. (B) Log_2 fold increase in expression was compared to the $\log_2$ fold change in immunogenicity at the low dose level administered IM (0.001 mg/kg). The five lead novel lipids and MC3 LNPs are labeled accordingly: MC3 (gray triangles), lipid H (green circles), lipid M (orange squares), lipid P (purple diamonds), lipid Q (tan inverted triangles), and lipid N (yellow hexagons). (C) Lipid pK_a versus fold increase in immunogenicity at 0.001 mg/kg IM for lipids A through E′. (D) Circulating IgG antibody (micrograms per milliliter of serum) 6 h after administration of 0.2 mg/kg modified mRNAs encoding the heavy chain and light chain of an influenza monoclonal antibody formulated at a 2:1 mass ratio in LNPs containing MC3 or novel lipids (n = 5 per group). *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001, ordinary one way ANOVA with Dunnett's multiple comparisons test of each novel lipid versus MC3.

expression and immunogenicity (r = 0.54). Of the 14 lipids yielding higher α H10 IgG titers than MC3, four lipids yielded significantly less luciferase expression relative to MC3, whereas four lipids yielded significantly greater luciferase activity (Figure 2B). The two lipids with the highest α H10 IgG titers were only 1.3 fold better than MC3 with regard to protein expression, illustrating that protein expression upon IM administration was a poor predictor of immunogenicity.

We also found little correspondence in rank between the LNPs with regard to IM versus IV expression (Figure 2A), illustrating that for mulations can behave differently when administered locally versus systemically. A possible explanation for the lack of correlation be tween IM and IV performance could be that the optimal physical or chemical properties differ between the two routes. One strong determinant of immunogenicity was the lipid pKa, with a range of 6.6 6.9 being optimal for IM immunogenicity (Figure 2C). This dif fers from the optimal pKa range for IV delivery of siRNAs and mRNAs, which has been reported as 6.2 6.6.[11,23] mRNA encapsula tion efficiencies and LNP sizes ranged from 69% to 100% and from 50 to 142 nm, respectively. While there was no relationship between encapsulation efficiency and either IM protein expression or immu nogenicity, there was a relationship between both readouts and LNP size, with the best performing formulations being 75 95 nm (Figures S1A and S1B).

For further study, we picked the five ionizable lipids exhibiting the greatest increase in α H10 IgG titers compared to MC3 (colored symbols in Figure 2; structures in Figure 3A). Notably, the pKa for all five lipids was very close to 6.75 (Figure 2C). As an additional measure of potency, we compared the ability of each lead LNP to drive the expression of a secreted IgG antibody after IM administra tion in mice (Figure 2D). With the exception of lipid Q, the other four lipids yielded higher IgG serum concentrations than MC3 ($p < 0.05$).

To understand the biodegradability of these lipids, we measured lipid levels after IM administration. As expected, IM delivery of these LNPs in CD 1 mice was followed by rapid clearance (Figures 3B 3D). All lead lipids degraded faster than MC3 in muscle (Figure 3B), spleen (Figure 3C), and liver (Figure 3D). 24 h post injection, the amount of lipid present in muscle dropped considerably from peak levels for all formulations tested, though lipids H and Q did not return to baseline levels by 48 h. Liver and spleen lipid levels closely followed

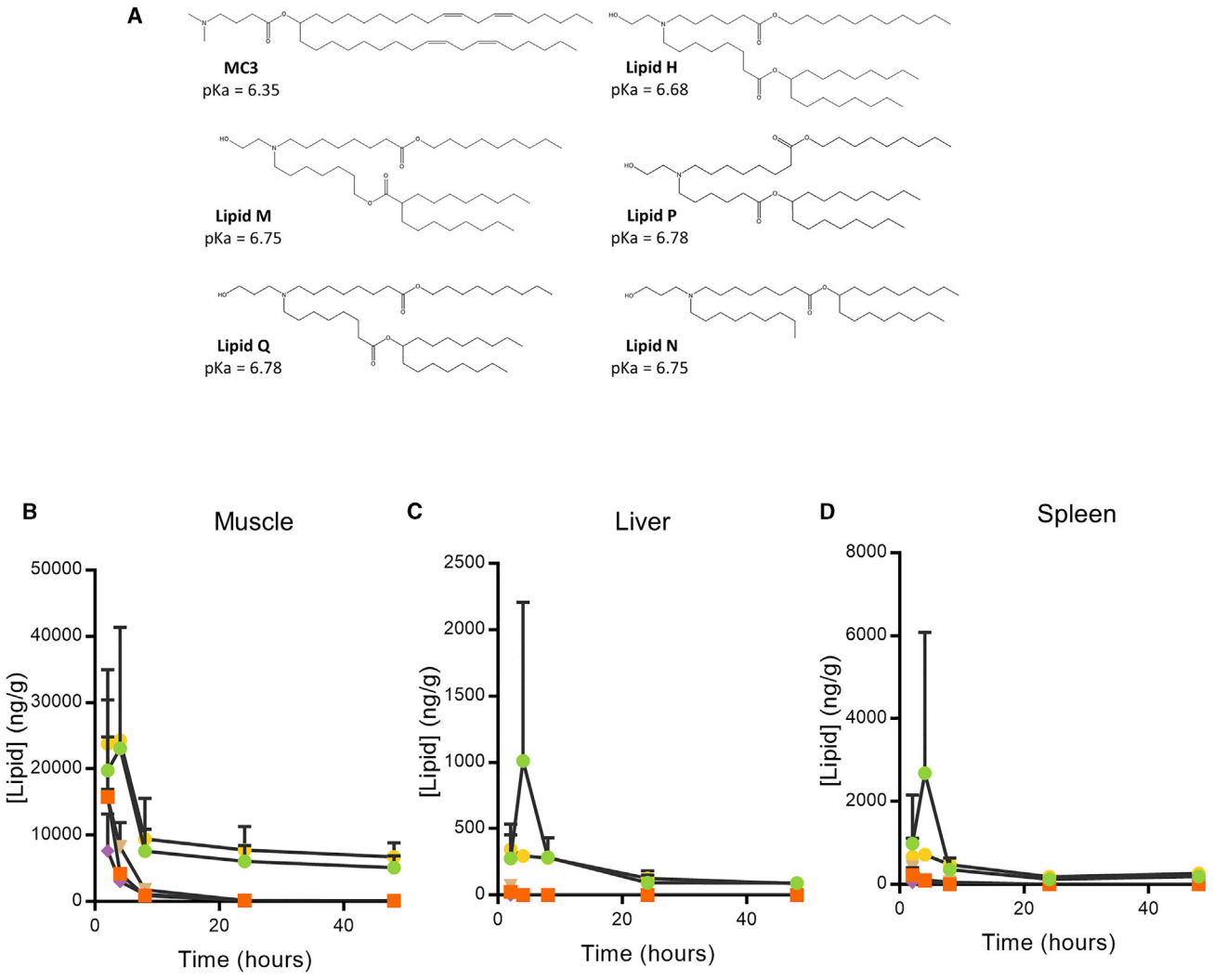

Figure 3. Chemical Structure and Pharmacokinetics of Lead Lipids

(A) Chemical structures and pK_a of MC3 and novel lipids. (B–D) Lipid concentration (nanograms per gram) after IM administration of modified mRNA encoding luciferase formulated in LNPs containing lipid H (green circles), lipid M (orange squares), lipid P (purple diamonds), lipid Q (tan inverted triangles), and lipid N (yellow hexagons) in (B) muscle, (C) liver, and (D) spleen up to 48 h post injection (n = 3 per group per time point).

IM lipid levels, though lipid H showed a peak at 6 h that dropped by 24 h in the spleen and liver.

Immunogenicity in non human primates (NHPs) was evaluated after IM injections of H10N8 mRNA formulated with the five lead lipids as LNPs. ELISA antibody titers (Figure 4A) and HAI titers (Figure 4B) were not statistically different for any group (one way ANOVA, $p > 0.05$), except lipid P was significantly lower than MC3 after the first dose (one way ANOVA, $p < 0.01$) by ELISA and after the second dose (one way ANOVA, $p < 0.001$) by HAI titer. Immune responses were measurable after a single dose by ELISA. After a second dose, both HAI and ELISA titers boosted considerably, indicating strong immune priming.

We also tested protein expression of the five lead lipids in NHPs. 500 μg IgG mRNA formulated in LNPs was injected IM, and serum antibody expression levels were monitored for 2 weeks. While three out of the five selected lipids yielded expression comparable to that of MC3 based LNPs, lipid H ($p < 0.001$) and lipid M ($p = 0.05$) showed significantly more expression over time then MC3 (Figure 4C). For lipid H, the maximum antibody concentration measured 24 h post injection was three times the antibody concentration measured with MC3 formulated material.

To assess tolerability in NHPs, the site of injection was monitored for edema (Figure 4D) and erythema (Figure 4E) 1 and 3 days after injection and was rated based on severity. Despite enhanced protein

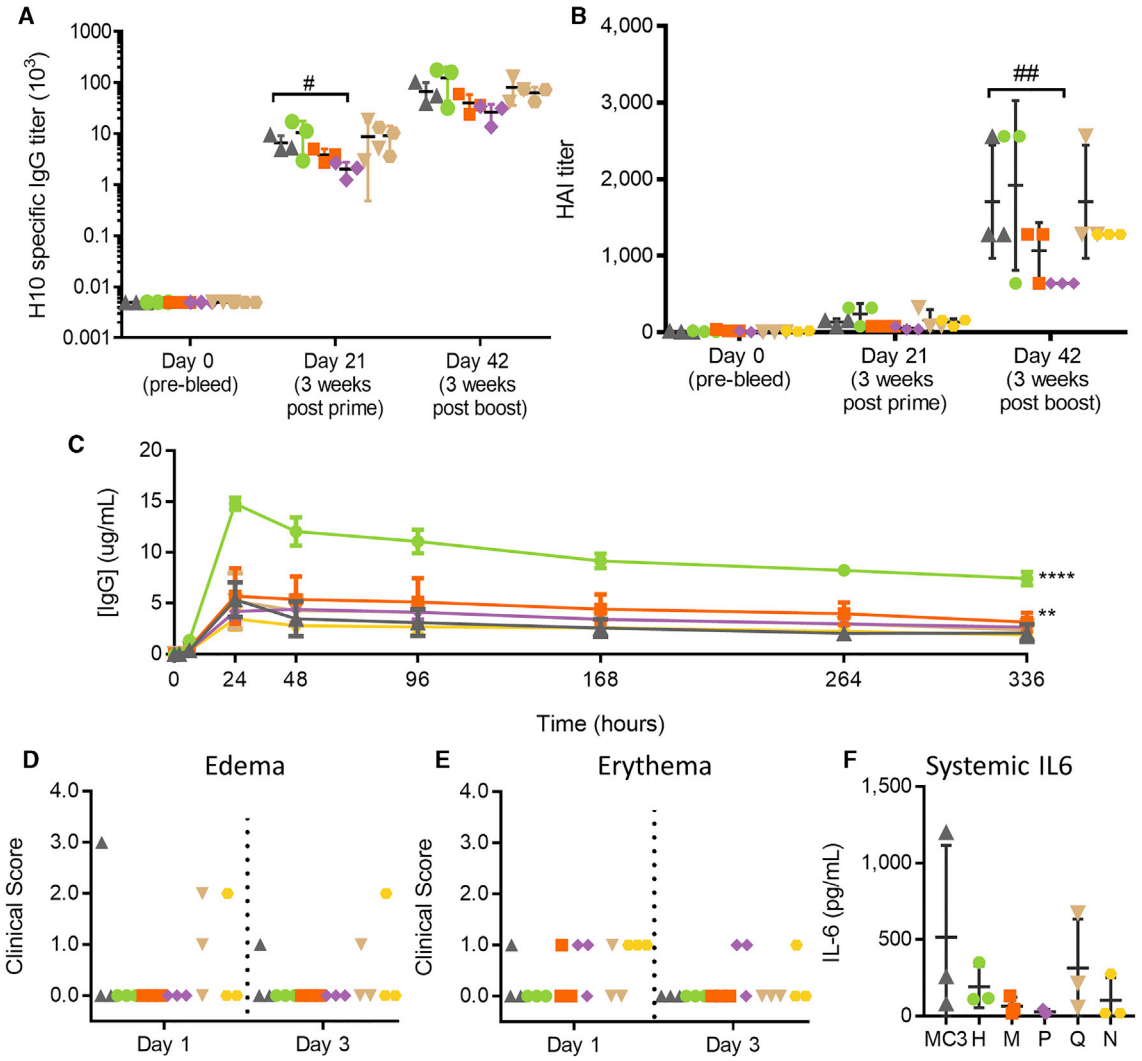

Figure 4. Expression and Immunogenicity in Non-human Primates

(A and B) Immunogenicity measured by H10 specific (A) ELISA or (B) HAI at days 0, 21 (3 weeks after the first dose), and 42 (3 weeks after the second dose). Each dose in cynomolgus monkeys contained 5 μg modified mRNA encoding H10N8 formulated in LNPs containing either MC3 (gray triangles), lipid H (green circles), lipid M (orange squares), lipid P (purple diamonds), lipid Q (tan inverted triangles), or lipid N (yellow hexagons) (n = 3 per group). (C) Circulating IgG levels (in micrograms per milliliter) after a 500 μg IM administration in cynomolgus monkeys of modified mRNA encoding heavy and light chain antibodies in a 2:1 weight ratio formulated in LNPs containing MC3 or novel lipids (n = 3 per group). (D and E) Site of injection was monitored for (D) edema and (E) erythema 1 and 3 days after injection. (F) Circulating IL 6 levels (in picograms per milliliter) 6 h after administration. $^{\#}p > 0.05$; $^{\#\#}p > 0.001$, two way ANOVA with Dunnett's multiple comparison test of each lipid versus MC3 at each time point. $^{**}p > 0.01$; $^{****}p > 0.0001$, z test of areas under the curve (AUCs) for each novel lipid versus MC3.

expression, NHPs injected with lipid H based LNPs exhibited no signs of swelling or redness 1 or 3 days post injection, with all NHPs receiving a score of 0 for both edema and erythema. All other novel lipids evaluated elicited mild to moderate scores for edema and erythema in at least 1 animal dosed. The MC3 group had one NHP receive a score of 3 for edema on day 1 post injection, resolving to a score of 1 on day 3 post injection. All lipids tested, except for lipid H, elicited an erythema score of 1 in at least one NHP. Serum interleukin (IL) 6 levels were comparable for all lipids based on one way ANOVA (Figure 4F). The NHPs in the MC3 group with the highest level of IL 6 also showed the highest level of edema, indicating a strong innate immune response in that individual animal.

To assess and compare the local tolerability of the different ionizable lipid LNPs, we administered 0.01 mg or 0.1 mg mRNA expressing prM E from the Zika virus formulated in either MC3, lipid H, lipid M, lipid P, lipid Q, or lipid N in Sprague Dawley rats IM. Serum cytokines in rats receiving both the high and low doses were measured 6 h after administration, using a 22 plex Luminex panel. Changes were observed in eotaxin, GRO alpha,

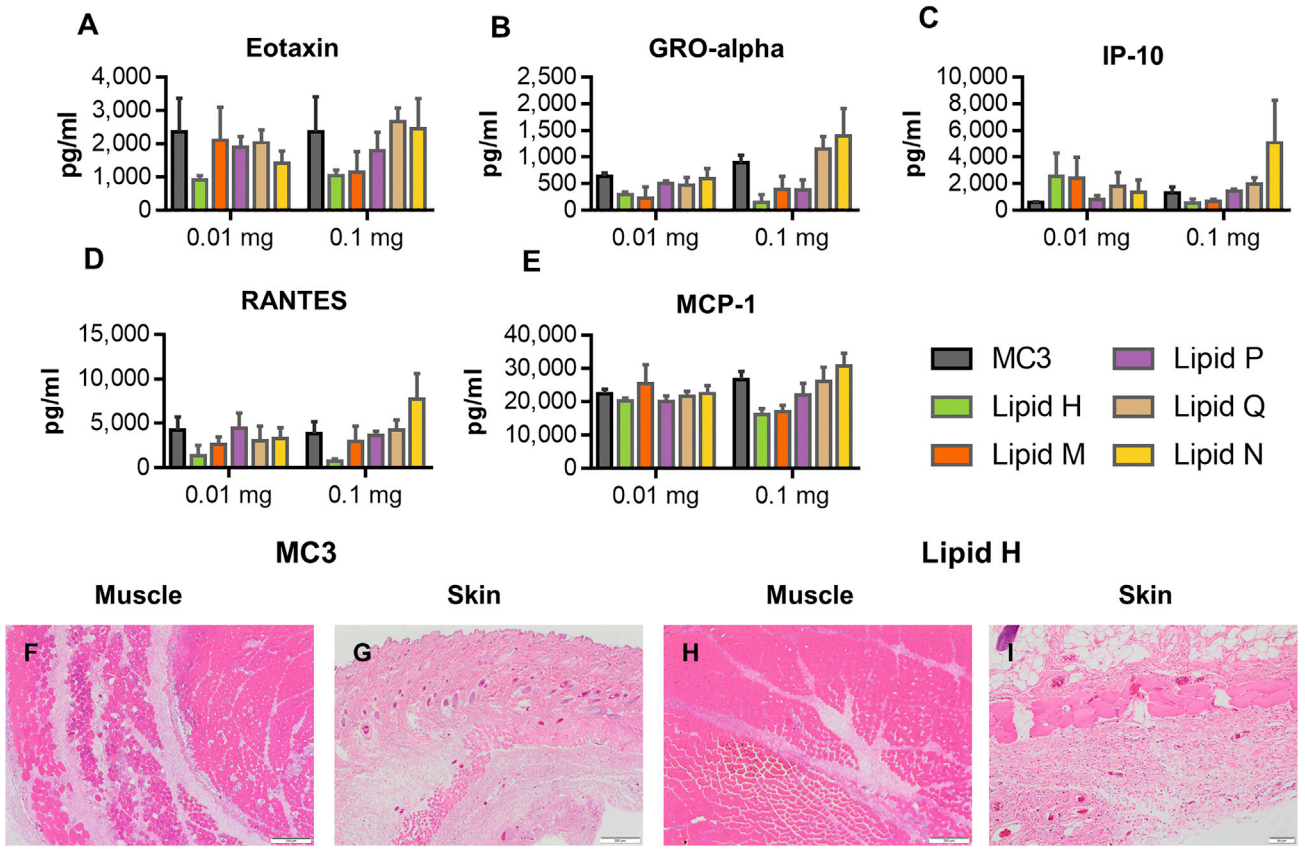

Figure 5. Tolerability in Rats

Serum concentrations (in picograms per milliliter) of cytokines (A) eotaxin, (B) GRO alpha, (C) IP 10, (D) RANTES, and (E) MCP 1 were measured 6 h after a single IM administration of 0.01 mg or 0.1 mg modified mRNA encoding prM E from Zika virus formulated in LNPs containing MC3 (gray), lipid H (green), lipid M (orange), lipid P (purple), lipid Q (tan), or lipid N (yellow) (n = 3 per group). (F I) Representative histology sections stained with H&E 2 days after a single IM administration of 0.1 mg of modified mRNA encoding prM E from Zika virus formulated in LNPs containing MC3 or lipid H in the (F and H) muscle and (G and I) skin. (F) MC3 muscle; (G) MC3 skin; (H) lipid H muscle; (I) lipid H skin.

IP 10, RANTES, and MCP 1 (Figures 5A 5E). With the exception of IP 10 at the 0.01 mg dose, lipid H induced the lowest systemic cytokine production.

Forty eight hours after administration, animals were sacrificed, and the injection sites were collected, paraffin embedded, sectioned, H&E stained, and blindly reviewed by a pathologist (Table 1). To evaluate, compare, and rank the local tolerability of each LNP, various endpoints were evaluated and graded, including mixed cell inflam mation at the injection site and in the dermis, myofiber necrosis, and relative number of degenerated neutrophils. MC3 formulated mRNA was the worst tolerated lipid tested, whereas lipid H was the best tolerated lipid tested (Figures 5F 5I).

Rats dosed with MC3 formulations at both the high and low doses dis played a dose dependent mixed cell inflammation characterized by edema; numerous intact and degenerate neutrophils; macrophages; and a few lymphocytes distending endomysium, epimysium, and adjacent connective tissue of the muscle and compressing myofibers at the injection site (Figures 5F and S3A). A dose dependent multi focal degeneration and/or necrosis of individual myofibers, infiltrated by inflammatory cells at times, was also observed. The mixed inflam mation observed in the muscle extended into the subcutaneous portion of the skin (Figures 5G and S3B). The subcutaneous tissue was expanded by edema and numerous intact and degenerate neutro phils, macrophages, and a few lymphocytes.

The dose related mixed cell inflammation observed in rats adminis tered lipid H was lower in magnitude and severity when compared to the rats given MC3 (Figure 5H). The relative amount of degenerate neutrophils was also lower, and it is worth noticing that there was less degeneration and/or regeneration and/or necrosis in the myofib ers. The extension and spillage of the inflammation from the muscular injection site into the subcutaneous tissue was also less severe and with much less edema than in animals given MC3 (Figure 5I).

Table 1. Pathology Summary

Formulation and Dose	Muscle Fiber Necrosis	Mixed-Cell Inflammation	Degenerate Neutrophils	Mixed-Cell Inflammation	Degenerate Neutrophils
MC3					
0.01 mg	2.3	2.4	1.7	2	0
0.1 mg	2.3	2.7	3.3	2	1
Lipid H					
0.01 mg	1	1.8	1	0	0
0.1 mg	1.3	2.9	2.3	1.3	0
Lipid M					
0.01 mg	2	2	1.3	1.7	0
0.1 mg	1.7	2.7	2	2	0
Lipid P					
0.01 mg	2.3	2.2	1.7	1.3	0
0.1 mg	2.3	2.8	2.3	2.3	0.7
Lipid Q					
0.01 mg	2.3	2.2	2	0.7	0
0.1 mg	2	2.9	3	2.5	1
Lipid N					
0.01 mg	0.7	1.4	2	0	0
0.1 mg	1.3	2	2.3	0	0

Rats (n = 3 per group) were injected IM with 0.01 or 0.1 mg modified mRNA encoding prM-E from the Zika virus formulated in LNPs containing MC3 or lipid H. Average histopathology scores on a 0–4 scale were recorded for events occurring in the muscle and skin.

DISCUSSION

mRNA vaccines delivered with LNPs have the potential to address numerous unmet medical needs not accessible with current vaccine technologies. Multiple reports from the siRNA field have shown that the ionizable lipid is the primary driver of LNP potency.[11–13] In this work, we observed the impact of ionizable lipid identity on expression, immunogenicity, and tolerability when delivered IM. Our working hypothesis was that the inclusion of a biodegradable lipid within an LNP would lead to vaccines with improved tolerability, as the lipid would be cleared quickly from the site of injection following mRNA delivery, and other tissues would also have minimal exposure to the lipid due to metabolic breakdown and clearance. Interestingly, throughout our initial screening, we noticed little correlation between expression and vaccine immunogenicity, indicating that expression alone is insufficient to identify improved mRNA vaccine formulations. We also observed a divergence in the best expressing formulations between the IV and IM routes of administration.

Ionizable lipid pK_a is thought to affect the protein opsonization of the particles, cellular uptake, and endosomal escape efficiency. The optimal lipid pK_a for siRNA mediated knockdown in the liver has been reported to be between 6.2 and 6.5, in line with our finding of the optimal pK_a for mRNA delivery to and expression in the liver as between 6.2 and 6.8.[11,13,23] However, the best lipids with respect to protein expression after IV administration generally had lower pK_as than the best lipids for protein expression after IM administration. Lipids such as V (pK_a = 6.87) and AC (pK_a = 7.09) show little to no expression after IV administration yet were some of the highest expressing lipids after IM administration, indicating a yet to be elucidated difference between these two routes of administration. Different cell types have shown variations in endosome acidification, demonstrating the need for additional work to better understand the performance of LNPs in the context of mRNA delivery across multiple tissues.[25,26] We also found that optimal lipid pK_a for immunogenicity was between 6.6 and 6.8. Independent of cytosolic mRNA delivery, lipid pK_a may also play a role in formulation interactions with the immune system. Although this research area has not been thoroughly explored, a recent report illustrates how ionizable lipids can drive uptake and transfection in immune cells, demonstrating potential areas of research for LNP mediated delivery of mRNA vaccines.[27] Although lipid pK_a was found to be an important factor for driving immunogenicity, it was not the only factor, as many lipids fell within that pK_a range and were no better than the MC3 control. In addition to differences in pK_a, lipid H also showed an improvement in endosomal escape efficiency, consistent with our previously published report on this class of lipids (Figure S4).[23]

Multiple previous reports speak to the need for a balance between expression and immune stimulation for optimal mRNA vaccine potency.[28,29] Pollard et al. documented the negative impact of interferon signaling on the magnitude of mRNA expression.[29] The mRNAs we used all contained a base modification on uridine to minimize innate immune activation.[24,30] As the mRNA is immune silent compared with canonical uridine containing mRNA, both antigen selection

and delivery system are important to generate potent immune responses. LNPs have been shown to be effective adjuvants for protein subunit vaccines, but it is unclear how important that adjuvant mechanism is for inducing immune responses from an mRNA vaccine. We previously showed that MC3 based LNPs generated innate immune activation and a potent cellular infiltrate.[31] The histopathology presented here for lipid H, compared to that for MC3, is consistent with improved tolerability and reduced innate immune stimulation. The reduction in inflammatory cell infiltrate, myofiber damage, and systemic cytokines support the hypothesis that mRNA vaccines may not require a strong adjuvant response for potent immune responses.

The improved tolerability and safety mediated by the inclusion of biodegradable lipids within LNPs correlate well with lipid half life after IV delivery.[23,32] The lead ionizable lipids in this study showed improved biodegradability while maintaining immune titers compared to MC3. The tolerability data suggest that this increased biodegradability leads to a reduction in injection site inflammation. Our data also show that extended residence time of the ionizable lipid post transfection is not required for a robust immune response. Indeed, clearance is preferred to extended residence, which results in undesirable inflammation at the site of injection beyond when the protein antigen is cleared. Interestingly, the data also indicate that biodegradability is not the only factor in tolerability lipid H was the best tolerated lipid yet showed a biodegradability similar to that of the other lead lipids tested. Degradation and tolerability of the lipid metabolites likely contribute to the tolerability of any formulation.

Other components, such as PEG, may play a role in vaccine potency due to the impact of anti PEG responses that have been well described for IV administered liposomal therapeutics. To date, there is no published information on the impact of anti PEG responses across other routes of administration. The field of viral vector delivery has described how anti vector immunity can substantially reduce immune response and can even completely prevent vaccine boosting when a homologous vector is used for both priming and boosting.[33] Given that we see a substantial increase in immune titers after a second dose, we do not believe that a neutralizing anti PEG response affects the LNP based vaccines we describe here.

The tolerability of any new vaccine is a key performance criterion, as vaccines are given to healthy individuals throughout different stages of life, from 1 day old neonates to the elderly. Here, we have described the identification, performance, and tolerability assessment of novel ionizable lipids for inclusion in mRNA vaccine formulations. We focused on the ionizable lipid component of the LNP, as it has been previously demonstrated to be the primary driver of LNP potency and tolerability. Given their improved tolerability and increased antigen expression, the formulations we identified have the potential for both active and passive immunization applications.

MATERIALS AND METHODS

mRNA Synthesis and Formulation

UTR sequences and mRNA production processes were performed as previously described.[19] Briefly, mRNA was synthesized *in vitro* by T7 RNA polymerase mediated transcription from a linearized DNA template, which incorporates the 5′ and 3′ UTRs and a poly(A) tail. The final mRNA utilizes Cap1 and full replacement of uridine with N1 methyl pseudouridine. mRNA encoding influenza HA genes originated from the H10N8 strain[34], and the mRNA encoding prM E from Zika utilized the signal sequences from human IgE (MDWTWILFLVAAATRVHS) and the prM and E genes from an Asian ZIKV strain (Micronesia 2007; GenBank: EU545988), which is >99% identical to circulating American strains.[35] All coding sequences were generated using a proprietary algorithm.

LNP formulations were prepared using a modified procedure of a method previously described.[17] Briefly, lipids were dissolved in ethanol at molar ratios of 50:10:38.5:1.5 (ionizable lipid:DSPC:cholesterol:PEG lipid). LNPs formulated with the ionizable lipid MC3 were used as a control throughout these studies and were produced as previously described.[11] Novel ionizable lipids were synthesized as described elsewhere.[36] The lipid mixture was combined with an acidification buffer of 50 mM sodium citrate (pH 4.0) or 25 mM sodium acetate (pH 5.0) containing mRNA at a volume ratio of 3:1 (aqueous:ethanol) using a microfluidic mixer (Precision Nanosystems, Vancouver, BC, Canada). The ratio of nitrogen present on the ionizable N:P ratio was set to 5.67 for each formulation. Formulations were dialyzed against PBS (pH 7.2) or 20 mM Tris (pH 7.4) with 8% sucrose in Slide A Lyzer dialysis cassettes (Thermo Scientific, Rockford, IL, USA) for at least 18 h. Formulations were concentrated using Amicon ultra centrifugal filters (EMD Millipore, Billerica, MA, USA), if needed, and then passed through a 0.22 μm filter and stored at 4°C (PBS) or 20°C (20 mM Tris 8% sucrose) until use. Formulations were tested for particle size, RNA encapsulation, and endotoxin. All LNPs were found to be between 50 and 142 nm in size by dynamic light scattering and with greater than 69% encapsulation and <3 EU/mL endotoxin. Lead lipids selected for further evaluation were between 66 and 107 nm, with greater than 72% encapsulation.

pK_a Analysis

Assay buffers (buffers containing 150 mM sodium chloride, 10 mM sodium phosphate, 10 mM sodium borate, and 10 mM sodium citrate) were pH adjusted with sodium hydroxide or hydrochloric acid to create buffers with pH ranges from pH 3 to pH 11.5. In a black bottom, 96 well plate, 300 μM 6 (*p* toluidino) 2 naphthalenesulfonic acid sodium salt in DMSO (TNS reagent) (Sigma Aldrich, St. Louis, MO, USA), LNP, and assay buffer were combined. Each pH unit of buffer was repeated in triplicate with TNS reagents and LNPs. Fluorescent measurements were taken using a Synergy H1 microplate reader (BioTek Instruments, Winooski, VT, USA), with excitation set to 325 nm and emission collected at 435 nm. Fluorescence intensity was plotted against the pH of the assay buffer. The log of the inflection point was assigned the apparent pK_a of the LNP.

Expression and Immunogenicity Screening Studies in a Murine Model

All animal experiments and husbandry followed guidelines from NIH (NIH publication #8023, eighth edition) and the U.S. National Research Council. Female BALB/c mice 5 8 weeks old were pur chased from Charles River Laboratories (Wilmington, MA, USA) and housed at Moderna Therapeutics (Cambridge, MA, USA). Mice were acclimated for at least 3 days before the initiation of a study. Initial murine screening studies evaluated expression and immunogenicity in the same study, as previous work showed that co formulation of the two mRNAs did not affect individual results (data not shown). On days 1 and 22, mice were injected in the quad riceps with 50 μL lipid nanoparticle formulations encapsulating an equal amount of luciferase and H10N8 mRNAs. 6 h post dose, ani mals received an intraperitoneal injection of 3 mg luciferin and were imaged on an *in vivo* imaging system (IVIS Spectrum, PerkinElmer, Waltham, MA, USA). On days 21 and 36, mice were bled through the submandibular cavity. Serum was separated from the blood by centrifugation and then used to evaluate immunoge nicity by ELISA. Group geometric means were calculated for each LNP evaluated and compared to the geometric mean of the MC3 group in the same study (expression) or of all MC3 groups tested (immunogenicity).

Lipid Clearance in a Murine Model

Female CD 1 mice were purchased from and housed at Charles River Laboratories. Mice were acclimated for at least 3 days before the initi ation of a study. Mice were injected IM with 50 μL containing 2 μg of luciferase mRNA formulated in LNPs. At 1, 2, 4, 8, and 24 h post in jection, 3 mice were sacrificed and the plasma, spleen, liver, site of in jection muscle, and draining lymph nodes were harvested. Tissues were frozen and sent to Agilux (Worcester, MA, USA) for evaluation of the remaining lipid by mass spectroscopy.

Quantification of Lipid by LC-MS/MS

Tissue samples were homogenized by Omni probe following the addi tion of 19 equivalents (w/v) of water. Lipid and proteins were precip itated and analyzed against calibration standards prepared in a matching blank. Chromatographic separation and quantification was accomplished with a liquid chromatography tandem mass spec troscopy (LC MS/MS) system. Samples were separated on a Clipeus C8 column (Higgins Analytical, Mountain View, CA, USA) equili brated with 35% solvent A containing 5 mM formic acid in 50% methanol (H_2O:MeOH:FA, 50:50:1) and 65% solvent B containing 5 mM formic acid in methanol (MeOH:FA, 100:1; Thermo Fisher Sci entific). A triple quadrupole MS/MS system (Applied Biosystems, API 5500) operated in positive ion mode was used for signal detection.

Tolerability in a Rat Model

Female Sprague Dawley rats were purchased from Charles River Lab oratories and housed at Moderna Therapeutics, Cambridge MA, USA. Rats were injected with 100 μL containing either 10 or 100 μg of mRNA formulated in LNPs. 6 h post injection, blood was drawn, and serum was used for Luminex cytokine analysis (Austin, TX, USA). 48 h post injection, rats were sacrificed, and the liver, site of injection, muscle, and skin were collected. Tissues were sectioned, stained with H&E, evaluated by a blinded board certified pathologist, and graded on a scale from 0 to 5 based on severity for myofiber ne crosis, mixed cell infiltration within muscle and skin, and degenerate neutrophils in muscle and skin.

Expression and Immunogenicity in NHPs

NHP studies were conducted at Charles River Laboratories (Sher brooke, QC, Canada) using naive cynomolgus monkeys, 2 5 years old and weighing 2 3 kg. Animals were housed in stainless steel, perforated floor cages, in a temperature and humidity controlled environment (21 26°C and 30 70%, respectively), with an automatic 12 h/12 h dark/light cycle. Animals were fed PMI Nutrition Certified Primate Chow No. 5048 twice daily. Tuberculin tests were carried out on arrival at the test facility. The study plan and procedures were approved by pre clinical services Sherbrook (PCS SHB) IACUC. An imal experiments and husbandry followed NIH (Publication no. 8023, eighth edition), U.S. National Research Council, and Canadian Council on Animal Care (CCAC) guidelines.

To evaluate expression, cynomolgus NHPs were injected IM with 300 μL containing a total of 500 μg mRNA (heavy chain and light chain in a 2:1 weight:weight ratio) encoding an antibody formulated in LNPs. The site of injection was monitored for erythema and edema and graded for severity from 0 (no reaction) to 4 (severe reaction). Blood was collected 6 h before dosing and then 2, 6, 24, 48, 96, 168, 264, and 336 h post injection to measure antibody levels. Blood from 6, 48, and 336 h was used to measure hematology, coagulation, D dimer, and clinical chemistry markers.

To evaluate immunogenicity, cynomolgus monkeys received IM in jections of 5 μg H10N8 mRNA formulated LNP in 100 μL on days 1 and 22. 0.5 mL blood was collected on day 22 and day 43 post dosing from a peripheral vein and centrifuged at 1200 × *g* for 10 min at 4°C for separation of serum. Serum was stored at 80°C until analysis by hemagglutination inhibition assay (HAI) and ELISA.

HAI Assay

The HAI titers of serum samples were determined using a protocol described previously.[17] Sera were first treated with receptor destroy ing enzyme (RDE) to inactivate nonspecific inhibitors. The RDE was inactivated by incubation at 56°C for 30 min. Treated sera were seri ally diluted in 96 well plates, mixed with a standardized amount of re combinant HA (8 HA units of H10N8; Medigen, Frederick, MD, USA), and incubated for 30 min at room temperature. Turkey red blood cells (RBCs) (Lampire Biological Laboratories, Everett, PA, USA) were then added to the wells of the 96 well plates, mixed, and incubated at room temperature for 45 min. The most dilute serum sample that completely inhibited HA was the reported titer for that replicate. Each serum sample was analyzed in triplicate, and the results are reported as the geometric mean of the 3 results.

Anti-H10N8 ELISA

Nunc MaxiSorp 96 well plates (Thermo Fisher, Rochester, NY, USA) were coated at 100 µL per well with 1 µg/mL H10 protein in PBS over night at 4°C. Plates were washed three times with PBS containing 0.1% Tween 20 (wash buffer). 200 µL Superblock (Pierce, Rockford, IL, USA) was added to each well and incubated at 37°C for at least 1.5 h and then washed three times with wash buffer. In each well, 100 µL PBS containing 5% goat serum (GIBCO, Gaithersburg, MD, USA) with 0.1% Tween 20 was added, and serum was serially diluted and incubated for 2 h at 37°C. Plates were washed three times, and 100 µL horseradish peroxidase (HRP) conjugated goat anti mouse IgG antibody (Southern Biotech, Birmingham, AL, USA) diluted 1:20,000 in PBS containing 5% goat serum with 0.1% Tween 20 was added and incubated for 1 h at 37°C. Plates were washed three times, and 100 µL SureBlue TMB Microwell Peroxidase substrate (Kirke gaard & Perry Labs, Milford, MA, USA) was added to each well and incubated for 15 min. 100 µL TMB Stop Solution (Kirkegaard & Perry Labs, Milford, MA, USA) was added to each well, and the plates were read at 450 nm. The average blank value was subtracted from each sample. Titers were defined as the reciprocal serum dilu tion at approximately $OD_{450\ nm}$ (optical density 450 nm) = 0.6 (normalized to a standard included on every plate).

Monoclonal Antibody Detection

QUICKPLEX 96 well plates (MSD) were coated with 100 µg of 1 µg/mL capture protein in PBS per well and incubated overnight at 4°C. Plates were washed with PBS with 0.5% Tween 20 three times. Serial dilutions for a reference standard and samples were performed into a 100 µL final volume in the plate and then were incubated at room temperature for 1.5 h, with shaking at 120 rpm. Plates were washed with PBS with 0.5% Tween 20 three times. 50 µL affinity pu rified goat anti human IgG (sulfo tagged) at 0.5 µg/mL was added to each well and incubated for 1 h at room temperature, with shaking at 120 rpm. After incubation, plates were washed six times, and 150 µL MSD Read Buffer T was added to each well. The plates were read on an MSD instrument (Meso Scale Diagnostics, Rockville, MD, USA).

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Methods and four figures and can be found with this article online at https://doi.org/10.1016/j.omtn.2019.01.013.

AUTHOR CONTRIBUTIONS

Conceptualization, G.C. and L.A.B.; Methodology, K.J.H., K.E.B., E.J., and L.A.B.; Formal analysis, K.J.H. and I.M.; Investigation, K.J.H., E.J., A. Lee, A.W., O.Y , S.H., J.D., B.M.G., T.K., and A. Lynn; Writing Original Draft, K.J.H , and L.A.B.; Writing Review and Editing, K.J.H., M.J.M., and L.A.B.; Visualization, K.J.H., I.M., and L.A.B.; Supervision, K.E.B., C.M., J.J.S , M.G.S., O.A , and G.C.

CONFLICTS OF INTEREST

All authors are either current or previous employees of Moderna Therapeutics and own stock options and/or shares in the company.

ACKNOWLEDGMENTS

We would like to thank Moderna's Preclinical Production group for production of mRNA and Moderna's Nonclinical Sciences group for *in vivo* experiments. This work was funded by Moderna Therapeutics.

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OMTN, Volume *15*

Supplemental Information

Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines

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Supplemental methods

Endosomal escape efficiency characterization

Endosomal escape efficiency was measured using single molecule imaging, as previously described (Sabnis, S. *et al*, 2018). Briefly, fluorescently labeled LNPs incorporating 0.1% ATTO 647 DOPE, and encapsulating Firefly Luciferase (FLuc) reporter mRNA were used to transfect HeLa cells in 96-well plates (Greiner BIO-ONE SensoPlate) at 25 ng (mRNA) per well in 100 uL cell culture media containing 10% Fetal Bovine Serum. Cells were incubated with LNPs for 4h, after that the samples were fixed in 4% paraformaldehyde (Ted Pella) and imaged on the Opera Phenix spinning disk confocal (Perkin Elmer) using a 63X water immersion objective (1.15 NA). Single particle imaging on glass substrate was used to normalize cellular uptake and to derive the number of LNPs internalized at the single cell level (Figure S4, D). Stellaris single molecule FISH (smFISH, Quasar 570, red signal, Figure S4) which detects both cytosolic mRNA and mRNA trapped in endocytic organelles, was employed to detect intracellular FLuc mRNA. mRNA molecules that egressed the endocytic organelles into the cytosol were identified through object based image analysis using the electroporated sample as benchmark for single mRNA intensity (Figure S4, grey signal). The selected single mRNA objects are pseudo-colored in grey, overlaid over the smFISH signal red. To quantitatively compare the endosomal escape efficiency for the two LNP formulations, we computed the ratio between the number of cytosolic mRNA and the number of internalized LNPs at the single cell level (Figure S4, B). Our results show significant increase in endosomal escape efficiency for lipid H compared to MC3.

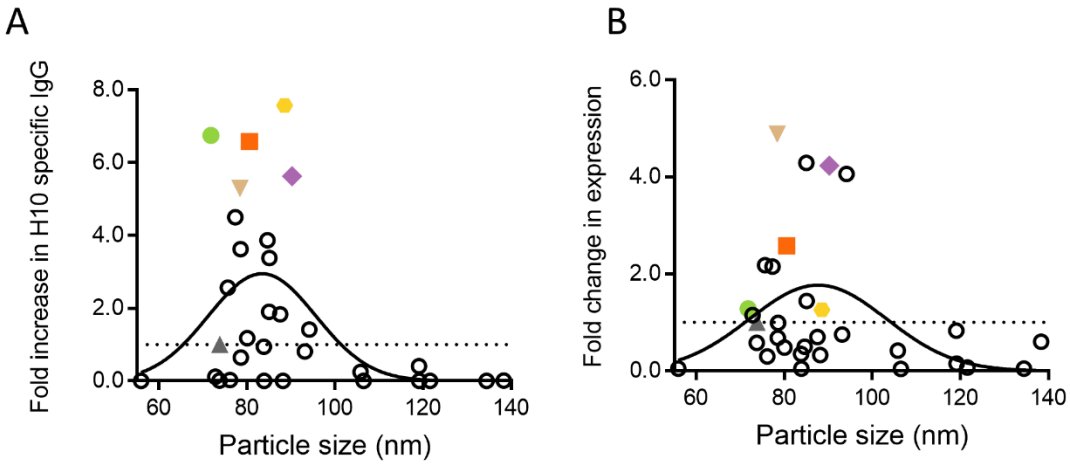

Figure S1: Impact of particle size on immunogenicity of different LNPs

Particle size measured by DLS of LNPs made with different ionizable lipids versus fold increase in **(A)** immunogenicity or **(B)** expression at 0.001 mg/kg IM for lipids A through E[1.]. The five lead novel lipids and MC3 LNPs are labeled accordingly: MC3 (▲), lipid H (●), lipid M (■), lipid P (◆), lipid Q (▼), and lipid N (⬢).

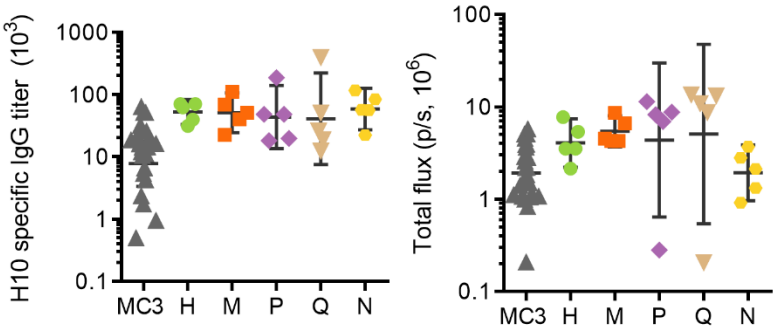

Figure S2: Immunogenicity and expression of lead lipids

The individual animal H10 specific IgG titers are shown for MC3 (n=24) and the five novel lipid leads (n=5 per group) delivered at 0.001 mg/kg IM in Balb/C mice. The individual animal total flux (photons/sec) values 6 hours after IM administration in Balb/C mice of 0.001 mg/kg modified mRNA encoding luciferase LNPs containing MC3 (n=24) or novel lipids (n=5 per group). The five lead novel lipids and MC3 LNPs are labeled accordingly: MC3 (▲), lipid H (●), lipid M (■), lipid P (◆), lipid Q (▼), and lipid N (⬢).

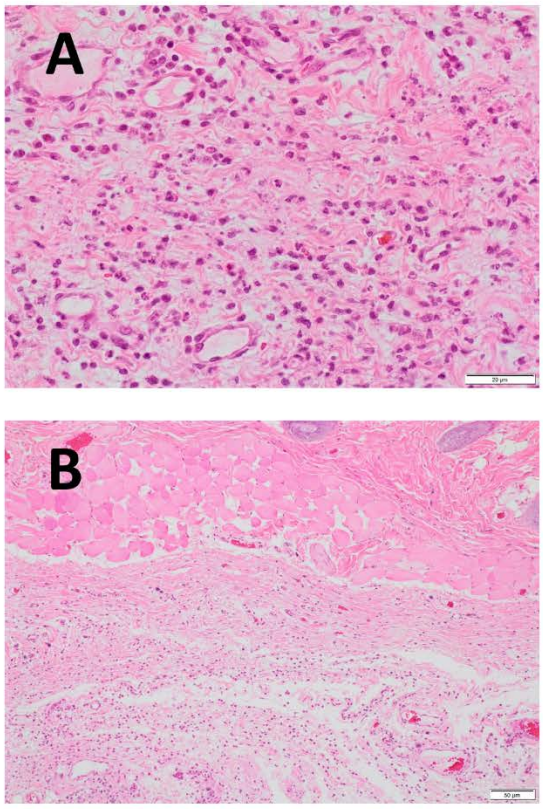

Figure S3: High magnification of MC3 LNP histology sections

Representative histology sections under high magnification stained with hematoxalin and eosin 2 days after a single IM administration of 0.1 mg of modified mRNA encoding PrMe from zika virus formulated in LNPs containing MC3 in the muscle **(A)** and skin **(B)**.

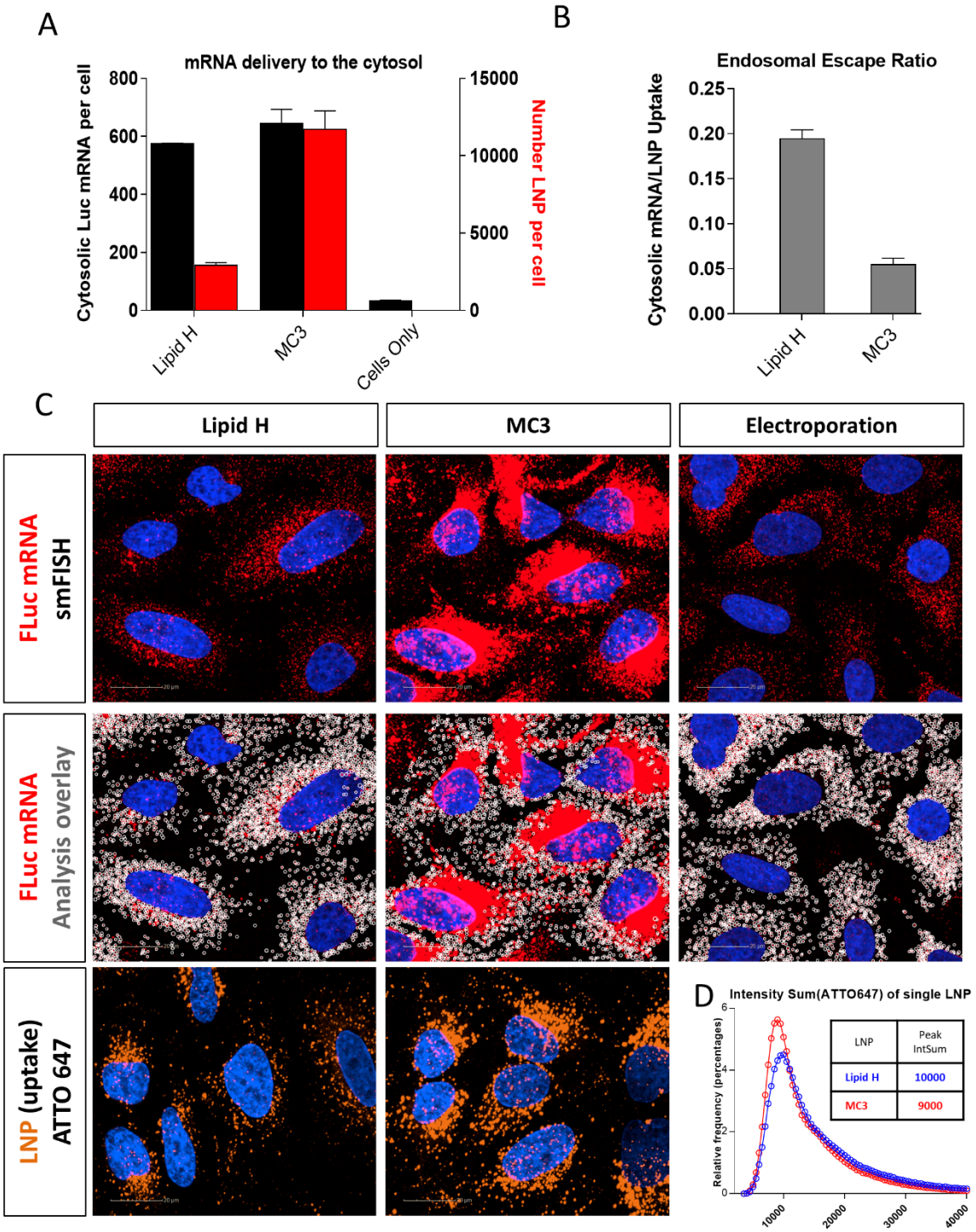

Figure S4: In-vitro endosomal escape of lipid H compared to MC3 in HeLa cells

(A) Quantitative image analysis of the number of cytosolic mRNAs (black bars) compared to the number of LNPs per cell (red bars) after delivery with either lipid H or MC3 at 25ng dose. **(B)** Endosomal escape ratio calculated by dividing the number of cytosolic mRNA by the number of LNPs taken up by the cell. **(C)** Representative fluorescent images showing labeled mRNA,

analysis and labeled LNP after delivery with lipid H, MC3, or electroporation in HeLa cells. **(D)** LNPs were imaged on glass substrate to determine the intensity distribution of a single LNP labeled with ATTO647.

EXHIBIT 5

Article

SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness

https://doi.org/10.1038/s41586-020-2622-0

Received: 10 June 2020

Accepted: 29 July 2020

Published online: 5 August 2020

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A vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is needed to control the coronavirus disease 2019 (COVID-19) global pandemic. Structural studies have led to the development of mutations that stabilize *Betacoronavirus* spike proteins in the prefusion state, improving their expression and increasing immunogenicity[1]. This principle has been applied to design mRNA-1273, an mRNA vaccine that encodes a SARS-CoV-2 spike protein that is stabilized in the prefusion conformation. Here we show that mRNA-1273 induces potent neutralizing antibody responses to both wild-type (D614) and D614G mutant[2] SARS-CoV-2 as well as $CD8^+$ T cell responses, and protects against SARS-CoV-2 infection in the lungs and noses of mice without evidence of immunopathology. mRNA-1273 is currently in a phase III trial to evaluate its efficacy.

Since its emergence in December 2019, SARS-CoV-2 has accounted for more than 30 million cases of coronavirus disease 2019 (COVID-19) worldwide in 9 months[3]. SARS-CoV-2 is the third novel *Betacoronavirus* in the past 20 years to cause substantial human disease; however, unlike its predecessors SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is transmitted efficiently from person to person. In the absence of a vaccine, public health measures such as quarantine of newly diagnosed cases, contact tracing, use of face masks and physical distancing have been put into place to reduce transmission[4]. It is estimated that until 60–70% of the population have immunity, COVID-19 is unlikely to be sufficiently well-controlled for normal human activities to resume. If immunity remains solely dependent on infection, even at a case fatality rate of 1%, more than 40 million people could succumb to COVID-19 globally[5]. Therefore, rapid development of vaccines against SARS-CoV-2 will be critical for changing the global dynamics of this virus.

The spike (S) protein, a class I fusion glycoprotein analogous to influenza haemagglutinin, respiratory syncytial virus (RSV) fusion glycoprotein (F) and human immunodeficiency virus gp160 (Env), is the major surface protein on the coronavirus virion and the primary target for neutralizing antibodies. S proteins undergo marked structural rearrangement to fuse virus and host cell membranes, enabling delivery of the viral genome into target cells. We previously showed that prefusion-stabilized protein immunogens that preserve neutralization-sensitive epitopes are an effective vaccine strategy for enveloped viruses such as RSV[6–10]. Subsequently, we identified 2 proline substitutions (2P) at the apex of the central helix and heptad repeat 1 that effectively stabilized MERS-CoV, SARS-CoV and human coronavirus HKU1 S proteins in the prefusion conformation[1,11,12]. Similar to other prefusion-stabilized fusion proteins, MERS-CoV S(2P) protein was more immunogenic at lower doses than wild-type S protein[1]. The 2P mutation has similar effects on the stability of S proteins from other betacoronaviruses, suggesting a generalizable approach for designing stabilized-prefusion *Betacoronavirus* S protein antigens for vaccination. Such generalizability is fundamental to the prototype pathogen approach for pandemic preparedness[13,14].

Coronaviruses have long been predicted to have a high probability of causing zoonotic disease and pandemics[15,16]. As part of our pandemic

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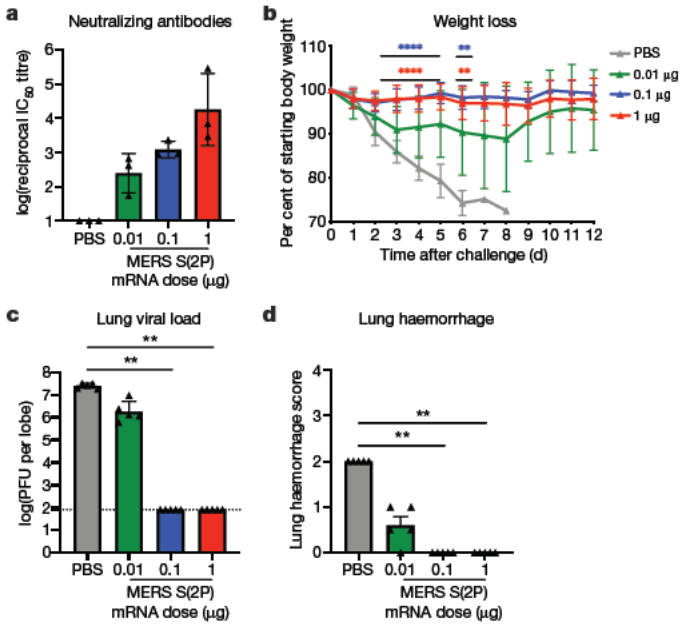

Fig. 1 | MERS-CoV S-2P mRNA protects mice from lethal challenge. **a**–**d**, 288/330$^{+/+}$ mice were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue) or 1 μg (red) MERS-CoV S(2P) mRNA. Control mice were administered phosphate-buffered saline (PBS) (grey). **a**, Two weeks post-boost, sera were collected from three mice per group and assessed for neutralizing antibodies against MERS m35c4 pseudovirus. **b**–**d**, Four weeks post-boost, 12 mice per group were challenged with a lethal dose of mouse-adapted MERS-CoV (m35c4). **b**, Following challenge, mice were monitored for weight loss. **c**, **d**, Two days post-challenge, at peak viral load, lung viral titres (**c**) and haemorrhage (scored as: 0, no haemorrhage, 4, severe haemorrhage in all lobes) (**d**) were assessed from five mice per group. In **c**, **d**, all dose levels were compared by Kruskal–Wallis analysis of variance (ANOVA) with Dunn's multiple comparisons test. In **b**, for weight loss, all comparisons are with PBS control mice at the same time point by two-sided Mann–Whitney *U*-test. $^{**}P < 0.01$, $^{****}P < 0.0001$. Data are GMT ± geometric s.d. (**a**, **c**) or mean ± s.d. (**b**, **d**). In **c**, the dotted line represents assay limit of detection.

preparedness efforts, we have studied MERS-CoV as a prototype *Betacoronavirus* pathogen to optimize vaccine design, dissect the humoral immune response to vaccination, and identify mechanisms and correlates of protection. Achieving an effective and rapid vaccine response to a newly emerging virus requires both the precision afforded by structure-based antigen design and a manufacturing platform to shorten time to product availability. Producing cell lines and clinical-grade subunit protein typically takes more than one year, whereas manufacturing nucleic acid vaccines can be achieved in a matter of weeks[17,18]. In addition to advantages in manufacturing speed, mRNA vaccines are potently immunogenic and elicit both humoral and cellular immunity[19–21]. We therefore evaluated mRNA formulated in lipid nanoparticles (mRNA–LNP) as a delivery vehicle for MERS-CoV S(2P), and found that transmembrane-anchored MERS-CoV S(2P) mRNA elicited more potent pseudovirus-neutralizing antibody responses than secreted MERS-CoV S(2P) (Extended Data Fig. 1a). Additionally, consistent with protein immunogens, MERS-CoV S(2P) mRNA was more immunogenic than wild-type MERS-CoV S mRNA (Extended Data Fig. 1b). Immunization with MERS-CoV S(2P) mRNA–LNP elicited potent pseudovirus-neutralizing activity with a dose as low as 0.1 μg and protected transgenic mice expressing human *DPP4* (288/330$^{+/+}$)[22] against lethal MERS-CoV challenge in a dose-dependent manner, establishing that mRNA encoding S(2P) protein is protective. Notably, a subprotective 0.01 μg dose of MERS-CoV S(2P) mRNA did not cause exaggerated disease following MERS-CoV infection, but instead resulted in partial protection against weight loss followed by full recovery without evidence of enhanced illness (Fig. 1).

SARS-CoV-2 was first identified as the cause of an outbreak of respiratory disease in Wuhan, China in early January 2020. Within 24 h of the release of genomic sequences of SARS-CoV-2 isolates on 10 January 2020, the 2P mutations were substituted into S protein residues 986 and 987 to produce prefusion-stabilized SARS-CoV-2 S(2P) protein for structural analysis[23] and serological assay development[24,25] in silico, without additional experimental validation. Within 5 days of the release of the sequence, current good manufacturing practice (cGMP) production of mRNA–LNP encoding the SARS-CoV-2 S(2P) as a transmembrane-anchored protein with the native furin cleavage site (mRNA-1273) was initiated in parallel with preclinical evaluation. This led to a first-in-human phase I clinical trial starting on 16 March 2020, 66 days after the viral sequence was released, and a phase II trial 74 days later on 29 May 2020 (Extended Data Fig. 2). Expression and antigenicity of the S(2P) antigen delivered by mRNA was confirmed in vitro before vaccination of the first human participant (Extended Data Fig. 3), and immunogenicity of mRNA-1273 was documented in several mouse strains. The results of those studies are detailed here.

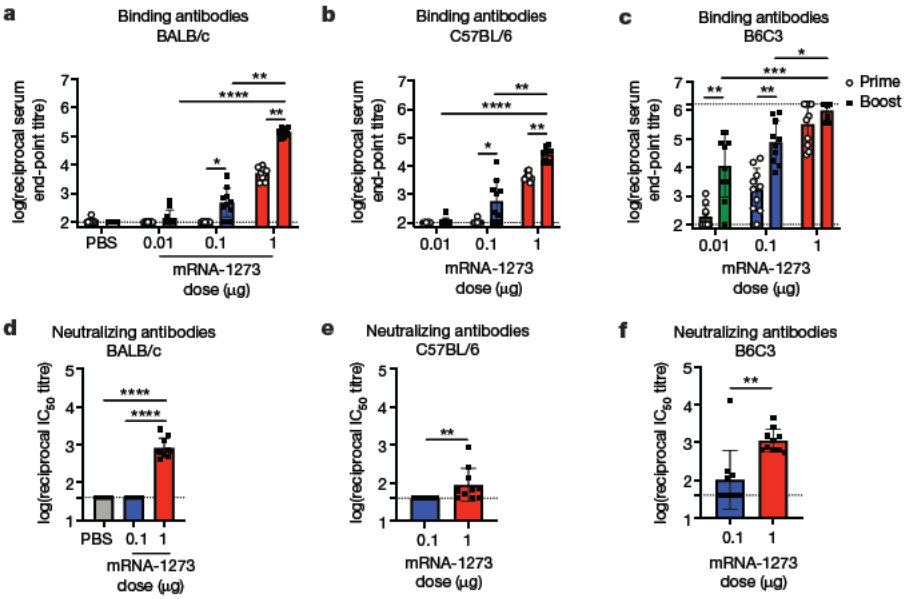

Fig. 2 | mRNA-1273 elicits robust binding and pseudovirus-neutralizing antibody responses in multiple mouse strains. **a**–**f**, BALB/cJ (**a**, **d**), C57BL/6J (**b**, **e**) or B6C3F1/J (**c**, **f**) mice ($n = 10$ per group) were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue) or 1 μg (red) mRNA-1273. Control BALB/cJ mice were administered PBS (grey). Sera were collected 2 weeks post-prime (unfilled circles) and 2 weeks post-boost (filled circles) and assessed for SARS-CoV-2 S-specific IgG by enzyme-linked immunosorbent assay (ELISA) (**a**–**c**), and for post-boost sera, neutralizing antibodies against homotypic SARS-CoV-2 pseudovirus (**d**–**f**). In **a**–**c**, time points were compared within each dose level by two-sided Wilcoxon signed-rank test, and doses were compared post-boost by Kruskal–Wallis ANOVA with Dunn's multiple comparisons test. In **d**–**f**, Vaccine groups were compared by two-sided Mann–Whitney *U*-test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Data are presented as GMT ± geometric s.d. Dotted lines represent assay limits of detection.

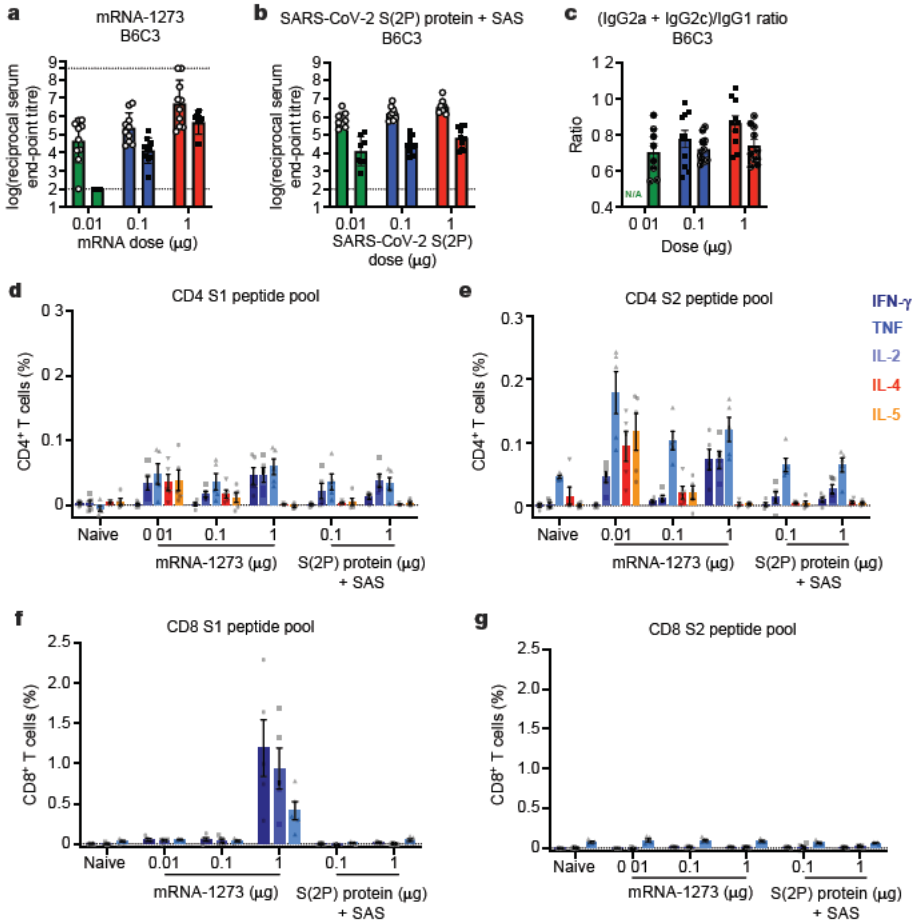

Fig. 3 | Immunizations with mRNA-1273 and S(2P) protein, delivered with TLR4 agonist, elicit S-specific T_H1-biased T cell responses. B6C3F1/J mice ($n = 10$ per group) were immunized at weeks 0 and 3 with 0.01, 0.1 or 1 µg of mRNA-1273 or SARS-CoV-2 S(2P) protein with SAS adjuvant. **a**–**c**, Sera were collected two weeks post-boost and assessed by ELISA for SARS-CoV-2 S-specific IgG1, and IgG2a and IgG2c. End-point titres (**a**, **b**) and end-point titre ratios of IgG2a plus IgG2c to IgG1 (**c**) were calculated. Ratios were not calculated for mice for which end-point titres did not reach the lower limit of detection (dotted line; N/A). **d**–**g**, Seven weeks post-boost, splenocytes were isolated from five mice per group and restimulated with vehicle or pools of overlapping peptides from SARS-CoV-2 S protein in the presence of a protein transport inhibitor cocktail. After 6 h, intracellular cytokine staining was performed to quantify $CD4^+$ and $CD8^+$ T cell responses. Cytokine expression in the presence of vehicle only was considered as background and subtracted from the responses measured from the S1 and S2 peptide pools for each individual mouse. **d**, **e**, Percentage of $CD4^+$ T cells expressing IFN-γ, TNF, IL-2, IL-4 and IL-5 in response to the S1 (**d**) and S2 (**e**) peptide pools. **f**, **g**, Percentage of $CD8^+$ T cells expressing IFN-γ, TNF and IL-2 in response to the S1 (**f**) and S2 (**g**) peptide pools.

Immunogenicity was assessed in six-week-old female BALB/cJ, C57BL/6J and B6C3F1/J mice by two intramuscular immunizations with 0.01, 0.1 or 1 µg mRNA-1273, separated by a 3-week interval. mRNA-1273 induced dose-dependent specific S-binding antibodies after prime and boost in all mouse strains (Fig. 2a–c). Potent pseudovirus-neutralizing activity was elicited by 1 µg mRNA-1273, reaching reciprocal half-maximal inhibitory concentration (IC_{50}) geometric mean titres (GMTs) of 819 (BALB/cJ), 89 (C57BL/6J) and 1,115 (B6C3F1/J) (Fig. 2d–f). Additionally, mice immunized with 1 µg mRNA-1273 had robust neutralizing antibodies against pseudoviruses that express S protein with the D614G substitution; SARS-CoV-2 expressing the D614G variant of the S protein has recently become dominant around the world[2] (Extended Data Fig. 4). To further gauge immunogenicity across a wide dose range, BALB/c mice were immunized with 0.0025–20 µg mRNA-1273, revealing a strong positive correlation between dose-dependent mRNA-1273-elicited binding and pseudovirus-neutralizing antibody responses (Extended Data Fig. 5). BALB/cJ mice that received a single dose of mRNA-1273 were evaluated to ascertain the utility of a single-dose vaccine. S-binding antibodies were induced in mice immunized with one 1 µg or 10 µg dose of mRNA-1273. The 10 µg dose elicited pseudovirus-neutralizing antibody activity that increased between week 2 and week 4, reaching 315 reciprocal IC_{50} GMT (Extended Data Fig. 6a, b). These data demonstrate that mRNA expressing SARS-CoV-2 S(2P) is a potent immunogen and that pseudovirus-neutralizing activity can be elicited with a single dose.

Vaccine-associated enhanced respiratory disease (VAERD) has been associated with T helper 2 cell (T_H2)-biased immune responses in children immunized with whole-inactivated-virus vaccines against RSV and measles virus[26,27]. A similar phenomenon has also been reported in some animal models with whole-inactivated vaccines and other types of experimental SARS-CoV vaccines[28–30]. We therefore evaluated the balance of T_H1 and T_H2 cells in immunized mice. We first compared levels of S-specific immunoglobulins, IgG2a and IgG2c, and IgG1—which are surrogates of T_H1 and T_H2 responses, respectively—elicited by mRNA-1273 with those elicited by immunization with SARS-CoV-2 S(2P) protein using the TLR4 agonist Sigma Adjuvant System (SAS). Both immunogens elicited S-binding antibodies in the IgG2a and IgG1 subclasses, indicating a balanced T_H1–T_H2 response (Fig. 3a–c, Extended Data Fig. 7). The S-specific IgG-subclass profile following a single dose of mRNA-1273 (Extended Data Fig. 6c) was similar to that observed following two doses. By contrast, T_H2-biased responses, with lower IgG2a/IgG1 ratios, were observed in mice immunized with

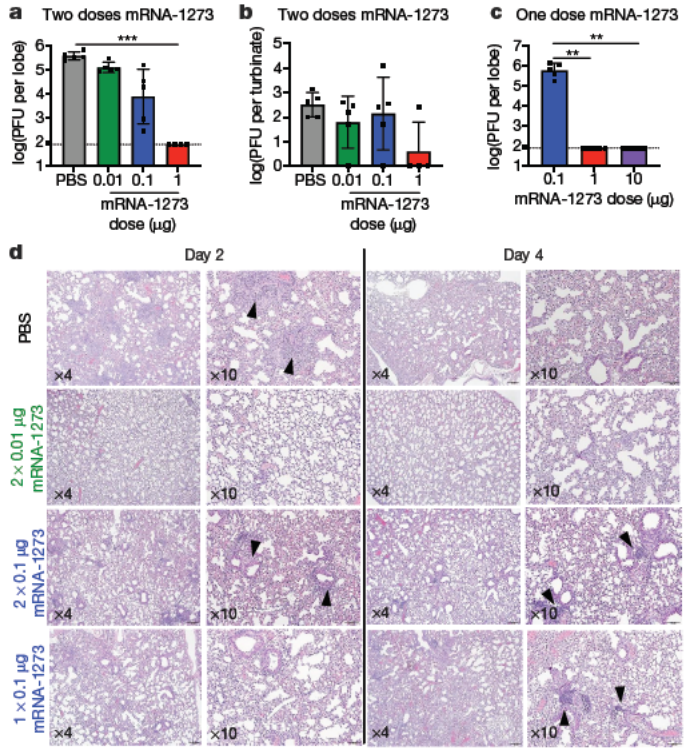

Fig. 4 | mRNA-1273 protects mice from upper- and lower-airway SARS-CoV-2 infection. a, **b**, BALB/cJ mice ($n = 10$ per group) immunized at weeks 0 and 3 with 0.01 μg (green), 0.1 μg (blue) or 1 μg (red) mRNA-1273 or PBS were challenged with SARS-CoV-2 MA five weeks post-boost. **c**, Other groups were immunized with single doses of 0.1 μg (blue), 1 μg (red) or 10 μg (purple) mRNA-1273 and challenged 7 weeks after immunization. Two days after challenge, at peak viral load, mouse lungs (**a**, **c**) and nasal turbinates (**b**) were collected from five mice per group to measure viral titres. **a**–**c**, Data are presented as GMT ± geometric s.d. and dotted lines represent assay limits of detection. Group comparisons were made by Kruskal–Wallis ANOVA with Dunn's multiple comparisons test. $^{**}P < 0.01$, $^{***}P < 0.001$. **d**, At days 2 and 4 after challenge, lung sections from 5 mice per group were stained with haematoxylin and eosin, and representative photomicrographs (original magnification ×4 (scale bars, 600 μm) and ×10 (scale bars, 300 μm) as indicated) from each group with detectable virus in lung are shown. Day 2 lungs from PBS control mice demonstrated moderate-to-severe, predominantly neutrophilic inflammation present within and surrounding small bronchioles (arrowheads); alveolar capillaries were markedly expanded by infiltrating inflammatory cells. In the 0.01 μg two-dose group, inflammation was minimal to absent. In the 0.1 μg two-dose group, occasional areas of inflammation intimately associated with small airways (bronchioles) and adjacent vasculature (arrowheads) were seen, primarily composed of neutrophils. In the single-dose 0.1 μg group, there were mild patchy expansions of alveolar septae by mononuclear and polymorphonuclear cells. At day 4, lungs from PBS control mice exhibited moderate-to-marked expansion of alveolar septae (interstitial pattern) with decreased prominence of adjacent alveolar spaces. In the 0.01 μg two-dose group, inflammation was minimal to absent. Lungs in the 0.1 μg two-dose group showed mild, predominantly lymphocytic inflammation, associated with bronchioles and adjacent vasculature (arrowheads). In the single-dose 0.1 μg group there was mild, predominantly lymphocytic inflammation around bronchovascular bundles (arrowheads).

SARS-CoV-2 S(2P) protein formulated in alum (Extended Data Fig. 8a, b). Following restimulation with peptide pools (one pool of overlapping peptides for each S subunit, S1 and S2) covering the entire S protein, splenocytes from mice immunized with mRNA-1273 secreted more IFN-γ (a prototypic T_H1 cytokine) than IL-4, IL-5 or IL-13 (classical T_H2 cytokines), whereas restimulation with SARS-CoV-2 S(2P) protein with alum adjuvant induced a T_H2-biased response (Extended Data Fig. 8c, d). We also directly measured cytokine patterns in vaccine-induced memory T cells by intracellular cytokine staining seven weeks after the boost injection; mRNA-1273-elicited $CD4^+$ T cells re-stimulated with S1 or S2 peptide pools exhibited a T_H1-dominant response, particularly at higher immunogen doses (Fig. 3d, e). Furthermore, 1 μg mRNA-1273 induced a robust $CD8^+$ T cell response to the S1 peptide pool (Fig. 3f, g). Together, the IgG subclass and T cell cytokine data demonstrate that immunization with mRNA-1273 elicits balanced T_H1 and T_H2 responses, in contrast to the T_H2-biased response seen when using S protein with alum adjuvant, suggesting that mRNA vaccination avoids T_H2-biased immune responses, which have been linked to VAERD.

Protective immunity was assessed in young adult BALB/cJ mice challenged with mouse-adapted (MA) SARS-CoV-2. SARS-CoV-2 MA contains the substitutions Q498Y/P499T in the receptor-binding domain[31]. The substitutions enable the virus to bind to the mouse angiotensin-converting enzyme 2 (ACE2) receptor and infect and replicate in the upper and lower respiratory tract[32]. BALB/cJ mice that received two 1 μg doses of mRNA-1273 were completely protected from viral replication in lungs after challenge 5 or 13 weeks after boost injection (Fig. 4a, Extended Data Fig. 9a). mRNA-1273-induced immunity also resulted in undetectable viral replication in nasal turbinates in 6 out of 7 mice (Fig. 4b, Extended Data Fig. 9b). The efficacy of mRNA-1273 was dose-dependent; two 0.1 μg doses of mRNA-1273 reduced lung viral load by about 100-fold, whereas two 0.01 μg doses reduced lung viral load by about 3-fold (Fig. 4a). Of note, mice challenged 7 weeks after a single dose of 1 or 10 μg mRNA-1273 were also completely protected against lung viral replication (Fig. 4c). Challenging animals immunized with subprotective doses provides an orthogonal assessment of safety signals such as increased clinical illness or pathology. Similar observations with MERS-CoV S(2P) mRNA, mice immunized with subprotective 0.1 or 0.01 μg doses of mRNA-1273 showed no evidence of enhanced lung pathology or excessive mucus production (Fig. 4d). In summary, mRNA-1273 is immunogenic, efficacious and does not produce evidence of VAERD when given at subprotective doses in mice.

Here we have shown that 1 μg of mRNA-1273 is sufficient to induce robust pseudovirus-neutralizing activity and CD8 T cell responses, balanced T_H1–T_H2 antibody isotype responses, and protection from viral replication for more than three months following a prime–boost regimen similar to the one being tested in humans. The level of pseudovirus-neutralizing activity induced by 1 μg mRNA-1273 in mice is similar in magnitude to that induced by 100 μg mRNA-1273 in humans[33], which is the dose selected for mRNA-1273 to advance into phase III clinical trials. The inclusion of lower subprotective doses demonstrates the dose-dependence of antibody, T_H1 CD4 T cell responses and protection, suggesting that immune correlates of protection can be further elucidated. Animal studies supporting candidate SARS-CoV-2 vaccines through clinical trials aim to demonstrate elicitation of potent protective immune responses as well as to show that subprotective responses do not cause VAERD[5]. Subprotective doses of mRNA-1273 did not prime mice for enhanced immunopathology following challenge. Moreover, the induction of protective immunity following a single dose suggests single-dose administration of this vaccine could be considered in the outbreak setting. These data, combined with immunogenicity data from non-human primates and human participants of early phase I clinical trials, have been used to inform the dose and regimen of mRNA-1273 in advanced clinical efficacy trials.

The COVID-19 pandemic of 2020 is the widely predicted 'pathogen X event'[13,14]. Here we provide a paradigm for rapid vaccine development. Combining structure-guided stabilization of the MERS-CoV S protein with a fast, scalable and safe mRNA–LNP vaccine platform has led to a generalizable vaccine solution for *Betacoronavirus* and a commercial mRNA vaccine delivery platform; these developments enabled a rapid response to the COVID-19 outbreak. This response demonstrates how new technology-driven concepts such as synthetic vaccinology can facilitate a vaccine development programme initiated on the basis of

pathogen sequences alone[11]. This study also provides a proof of concept for the prototype-pathogen approach to pandemic preparedness and response that is predicated on identifying generalizable solutions for medical counter measures within virus families or genera[13]. Although the response to the COVID-19 pandemic has been unprecedented in its speed and breadth, we envision further improvements in rapid responses to such threats. There are 24 other virus families that are known to infect humans, and sustained investigation of those potential threats will improve our readiness for future pandemics[14].

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2622-0.

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Methods

Data reporting

No statistical methods were used to predetermine sample size. The experiments were not randomized. The investigators were not blinded to allocation during experiments and outcome assessment.

Pre-clinical mRNA-1273 mRNA and LNP production process

A sequence-optimized mRNA encoding SARS-CoV-2 S(2P) protein was synthesized in vitro using an optimized T7 RNA polymerase-mediated transcription reaction with complete replacement of uridine by N1-methyl-pseudouridine[34]. The reaction included a DNA template containing the immunogen open reading frame flanked by 5′ untranslated region (UTR) and 3′ UTR sequences and was terminated by an encoded polyA tail. After transcription, the Cap 1 structure was added to the 5′ end using vaccinia capping enzyme (New England Biolabs) and Vaccinia 2′ *O*-methyltransferase (New England Biolabs). The mRNA was purified by oligo-dT affinity purification, buffer exchanged by tangential flow filtration into sodium acetate, pH 5.0, sterile filtered, and kept frozen at −20 °C until further use.

The mRNA was encapsulated in a lipid nanoparticle through a modified ethanol-drop nanoprecipitation process as described previously[20]. In brief, ionizable, structural, helper and polyethylene glycol lipids were mixed with mRNA in acetate buffer, pH 5.0, at a ratio of 2.5:1 (lipids:mRNA). The mixture was neutralized with Tris-Cl pH 7.5, sucrose was added as a cryoprotectant, and the final solution was sterile filtered. Vials were filled with formulated LNP and stored frozen at −70 °C until further use. The drug product underwent analytical characterization, which included the determination of particle size and polydispersity, encapsulation, mRNA purity, double stranded RNA content, osmolality, pH, endotoxin and bioburden, and the material was deemed acceptable for in vivo study.

MERS-CoV and SARS-CoV protein expression and purification

Vectors encoding MERS-CoV S-2P[1] and SARS-CoV S-2P[23] were generated as previously described with the following small amendments. Proteins were expressed by transfection of plasmids into Expi293 cells using Expifectamine transfection reagent (ThermoFisher) in suspension at 37 °C for 4–5 days. Transfected cell culture supernatants were collected, buffer exchanged into 1× PBS, and protein was purified using Strep-Tactin resin (IBA). For proteins used for mouse inoculations, tags were cleaved with addition of HRV3C protease (ThermoFisher) (1% wt/wt) overnight at 4 °C. Size-exclusion chromatography using Superose 6 Increase column (GE Healthcare) yielded final purified protein.

Design and production of recombinant minifibritin foldon protein

A mammalian codon-optimized plasmid encoding foldon inserted minifibritin (ADIVLNDLPFVDGPPAEGQSRISWIKNGEEILGADTQYGSE GSMNRPTVSVLRNVEVLDKNIGILKTSLETANSDIKTIQEAGYIPEAPRDGQA YVRKDGEWVLLSTFLSPALVPRGSHHHHHHSAWSHPQFEK) with a C-terminal thrombin cleavage site, 6×His tag, and Strep-TagII was synthesized and subcloned into a mammalian expression vector derived from pLEXm. The construct was expressed by transient transfection of Expi293 (ThermoFisher) cells in suspension at 37 °C for 5 days. The protein was first purified with a Ni^{2+}-nitrilotriacetic acid resin (GE Healthcare) using an elution buffer consisting of 50 mM Tris-HCl, pH 7.5, 400 mM NaCl and 300 mM imidazole pH 8.0, followed by purification with StrepTactin resin (IBA) according to the manufacturer's instructions.

Cell lines

HEK293T/17 (ATCC CRL-11268), Vero E6 (ATCC), Huh7.5 cells (provided by D. R. Taylor, US Food and Drug Administration) and ACE2-expressing 293T cells (provided by M. Farzan, Scripps Research Institute) were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS, 2 mM glutamine and 1% penicillin–streptomycin at 37 °C and 5% CO_2. Vero E6 cells used in plaque assays to determine lung and nasal turbinate viral titres were cultured in DMEM supplemented with 10% Fetal Clone II and 1% antibiotic–antimycotic at 37 °C and 5% CO2. Vero E6 cells used in plaque-reduction neutralization test (PRNT) assays were cultured in DMEM supplemented with 10% Fetal Clone II and amphotericin B (0.25 μg ml^{-1}) at 37 °C and 5% CO_2. Lentivirus encoding hACE2-P2A-TMPRSS2 was made to generate A549-hACE2-TMPRSS2 cells, which were maintained in DMEM supplemented with 10% FBS and 1 μg ml^{-1} puromycin. Expi293 cells were maintained in the manufacturer's suggested medium. BHK-21/WI-2 cells were obtained from Kerafast and cultured in DMEM with 5% FBS at 37 °C and 6–8% CO_2. Cell lines were not authenticated. All cells lines were tested for mycoplasma and remained negative.

In vitro mRNA expression

HEK293T cells were transiently transfected with mRNA encoding SARS-CoV-2 wild-type S or S(2P) protein using a TranIT mRNA transfection kit (Mirus). After 24 h, the cells were collected and resuspended in fluorescence-activated cell sorting (FACS) buffer (1× PBS, 3% FBS, 0.05% sodium azide). To detect surface-protein expression, the cells were stained with 10 μg ml^{-1} ACE2–Flag (Sigma) or 10 μg ml^{-1} CR3022[35] in FACS buffer for 30 min on ice. Thereafter, cells were washed twice in FACS buffer and incubated with FITC–anti-Flag (Sigma) or Alexa Fluor 647–goat anti-human IgG (Southern Biotech) in FACS buffer for 30 min on ice. Live/Dead aqua fixable stain (Invitrogen) were used to assess viability. Data acquisition was performed on a BD LSRII Fortessa instrument (BD Biosciences) and analysed by FlowJo software v.10 (Tree Star).

Mouse models

Animal experiments were carried out in compliance with all pertinent US National Institutes of Health regulations and approval from the Animal Care and Use Committee (ACUC) of the Vaccine Research Center, Moderna Inc., or University of North Carolina at Chapel Hill. For immunogenicity studies, 6- to 8-week-old female BALB/c (Charles River), BALB/cJ, C57BL/6J or B6C3F1/J mice (Jackson Laboratory) were used. mRNA formulations were diluted in 50 μl 1× PBS, and mice were inoculated intramuscularly in the same hind leg for both prime and boost. Control mice received PBS because previous studies have demonstrated the mRNA formulations being tested do not create substantial levels of nonspecific immunity beyond a few days[36–38]. For all SARS-CoV-2 S(2P) protein vaccinations, mice were inoculated intramuscularly with SAS as previously described[1]. For S(2P) + alum immunizations, SARS-CoV-2 S(2P) protein + 250 μg alum hydrogel was delivered intramuscularly. For challenge studies to evaluate MERS-CoV vaccines, 16- to 20-week-old male and female 288/330$^{+/+}$mice[22] were immunized. Four weeks post-boost, pre-challenge sera were collected from a subset of mice, and the remaining mice were challenged with 5×10^5 PFU of a mouse-adapted MERS-CoV EMC derivative, m35c4[39]. On day 3 post-challenge, lungs were collected and haemorrhage and viral titre were assessed according to previously published methods[40]. For challenge studies to evaluate SARS-CoV-2 vaccines, BALB/cJ mice were challenged with 10^5 PFU SARS-CoV-2 MA. This virus contains two mutations (Q498T/P499Y) in the receptor binding domain that enable binding of SARS-CoV-2 S protein to the mouse ACE2 receptor and infection and replication in the upper and lower respiratory tract[32]. On day 2 post-challenge, lungs and nasal turbinates were collected for viral titre assessment according to previously published methods[32]. Sample size for animal experiments was determined on the basis of criteria set by institutional ACUC. Experiments were not randomized or blinded.

Histology

Lungs were collected from mice at the indicated study end points and placed in 10% neutral-buffered formalin until adequately fixed. Thereafter, tissues were trimmed to a thickness of 3–5 mm, processed and paraffin

embedded. The respective paraffin tissue blocks were sectioned at 5 µm and stained with haematoxylin and eosin. All sections were examined by a board-certified veterinary pathologist using an Olympus BX51 light microscope, and photomicrographs were taken using an Olympus DP73 camera.

ELISA

Nunc Maxisorp ELISA plates (ThermoFisher) were coated with 100 ng per well of protein in 1× PBS at 4 °C for 16 h. Where applicable, to eliminate fold-on-specific binding from MERS-CoV S(2P) or SARS-CoV-2 S(2P) protein-immune mouse serum, 50 µg ml^{-1} of fold-on protein was added for 1 h at room temperature. After standard washes and blocks, plates were incubated with serial dilutions of heat-inactivated sera for 1 h at room temperature. Following washes, anti-mouse IgG, IgG1 or IgG2a and/or IgG2c–horseradish peroxidase conjugates (ThermoFisher) were used as secondary antibodies, and 3,5,3′5′-tetramethylbenzidine (TMB) (KPL) was used as the substrate to detect antibody responses. End-point titres were calculated as the dilution that emitted an optical density exceeding 4× background (secondary antibody alone).

Lentivirus-based pseudovirus-neutralization assay

The pseudovirus-neutralization assay measures the inhibition of pseudovirus attachment and entry including fusion-inhibiting activity. It is a single-round virus, does not replicate, and does not express the S protein in transduced cells. Therefore, pseudovirus infection will not cause cell-to-cell fusion or plaque formation that can be measured in a classical neutralization assay using live virus. This pseudovirus neutralization assay has been shown to correlate with live virus plaque-reduction neutralization[33], and because it does not require BL3 containment, was chosen as the preferred assay for measuring neutralizing activity in these studies. We introduced divergent amino acids, as predicted from translated sequences, into the CMV/R-MERS-CoV EMC S (GenBank: AFS88936) gene[41] to generate a MERS-CoV m35c4 S gene[39]. To produce SARS-CoV-2 pseudoviruses, a codon-optimized CMV/R-SARS-CoV-2 S (Wuhan-1, GenBank: MN908947.3) plasmid was constructed. Pseudoviruses were produced by co-transfection of plasmids encoding a luciferase reporter, lentivirus backbone, and S genes into HEK293T/17 cells (ATCC CRL-11268), as previously described[41]. For SARS-CoV-2 pseudovirus, human transmembrane protease serine 2 (TMPRSS2) plasmid was also co-transfected[42]. Pseudoneutralization assay methods have been previously described[1,33]. In brief, heat-inactivated serum was mixed with pseudoviruses, incubated, and then added to Huh7.5 cells or ACE-2-expressing 293T cells for MERS-CoV and SARS-CoV-2 respectively. Seventy-two hours later, cells were lysed and luciferase activity (in relative light units (RLU)) was measured. Per cent neutralization was normalized considering uninfected cells as 100% neutralization and cells infected with only pseudovirus as 0% neutralization. IC_{50} titres were determined using a log (agonist) vs normalized-response (variable slope) nonlinear function in Prism v8 (GraphPad).

Recombinant VSVΔG-based pseudovirus neutralization assay

Codon-optimized wild-type (D614) or D614G spike gene (Wuhan-Hu-1 strain, NCBI reference sequence: NC_045512.2) was cloned into pCAGGS vector. To generate VSVΔG-based SARS-CoV-2 pseudovirus, BHK-21/WI-2 cells were transfected with the spike expression plasmid and infected VSVΔG-firefly-luciferase as previously described[43]. A549-hACE2-TMPRSS2 cells were infected by pseudovirus for 1 h at 37 °C. The inoculum virus or virus-antibody mix was removed after infection. Eighteen hours later, an equal volume of One-Glo reagent (Promega) was added to culture medium for readout using a BMG PHERastar-FS plate reader. The neutralization procedure and data analysis are the same as mentioned above for the lentivirus-based pseudovirus neutralization assay.

PRNT assays

Heat-inactivated sera were diluted in gelatin saline (0.3% (wt/vol) gelatin in PBS supplemented with $CaCl_2$ and $MgCl_2$ to generate a 1:5 dilution of the original specimen, which served as a starting concentration for further serial log_4 dilutions terminating in 1:81,920. Sera were combined with an equal volume of SARS-CoV-2 clinical isolate 2019-nCoV USA-WA1-F6/2020 in gelatin saline, resulting in an average concentration of 730 PFU per ml (determined from plaque counts of 24 individual wells of untreated virus) in each serum dilution. Thus, final serum concentrations ranged from 1:10 to 1:163,840 of the original. Virus–serum mixtures were incubated for 20 min at 37 °C, followed by adsorption of 0.1 ml to each of two confluent Vero E6 cell monolayers (in 10 cm^2 wells) for 30 min at 37 °C. Cell monolayers were overlaid with DMEM containing 1% agar and incubated for 3 d at 37 °C in humidified 5% CO_2. Plaques were enumerated by direct visualization. The average number of plaques in virus + serum (duplicate) and virus-only (24 repeats) wells was used to generate percent neutralization curves according the following formula: 1 – (ratio of mean number of plaques in the presence and absence of serum). The PRNT IC_{50} titre was defined as the reciprocal serum dilution at which the neutralization curve crossed the 50% threshold.

Intracellular cytokine staining

Mononuclear single-cell suspensions from whole mouse spleens were generated using a gentleMACS tissue dissociator (Miltenyi Biotec) followed by 70-µm filtration and density gradient centrifugation using Fico/Lite-LM medium (Atlanta Biologicals). Cells from each mouse were resuspended in R10 media (RPMI 1640 supplemented with penicillin–streptomycin antibiotic, 10% heat-inactivated FBS, Glutamax and HEPES) and incubated for 6 h at 37 °C with protein transport inhibitor cocktail (eBioscience) under three conditions: no peptide stimulation, and stimulation with two S-protein peptide pools (JPT product PM-WCPV-S-1). Peptide pools were used at a final concentration of 2 µg ml per peptide. Cells from each group were pooled for stimulation with cell stimulation cocktail (eBioscience) as a positive control. Following stimulation, cells were washed with PBS before staining with LIVE/DEAD Fixable Blue Dead Cell Stain (Invitrogen, L23105; 1:800) for 20 min at room temperature. Cells were then washed in FC buffer (PBS supplemented with 2% heat-inactivated FBS and 0.05% NaN_3) and resuspended in Fc Block (BD, 553141, clone 2.4G2; 1:100) for 5 min at room temperature before staining with a surface stain cocktail containing the following antibodies: I-A/I-E PE (BD, 557000, clone M5/114.15.2; 1:2,500), CD8a BUV805 (BD, 612898, clone 53-6.7; 1:80), CD44 BUV395 (BD, 740215, clone IM7; 1:800), CD62L BV605 (Biolegend, 104418, clone MEL-14; 1:5,000) and CD4 BV480 (BD, 565634, clone RM4-5; 1:500) in brilliant stain buffer (BD). After 15 min, cells were washed with FC buffer then fixed and permeabilized using the BD Cytofix/Cytoperm fixation/permeabilization solution kit according to the manufacturer's instructions. Cells were washed in perm/wash solution and stained with Fc Block (5 min at room temperature), followed by intracellular staining (30 min at 4 °C) using a cocktail of the following antibodies: CD3e BUV737 (BD, 741788, clone 17A2; 1:80), IFN-γ BV650 (BD, 563854, clone XMG1.2; 1:500), TNF BV711 (BD, 563944, clone MP6-XT22; 1:80), IL-2 BV421 (BD, 562969, clone JES6-5H4; 1:80), IL-4 Alexa Fluor 488 (Biolegend, 504109, clone 11B11; 1:80) and IL-5 APC (Biolegend, 504306, clone TRFK5; 1:320) in 1× perm/wash diluted with brilliant stain buffer. Finally, cells were washed in perm/wash solution and resuspended in 0.5% PFA–FC stain buffer before running on a Symphony A5 flow cytometer (BD). Analysis was performed using FlowJo software, v.10.6.2 according to the gating strategy outlined in Extended Data Fig. 10. Background cytokine expression in the no-peptide condition was subtracted from that measured in the S1 and S2 peptide pools for each individual mouse.

T cell stimulation and cytokine analysis

Spleens from immunized mice were collected two weeks post-boost. Two-million splenocytes per well (96-well plate) were stimulated in vitro with two peptide libraries, JPT1 and JPT2, (15mers with 11 amino acid overlap) covering the entire SARS-CoV-2 S protein (JPT product

PM-WCPV-S-1). Both peptide libraries were used at a final concentration of 1 μg ml^{-1}. After 24 h of culture at 37 °C, the plates were centrifuged and supernatant was collected and frozen at −80 °C for cytokine detection. Measurements and analyses of secreted cytokines from a murine 35-plex kit were performed using a multiplex bead-based technology (Luminex) assay with a Bio-Plex 200 instrument (Bio-Rad) after twofold dilution of supernatants.

Statistical analysis

Geometric means or arithmetic means are represented by the heights of bars, or symbols, and error bars represent the corresponding s.d. Dotted lines indicate assay limits of detection. Two-sided Mann–Whitney *U*-tests were used to compare two experimental groups and two-sided Wilcoxon signed-rank tests to compare the same animals at different time points. To compare more than two experimental groups, Kruskal–Wallis ANOVA with Dunn's multiple comparisons tests were applied. In Extended Data Fig. 5a, b, all doses were compared to the 20 μg dose by two-sided Mann–Whitney *U*-test in a stepwise fashion, such that lowest doses were tested first at $\alpha = 0.05$ and higher doses were tested only if the lower doses were significant. In Extended Data Fig. 5c, a Spearman correlation test was used to correlate binding antibody titres to pseudovirus-neutralizing antibody titres. Statistical analyses were performed using R v.4.0.0 or Prism v.8 (GraphPad). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

The authors declare that the data supporting the findings of this study are available within this Article and its Supplementary Information. Source data are provided with this paper.

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Acknowledgements We thank K. Bok, K. Carlton, M. Kanekiyo, R. Seder and other members of all included laboratories for critical discussions, advice and review of the manuscript; J. Stein for technology transfer; M. Young for administrative support; members of the NIH NIAID VRC Translational Research Program for technical assistance with mouse experiments; B. Hartman for assistance with graphics; H. Mu and M. Farzan for the ACE2-overexpressing 293 cells; and M. Whitt for support on VSV-based pseudovirus production. This work was supported by the Intramural Research Program of the VRC and the Division of Intramural Research, NIAID, NIH (B.S.G.), NIH NIAID grant R01-AI127521 (J.S.M.), and NIH grants AI149644 and AI100625 (R.S.B.). mRNA-1273 has been funded in part with Federal funds from the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract 75A50120C00034. PRNT assays were funded under NIH contract HHSN261200800001E agreement 17x198 (to J.D.C.), furnished through Leidos Biomedical Research. MERS-CoV mRNA mouse challenge studies were funded under NIH contract HHSN272201700036I task order no. 75N93019F00132 requisition no. 5494549 (to R.S.B.). K.S.C.'s research fellowship was partially funded by the Undergraduate Scholarship Program, Office of Intramural Training and Education, Office of the Director, NIH. D.R.M. was funded by NIH NIAID grant T32-AI007151 and a Burroughs Wellcome Fund Postdoctoral Enrichment Program Award.

Author contributions K.S.C., D.K.E., S.R.L., O.M.A, S.B.-B., R.A.G., S.H., A.S., C.T.Z., A.T.D., K.H.D., S.M.E., C.A.S., A. Woods, E.J.F., D.R.M., K.W.B., M. Minai, B.M.N., G.B.H., K.W., C.H., K.B., D.G.-D., L.M., I.R., W.-P.K., S.D.S., L.W., Y.Z., E.P., L.A.C., R.J.L., N.E.A., E.N., M. Metkar, V.P., C.L., M.K.L., W.S., K.L., E.S.Y., A. West, K.L.G., L.J.S., N.A.D.-R., G.S.-J., H.B., G.S.A., M.C.N., T.J.R., M.R.D., J.D.C., I.N.M., K.M.M., J.R.M., R.S.B., A.C. and B.S.G. designed, completed and/or analysed experiments. K.S.C., O.M.A., G.B.H., N.W., D.W., J.S.M. and B.S.G. contributed new reagents and/or analytic tools. K.S.C., K.M.M. and B.S.G. wrote the manuscript. All authors contributed to discussions in regard to and editing of the manuscript.

Competing interests K.S.C., N.W., J.S.M. and B.S.G. are inventors on International Patent Application no. WO/2018/081318 entitled 'Prefusion Coronavirus Spike Proteins and Their Use'. K.S.C., O.M.A., G.B.H., N.W., D.W., J.S.M. and B.S.G. are inventors on US Patent Application no. 62/972,886 entitled '2019-nCoV Vaccine'. R.S.B. filed an invention report for the SARS-CoV-2 MA virus (UNC ref. 18752).

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41586-020-2622-0.

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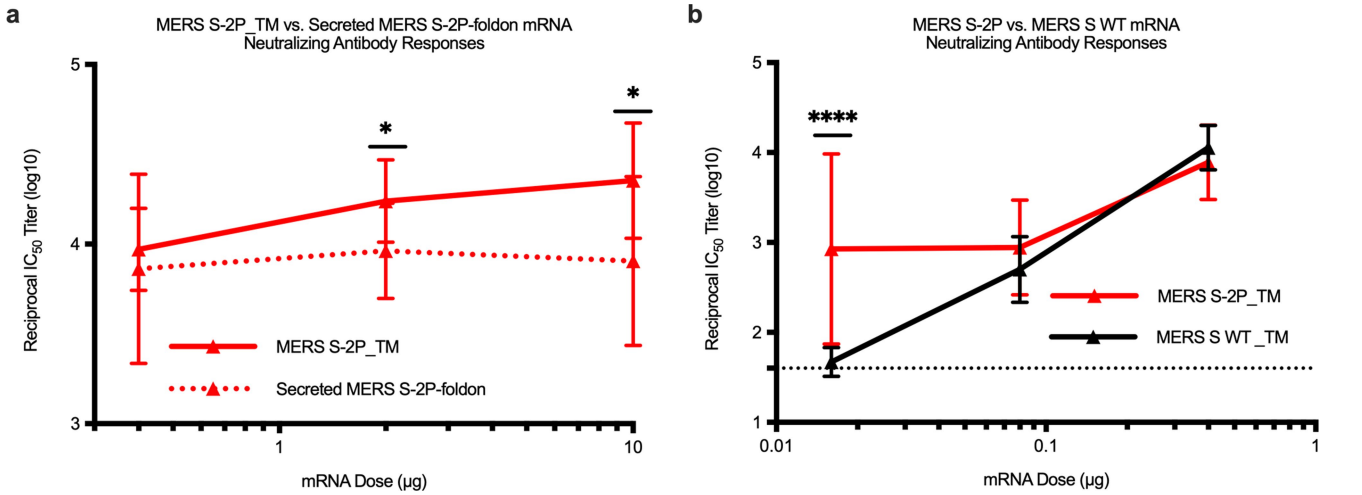
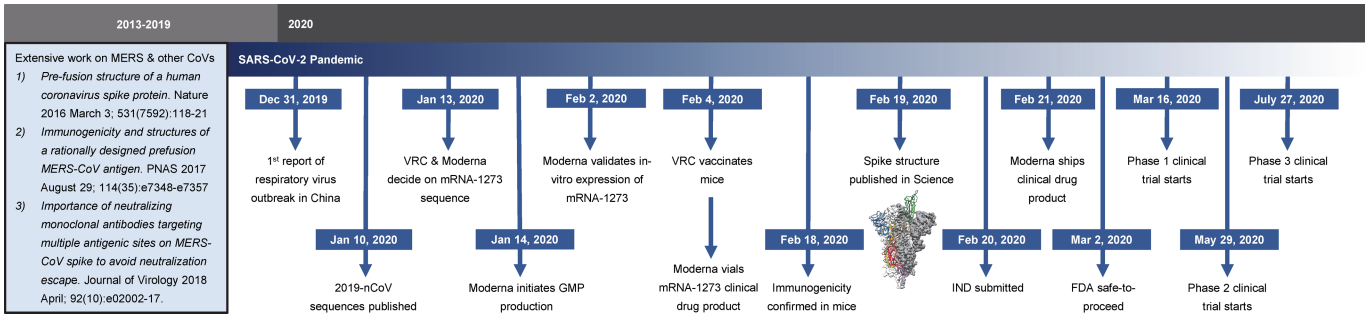
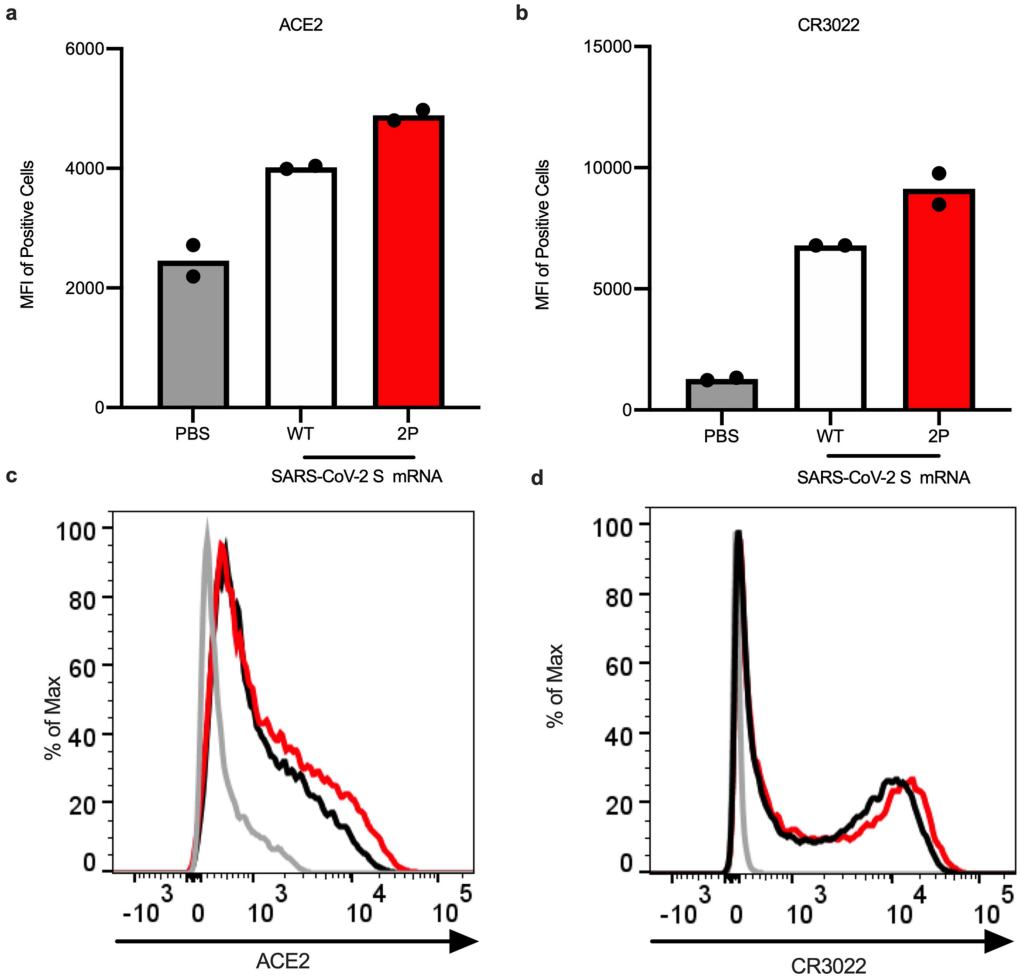
Peer review information *Nature* thanks Rino Rappuoli, Patrick C. Wilson and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.



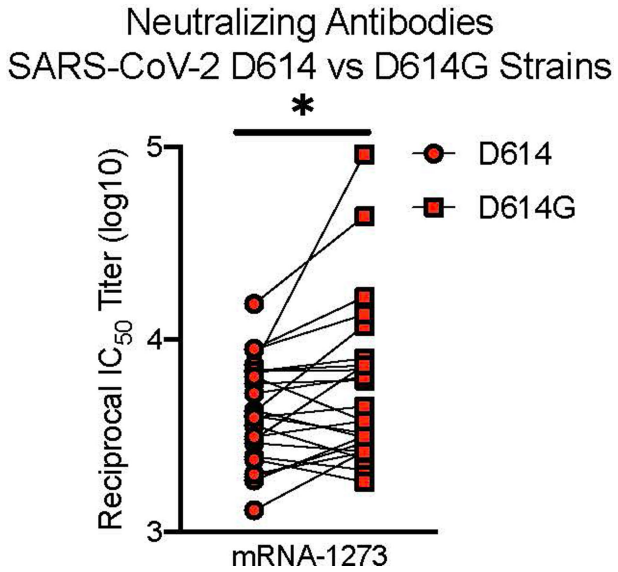
Extended Data Fig. 1 | Transmembrane-anchored MERS-CoV S-2P (S-2P_TM) mRNA elicits more potent pseudovirus neutralizing antibody responses than secreted MERS-CoV S(2P) and S WT mRNA. a, **b**, C57BL/6J mice ($n = 10$/group) were immunized at weeks 0 and 4 with (**a**) 0.4, 2, or 10 µg of MERS-CoV S-2P_TM (red) or MERS S-2P_secreted (red hashed) or (**b**) 0.016 µg, 0.08 µg, or 0.4 µg of MERS-CoV S(2P) or MERS-CoV S WT_TM (black) mRNA. Sera were collected 4 weeks post-boost and assessed for neutralizing antibodies against MERS-CoV m35c4 pseudovirus. Immunogens were compared at each dose level by two-sided Mann–Whitney *U*-test. $^{*}P < 0.05$, $^{****}P < 0.0001$. Data are presented as GMT ± geometric s.d.



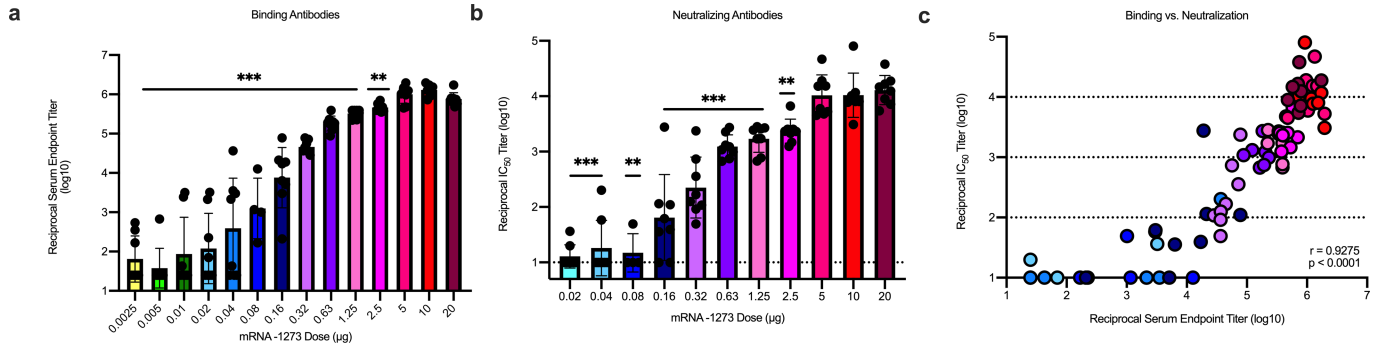
Extended Data Fig. 2 | Timeline for mRNA-1273's progression to clinical trial. The morning after novel coronavirus (nCoV) sequences were released, spike sequences were modified to include prefusion stabilizing mutations and synthesized for protein production, assay development, and vaccine development. Twenty-five days after viral sequences were released, clinically-relevant mRNA-1273 was received to initiate animal experiments. Immunogenicity in mice was confirmed 15 days later. Moderna shipped clinical drug product 41 days after GMP production began, leading to the phase I clinical trial starting 66 days following the release of nCoV sequences.



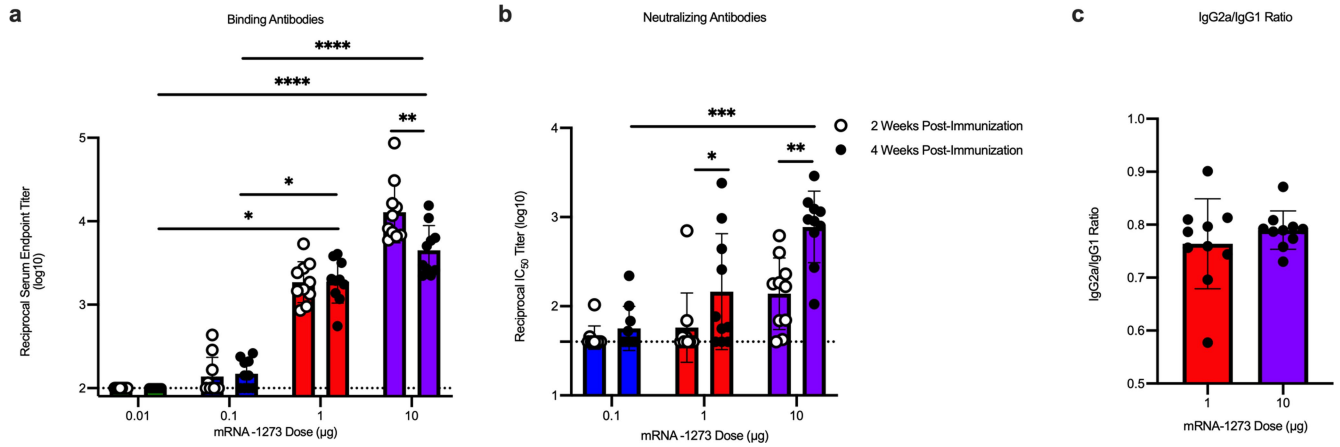
Extended Data Fig. 3 | In vitro expression of SARS-CoV-2 spike mRNA on the cell surface. a–**d**, 293T cells were transfected in duplicate with mRNA expressing SARS-CoV-2 wild-type spike (white bars, black lines) or S-2P (red), stained with ACE2 (**a**, **c**) or CR3022 (**b**, **d**), and evaluated by flow cytometry 24 post-transfection. Mock-transfected (PBS) cells served as a control (grey). (**a**, **b**) Data are presented as mean.



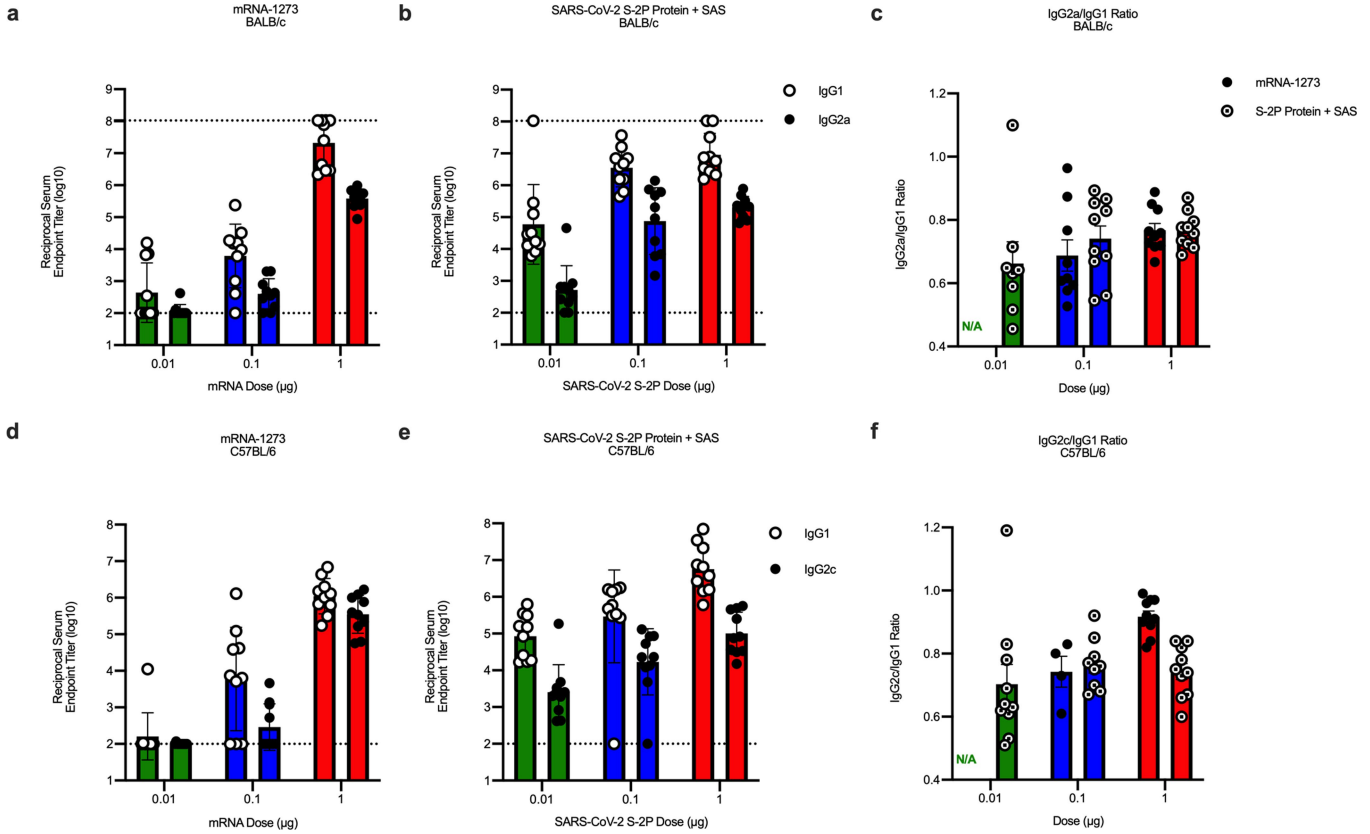
Extended Data Fig. 4 | mRNA-1273 elicits robust pseudovirus neutralizing antibody responses to SARS-CoV-2_D614G. BALB/c mice ($n = 24$) were immunized at weeks 0 and 3 weeks with 1 µg (red) of mRNA-1273, in three individual studies ($n = 8$/study). Sera were collected 2 weeks post-boost and assessed for neutralizing antibodies against homotypic SARS-CoV-2_D614 pseudovirus (circles) or SARS-CoV-2_D614G (squares). Comparisons between D614 and D614G were made by two-sided Wilcoxon signed rank test. *$P < 0.05$.



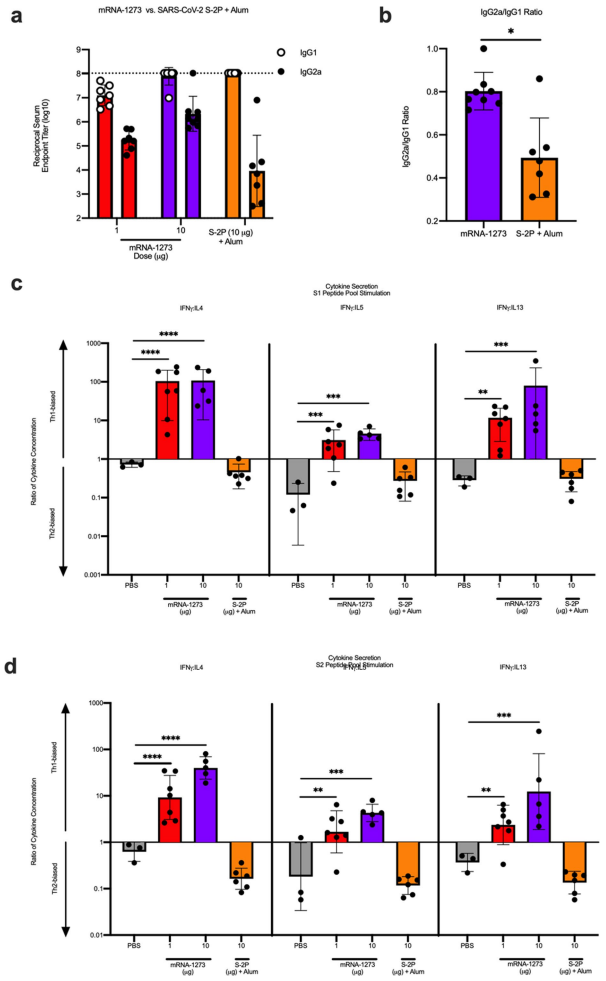
Extended Data Fig. 5 | Dose-dependent mRNA-1273-elicited antibody responses reveal strong positive correlation between binding and pseudovirus neutralization titres. a–**c**, BALB/c mice ($n = 10$/group) were immunized at weeks 0 and 3 weeks with various doses (0.0025–20 µg) of mRNA-1273. Sera were collected 2 weeks post-boost and assessed for SARS-CoV-2 S-specific IgG by ELISA (**a**) and neutralizing antibodies against homotypic SARS-CoV-2 pseudovirus (**b**). **a**, **b**, All doses were compared to the 20 µg dose by two-sided Mann–Whitney *U*-test in a stepwise fashion, such that lowest doses were tested first at $\alpha = 0.05$ and higher doses tested only if the lower doses were significant. Data are presented as GMT ± geometric s.d., and dotted lines represent assay limits of detection. **c**, Spearman correlation test was used to correlate binding antibody titres to pseudovirus neutralizing antibody titres ($P < 0.0001$). Each dot represents an individual mouse. Dotted lines highlight $\log_{10}$ IC_{50} boundaries. $^{**}P < 0.01$, $^{***}P < 0.001$.



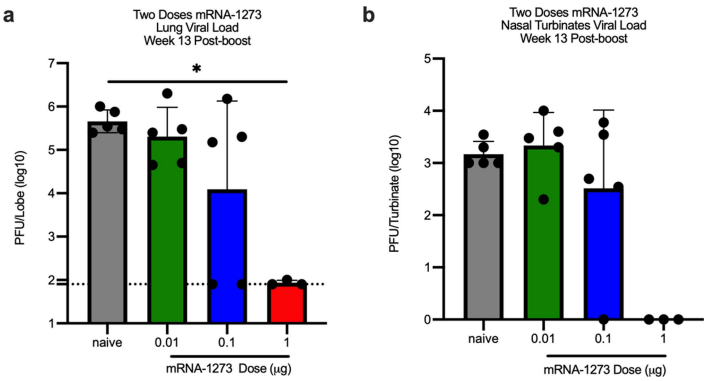
Extended Data Fig. 6 | A single dose of mRNA-1273 elicits robust antibody responses. a–**c**, BALB/cJ mice ($n = 10$/group) were immunized with 0.01 (green), 0.1 (blue), 1 µg (red), or 10 µg (purple) of mRNA-1273. Sera were collected 2 (unfilled circles) and 4 (filled circles) weeks post-immunization and assessed for SARS-CoV-2 S-specific total IgG by ELISA (**a**) and neutralizing antibodies against homotypic SARS-CoV-2 pseudovirus (**b**). **c**, S-specific IgG2a and IgG1 were also measured by ELISA, and IgG2a to IgG1 subclass ratios were calculated. In **a**, **b**, Time points were compared within each dose level by two-sided Wilcoxon signed-rank test, and doses were compared 4 weeks post-boost by Kruskal–Wallis ANOVA with Dunn's multiple comparisons test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. **c**, Doses were compared by two-sided Mann–Whitney *U*-test, and no significance was found. Data are presented as GMT ± geometric s.d. (**a**, **b**) or mean ± s.d. (**c**), and dotted lines represent assay limits of detection.



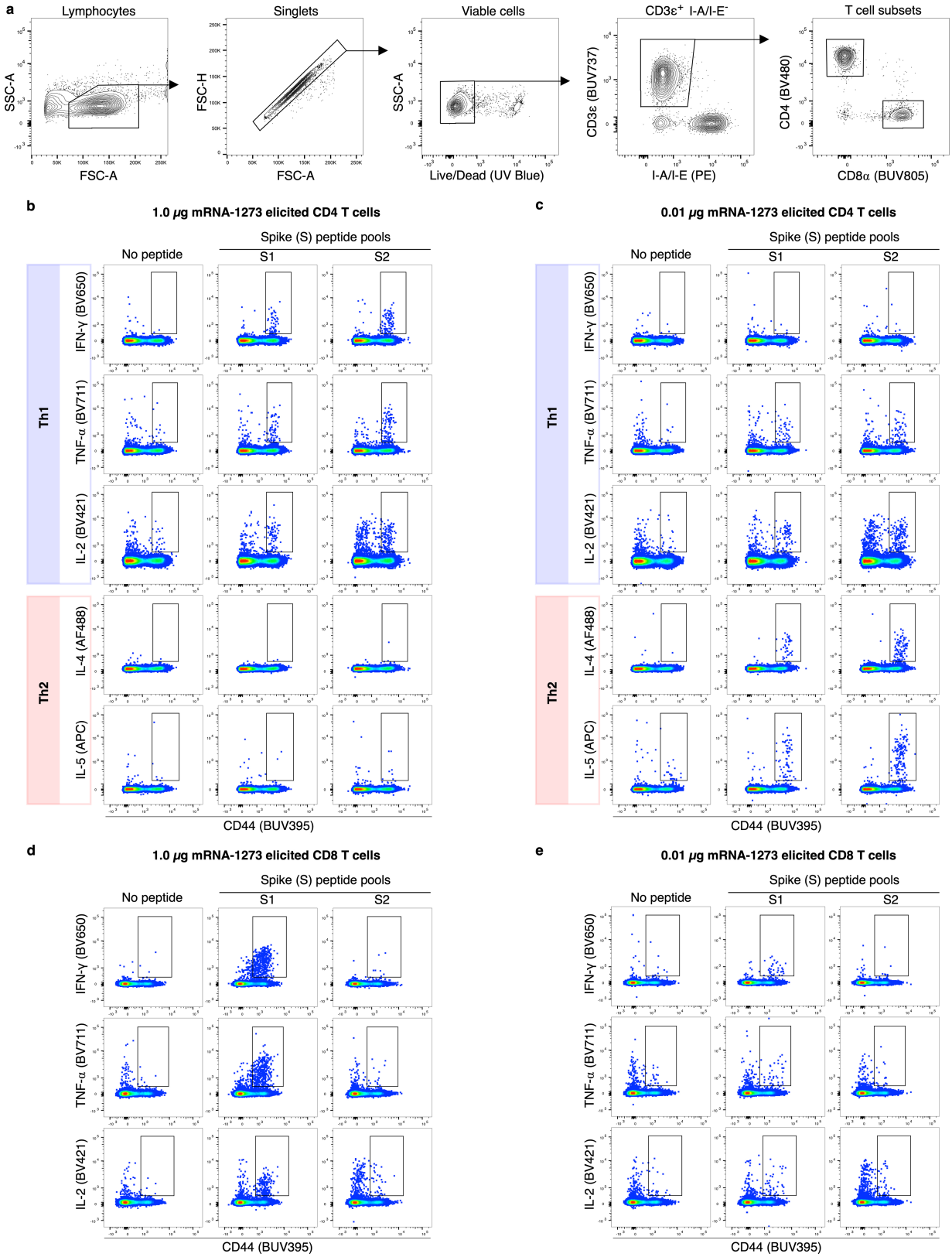
Extended Data Fig. 7 | mRNA-1273 and SAS-adjuvanted S-2P protein elicit both IgG2a and IgG1 subclass S-binding antibodies. a–**f**, BALB/cJ (**a**–**c**) or C57BL/6J (**d**–**f**) mice ($n = 10$/group) were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue), or 1 µg (red) of mRNA-1273 or SARS-CoV-2 S-2P protein adjuvanted with SAS. Sera were collected 2 weeks post-boost and assessed by ELISA for SARS-CoV-2 S-specific IgG1 and IgG2a or IgG2c for BALB/cJ and C57BL/6J mice, respectively. End-point titres (**a**, **b**, **d**, **e**) and end-point titre ratios of IgG2a to IgG1 (**c**) and IgG2c to IgG1 (**f**) were calculated. For mice for which end-point titres did not reach the lower limit of detection (dotted line), ratios were not calculated (N/A). Data are presented as GMT ± geometric s.d. (**a**, **b**, **d**, **e**) or mean ± s.d. (**c**, **f**).



Extended Data Fig. 8 | mRNA-1273 elicits T_H1-skewed responses compared to S-2P protein adjuvanted with alum. BALB/c mice ($n = 6$/group) were immunized at weeks 0 and 2 weeks with 1 (red) or 10 µg (purple) of mRNA-1273 or 10 µg of SARS-CoV-2 S-2P protein adjuvanted with alum hydrogel (orange). Control mice were administered PBS (grey) ($n = 3$). **a**, **b**, Sera were collected 2 weeks post-boost and assessed by ELISA for SARS-CoV-2 S-specific IgG1 and IgG2a. End-point titres (**a**) and end-point titre ratios of IgG2a to IgG1 (**b**) were calculated. **c**, **d**, Splenocytes were collected 4 weeks post-boost to evaluate IFN-γ, IL-4, IL-5, and IL-13 cytokine levels secreted by T cells re-stimulated with S1 (**c**) and S2 (**d**) peptide pools, measured by Luminex. In **b**, immunogens were compared by two-sided Mann–Whitney *U*-test. In **c**, **d**, for cytokines, all comparisons were compared to PBS control mice by Kruskal–Wallis ANOVA with Dunn's multiple comparisons test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. Data are presented as GMT ± geometric s.d. (**a**) or mean ± s.d. (**b**–**d**). Dotted line represents assay limit of detection.



Extended Data Fig. 9 | mRNA-1273 protects mice from upper- and lower-airway SARS-CoV-2 infection, 13 weeks post-boost. a, **b**, BALB/cJ mice were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue), or 1 µg (red) of mRNA-1273. Age-matched naive mice (grey) served as controls. Thirteen weeks post-boost, mice were challenged with mouse-adapted SARS-CoV-2. Two days post-challenge, at peak viral load, mouse lungs (**a**) and nasal turbinates (**b**) were collected from 5 mice per group (3 mice for the 1 µg group) for analysis of viral titres. All dose levels were compared by Kruskal–Wallis ANOVA with Dunn's multiple comparisons test. *$P < 0.05$. Data are presented as GMT ± geometric s.d. Dotted line represents assay limit of detection.



Extended Data Fig. 10 | Flow cytometry panel to quantify SARS-CoV-2 S-specific T cells in mice. a, Related to Fig. 3d–g, a hierarchical gating strategy was used to unambiguously identify single, viable $CD4^+$ and $CD8^+$ T cells. **b**–**e**, Gating summary of SARS-CoV-2 S-specific (**b**, **c**) $CD4^+$ and (**d**, **e**) $CD8^+$ T cells elicited by 0.01 and 1 μg mRNA-1273 immunization. Antigen-specific T cell responses following peptide pool re-stimulation were defined as $CD44^{hi}$/cytokine$^+$. Concatenated files shown were generated using the same number of randomly selected events from each animal across the different stimulation conditions using FlowJo software, v.10.6.2.

nature research

Corresponding author(s): Barney S. Graham and Andrea Carfi

Last updated by author(s): Jul 21, 2020

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one or two sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software used
Data analysis	R v4.0.0, Prism v8 (Graph Pad), FlowJo v10.6.2

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The authors declare that the data supporting the findings of this study are available within the paper and it's supplementary information files.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr_reporting_summary_flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size for animal experiments was determined based on criteria set by institutional ACUC.
Data exclusions	No data were excluded.
Replication	Animal studies were completed once. All immunoassay testing was completed in duplicate or triplicate with 1 replicate, unless otherwise stated.
Randomization	Allocation of animals was not random.
Blinding	Blinding was not completed as assays were completed by the same team that immunized animals.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP seq
☐	☒ Flow cytometry
☒	☐ MRI based neuroimaging

Antibodies

Antibodies used	CR3022 (made in house, citation below) | For ICS, a surface stain cocktail containing the following antibodies: I A/I E PE (BD, cat. 557000, clone M5/114.15.2, 1/2500), CD8a BUV805 (BD, cat. 612898, clone 53 6.7, 1/80), CD44 BUV395 (BD, cat. 740215, clone IM7, 1/800), CD62L BV605 (Biolegend, cat. 104418, clone MEL 14, 1/5000), and CD4 BV480 (BD, cat. 565634, clone RM4 5, 1/500)
Validation	Jan ter Meulen, J. et al. Human Monoclonal Antibody Combination against SARS Coronavirus: Synergy and Coverage of Escape Mutants. PLOS Medicine 3, e237, doi:10.1371/journal.pmed.0030237 (2006).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Expi293 (ThermoFisher), HEK293T/17 (ATCC #CRL 11268), Vero E6 (ATCC), Huh7.5 cells (provided by Deborah R. Taylor, US Food and Drug Administration), ACE 2 expressing 293T (ATCC) cells (provided by Michael Farzan, Scripps Research Institute). Huh7.5 cells are a derivative of Huh7 cells (ATCC).
Authentication	Cell lines were not authenticated.
Mycoplasma contamination	All cells tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines are in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	6 8 week old female BALB/c (Charles River), BALB/cJ, C57BL/6J, or B6C3F1/J mice (Jackson Laboratory) | 16 20 week old male and female 288/330+/+mice
Wild animals	There were no wild animals used in this study
Field collected samples	There were no field collected samples.
Ethics oversight	Animal experiments were carried out in compliance with all pertinent US National Institutes of Health regulations and approval from the Animal Care and Use Committee of the Vaccine Research Center, Moderna Inc., or University of North Carolina at Chapel Hill.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4 FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Mononuclear single cell suspensions from whole mouse spleens were generated using a gentleMACS tissue dissociator (Miltenyi Biotec) followed by 70 µm filtration and density gradient centrifugation using Fico/Lite LM medium (Atlanta Biologicals). Cells from each mouse were resuspended in R10 media (RPMI 1640 supplemented with Pen Strep antibiotic, 10% HI FBS, Glutamax, and HEPES) and incubated for 6 hr at 37°C with protein transport inhibitor cocktail (eBioscience) under three conditions: no peptide stimulation, and stimulation with two spike peptide pools (JPT product PM WCPV S 1). Peptide pools were used at a final concentration of 2 µg/mL each peptide. Cells from each group were pooled for stimulation with cell stimulation cocktail (eBioscience) as a positive control. Following stimulation, cells were washed with PBS prior to staining with LIVE/DEAD Fixable Blue Dead Cell Stain (Invitrogen) for 20 min at RT. Cells were then washed in FC buffer (PBS supplemented with 2% HI FBS and 0.05% NaN3) and resuspended in BD Fc Block (clone 2.4G2) for 5 min at RT prior to staining with a surface stain cocktail containing the following antibodies purchased from BD and Biolegend: I A/I E (M5/114.15.2) PE, CD8a (53 6.7) BUV805, CD44 (IM7) BUV395, CD62L (MEL 14) BV605, and CD4 (RM4 5) BV480 in brilliant stain buffer (BD). After 15 min, cells were washed with FC buffer then fixed and permeabilized using the BD Cytofix/Cytoperm fixation/permeabilization solution kit according to manufacturer instructions. Cells were washed in perm/wash solution and stained with Fc Block (5 min at RT), followed by intracellular staining (30 min at 4°C) using a cocktail of the following antibodies purchased from BD, Biolegend, or eBioscience: CD3e (17A2) BUV737, IFN γ (XMG1.2) BV650, TNF α (MP6 XT22) BV711, IL 2 (JES6 5H4) BV421, IL 4 (11B11) Alexa Fluor 488, and IL 5 (TRFK5) APC in 1x perm/wash diluted with brilliant stain buffer. Finally, cells were washed in perm/wash solution and resuspended in 0.5% PFA FC stain buffer prior to running on a Symphony A5 flow cytometer (BD). Analysis was performed using FlowJo software, version 10.6.2 according to the gating strategy outlined in Extended Data Figure 9. Background cytokine expression in the no peptide condition was subtracted from that measured in the S1 and S2 peptide pools for each individual mouse.
Instrument	Symphony A5 flow cytometer (BD)
Software	FlowJo software, version 10.6.2
Cell population abundance	Concatenated files shown were generated using the same number of randomly selected events from each animal across the different stimulation conditions.
Gating strategy	Extended Data Fig. 10 shows a hierarchical gating strategy was used to unambiguously identify single, viable CD4+ and CD8+ T cells. Gating summary of SARS CoV 2 S specific CD4 (b c) and CD8 (d e) T cells. Antigen specific T cell responses following peptide pool re stimulation were defined as CD44hi/cytokine+.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

EXHIBIT 6

REFINITIV STREETEVENTS

EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc Corporate Analyst Meeting

EVENT DATE/TIME: SEPTEMBER 17, 2020 / 12:00PM GMT

REFINITIV

That review by FDA is also an independent regulatory review, and they themselves also seek independent advice from a committee called VRBPAC or the Vaccines and Related Biological Products Advisory Committee. So the point I would like to underscore is that throughout this process, there are independent reviews of data, both in an ongoing way and once the analyses have been concluded. And that independent review really gives confidence that the data generated in this trial are representative and can be relied upon to give confidence to implementation of a vaccine program.

So let's move to the next slide, where I'm going to speak a little bit more about the DSMB monitoring of the primary efficacy endpoint in a bit more detail. And I'm going to take a couple of minutes with this slide because it is a bit complicated. I'd like to start the graph on the right.

So what the graph on the right shows you is the cumulative boundary crossing probability on the y axis as a function of vaccine efficacy on the x axis. In any efficacy trial, the likelihood of meeting your endpoints is really based on 3 factors: the overall efficacy of the vaccine; secondly, the sample size, so larger sample sizes lead to closer refinements of point estimates to the actual efficacy; and then third, the random distribution of events as you go through a trial. So in any given trial, you don't necessarily receive cases that occur in the vaccine group and control group in an alternating fashion. They come into the trial and are reported randomly.

So how does this graph help us understand how likely we are at various interim analyses to meet the statistical criteria? Well, if we move to the next slide, what we see is a vaccine efficacy highlighted in blue at 60%. And this is important because 60% is the conservative assumption that we used when we designed the trial. Obviously, we are quite hopeful that the true vaccine efficacy will be higher. And what you see on the left-hand side of the grid is that the first efficacy interim analysis will be performed when 53 cases are accumulated. That's shown in the fine dotted line labeled interim analysis 1 on the graph. At interim analysis 1, if the vaccine efficacy is 60%, there's a 10% probability that we are able to meet the statistical criteria successfully.

But as we capture more cases, on the next slide, so now we're talking about the second interim analysis, where there are 106 cases accumulated, you see that with the higher sample size, the likelihood of meeting our statistical criteria increases to 65%. And by the time we reach the final analysis on Slide 136, at 151 cases accumulated, we have a 90% probability of successfully meeting that statistical criterion. And that's really what we're speaking about when we refer to a study having 90% power.

So the study was really designed to look at 151 cases, but because we believe that our vaccine may be more efficacious than 60%, we've designed these interim analysis to allow ourselves the opportunity to investigate the data and potentially conclude the trial earlier based on meeting those criteria.

So if we go to the next slide, now we're going to go through the same 3 different analyses, but see what happens when we land at 75% efficacy. So if we move to Slide 138, what you can see is with just a 15% increase in efficacy, at the first interim analysis, there's now a 50% probability of successfully meeting our statistical criteria.

On the next slide, 139, you see that once you get to then the second interim analysis or 106 cases of COVID-19 accumulated, the likelihood of meeting statistical criteria exceeds 95%. So I hope that that helps demystify a bit how we will be monitoring the safety and the efficacy of our data while we go through the study. And we really look forward to bringing you more updates of these data as they occur.

I'll conclude my presentation, and I'm going to hand over to my colleague, Juan Andres, who will speak to you about the manufacturing and distribution of the COVID-19 vaccine.

Juan Andres - *Moderna, Inc. - Chief Technical Operations & Quality Officer*

Thank you, Jackie. Good morning, good afternoon or good evening. My name is Juan Andres, and I have responsibility for clinical development, manufacturing and quality in Moderna.

Slide 141, please. As we discussed in previous meetings, we are a platform, which in manufacturing terms mean that all our products are made in a very similar way. This allows that any learning and improvements that we have had over the years can be applied across our pipeline.

Next slide. Because we know the importance of improving our platform, it has been a top company priority to invest in CM and C, chemistry, manufacturing and controls. The fundamental product understanding has allowed us to make tremendous progress in shelf life, storage temperature, safety and tolerability, potency and consistency of manufacture.

Next slide. Specifically, mRNA-1273, our COVID vaccine candidate, benefits from the progress we have made with all the other vaccines in the pipeline. On the left-hand side, you can see 3 different graphs. Each graph represents a critical quality attribute for the product. Each dot in its graph represents a real GMP batch manufactured during the development of 1273. The values show very high consistency, and you would not be able to differentiate that there are 3 different scales in each graph, small, medium and large. This level of consistency is what you want to see during the scale-up of a product.

Next, please. We presented extensively in March our manufacturing site in Massachusetts. We wanted it fully integrated, end-to-end, to ensure we mastered all parts of our process. In addition, we designed a plan with a high degree of automation and digital integration to allow rapid growth and scale. Little we knew then that this thinking was going to be essential for scaling up COVID mRNA-1273. Having produced here over 100 GMP batches, in addition to thousands of preclinical and development batches, give us a good and tremendous confidence that we can deliver on our mission to manufacture high quantities of mRNA-1273 COVID vaccine.

Next slide. As a reminder, our process is not a traditional biotech monoclonal antibody that requires huge bioreactors. We do not need cells to produce mRNA. No need for product-dedicated plant. Having our manufacturing plant and being an [ancillary] cell-free process allows us to scale very fast.

Next. Now we are producing a commercial engine. And this is in addition to the ones we have before and we will be able to produce hundreds of millions of doses in this infrastructure. Also importantly, this capacity can be used beyond the COVID vaccine for other products that we commercialize after it. We believe this experience is a competitive advantage.

Next slide. So how are we scaling up? Once we decided in our industrial scale, we are replicating units of the same equipment inside our plant and those of our partners. Having the same kit allows for easier replication, faster technical transfer and a much reduced risk of surprises among [different] plants.

Next. We have designed 2 different supply chains using this concept. One in the U.S. for the U.S. and another one in Europe for international markets. The magnitude of this effort required us to partner with very reliable companies. So let me expand about them in the next slide. So these companies have -- are very experienced commercial manufacturers, all with extensive experience launching and supplying medicines worldwide.

Lonza. Lonza will help Moderna to produce active ingredients, both in the U.S. and in Switzerland. Lonza has an impressive track record of healthy pharmaceutical companies with more than 45 BLAs, MAAs to market, commercializing in more than 80 countries and with many expedited review designations.

Catalent; for formulation, fill and finish in the U S., definitely, one of the top aseptic manufacturing companies producing vials with isolated technology.

ROVI for formulation, fill and finish for international countries. Experienced in 65 markets including the U S. and with a lot of vaccine experience. We are also finalizing agreements with other partners. I cannot thank enough our manufacturing partners. I have not seen in my career such a tremendous collaboration and purpose from employees of different companies.

Next slide. So how are we designing the product to be in the market? We will have multi-dose vials with 10 doses in each vial. 10 vials will go into a carton, cartons will go into a case and cases into pallets. The pallet will be stored at negative 20 degrees Celsius or negative 4 Fahrenheit, which is the normal, a standard freezing temperature. Frozen food and freezers at home target the same temperature. We all are familiar with it.

Next slide. We are designing the supply chain for COVID mRNA-1273 to be fully flexible. We expect the product to be stored at minus 20 degrees Celsius for a minimum of 6 months. As we get more real-time stability information, we may go beyond 6 months. In addition, the product can be up to 7 days in the refrigerator at positive 2 to 8 degrees Celsius. Again, this could be longer once we have more real-time stability.

In addition, the product can be up to 1 day at room temperature during administration. All of this allows to use existing market infrastructure. Finally, the product is ready-to-use as is. No dilution or special handling is required.

Next slide. By using existing infrastructure, there is flexibility to send different quantities to the different needed locations, bigger quantities to large immunization centers, or for instance, a single pack to a small nursing home or doctor's office. For immunization, just draw 0 5 mL and inject.

Next slide. COVID mRNA-1273 is a liquid vial. The other vaccines in our pipeline are designed to be lyophilized or freeze dried as you refer to call it, which could allow for 18 months or more of refrigerated conditions, positive 2 to 8 degrees Celsius. For instance, our CMV vaccine candidate is, as you can see already in lyo form.

You may be asking yourselves why we didn't go lyo for COVID 1273. While there is not enough lyo capacity in the world for a global pandemic of this nature to be produced in lyo. I can also tell you that we have an active technical development program, intended to have a stable to 2 to 8 degree liquid formulation.

Next slide. Our CM and C readiness is well advanced for a BLA and emergency use authorization. First, we count with a very experienced management team with an impressive track record in product development, BLA preparation and launch and running commercial operations. As discussed before, we are privileged to have second to none partners to help us in our mission. Third, we have validated our first commercial scale, and the next scale is well in progress.

Our manufacturing plant has produced above 100 GMP mRNA batches. And finally, we are having real-time and constructive dialogue with regulators. In the right-hand side, you can see a picture of real COVID mRNA-1273 vials intended to go to market. I have personally brought numerous products to market in my 30-year career. And I'm very confident to make this one happen, too.

Next slide. We are on target. We are bringing together the infrastructure to produce 500 million to 1 billion doses per year. We are already actively manufacturing for market use, and so far, our scale-up and documentation is on track to deliver.

Next slide. Before I hand it over to Stephen, I want to sincerely thank employees, manufacturing partners, supplier partners and regulators and government agencies for an incredible collaboration and tireless effort. This is indeed unprecedented. Stephen?

Stephen Hoge - *Moderna, Inc. - President*

Thank you very much, Juan. So I'd like to take the closing few minutes of our prepared remarks today and update on a couple of activities in the new research and development space.

I'll remind you that we generally do not talk about all of our preclinical research and our extensive investments there, but we have a longstanding and major strategic commitment to continue to push the boundaries of how we use our mRNA technologies and to create an expanding pipeline in all of our core and noncore therapeutic areas. But we do regularly update when we do deals. And in this case, in particular, we announced 2 partnerships today that we wanted to provide a little more context on it.

So the first on Slide 158 is a new partnership with Vertex, expanding on our multiyear collaboration with them in the field of cystic fibrosis. This new announcement that was made yesterday is aimed at expanding into gene editing and gene therapy technologies as an alternative approach to treatment of cystic fibrosis. And I'll provide in just a minute, a little more context of how these 2 different approaches to addressing this disease will operate in parallel and the difference in to do it [personally].

EXHIBIT 7

EXHIBIT 8

From: Sheh, Anthony
To: Dean, Caitlin; Genevant Team; Arbutus_MoFo
Cc: #KEModernaSpikevaxService; Blumenfeld, Jack; Egan, Brian P.; Murray, Travis; "kkeller@shawkeller.com"; "nhoeschen@shawkeller.com"; *jshaw@shawkeller.com
Subject: RE: Arbutus v. Moderna, 1-22-cv 00252 - Moderna"s RFP No. 106
Date: Thursday, November 30, 2023 6:28:45 PM

Caitlin,

We've repeatedly explained the challenge and burden on our end regarding INDs due to the lack of a centralized database of regulatory submissions. The burden of conducting a search among loose files is both undue and disproportionate relative to the minimal relevance that Moderna has identified to date.

Nevertheless, Plaintiffs will agree to conduct a reasonable and proportionate search for IND documents that you requested in your November 29, 2023 email within the scope of the asserted patents—as we have flagged before, we can make no guarantees that we will be able to locate a complete set of responsive documents, the draft or final status of the documents, whether they were ever submitted to FDA, etc. We are unsure of exactly when we will be able make a production, but will work diligently to provide what we can responsive to Moderna's request.

We understand that it remains Moderna's position that it refuses to search for its own INDs within the scope of the asserted patents responsive to Plaintiffs' RFPs 164–167 despite (1) those documents being readily available in a regulatory document database, (2) Moderna's repeated insistence that Plaintiffs produce equivalent documents, and (3) Plaintiffs' previously expressed willingness to narrow these RFPs to remove Module 5. Plaintiffs intend to seek the Court's assistance to obtain these highly relevant documents.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: Dean, Caitlin <caitlin.dean@kirkland.com>
Sent: Wednesday, November 29, 2023 5:27 PM
To: Sheh, Anthony <ASheh@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Blumenfeld, Jack <JBlumenfeld@morrisnichols.com>; Egan, Brian P. <began@morrisnichols.com>; Murray, Travis <tmurray@morrisnichols.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>
Subject: Arbutus v. Moderna, 1-22-cv 00252 - Moderna's RFP No. 106

Counsel,

Pursuant to your offer to compromise on yesterday's meet-and-confer regarding Moderna's RFP No. 106, will Plaintiffs agree to produce INDs sponsored by Plaintiffs or their predecessors for products within the scope of the Patents-in-Suit excluding Module 5? As you know, Moderna agreed to produce FDA filings for the Accused Product, including correspondence and all Modules except Module 5. Please let us know or confirm that the parties are at an impasse by **Friday, December 1, 2023**.

Best,
Caitlin

Caitlin Dean

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F +1 212 446 4900

caitlin.dean@kirkland.com

EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Plaintiffs, v. MODERNA, INC. and MODERNATX, INC., Defendants.	)	C. A. No. 22-252 (MSG)
MODERNA, INC. and MODERNATX, INC., Counterclaim-Plaintiffs, v. ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Counterclaim-Defendants.	)	

PLAINTIFFS' FIRST SET OF REQUESTS FOR PRODUCTION TO DEFENDANTS (NOS. 1–98)

Pursuant to Fed. R. Civ. P. 34, Plaintiffs Arbutus Biopharma Corporation ("Arbutus") and Genevant Sciences GmbH ("Genevant," together "Plaintiffs"), direct the following requests for production to Defendants Moderna, Inc. and ModernaTX Inc. (collectively, "Moderna" or "Defendants"). Responses to these requests shall be served upon Plaintiffs' undersigned counsel within 30 days of service of these requests, or at such time and location as may be mutually agreed upon by the parties. Copies shall be produced as they are kept in the ordinary course of business, including their labeling as to the source of the documents. Pursuant to Fed. R. Civ. P.

26(e), these requests are continuing and require supplemental answers.

DEFINITIONS

1. The "Accused Product" shall be construed to include, but not be limited to, Moderna's mRNA-1273 COVID-19 mRNA LNP vaccine product ("Moderna's COVID-19 vaccine") or any supplemental or booster COVID-19 mRNA LNP vaccine product, including the mRNA-1273.214 Omicron bivalent booster.

2. "And" and "or" shall be construed either disjunctively or conjunctively as necessary to bring within the scope of these requests any information or documents that might be deemed outside their scope.

3. "Complaint" means the complaint filed by Plaintiffs in the United States District Court for the District of Delaware on February 28, 2022 as Civil Action No. 1:22-cv-00252-MN.

4. The term "communication" means any transmission of information from one person to another, including, without limitation, by personal meeting, telephone, facsimile, electronic transmission, including electronic mail, and teleconference.

5. "Document" is used in its broadest sense, and includes any written, printed, typed, recorded, electronic or graphic matter of every type, however and by whomever prepared, produced, reproduced, disseminated or made, in any form, including but not limited to, letters, calendars, correspondence, email, telegrams, memoranda, electronic files, spreadsheets, databases, records, minutes, contracts, agreements, leases, communications, microfilm, bulletins, circulars, pamphlets, studies, reports, notices, diaries, summaries, books, messages, instructions, work assignments, notes, notebooks, drafts, data sheets, data compilations, worksheets, statistics, speeches, tapes, tape recordings, magnetic, photographic, an any other writings or sound

recordings. "Document" includes any version, copy, or reproduction not identical to the original or a produced copy.

6. "You," "your," and "Defendants" means, collectively and singly, Moderna, Inc. and ModernaTX Inc., and their officers, directors, employees, agents, consultants, any divisions, subsidiaries, affiliates, parent companies, any joint ventures to which they may be a party, consultants, agents, and accountants, including any person who served in such a capacity at any time.

7. "Refer," "refer to," "relate," or "relate to" shall mean any document or electronically stored information that evidences, reflects, mentions, discusses, constitutes, concerns, relates to (directly or indirectly), contradicts, or in any other way is factually or logically connected to the matter discussed, or pertains to its subject matter.

8. The use of the singular form of any word shall include the plural and vice versa.

9. The terms "all," "each," and "any" shall be construed as all and any.

10. The term "LNP" means "lipid nanoparticle."

11. "Test" or "testing" shall be construed to include but not be limited to any test, evaluation, comparison, analysis, study, experiment or trial for any purpose, including clinical trials or results, including any submissions to any governmental, regulatory, contracting, or granting agency or entity, whether published or unpublished.

12. "Operation Warp Speed" shall refer to the public-private partnerships, individually and collectively, initiated by the U.S. government to facilitate and accelerate the development, manufacture, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.

13. "Patents-in-Suit" shall mean any patents presently or later asserted in this litigation. Presently, this means U.S. Patent Nos. 8,058,069 (the "'069 patent"), 8,492,359 (the "'359 patent"), 8,822,668 (the "'668 patent"), 9,364,435 (the "'435 patent"), 9,504,651 (the "'651 patent"), and 11,141,378 (the "'378 patent").

14. "The Alnylam litigation" refers to *Alnylam Pharmaceuticals, Inc. v. Moderna, Inc., ModernaTX, Inc., and Moderna US, Inc.*, C.A. No. 22-cv-335-CFC (D. Del.).

REQUESTS FOR PRODUCTION

REQUEST FOR PRODUCTION NO. 1

A copy of Biologics License Application 125752, including all correspondence, amendments, and supplements relating thereto.

REQUEST FOR PRODUCTION NO. 2

All documents related to the preparation of Biologics License Application 125752.

REQUEST FOR PRODUCTION NO. 3

A copy of any other U.S. or foreign regulatory submission relating to approval or emergency authorization of the Accused Product, including all correspondence, amendments, and supplements relating thereto.

REQUEST FOR PRODUCTION NO. 4

All documents related to the research and development of the Accused Product.

REQUEST FOR PRODUCTION NO. 5

All documents related to the manufacture of the Accused Product.

REQUEST FOR PRODUCTION NO. 6

All documents related to Operation Warp Speed.

REQUEST FOR PRODUCTION NO. 7

Documents sufficient to show the time it took to develop the Accused Product.

REQUEST FOR PRODUCTION NO. 8

All documents related to the decision to utilize LNPs in the Accused Product, including but not limited to any document concerning the advantages of LNPs compared to other technologies; the consideration of alternatives to LNPs for use in the Accused Product; and the testing or development of any COVID-19 vaccine product without LNPs.

REQUEST FOR PRODUCTION NO. 9

All documents related to any comparisons between LNPs including but not limited to comparisons of LNPs with different lipid compositions or different lipid molar ratios.

REQUEST FOR PRODUCTION NO. 10

All patents, publications, or other documents relied on or considered in the development and selection of LNPs for the Accused Product.

REQUEST FOR PRODUCTION NO. 11

All documents related to any comparison between the Accused Product and any other COVID-19 vaccine product, including but not limited to comparisons between potential vaccine products in connection with the research and development, preclinical testing, clinical testing, or regulatory approval of the Accused Product.

REQUEST FOR PRODUCTION NO. 12

All documents related to the formulation of the Accused Product.

REQUEST FOR PRODUCTION NO. 13

All documents related to the selection of the formulation of the Accused Product, including but not limited to documents related to the consideration, research and development, and/or testing

of that formulation or any alternative formulations.

REQUEST FOR PRODUCTION NO. 14

All documents related to the lipid composition or lipid molar ratio of the LNPs in the Accused Product.

REQUEST FOR PRODUCTION NO. 15

All documents related to the selection of the lipid composition or lipid molar ratio of, or to the determination of any variability of the lipid molar ratio in, the LNPs in the Accused Product, including but not limited to documents related to the consideration, research and development, and/or testing of the lipid composition or lipid molar ratio of the LNPs in the Accused Product or any alternative lipid compositions or lipid molar ratios.

REQUEST FOR PRODUCTION NO. 16

All documents related to the manufacturing process for the Accused Product, including but not limited to the manufacturing process for the LNPs in the Accused Product.

REQUEST FOR PRODUCTION NO. 17

All documents related to the selection of the manufacturing process for the Accused Product, including but not limited to the manufacturing process for the LNPs in the Accused Product, and including but not limited to documents related to the consideration, research and development, and/or testing of those manufacturing processes or any alternative manufacturing processes.

REQUEST FOR PRODUCTION NO. 18

All documents related to the identity of each manufactured batch of the Accused Product, including but not limited to documents sufficient to show the identity of the manufacturer, the date and location the batch was manufactured, the size of the batch, the intended market for the batch,

the characteristics and testing of the batch, the specification for the batch, the lipid molar ratio of the batch, and the status of the batch.

REQUEST FOR PRODUCTION NO. 19

All documents relating to the analytical procedures used to characterize the Accused Product at any point during or after manufacturing.

REQUEST FOR PRODUCTION NO. 20

All documents related to the selection of the analytical procedures used to characterize the Accused Product at any point during or after manufacturing, including but not limited to documents related to the consideration, research and development, and/or testing of those procedures or any alternative procedures.

REQUEST FOR PRODUCTION NO. 21

All documents related to any changes to the formulation, lipid composition, lipid molar ratio, manufacturing process, product characteristics, or methods used to characterize the Accused Product and any reasons for such changes.

REQUEST FOR PRODUCTION NO. 22

All documents related to any efforts by or on behalf of Defendants to avoid infringement of or design around the Patents-in-Suit, including but not limited to any modifications considered or made to the Accused Product to avoid infringement.

REQUEST FOR PRODUCTION NO. 23

All documents related to any regulatory or manufacturing specifications for the Accused Product, including but not limited to the selection of such specifications.

REQUEST FOR PRODUCTION NO. 24

All documents related to any batch of the Accused Product found to be out of specification.

REQUEST FOR PRODUCTION NO. 25

All documents related to any testing conducted to characterize the Accused Product including but not limited to any testing related to: the lipid composition of the LNPs, the lipid molar ratio of the LNPs; the mRNA content of the LNPs; the percentage encapsulation of mRNA in the LNPs; and the structural characteristics of the LNPs (including but not limited to diameter, polydispersity, and microstructure).

REQUEST FOR PRODUCTION NO. 26

All documents related to any testing conducted to characterize LNPs during development or manufacturing of the Accused Product, including but not limited to testing of: the lipid composition of the LNPs; the lipid molar ratio of the LNPs; the mRNA content of the LNPs; the percentage encapsulation of mRNA in the LNPs; and the structural characteristics of the LNPs (including but not limited to diameter, polydispersity, and microstructure).

REQUEST FOR PRODUCTION NO. 27

All documents related to the development of any analytical procedure for characterizing LNPs during development or manufacturing of the Accused Product, including but not limited to the development of any analytical procedure for characterizing: the lipid composition of the LNPs; the lipid molar ratio of the LNPs; the mRNA content of the LNPs; the percentage encapsulation of mRNA in the LNPs; and the structural characteristics of the LNPs (including but not limited to diameter, polydispersity, and microstructure), and any results from using such analytical procedure.

REQUEST FOR PRODUCTION NO. 28

Any internal communications or communications with third parties, including but not limited to collaborators, contractors, or regulatory entities, regarding the development or selection of any analytical procedure for characterizing LNPs, including but not limited to the lipid

composition of the LNPs, including the lipid molar ratio; the mRNA content of the LNPs; the percentage encapsulation of mRNA in the LNPs; and the structural characteristics of the LNPs, including diameter, polydispersity, and microstructure, and any results from such analytical procedures.

REQUEST FOR PRODUCTION NO. 29

All documents relating to the selection of regulatory acceptance criteria for the Accused Product and justifications therefore, including but not limited to criteria for: pH, impurities, LNP size and polydispersity, mRNA content, mRNA encapsulation, identity of lipid components and lipid molar ratio.

REQUEST FOR PRODUCTION NO. 30

All documents relating to the characterization of LNPs before and after storage or transport under different conditions, including protocols for and results of any stability studies.

REQUEST FOR PRODUCTION NO. 31

All documents related to any testing conducted during the manufacture of any batch of the Accused Product.

REQUEST FOR PRODUCTION NO. 32

All documents, including but not limited to testing protocols, regarding variation in lipid ratios, including molar ratios, within each batch and between batches of the Accused Product.

REQUEST FOR PRODUCTION NO. 33

All documents, including but not limited to testing protocols, regarding the variation in lipid ratios, including molar ratios, in each batch of the Accused Product before and after manufacture.

REQUEST FOR PRODUCTION NO. 34

All documents related to any testing conducted on the materials used to manufacture the

Accused Product, including but not limited to any testing on any of the lipids used to manufacture the LNPs in the Accused Product.

REQUEST FOR PRODUCTION NO. 35

All documents related to, or constituting, communications with the FDA concerning the Accused Product.

REQUEST FOR PRODUCTION NO. 36

All documents related to, or constituting, communications with any U.S. government agency concerning the Accused Product.

REQUEST FOR PRODUCTION NO. 37

All documents related to the FDA emergency authorization and/or approval process for the Accused Product.

REQUEST FOR PRODUCTION NO. 38

All documents related to any preclinical or clinical testing conducted in connection with the authorization or approval process for the Accused Product.

REQUEST FOR PRODUCTION NO. 39

All documents relating to the preclinical study of Moderna's COVID-19 vaccine authored by Corbett et al. and published on the website of *The New England Journal of Medicine* on July 28, 2020.[1]

REQUEST FOR PRODUCTION NO. 40

All documents related to any proposed, contemplated, or actual package insert or labeling,

[1] *See* Corbett et al., "Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates," NEJM 383;16:1544-1555, 1546 (2020) (citing Hassett et al., "Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines," *Mol. Ther. Nucl. Acids* 15:1-11, 8 (2019)), *available at* https://www.nejm.org/doi/full/10.1056/nejmoa2024671#.

including revisions thereto, concerning the Accused Product.

REQUEST FOR PRODUCTION NO. 41

All documents related to or generated in connection with any research collaborations, research partnerships, or funding arrangements between Defendants and any other entities or individuals in connection with the research and development of the Accused Product.

REQUEST FOR PRODUCTION NO. 42

All documents that constitute, or refer or relate to, documents or publications that Defendants assert (i) constitute prior art to the Patents-in-Suit, or (ii) render the Patents-in-Suit invalid.

REQUEST FOR PRODUCTION NO. 43

All documents related to the Patents-in-Suit, or any related patents or patent applications.

REQUEST FOR PRODUCTION NO. 44

All documents that Defendants may rely on to assert the invalidity, unenforceability, or non-infringement of any claim of the Patents-in-Suit or which otherwise refer or relate to any defense asserted by Defendants.

REQUEST FOR PRODUCTION NO. 45

All documents that constitute, or refer or relate to, any opinions regarding the Patents-in-Suit, including but not limited to (a) opinions relating to the validity, enforceability, or infringement of the Patents-in-Suit, or (b) freedom-to-operate opinions, as well as drafts of said opinions, and any documents considered, reviewed, used, or relied on in formulating and/or rendering said opinions.

REQUEST FOR PRODUCTION NO. 46

All documents related to, or reflecting, Defendants' knowledge or awareness of the Patents-

in-Suit, or any related patents or patent applications.

REQUEST FOR PRODUCTION NO. 47

All documents reflecting or related to communications by or on behalf of Defendants referring to Plaintiffs or any related companies (*e.g.*, Tekmira Pharmaceuticals or Protiva Biotherapeutics), including but not limited to any communications related to Plaintiffs' work on LNP technology.

REQUEST FOR PRODUCTION NO. 48

All documents related to any testing of the lipid formulations or LNP manufacturing methods described or claimed in the Patents-in-Suit, including but not limited to any testing by Defendants to reproduce any of the experiments in the Patents-in-Suit.

REQUEST FOR PRODUCTION NO. 49

All documents related to communications by or on behalf of Defendants to financial or securities analysts regarding the Patents-in-Suit, or any related patents or patent applications, or this lawsuit.

REQUEST FOR PRODUCTION NO. 50

All documents related to press releases or communications by or on behalf of Defendants to reporters regarding the Patents-in-Suit, or any related patents or patent applications, or this lawsuit.

REQUEST FOR PRODUCTION NO. 51

All documents related to communications between Defendants and any purchaser of the Accused Product regarding the Patents-in-Suit, or any related patents or patent applications, or this lawsuit.

REQUEST FOR PRODUCTION NO. 52

Any presentations regarding LNP technology or the Accused Product given by Defendants to FDA or any other regulatory body or any purchaser.

REQUEST FOR PRODUCTION NO. 53

All documents related to any indemnification agreement or warranty between Defendants and any purchaser of the Accused Product.

REQUEST FOR PRODUCTION NO. 54

All documents related to Defendants' knowledge of any USPTO proceedings or any foreign patent office proceedings that concern the Patents-in-Suit, or any related patents or patent applications.

REQUEST FOR PRODUCTION NO. 55

All documents related to Defendants' involvement in any USPTO proceedings or any foreign patent office proceedings related to the Patents-in-Suit, or any related patents or patent applications.

REQUEST FOR PRODUCTION NO. 56

All documents related to any consideration given by Defendants to seeking a license under the Patents-in-Suit, or any related patents or patent applications, including but not limited to all communications related to a potential license.

REQUEST FOR PRODUCTION NO. 57

A copy of any patent license agreement relating to the Accused Product, including any agreement relating to the manufacture, use, or sale of the Accused Product, as well as documents sufficient to show any royalty payments Defendants made or received pursuant to those license agreements.

REQUEST FOR PRODUCTION NO. 58

A copy of any patent license agreement between Defendants and any entity relating to COVID-19 vaccines, as well as documents sufficient to show any royalty payments Defendants made or received pursuant to those license agreements.

REQUEST FOR PRODUCTION NO. 59

A copy of any patent license agreement between Defendants and any entity relating to LNP technology, as well as documents sufficient to show any royalty payments Defendants made or received pursuant to those license agreements.

REQUEST FOR PRODUCTION NO. 60

A copy of any written agreement, contract, or license concerning the development, manufacture, sale, or distribution ofthe Accused Product, including any exhibits or annexes to such written agreement, contract, or license.

REQUEST FOR PRODUCTION NO. 61

A copy of any written agreement, contract, grant, or license between Defendants and the U.S. Government concerning the development, manufacture, sale, or distribution of the Accused Product, including any exhibits or annexes to such written agreement, contract, or license.

REQUEST FOR PRODUCTION NO. 62

All documents related to any written agreement, contract, grant, or license between Defendants and the U.S. Government concerning the development, manufacture, sale, or distribution of the Accused Product.

REQUEST FOR PRODUCTION NO. 63

A copy of any written agreement, contract, grant, or license concerning funding from the U.S. Government relating to LNP therapeutics.

REQUEST FOR PRODUCTION NO. 64

All documents related to any negotiations between Defendants and any third party, including but not limited to the U.S. Government, related to any written agreement, contract, or grant, concerning the development, manufacture, sale, or distribution of the Accused Product.

REQUEST FOR PRODUCTION NO. 65

All documents related to the nature and extent of the U.S. government's involvement, if any, in the development, manufacture, sale, or distribution of the Accused Product.

REQUEST FOR PRODUCTION NO. 66

All documents related to how doses of the Accused Product were distributed and to whom (including but not limited to customers of drug stores, grocery stores, private medical practices, or on military bases).

REQUEST FOR PRODUCTION NO. 67

All documents related to Defendants' understanding of who was the true beneficiary of any contract with the U.S. Government concerning the development, manufacture, sale, or distribution of the Accused Product.

REQUEST FOR PRODUCTION NO. 68

All correspondence between Defendants and the U.S. Government relating to who was the true beneficiary of any contract with the U.S. Government concerning the development, manufacture, sale, or distribution of the Accused Product.

REQUEST FOR PRODUCTION NO. 69

All documents related to any negotiations or communications between Defendants and third parties, including but not limited to the U.S. Government, about the price of the Accused Product.

REQUEST FOR PRODUCTION NO. 70

All regulatory submissions regarding the Accused Product submitted to U.S. or foreign regulatory bodies.

REQUEST FOR PRODUCTION NO. 71

All communications and documents concerning communications with any regulatory agency regarding the Accused Product, including but not limited to communications with the FDA, European Medicines Agency/European Medicines Evaluation Agency, or any other U.S. or foreign regulatory body.

REQUEST FOR PRODUCTION NO. 72

Any Investigational New Drug ("IND") applications involving the Accused Product.

REQUEST FOR PRODUCTION NO. 73

Organization charts and/or employee directories sufficient to identify any officers, directors or employees of Defendants involved in any stage of the conceptualization, design, research, development, testing, commercialization, marketing, manufacturing, or regulatory authorization or approval process for the Accused Product.

REQUEST FOR PRODUCTION NO. 74

All documents related to any brand plans, long range plans, competitive analyses, market surveys, sales projections, and contracting strategies for the Accused Product.

REQUEST FOR PRODUCTION NO. 75

All documents related to Defendants' efforts to market, promote, or publicize the Accused Product, including but not limited to documents describing any advantages related to the LNP technology of the Accused Product.

REQUEST FOR PRODUCTION NO. 76

All documents related to any forecasting or other model used by Defendants to develop their market and/or sales projections for the Accused Product.

REQUEST FOR PRODUCTION NO. 77

All documents related to any forecasts or budgets relating to the Accused Product, including historical forecasts or budgets and current forecasts and budgets.

REQUEST FOR PRODUCTION NO. 78

A copy of all profit-and-loss statements, whether historical, current, or projected, for the Accused Product.

REQUEST FOR PRODUCTION NO. 79

All documents related to the projected sales of the Accused Product, including projected profits.

REQUEST FOR PRODUCTION NO. 80

Documents sufficient to show, on a monthly basis, the following information for the Accused Product:

(a) Units made in the United States;

(b) Units sold in the United States to the United States Government;

(c) Units sold in the United States to entities other than the United States Government;

(d) Units made in the United States and sold outside the United States;

(e) Revenue from those sales;

(f) Costs attributable to those sales;

(g) Profits from those sales.

REQUEST FOR PRODUCTION NO. 81

A copy of any commercial agreement Defendants have made with any third party relating to the Accused Product, including but not limited to any document relating to a payment or financial commitment made by Defendants to develop and/or market the Accused Product.

REQUEST FOR PRODUCTION NO. 82

Documents sufficient to show the first commercial offer for sale of the Accused Product, including when the first commercial offer for sale occurred.

REQUEST FOR PRODUCTION NO. 83

All documents related to the offer for sale of the Accused Product, including without limitation documents identifying Defendants' role in those activities and all efforts by Defendants or any third party working with Defendants or on Defendants' behalf to design, develop, make, and/or market the Accused Product.

REQUEST FOR PRODUCTION NO. 84

All documents related to any studies, preprints, or other publications relating to the development or testing of the Accused Product, including but not limited to all manuscripts of the same, reviews of same, and correspondence relating to same.

REQUEST FOR PRODUCTION NO. 85

A copy of each U.S. or foreign patent or patent application owned by, assigned to, or licensed to Defendants that describes, claims, or otherwise relates to the Accused Product.

REQUEST FOR PRODUCTION NO. 86

A copy of each U.S. or foreign patent or patent application owned by, assigned to, or licensed to Defendants that relates to COVID-19 or LNPs.

REQUEST FOR PRODUCTION NO. 87

All communications with any third party, including any U.S. government agency, referring or relating to any patent or patent application owned by, assigned to, or licensed to Defendants that describes, claims, or otherwise relates to the Accused Product or relates to COVID-19 or LNPs.

REQUEST FOR PRODUCTION NO. 88

All documents relating to Defendants' seeking indemnification from the U.S. Government for infringing the Patents-in Suit.

REQUEST FOR PRODUCTION NO. 89

All documents related to any work performed by third parties related to the Accused Product, including but not limited to any development, testing, or manufacturing work performed by third parties related to the Accused Product.

REQUEST FOR PRODUCTION NO. 90

Curricula vitae or resumes for each witness listed in Defendants' initial disclosures.

REQUEST FOR PRODUCTION NO. 91

A copy of any document referred to in any of Defendants' responses to interrogatories served on Defendants in this case, or the identification of which is sought by any such interrogatories.

REQUEST FOR PRODUCTION NO. 92

A copy of any document reviewed, considered, or relied upon when answering any interrogatories served on Defendants in this case.

REQUEST FOR PRODUCTION NO. 93

A copy of any document reviewed, considered, or relied upon by Defendants in preparation of their invalidity contentions.

REQUEST FOR PRODUCTION NO. 94

A copy of any document that Defendants intend to introduce at trial, or introduce with respect to any motion, opposition, or hearing in this action.

REQUEST FOR PRODUCTION NO. 95

All documents produced in the Alnylam litigation, *Alnylam Pharmaceuticals, Inc. v. Moderna, Inc., ModernaTX, Inc., and Moderna US, Inc.*, C.A. No. 22-cv-335-CFC (D. Del.).

REQUEST FOR PRODUCTION NO. 96

All pleadings, correspondence, transcripts, discovery requests, discovery responses, or other documents associated with the Alnylam litigation, *Alnylam Pharmaceuticals, Inc. v. Moderna, Inc., ModernaTX, Inc., and Moderna US, Inc.*, C.A. No. 22-cv-335-CFC (D. Del.), including but not limited to requests for production, responses to requests for production, interrogatories, interrogatory responses, discovery correspondence, briefs, deposition transcripts, and hearing transcripts.

REQUEST FOR PRODUCTION NO. 97

50 vials of the Accused Product from each lot referenced in Biologics License Application 125752 or that has otherwise been manufactured by or on behalf of Moderna, and the material safety data sheet and any handling and storage instructions and histories for each sample.

REQUEST FOR PRODUCTION NO. 98

A 10 g sample (divided into five 2 g aliquots) of each ingredient in the Accused Product, and the material safety data sheet and any handling and storage instructions and histories for each sample.

/s/ Nathan R. Hoeschen
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Dated: December 20, 2022

CERTIFICATE OF SERVICE

I, Nathan R. Hoeschen, hereby certify that on December 20, 2022 this document was served on the persons listed below in the manner indicated:

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EXHIBIT 10

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ARBUTUS BIOPHARMA CORPORATION and GENEVANT SCIENCES GmbH, Plaintiffs, v. MODERNA, INC. and MODERNATX, INC., Defendants.	)	**CONTAINS INFORMATION MODERNA DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL EYES ONLY** C.A. No. 22-252-MSG

PLAINTIFFS' SECOND SET OF INTERROGATORIES TO DEFENDANTS

Pursuant to Federal Rules of Civil Procedure 26 and 33, Plaintiffs Arbutus Biopharma Corporation ("Arbutus") and Genevant Sciences GmbH ("Genevant") request that Defendants Moderna, Inc. and ModernaTX Inc. (collectively, "Moderna" or "Defendants") respond fully, in writing, under oath, separately to each interrogatory below. Plaintiffs request that Defendants serve their written responses to these interrogatories upon Williams & Connolly LLP, 680 Maine Avenue SW, Washington, DC, 20024, within 30 days after service hereof.

DEFINITIONS & INSTRUCTIONS

Plaintiffs incorporate herein by reference as though fully set forth herein the definitions and instructions of Plaintiffs First Set of Interrogatories to Defendants served February 16, 2023.

INTERROGATORIES

INTERROGATORY NO. 11

Identify all final and intermediate batches and/or lots of the Accused Product by all batch numbers and/or lot numbers, including any batch and/or lot numbers used or assigned by Moderna or any third party, including:

(1) all batches and/or lots of mRNA-1273 Drug Product and any supplemental or booster COVID-19 mRNA vaccine product thereof, including any batches and/or lots of mRNA-1273.214 and mRNA-1273.222;

(2) all batches and/or lots of mRNA-1273 Lipid Nanoparticle ("LNP"), including all batches and/or lots of mRNA-1273 LNP-B, mRNA-1273.529 LNP, and mRNA-1273.045 LNP;

(3) all batches and/or lots of [redacted];

(4) all batches and/or lots of SM-102, DSPC, Cholesterol, and PEG2000-DMG; and

(5) all batches and/or lots of mRNA, including all batches and/or lots of CX-024414, CX-034476, and CX-031302,

and for each batch and/or lot:

describe in detail the genealogy of the batch and/or lot, including the source and disposition of the batch and/or lot, including: the batches of SM-102, DSPC, Cholesterol, and PEG2000-DMG used to manufacture each batch of [redacted] and/or mRNA-1273 LNP; the batches of mRNA and batches of [redacted] used to manufacture each batch of mRNA-1273 LNP; the batches of mRNA-1273 LNP used to manufacture each batch of mRNA-1273 Drug Product and/or other final drug product; the parties to whom or by whom the batch and/or lot was manufactured, sold, offered for sale, distributed, transferred, shipped, administered and/or used; where that manufacturing, sale, offer for sale, distribution, transfer, shipment, administration and/or use occurred; and the dates on which that manufacturing, sale, offer for sale, distribution, transfer, shipment, administration and/or use occurred; and

identify the unit sales, revenues, gross profit, net profit, average unit sales price to end users, average unit sales price to distributors (if any), list price to end users, list price to distributors

(if any), cost of goods sold (including identification of the items included in cost of goods sold), and operating costs (*i.e.*, other costs not included in cost of goods sold, such as selling, general, and administrative expenses) associated with the batch and/or lot.

/s/ Nathan R. Hoeschen
John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
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Dated: March 16, 2023

CERTIFICATE OF SERVICE

I, Nathan R. Hoeschen, hereby certify that on March 16, 2023, this document was served on the persons listed below in the manner indicated:

BY EMAIL:

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EXHIBIT 11

From:	Li, Yan-Xin
To:	Afinogenova, Alina; Sheh, Anthony; Haunschild, Philip; McLennan, Mark C.
Cc:	#KEModernaSpikevaxService; Horstman, N. Kaye; "Arbutus_MoFo"; Parrado, Alvaro; Elenberg, Falicia; Komis, Jihad; Genevant Team; Berl, David; Mahaffy, Shaun; Harber, Adam; Fletcher, Thomas; Ryen, Jessica; "NTan@mofo.com"; Bolte, Erik; *jshaw@shawkeller.com; "kkeller@shawkeller.com"; "nhoeschen@shawkeller.com"; "EWiener@mofo.com"; "began@mnat.com"; "tmurray@morrisnichols.com"; "jblumenfeld@morrisnichols.com"; Hurst, James F.; Carson, Patricia A.; Wacker, Jeanna
Subject:	RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO
Date:	Thursday, December 7, 2023 9:51:49 PM

Tony and Philip:

Further to your email of November 15 and the parties' meet and confer on November 17, we understand that Plaintiffs are seeking production of Moderna's contracts associated with batches manufactured outside the United States ("OUS") and sold to customers OUS. Plaintiffs proposed that Moderna produce these documents first for Plaintiffs to assess whether additional information about the OUS batches should be produced (e.g., COAs).

Plaintiffs appear to suggest that Moderna's OUS batches are a "sale" within the ambit of 35 U.S.C. § 271(a). We disagree. As the *Cal. Inst. of Tech. v. Broadcom Ltd.* court noted, there is no dispute that § 271(a) "appl[ies] only domestically," and the issue is whether "the relevant transactions [] were domestic or extraterritorial in nature." *Cal. Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 992 (Fed. Cir. 2022). Yet as your November 15 email concedes, OUS batches are manufactured OUS and sold to customers OUS—i.e., extraterritorial in nature. *See* 11/15/2023 P. Haunschild Email ("certain batches were simply manufactured abroad"). Plaintiffs have not identified any relevance or basis for seeking discovery of extraterritorial sales or activities. And indeed, the *Broadcom* court further noted that "the key question" is "whether there were such ***substantial activities*** in the United States," which there are not for Moderna's OUS batches. *See Broadcom*, 25 F.4th at 993 (discussing *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 831 F.3d 1369 (Fed. Cir. 2016), including how pricing and contracting negotiations in the United States alone ***do not*** constitute or transform those extraterritorial activities into a sale under § 271(a) (emphasis added)). In addition, the Federal Circuit noted that the place of signing a contract is only one of many factors to consider in determining the location of a "sale" under § 271(a). *See Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1309 (Fed. Cir. 2015). To hold otherwise would effectively extend the scope of § 271(a) to "confer a worldwide exclusive right to a U.S. patent holder, which is contrary to the statute and case law." *Halo*, 831 F.3d at 1379.

Batches that were manufactured OUS and sold to customers OUS are therefore beyond the scope of Plaintiffs' accusations of infringement. This is not because of "Moderna's own self-serving analysis," but rather precedential case law on this issue, including cases Plaintiffs identified. Moderna will not permit an unduly burdensome fishing expedition by Plaintiffs into its extraterritorial business.

Best regards,
Yan-Xin

Yan-Xin Li

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F +1 415 439 1500

yanxin.li@kirkland.com

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Tuesday, December 5, 2023 6:48 PM
To: Sheh, Anthony <ASheh@wc.com>; Haunschild, Philip <phaunschild@wc.com>; McLennan, Mark

C. <mark.mclennan@kirkland.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

Tony,

In follow-up to our November 10 email relating to the production of samples from 400+ lots of expired drug product, we are continuing to work through the burdensome exercise of setting up the logistics to make said production, which we now expect to be in a position to do in January. We will provide an update with additional information as soon as we are able.

Regards,
Alina

Alina Afinogenova

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200 Clarendon Street, Boston, MA 02116
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F +1 212 446 4900

alina.afinogenova@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Wednesday, November 29, 2023 6:16 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Haunschild, Philip <phaunschild@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>;

Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

Mark,

Could you please let us know if Moderna has an update regarding our questions on sample shipping and storage? If there additional arrangements that need to be made, we'd like to start putting them in place. Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

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From: Sheh, Anthony <ASheh@wc.com>
Sent: Monday, November 20, 2023 6:06 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Haunschild, Philip <phaunschild@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

Mark and Alina,

Further to Moderna's November 10 email and the meet-and-confer on November 17, Plaintiffs

understand that Moderna's production of the ~480 batches/lots referenced below does not resolve the parties' dispute as to the remaining batches, but we appreciate Moderna's efforts to narrow the scope of the parties' dispute. We understand that the ~480 batches Moderna is agreeing to produce are being transferred by a third-party to another location. We also understand that Moderna is not withholding samples as to post-complaint batches. We understand that Moderna is looking into whether there are post-complaint batches that are due to imminently expire and that the parties' should have ample time before expiry to address samples from Moderna's ongoing booster production.

Plaintiffs are willing to consider covering the cost for Moderna to ship the samples and/or for a courier. As discussed, please let us know an estimate of the shipping costs. Additionally, we'd appreciate information regarding storage conditions and the capacity needed to store the samples. Assuming that the conditions are as before [redacted] Plaintiffs currently have 90% capacity left in a 19.4 cubic feet (549 L) freezer with interior dimensions of 51.2 in x 23.1 in x 28.3 (H x W x D, 130.1 cm x 58.8 cm x 97.37 cm) and will acquire additional space if needed. The shipping address would be:

Triclinic Labs, Inc.
Attn: Sample Submission
2660 Schuyler Ave. Ste. A.
Lafayette, IN 47905

Plaintiffs understand that Moderna considers batches that were not manufactured or imported into the U.S. to be batches "not accused of infringement." As outlined in previous correspondence, Plaintiffs disagree that such batches are not accused. *See, e.g.*, *E.g.*, D.I. 1 ¶¶ 50–54, 70, 89, 108, 130, 154. Plaintiffs understand that Moderna is investigating the scope of documents it is willing to produce concerning these batches, including its agreements with the relevant third-parties for sales of such batches (besides the U.S. Government, and whether located in the United States or abroad, and whether to a public or private entity), its communications with such third-parties concerning sales or offers to sell batches of the Accused Product, documents evidencing the location and timing of any negotiations or meetings regarding such sales, and Moderna's marketing and strategic plans regarding such sales. Such documents are responsive to at least Plaintiffs' RFPs 51, 53, 60, 64, 69, 74, 75, 81, and 83. Please confirm the scope of documents that Moderna will agree to produce by December 1, 2023.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Thursday, November 16, 2023 11:07 AM
To: Haunschild, Philip <phaunschild@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Sheh, Anthony <ASheh@wc.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin

<yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

Hi Philip,

We are not available before 3pm ET today, but can be available tomorrow before 12pm ET or between 1 and 3pm ET.

Thank you,
Alina

Alina Afinogenova

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alina.afinogenova@kirkland.com

From: Haunschild, Philip <phaunschild@wc.com>
Sent: Wednesday, November 15, 2023 11:20 AM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Sheh, Anthony <ASheh@wc.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com'

<began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

Hi Mark,

Thank you for your email. Please let us know when Moderna is available to meet-and-confer tomorrow before 3:00 PM (ET) regarding Moderna's proposal as to the samples that Moderna has agreed to produce. We have a number of questions that we would like to address on the meet-and-confer, including at least the following:

- Does your email mean to draw a distinction between the "lots" that Moderna is agreeing to produce and the "batches" that the parties have previously been discussing? We understand these to be interchangeable terms, but please let us know if that is wrong.

- How did Moderna select the approximately 480 lots that it has agreed to produce samples from?

- Is Moderna refusing to produce samples from any unexpired lots?

- Will Moderna be producing samples from lots manufactured after February 28, 2022, the date of the filing of the complaint?

- For part numbers with unexpired lots, will Moderna be producing both expired and unexpired lots from the same part number?

- What is Moderna's position as to representativeness and the ability to argue non-infringement of lots that Moderna is not agreeing to produce samples from?

- Has Moderna determined whether there are additional part numbers for Drug Product or mRNA-LNP beyond those that we have identified in our October 31, 2023 email?

Further, regarding the batches that Moderna will be providing samples from, we have made clear in multiple meet-and-confers in March, April, and November, and in separate correspondence, *e.g.,* March 3, 2023 Letter from A. Sheh; May 11, 2023 Letter from L. Cash, that Moderna's refusal to provide discovery on the basis that certain batches were simply manufactured abroad is improper. Moderna cannot shield batches from discovery based on Moderna's own self-serving analysis of whether such batches infringe. *See*, *e.g.*, *California Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 992 (Fed. Cir. 2022); *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1308 (Fed. Cir. 2015). Plaintiffs are entitled to take relevant discovery regarding all batches that have been accused of infringement. Please be prepared to discuss this on our meet-and-confer. Please also be prepared to explain how Moderna is determining what batches "can be accused of infringement."

Thank you,

Philip N. Haunschild
Associate | Williams and Connolly LLP
680 Maine Avenue SW, Washington, DC 20024
202-434-5979 phaunschild@wc.com | www.wc.com

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Friday, November 10, 2023 3:00 PM
To: Sheh, Anthony <ASheh@wc.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information) - HIGHLY CONFIDENTIAL OCEO

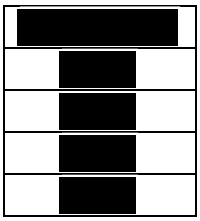
CONTAINS INFORMATION MODERNA HAS DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL'S EYES ONLY

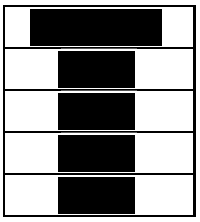
Counsel,

Regarding Plaintiffs' questions from the meet-and-confer on the number of vials per lot Moderna is able to produce from regulatory retains, we confirm that Moderna maintains its agreement to produce 3 vials per lot. This is proportional to the needs of the case in light of the extensive data Moderna is agreeing to produce about each lot, in the absence of any explanation from Plaintiffs as to why more than 3 vials is needed, and due to Moderna's need to retain samples for regulatory and compliance purposes, as laid out in detail in our October 20, 2023 letter.

With regard to the number of accused lots that Moderna will produce samples from, in the spirit of compromise and in an effort to narrow the dispute, Moderna is preparing to produce samples of 3 vials of expired drug product from approximately 480 lots. We will provide the lot numbers shortly, but can confirm they correspond to the part numbers below. Moderna will produce (if not already produced) specifications for these part numbers and CoAs for each lot later today or Monday (we

are still waiting for the final production volume). Moderna will continue to making rolling productions of additional CoAs and specifications for accused batches as we review them, but we wanted to prioritize these 480 lots first.





Moderna will make this production in the spirit of compromise and does so without waiving any objections to Plaintiffs' RFPs for samples from the remaining accused batches (both the number of samples and quantity of lots). Moderna also makes this production without any representations that the expired drug product is representative of its characteristics at release. Moderna will agree to this production if Plaintiffs agree to pay for the shipping costs or arrange a courier to collect the vials in a single shipment – please confirm Plaintiffs' position by COB November 15, including confirmation of a shipping address if Plaintiffs request that Moderna ship the samples.

We are confirming the exact timing of the production but we understand it can be made in the next two weeks.

Regarding your questions on the batches at issue in this case, we're surprised by Plaintiffs' recent change in position, attempting to dramatically expand the scope of discovery at this late stage. Moderna has been consistent and clear in its position that it would not provide discovery on batches not accused of infringement:

- Moderna's February 2, 2023 Objections to 1st RFPs (including general objection: "Moderna objects to Plaintiffs' requests to the extent they seek information, documents, and/or things relating to batches and doses of the Accused Products not accused of infringement, including batches of doses of the Accused Products not made, used, offered for sale, or sold within the United States or imported into the United States, which are not accused of infringement. Moderna will not produce irrelevant information, documents, and/or things concerning such batches and doses.")
- Moderna's April 17, 2023 Objections to Rog. 11 ("Moderna objects to this Interrogatory to the extent it seeks information related to the identity of manufactured lots and/or batches that were not made, used, offered for sale, or sold within the United States or imported into the United States.")
- McLennan Sept. 19, 2023 Letter (" Moderna offered to produce samples of drug product that were made with each part number of mRNA-LNP that was made, sold, or imported into the

U.S.")

- McLennan July 21, 2023 Email ("Moderna confirms it has produced information in MRNA-GEN-00456085 and MRNA-GEN-00456086 showing batches of Moderna's COVID-19 Vaccine manufactured ***in the U.S.***")

Our objections to Interrogatory No. 11, and all correspondence concerning it since then have been crystal clear that Moderna is properly limiting discovery concerning batches to those that can be accused of infringement. Although you take statements from our August 1, 2023 letter out of context, in reality we repeated the same objection in that letter. McLennan August 1, 2023 Letter ("Moderna did not agree that Moderna is broadly required to "produce information regarding that foreign activity." . . . If you have support indicating that batches made outside the U.S. and never imported into the U.S. can constitute infringement of a U.S. patent, we remain willing to consider it."). Despite Moderna consistently placing Plaintiffs on notice of its position, Plaintiffs delayed raising this purported issue for months. Unfortunately this appears to be yet another attempt to delay resolution of the sample dispute and ***exponentially*** increase the burden of Moderna's discovery.

Regards,
Mark

Mark C. McLennan

KIRKLAND & ELLIS LLP
601 Lexington Avenue, New York, NY 10022
T +1 212 909 3451

mark.mclennan@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Tuesday, November 7, 2023 11:42 AM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>

Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Alina,

Thanks for your email and for confirming that Moderna will be producing CoAs and specifications, as well as responding to Plaintiffs' inquiry regarding the number of vials Moderna is willing to produce per batch, this week. The part numbers below were intended to assist Moderna, necessitated by Moderna's incomplete responses to Plaintiffs' Interrogatories Nos. 6 and 11, and based on Plaintiffs' efforts to analyze information that has been readily available in the first instance to Moderna, not Plaintiffs. We appreciate that Moderna will be producing CoAs and specifications this week, but both of these have been the subject of months-long requests. Plaintiffs have been prejudiced and continue to be prejudiced by Moderna's delays.

With respect your points below regarding batches purportedly "not accused of infringement," Plaintiffs' Complaint alleges that Moderna infringes the patent-in-suit by *inter alia* "manufacturing, offering to sell, selling, or using within the United States, the Accused Product." *E.g.*, D.I. 1 ¶¶ 70, 89, 108, 130, 154. The Complaint further addresses "doses made in the United" but "administered abroad," contracts Moderna has entered worldwide, and "emergency authorizations" for Moderna's COVID-19 vaccine "from more than 70 countries, including Canada, Israel, the United Kingdom, Switzerland, Singapore, Qatar, Taiwan, and the Philippines, as well as from the European Union." D.I. 1 ¶¶ 50–54. With respect to "foreign" batches, Moderna's August 1, 2023 letter (at 7) acknowledges that Moderna's response to Plaintiffs' Interrogatory No. 11 "may provide all of the information Plaintiffs want and/or need," but Moderna has not supplemented its response to Interrogatory No. 11. In any event, Moderna cannot unilaterally shield from discovery batches it contends were assertedly "not made, sold, used, or imported into the U.S." *See, e.g.*, *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1308 (Fed. Cir. 2015) ("Places of seeming relevance [to a sale] include a place of inking the legal commitment to buy and sell and a place of delivery . . . and perhaps also a place where other 'substantial activities of the sales transactions' occurred."). Plaintiffs are entitled to discovery into these issues and to test Moderna's as-of-yet unsupported contentions. Moderna's email suggests, contrary to its August 1, 2023 letter, that Moderna's response to Interrogatory No. 11 in fact will *not* include information on batches Moderna contends to be "not accused of infringement" on the basis of such batches being "ex-US" or "OUS," which is improper.

Please therefore confirm (1) that the batches Moderna has "identified to date" extends to *all* of the batches Moderna has manufactured and/or sold, regardless of whether that activity occurred in the United States or purportedly not, (2) that Moderna's responses to Plaintiffs' Interrogatory Nos. 6 and 11 will not exclude batches simply because Moderna deems them to be batches "not accused of infringement," and (3) that Moderna's listing or identification of part numbers for the purpose of sample production will include *all* batches. To the extent that Moderna has been excluding "ex-US" or "OUS" batches from discovery, please inform us of Moderna's basis for doing so. Please provide Moderna's confirmation by this Friday, November 10, 2023, so that Plaintiffs can promptly seek relief from the Court if necessary.

Best,

Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Friday, November 3, 2023 5:35 PM
To: Sheh, Anthony <ASheh@wc.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

CONTAINS INFORMATION MODERNA HAS DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL'S EYES ONLY

Tony,

As we will explain in more detail when we respond to your letter on Plaintiffs' 2nd set of RFPs, in the spirit of compromise, next week we expect to produce Moderna's CoAs for accused batches of DP, mRNA-1273 LNP, and [redacted] identified to-date. We trust this (in addition to the drug product genealogy spreadsheet) will resolve many, if not all, of your questions below. We expect to produce additional specifications next week too, and are still investigating whether a complete listing of part numbers exists.

We note that from your email below, which lists many part numbers not referenced in earlier correspondence, Plaintiffs appear to now be seeking information concerning batches that were not made, sold, used, or imported into the U.S. and thus not accused of infringement. Moderna has been clear in its objections to the RFPs, and in correspondence concerning samples since then, that Moderna is not producing samples from batches that are not accused of infringement. We maintain that such batches bear no relevance to this litigation, and thus collection of samples and information from those batches is unduly burdensome and not proportionate to the needs of the case.

We hope to get back to you next week on whether Moderna agrees to produce more than 3 vials per batch.

Have a nice weekend,
Alina

Alina Afinogenova

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200 Clarendon Street, Boston, MA 02116
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F +1 212 446 4900

alina.afinogenova@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Tuesday, October 31, 2023 2:53 PM
To: Parrado, Alvaro <alvaro.parrado@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

CONTAINS INFORMATION MODERNA HAS DESIGNATED HIGHLY CONFIDENTIAL – OUTSIDE COUNSEL'S EYES ONLY

Mark,

Plaintiffs understood from our meet-and-confer on October 23, 2023, that Moderna would be getting back to us last week regarding whether it would be willing to produce more than three vials from a batch. Could you please let us know by COB tomorrow the results of Moderna's investigation?

Likewise, Plaintiffs have been working to narrow the parties' dispute regarding samples with respect to the number of vials. For Moderna's convenience, we have been able to identify the following

drug product part numbers based on information Moderna has produced to date: [redacted] Could you please confirm whether there are any other drug product part numbers that are at issue, including for ex-US batches? We have excluded "unlabeled" drug product part numbers from this set, but if those are relevant, please let us know. For the part numbers that are *not* in bold, we have been unable to identify a specification sheet in MRNA-GEN-VOL013 to ascertain the lipid content per vial. Could you please confirm that Moderna will produce these specification sheets this week?

We'd also like to make sure that the parties share an understanding of the mRNA LNP part numbers that are at issue with respect to Moderna's proposal. As set forth in Plaintiffs' September 6, 2023 letter, we are aware of the following part numbers: [redacted] Please confirm whether there are any other mRNA LNP part numbers at issue. We understand from Moderna's August 24, 2023 letter that it has been working to collect and produce specifications for each part number relevant to batches of the Accused Product.

We are happy to discuss any of the foregoing by phone if helpful. Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

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From: Parrado, Alvaro <alvaro.parrado@kirkland.com>
Sent: Friday, October 20, 2023 6:28 PM
To: Sheh, Anthony <ASheh@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

Please see the attached case correspondence.

Thank you,

Alvaro R. Parrado
Senior Paralegal | Intellectual Property

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F +1 212 446 4900

alvaro.parrado@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Friday, October 20, 2023 5:58 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Thanks Alina. We can use the following dial-in:

Call in (audio only)
+1 872-242-8083,,149140221# United States, Chicago
Phone Conference ID: 149 140 221#
Find a local number

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Friday, October 20, 2023 1:11 PM
To: Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>;

Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

We are available at 2:30pm ET on Monday.

Regards,
Alina

Alina Afinogenova

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F +1 212 446 4900

alina.afinogenova@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Friday, October 20, 2023 11:39 AM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com'

<began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Mark,

Since it appears that Moderna believes that the parties may still have a dispute, please let us know when you are available to meet and confer on Monday with Delaware counsel present. Plaintiffs are available after 12 p.m. ET. We look forward to receiving Moderna's response regarding samples later today. Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Friday, October 20, 2023 10:52 AM
To: Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

Thanks for your email. We're still investigating a couple of outstanding issues concerning the samples in an effort to try to narrow the issues in dispute, and hope to respond later today. We'll be available to meet and confer after that whenever Plaintiffs are ready.

We disagree that Moderna has delayed this process; instead Moderna has worked expeditiously to investigate ways to reach a compromise on Plaintiffs' unreasonable demands.

Thanks,
Mark

Mark C. McLennan

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T +1 212 909 3451

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From: Sheh, Anthony <ASheh@wc.com>
Sent: Friday, October 20, 2023 8:35 AM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Elenberg, Falicia <felenberg@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Mark,

Thanks for your note. Plaintiffs understood that we would be hearing back from Moderna yesterday regarding sample production, which is a months (if not years) long dispute that Plaintiffs have taken significant efforts to resolve with Moderna to no avail. Plaintiffs have been prejudiced by Moderna's delays in this process.

Please let us know your availability to meet and confer today so that we can promptly raise this dispute with the Court.

We will await Moderna's response to our October 6, 2023 letter regarding Moderna's R&D documents, but note that Plaintiffs raised the issues therein in our meet-and-confer on September 15, 2023, and we have been waiting over a month for a response.

Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

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From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Wednesday, October 18, 2023 10:09 AM
To: Elenberg, Falicia <felenberg@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Falicia,

Thank you for your email. We are hoping to get back to you today or tomorrow on the samples issue.

We are also reviewing your October 6 letter on "R&D-related documents" which addresses the same RFPs that Plaintiffs separately wrote to us about in two other letters on October 9. We are preparing a response to those three letters and will get back to you as soon as possible. We note we've been waiting for a response to our September 7 letter on Moderna's 1st set of RFPs for six weeks now.

Thanks,
Mark

Mark C. McLennan

KIRKLAND & ELLIS LLP
601 Lexington Avenue, New York, NY 10022
T +1 212 909 3451

mark.mclennan@kirkland.com

From: Elenberg, Falicia <felenberg@wc.com>
Sent: Wednesday, October 18, 2023 9:59 AM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

You have not responded to our October 6th letters regarding sample production and R&D-related documents, nor have we heard back from you regarding your availability to meet-and-confer on the matter. Plaintiffs are highly prejudiced by Defendants' refusal to produce and resolve these crucial categories of material. Please let us know your availability to meet-and-confer today (Oct. 18th) or tomorrow (Oct. 19th). If we do not hear from you regarding a time to meet-and-confer by close of business today, Plaintiffs' will consider the parties to be at an impasse.

Best,
Falicia

Falicia Elenberg
Law Clerk | Williams & Connolly LLP
680 Maine Avenue, S.W., Washington, DC 20024
202-434-5989 | felenberg@wc.com | www.wc.com

From: Elenberg, Falicia
Sent: Monday, October 16, 2023 8:57 AM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com

Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

We have not received response to our October 6, 2023 letters concerning sample production and Moderna's production of documents relating to its research and development of the Accused Product. So that Plaintiffs can promptly resolve these disputes, could you please let us know your availability tomorrow or Wednesday to meet and confer? We are available tomorrow (Tuesday) from 11 a.m. – 12 p.m. and 2p.m. – 3 p.m. ET or Wednesday before 2 p.m. ET. Thanks.

Best,
Falicia
Falicia Elenberg
Law Clerk | Williams & Connolly LLP
680 Maine Avenue, S.W., Washington, DC 20024
202-434-5989 | felenberg@wc.com | www.wc.com

From: Elenberg, Falicia <felenberg@wc.com>
Sent: Friday, October 6, 2023 6:04 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Hello all,

Please see the attached correspondence.

Falicia Elenberg
Law Clerk | Williams & Connolly LLP
680 Maine Avenue, S.W., Washington, DC 20024

202-434-5989 | felenberg@wc.com | www.wc.com

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Tuesday, October 3, 2023 8:17 PM
To: Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Hi Tony,

Based on the meet-and-confer last week, we understand the parties are each going to reconsider their positions and respond.

In the meantime, please confirm that Plaintiffs will reimburse Moderna for the doses and the associated shipping and handling costs. For example, Plaintiffs' current request for the equivalent of 100 mg of lipids per batch, and samples from 10% of batches, could exceed 10,000 doses, which is clearly a significant expense and burden on Moderna.

Thank you,
Alina

Alina Afinogenova

KIRKLAND & ELLIS LLP
200 Clarendon Street, Boston, MA 02116
T +1 617 385 7526 **M** +1 917 324 5094
F +1 212 446 4900

alina.afinogenova@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Wednesday, September 27, 2023 6:32 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David

<DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Thanks Alina, that works for us. We can use the following dial-in:

Call in (audio only)
+1 872-242-8083,,631822421# United States, Chicago
Phone Conference ID: 631 822 421#
Find a local number

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Wednesday, September 27, 2023 11:08 AM
To: Sheh, Anthony <ASheh@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

We can be available at 2pm ET on Thursday.

Regards,
Alina

Alina Afinogenova

KIRKLAND & ELLIS LLP
200 Clarendon Street, Boston, MA 02116
T +1 617 385 7526 **M** +1 917 324 5094
F +1 212 446 4900

alina.afinogenova@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Tuesday, September 26, 2023 9:28 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Hi Mark,

Unfortunately 4 p.m. tomorrow doesn't work for us. Would sometime on Thursday from 1–4 p.m. ET work? Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Monday, September 25, 2023 4:31 PM
To: Sheh, Anthony <ASheh@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F.

<james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

We're available on Wednesday at 4pm ET.

Thanks,
Mark

Mark C. McLennan

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601 Lexington Avenue, New York, NY 10022
T +1 212 909 3451

mark.mclennan@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Friday, September 22, 2023 10:01 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

With apologies to all who celebrate—I forgot that Monday is Yom Kippur. As such, please let us know if Tuesday or Wednesday would work. Thanks.

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

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From: Sheh, Anthony <ASheh@wc.com>
Sent: Friday, September 22, 2023 9:45 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>;

Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Mark,

Could you please let us know your availability to meet and confer regarding your September 19 letter this Monday or Tuesday? Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Tuesday, September 19, 2023 5:05 PM
To: Sheh, Anthony <ASheh@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

Please see the attached letter. We're available to meet and confer.

Thanks,
Mark

Mark C. McLennan

KIRKLAND & ELLIS LLP

601 Lexington Avenue, New York, NY 10022
T +1 212 909 3451

mark.mclennan@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Monday, September 18, 2023 8:21 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Mark,

Could you please provide Moderna's response to Plaintiffs' September 6 letter regarding samples? As we noted in the letter, this dispute has been pending for more than 8 months, and Plaintiffs intend to raise this dispute with the Court shortly if the parties cannot reach agreement. Thanks.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Friday, September 8, 2023 5:14 PM
To: Sheh, Anthony <ASheh@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna

<jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Tony,

We're in receipt of your letter from Wednesday night. We note that you took two weeks to respond to our August 24 letter and demanded a response within two days. We are looking into questions raised in your letter, including numerous new inquiries, and will respond next week.

Best,
Mark

Mark C. McLennan

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601 Lexington Avenue, New York, NY 10022
T +1 212 909 3451

mark.mclennan@kirkland.com

From: Sheh, Anthony <ASheh@wc.com>
Sent: Wednesday, September 6, 2023 10:31 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

Please see the attached correspondence. Thank you.

Best,
Tony

Anthony Sheh | Associate | Williams & Connolly LLP | (202) 434-5436 | vcard

---

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Thursday, August 24, 2023 12:23 PM

To: Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

Please see the attached correspondence.

Regards,
Alina

Alina Afinogenova

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From: Komis, Jihad <JKomis@wc.com>
Sent: Wednesday, August 16, 2023 6:10 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

Counsel,

Please see the attached correspondence. Thanks.

Regards,
Jihad

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JKomis@wc.com | www.wc.com

From: McLennan, Mark C. <mark.mclennan@kirkland.com>
Sent: Friday, July 21, 2023 2:18 PM
To: Komis, Jihad <JKomis@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel (Batch Information)

CONFIDENTIAL

Jihad,

Moderna confirms it has produced information in MRNA-GEN-00456085 and MRNA-GEN-00456086 showing batches of Moderna's COVID-19 Vaccine manufactured in the U.S. As we've noted to Plaintiffs many times, the information is burdensome to investigate, and we produced this listing now based on our current investigation to date at Plaintiffs' request. We are still months from close of fact discovery and we will update it as our investigation continues, if needed.

As you know, the parties repeatedly agreed to continue discussing further sample availability once we were able to produce batch history information. Now that Plaintiffs have this batch listing showing more than one thousand batches, please let us know if Plaintiffs are maintaining their request for "50 vials . . . from each" batch. As you can imagine, investigating the availability of this unreasonable and unjustified number of vials across more than one thousand batches is extremely burdensome. We have repeatedly asked Plaintiffs for months to explain why they need 50 vials from

each lot, and have not received a response. Moderna maintains its objections to Plaintiffs' RFPs and Interrogatories in the meantime and reserves all rights.

We look forward to hearing from Plaintiffs about the availability of samples in response to Moderna's RFP No. 125 too.

Regards,
Mark

Mark C. McLennan

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T +1 212 909 3451

mark.mclennan@kirkland.com

From: Komis, Jihad <JKomis@wc.com>
Sent: Thursday, July 20, 2023 6:04 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel

Counsel,

We are in receipt of Moderna's production of July 19, 2023, including the natives produced at MRNA-GEN-00456085 and MRNA-GEN-00456086, which purport to identify batches of Moderna's finished drug product. Could you please confirm whether these documents identify the batches of the Accused Product that Moderna has manufactured to date? Relatedly, we have not heard from Moderna regarding Plaintiffs' email below dated July 13, 2023, regarding the availability of samples from batches of the Accused Product. Could you please confirm that Moderna will provide this information this week?

Regards,
Jihad

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From: Komis, Jihad <JKomis@wc.com>
Sent: Thursday, July 13, 2023 4:57 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel

Counsel,

Thank you for your response. Plaintiffs understand that Moderna has agreed to provide a listing of batch/lot numbers of Moderna's finished drug product by next week. However, Moderna's July 12, 2023 letter does not address Plaintiffs' other longstanding inquiry regarding the availability of samples from those batches. Please confirm that Moderna will provide this information next week, as well.

For avoidance of doubt, Plaintiffs have not agreed to modify the scope of information sought by Interrogatory Nos. 6 and 11, which we understand that Moderna intends to answer substantively later this month. Plaintiffs expect that Moderna will answer the full scope of those interrogatories, and not just provide the "simple listing" referred to in your letter. We disagree with Moderna's assertion that the scope of Interrogatories No. 6 and 11, which seek highly relevant information regarding infringement and damages, imposes any burden with respect to information that Moderna agreed to provide *four months ago*, *i.e.*, a "simple listing" of batches and the availability of samples from those batches. In any event, please confirm that Moderna intends to answer the full scope of Interrogatories Nos. 6 and 11, and is not unilaterally limiting the scope of Plaintiffs' interrogatories based on a misunderstanding of the information Plaintiffs need regarding samples.

Finally, we disagree with the implications in your letter that Moderna's ongoing failure to provide routine discovery information is in any way justified by its request for thousands of prototype formulations sought by RFP No. 125, including those that are not sold or manufactured by Plaintiffs. Moderna's unjustified delay continues to prejudice Plaintiffs' ability to discuss the production of samples of the Accused Product which are at the heart of this case. Plaintiffs reserve all rights.

Regards,
Jihad

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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Wednesday, July 12, 2023 8:50 AM
To: Komis, Jihad <JKomis@wc.com>; McLennan, Mark C. <mark.mclennan@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye <kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel

Counsel,

Please see the attached correspondence.

Best regards,
Alina

Alina Afinogenova

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F +1 212 446 4900

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From: Komis, Jihad <JKomis@wc.com>
Sent: Tuesday, July 11, 2023 5:17 PM
To: McLennan, Mark C. <mark.mclennan@kirkland.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Li, Yan-Xin <yanxin.li@kirkland.com>; Horstman, N. Kaye

<kaye.horstman@kirkland.com>; began@mnat.com; tmurray@morrisnichols.com; jblumenfeld@morrisnichols.com; Hurst, James F. <james.hurst@kirkland.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Wacker, Jeanna <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; NTan@mofo.com; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; kkeller@shawkeller.com; nhoeschen@shawkeller.com; EWiener@mofo.com
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel

Counsel,

We have not received any response to our June 29, 2023 correspondence once again requesting that Moderna identify batches of the Accused Product and the availability of samples. As set forth in our correspondence, despite Moderna agreeing months ago to provide this information so that the parties could continue discussing sample production, as well as multiple letters and meet-and-confers on this issue, Moderna continues to withhold this information and has failed to even provide a date certain when it intends to supply it. To date, Moderna has not articulated any reasonable basis for not promptly providing this basic accounting information, and Moderna's unjustified delay continues to prejudice Plaintiffs' ability to litigate this case.

Given Plaintiffs' multiple letters and the parties' multiple meet-and-confers on this issue, Plaintiffs understand that the parties are at an impasse. Plaintiffs thus intend to move the Court this Friday, July 14, 2023, for an order compelling Moderna to identify all batches of the Accused Product and the availability of samples unless Moderna immediately provides this information.

Thank you.

Regards,
Jihad

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JKomis@wc.com | www.wc.com

From: Komis, Jihad
Sent: Thursday, June 29, 2023 5:17 PM
To: 'mark.mclennan@kirkland.com' <mark.mclennan@kirkland.com>; 'alina.afinogenova@kirkland.com' <alina.afinogenova@kirkland.com>; 'yanxin.li@kirkland.com' <yanxin.li@kirkland.com>; 'kaye.horstman@kirkland.com' <kaye.horstman@kirkland.com>;

'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; 'james.hurst@kirkland.com' <james.hurst@kirkland.com>; 'patricia.carson@kirkland.com' <patricia.carson@kirkland.com>; 'jeanna.wacker@kirkland.com' <jeanna.wacker@kirkland.com>
Cc: Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; 'KEModernaSpikevaxService@kirkland.com' <KEModernaSpikevaxService@kirkland.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Sheh, Anthony <ASheh@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; 'jshaw@shawkeller.com' <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>
Subject: Arbutus v. Moderna, 1-22-cv-00252 - Letter to Counsel

Counsel,

Please see the attached correspondence. Thank you.

Regards,
Jihad

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EXHIBIT 12

Nos. 2020-2222, 2021-1527

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

THE CALIFORNIA INSTITUTE OF TECHNOLOGY,

Plaintiff-Appellee,

v.

BROADCOM LIMITED, nka Broadcom Inc., BROADCOM CORPORATION, AVAGO TECHNOLOGIES LIMITED, nka Avago Technologies International Sales Pte. Limited, APPLE INC.,

Defendants-Appellants.

On Appeal from the United States District Court for the Central District of California in Case No. 2:16-cv-03714-GW-AGR, Judge George H. Wu

NON-CONFIDENTIAL JOINT APPENDIX VOLUME I OF IV (Appx1-Appx2390)

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May 6, 2021

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UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

CALIFORNIA INSTITUTE OF TECHNOLOGY, Plaintiff, v. BROADCOM LIMITED AND APPLE, INC., Defendants.	No. CV 16-3714-GW-AGRx **FINAL JURY INSTRUCTIONS**

Final Jury Instructions

I. Introductory Instructions

Members of the Jury: Now that you have heard all of the evidence, it is my duty to instruct you on the law that applies to this case. Each of you has received a copy of these instructions that you may take with you to the jury room.

It is your duty to find the facts from all the evidence in the case. To those facts you will apply the law as I give it to you. You must follow the law as I give it to you whether you agree with it or not. And you must not be influenced by any personal likes or dislikes, opinions, prejudices, or sympathy. That means that you must decide the case solely on the evidence before you. You will recall that you took an oath to do so.

Please do not read into these instructions or anything that I may say or do or have said or done that I have an opinion regarding the evidence or what your verdict should be.

This case is a civil lawsuit alleging patent infringement. In this case, the California Institute of Technology, which I will refer to as "Caltech," is suing Defendants Apple Inc., Broadcom Corporation, Broadcom Limited, and Avago Technologies, Limited, for what it claims is unauthorized use of three Caltech patents, in products sold by Defendants. Broadcom Corporation, Broadcom Limited, and Avago Technologies, Limited are related entities and can be treated as a single defendant which I will refer to as "Broadcom."

Caltech owns three patents issued by the United States Patent and Trademark Office in 2006, 2008 and 2011, related to encoders and decoders that use a specific type of error correction coding. Caltech claims and bears the burden of proof by a preponderance of the evidence that Apple's products that support Wi-Fi (including its iPhones, iPads, iMacs, MacBooks, and AppleTV) and Broadcom's chips (that support Wi-Fi) infringe Caltech's patents.

Broadcom and Apple claim that their products do not use Caltech's technology, and that their products instead use a form of error correction coding that is different from the specific type of error correction coding claimed by Caltech's patents.

Caltech is seeking what it believes to be a reasonable royalty from Broadcom and Apple to compensate for the alleged infringement. Broadcom and Apple deny that Caltech is entitled to any damages because: (1) they deny infringement, and (2) they believe that what Caltech is seeking is not reasonable.

When a party has the burden of proving any claim or affirmative defense by a "preponderance of the evidence," it means you must be persuaded by the evidence that the claim or affirmative defense is more probably true than not true.

You should base your decision on all of the evidence, regardless of which party presented it. Unless I instruct you otherwise, all issues in this case must be established by a preponderance of the evidence.

You should decide the case as to each Defendant separately. Unless otherwise stated, the instructions apply to all parties.

The evidence you are to consider in deciding what the facts are consists of:

1. the sworn testimony of any witness;
2. the exhibits that are admitted into evidence;
3. any facts to which the lawyers have agreed; and
4. any facts that I have instructed you to accept as proved.

In reaching your verdict, you may consider only the testimony and exhibits received into evidence. Certain things are not evidence, and you may not consider them in deciding what the facts are. I will list them for you:

1. Arguments and statements by lawyers are not evidence. The lawyers are not witnesses. What they have said in their opening statements, closing arguments and at other times is intended to help you interpret the evidence, but it is not evidence. If the facts as you remember them differ from the way the lawyers have stated them, your memory of them controls.

2. Questions and objections by lawyers are not evidence. Attorneys have a duty to their clients to object when they believe a question is improper under the rules of evidence. You should not be influenced by the objection or by the court's ruling on it.

3. Testimony that is excluded or stricken, or that you have been instructed to disregard, is not evidence and must not be considered.

4. Anything you may have seen or heard when the court was not in session is not evidence. You are to decide the case solely on the evidence received at the trial.

Evidence may be direct or circumstantial. Direct evidence is direct proof of a fact, such as testimony by a witness about what that witness personally saw or heard or did. Circumstantial evidence is proof of one or more facts from which you could find another fact. You should consider both kinds of evidence. The law makes no distinction between the weight to be given to either direct or circumstantial evidence. It is for you to decide how much weight to give to any evidence.

There are rules of evidence that control what can be received into evidence. When a lawyer asked a question or offers an exhibit into evidence and a lawyer on the other side thought that it was not permitted by the rules of evidence, that lawyer raised an objection. If I overruled the objection, the question was answered or the exhibit received. If I sustained the objection, the question was not answered, and the exhibit not admitted. Whenever I sustained an objection to a question, you must ignore the question and must not guess what the answer might have been.

Sometimes I may order that evidence be stricken from the record and that you disregard or ignore that evidence. That means when you are deciding the case, you must not consider the stricken evidence for any purpose.

In deciding the facts in this case, you may have to decide which testimony to believe and which testimony not to believe. You may believe everything a witness says, or part of it, or none of it. In considering the testimony of any witness, you may take into account:

1. the opportunity and ability of the witness to see or hear or know the things testified to;

2. the witness's memory;
3. the witness's manner while testifying;
4. the witness's interest in the outcome of the case, if any;
5. the witness's bias or prejudice, if any;
6. whether other evidence contradicted the witness's testimony;
7. the reasonableness of the witness's testimony in light of all the evidence; and
8. any other factors that bear on believability.

Sometimes a witness may say something that is not consistent with something else he or she said. Sometimes different witnesses will give different versions of what happened. People often forget things or make mistakes in what they remember. Also, two people may see the same event but remember it differently. You may consider these differences, but do not decide that testimony is untrue just because it differs from other testimony.

However, if you decide that a witness has deliberately testified untruthfully about something important, you may choose not to believe anything that witness said. On the other hand, if you think the witness testified untruthfully about some things but told the truth about others, you may accept the part you think is true and ignore the rest.

The weight of the evidence as to a fact does not necessarily depend on the number of witnesses who testify. What is important is how believable the witnesses were, and how much weight you think their testimony deserves.

During your deliberations, you will not have a transcript of the trial testimony.

You have been allowed to take notes during the trial to help you remember the evidence. If you did take notes, please keep them to yourself until you go to the jury room to decide the case. When you leave, your notes should be left in the jury room. No one will read your notes.

Whether or not you take notes, you should rely on your own memory of the evidence. Notes are only to assist your memory. You should not be overly influenced by your notes or those of other jurors.

A deposition is the sworn testimony of a witness taken before trial. The witness is placed under oath to tell the truth and lawyers for each party asked questions. The questions and answers are recorded either in written form or by means of a video recording.

Certain depositions were presented to you in the form of playing the recording of the witness's deposition testimony in lieu of those witnesses' live testimony during the trial. Insofar as possible, you should consider deposition testimony, presented to you in court in lieu of live testimony, in the same way as if the witness had been present to testify. During the playing of those depositions, not only were you able to see and hear that testimony but also a transcription of the testimony was simultaneously scrolled at the bottom of the screen to assist you when listening to the recordings. However, bear in mind that the recording is the evidence, not the transcript. If you heard something different from what appeared in the transcript, what you heard is controlling.

During the trial, you heard testimony from certain witnesses who because of their education,

training and/or experience were allowed to give opinions on issues in the case and the reasons for their opinions.

Such opinion testimony should be judged like any other testimony. You may accept it or reject it, and give it as much weight as you think it deserves, considering the witness's education and experience, the reasons given for the opinion, and all the other evidence in the case.

Certain charts and summaries *not* admitted into evidence have been shown to you in order to help explain the contents of books, records, documents, or other evidence in the case. Charts and summaries are only as good as the underlying evidence that supports them. You should, therefore, give them only such weight as you think the underlying evidence deserves.

Certain charts and summaries have been admitted into evidence to illustrate information brought out in the trial. Charts and summaries are only as good as the testimony or other admitted evidence that supports them. You should, therefore, give them only such weight as you think the underlying evidence deserves.

Corporations and other legal entities are allowed to sue and be sued in court. All parties are equal before the law and a corporation is entitled to the same fair and conscientious consideration by you as any party.

Under the law, a corporation is considered to be a person. It can only act through its employees, agents, directors, or officers. Therefore, a corporation is responsible for the acts of its employees, agents, directors, and officers performed within the scope of authority.

From time to time during the trial, the parties presented information that is confidential to one or more of the parties. At those times, it became necessary for measures to be taken to protect the confidentiality of the information, such as sealing the courtroom. The parties agreed to these procedures to protect the confidentiality of the information and undue weight should not be given to these measures.

Each of you are required to maintain the confidentiality of the information that was presented under seal. You may discuss this information in your deliberations with other jurors, but may not discuss it with any other individuals or after the completion of your jury service.

II. Stipulated Facts

The parties have agreed to the following and you must therefore treat these facts as having been proved.

1. Caltech is the owner of all right, title and interest in U.S. Patent No. 7,116,710.
2. Caltech is the owner of all right, title and interest in U.S. Patent No. 7,421,032.
3. Caltech is the owner of all right, title and interest in U.S. Patent No. 7,916,781.
4. U.S. Patent No. 7,116,710 (the "'710 patent") is titled "Serial Concatenation of

Interleaved Convolution Codes Forming Turbo-Like Codes."

5. The '710 patent issued on October 3, 2006.

6. The named inventors listed on the '710 patent are Hui Jin, Aamod Khandekar, and Robert J. McEliece.

7. The '710 patent expires on August 23, 2022.

8. U.S. Patent No. 7,421,032 (the "'032 patent") is titled "Serial Concatenation of Interleaved Convolution Codes Forming Turbo-Like Codes."

9. The '032 patent issued on September 2, 2008.

10. The named inventors listed on the '032 patent are Hui Jin, Aamod Khandekar, and Robert J. McEliece.

11. The '032 patent expires on August 18, 2020.

12. U.S. Patent No. 7,916,781 (the "'781 patent") is titled "Serial Concatenation of Interleaved Convolution Codes Forming Turbo-Like Codes."

13. The '781 patent issued on March 29, 2011.

14. The named inventors listed on the '781 patent are Hui Jin, Aamod Khandekar, and Robert J. McEliece.

15. The '781 patent expires on October 16, 2021.

16. Broadcom Corporation is a California corporation with a principal place of business at 5300 California Avenue, Irvine, California 92617.

17. Avago Technologies Ltd. is a corporation organized under the laws of the country of Singapore with principal places of business at 1320 Ridder Park Dr., San Jose, California 95131 and 1 Yishun Avenue 7, Singapore 768923.

18. Apple Inc. is a corporation organized under the laws of the State of California, with principal place of business at One Apple Park Way, Cupertino, California 95014.

19. The California Institute of Technology is a non-profit private university located in Pasadena, California.

20. The parties entered a stipulation identifying the representative products for purposes of the infringement and non-infringement analysis.

The parties have further agreed to the following:

1. For purposes of evaluating infringement or noninfringement of the claims asserted in this case, the RU encoder is representative of the Prediction Correction encoder (also known as the "PC encoder"). No evidence regarding the Prediction Correction Encoder shall be offered or discussed at trial.

2. If Caltech proves by a preponderance of the evidence that any accused product meets all limitations of one or more asserted claims based on its incorporation of the RU

encoder shall constitute proof that all other accused products incorporating the RU encoder or the PC encoder, as listed in Exhibit 1, Sections II and IV, meet all limitations of the same one or more claims.

3. If Caltech fails to prove by a preponderance of the evidence that any accused product meets all limitations of one or more asserted claims based on its incorporation of the RU encoder, that failure shall mean that all other accused products incorporating the RU encoder or the PC encoder, as listed in Exhibit 1, Sections II and IV, also do not meet all limitations of the same one or more claims.

4. For purposes of evaluating infringement or noninfringement, the Permuted Layer decoder is representative of the Submatrix Layer decoder with regard to the limitations of claim 18 of the '032 patent. No evidence regarding the Sub-Matrix Layer decoder shall be offered or discussed at trial.

5. If Caltech proves by a preponderance of the evidence that any accused product meets all limitations of claim 18 of the '032 patent based on its incorporation of the Permuted Layer decoder shall constitute proof that all other accused products incorporating the Permuted Layer decoder or the Sub-Matrix Layer decoder, as listed in Exhibit 1, Sections V and VI, meet all limitations of the same claim.

6. If Caltech fails to prove by a preponderance of the evidence that any accused product meets all limitations of claim 18 of the '032 patent based on its incorporation of the Permuted Layer decoder, that failure shall mean that all other accused products incorporating the Permuted Layer decoder or the Sub-Matrix Layer decoder, as listed in Exhibit 1, Sections V and VI, also do not meet all limitations of the same claim.

III. Patents in General and the Three Patents Involved in This Case

Patents are granted by the United States Patent and Trademark Office (referred to herein as "PTO"). A valid United States patent gives the patent holder the right to prevent others from making, using, offering to sell, or selling the patented invention within the United States, or from importing it into the United States, during the term of the patent without the patent holder's permission. A violation of the patent holder's rights is called "infringement." The patent holder can try to enforce its patent against persons believed to be infringers by means of a lawsuit filed in federal court.

This case involves three patents that were issued by the PTO which were "assigned" to Caltech. An assignment is the transfer of ownership of a patent application or a patent from one entity or person to another.

The three patents are: (1) Patent No. 7,116,710 issued on October 3, 2006, (2) Patent No. 7,421,032 issued on September 2, 2008, and (3) Patent No. 7,916,781 issued on March 29, 2011. Copies of the three patents are included in the Jury Notebook at Tabs 2, 3 and 4, respectively. Henceforth, the patents will be referred to by their last three digits – for example the 7,116,710 patent will be called the '710 Patent.

A patent and the claims contained in the patent issued by the PTO are presumed to be valid. The validity or invalidity of the three patents herein is not an issue in this case. Your job in this trial is to determine whether Caltech has proved by a preponderance of the evidence that Broadcom and/or Apple infringed any of the claims in Caltech's patents and, if so, the amount of damages to be awarded because of the acts of infringement.

A patent usually has three main parts. The first part will contain informational items such as (but not limited to) the patent number, the date the patent application was filed, the date it was issued, the names of the inventors of the patent, whether the patent has been assigned, a list of other patent documents that the PTO looked at in evaluating the patent application, and a section sometimes called "Other Publications" which sets out books and articles which discuss the technology involved and what was generally known about the specific area at the time of the application. For example, if you look at the '710 Patent at Tab 2 at the pages marked at the bottom as JTX 1-1 and JTX 1-2, that is the first part of that patent.

The second part of a patent is referred to as the "specification" which typically includes: (1) a paragraph entitled "Abstract" which briefly summarizes the invention, (2) a background section that describes the nature of the problem the invention is supposed to solve, (3) one or more drawings called "figures" that assist in delineating the invention and/or illustrate various aspects of the application, and (4) a detailed description of one or more embodiments of the invention. An embodiment is a specific device or method that uses the invention; for example as to Thomas Edison's lightbulb patent, it would be a particular form of a lightbulb. In the '710 patent, the specification section begins at the lower right-hand corner of page JTX 1-1, skips page JTX 1-2, and goes from JTX 1-3 through 1-11. You will notice that starting on page JTX 1-8, there are two columns which are numbered sequentially on each page and there are numbers in the center of each page going from 5 to 65. Those numbers are to assist in locating references; for example in the '710 patent, a reference to column 6 lines 33 through 49 would be to Table 1 on page JTX 1.10.

The third (and most important) part of a patent is a statement of the "claims" in the patent. The claims are what give the public notice of the definitions or boundaries of the invention. They are similar to the description of property you may have seen in a deed, referring to precise measurements taken on the ground. The claims are numbered and appear at the end of the patent document. Each claim constitutes a separate definition of the invention. For example, as to the '710 Patent, there are 33 separate claims numbered from 1 to 33 on page JTX 1-11 starting on Column 7 line 14 and ending on Column 8 line 63.

A claim sets forth, in words, a set of requirements. Each claim sets forth its requirements in a single sentence. If a device or a method satisfies each of these requirements, then it is covered by the claim.

The coverage of a patent is assessed claim-by-claim. In patent law, the requirements of a claim are often referred to as "claim elements" or "claim limitations." When a thing (such as a product or a process) meets all of the requirements of a claim, the claim is said to "cover" that thing, and that thing is said to "fall" within the scope of that claim. In other words, a claim covers

a product or process where each of the claim elements or limitations is present in that product or process.

Claims can either be "independent" or "dependent." An "independent claim" sets forth all of the requirements that must be met in order to be covered by that claim. Thus, it is not necessary to look at the language in any other claim to determine what an independent claim covers. In this case, claims 11 and 18 of the '032 patent, and claim 13 of the '781 patent are each independent claims.

Claims 20 and 22 of the '710 patent are "dependent claims." A dependent claim does not itself recite all of the requirements of the claim but refers to another claim for some of its requirements. In this way, the claim "depends" on another claim. A dependent claim incorporates all of the requirements of the claim(s) to which it refers. The dependent claim then adds its own additional requirements. To determine what a dependent claim covers, it is necessary to look at both the dependent claim and any other claim(s) to which it refers. A product or method that meets all of the requirements of both the dependent claim and the claim(s) to which it refers is covered by that dependent claim. Normally, a dependent claim will begin by referencing the earlier claim which it is incorporating. For example, claim 20 of the '710 Patent is a dependent claim because it begins by including "the coder of claim **15**."

IV. Claims Construction

Before you decide whether Apple and/or Broadcom have infringed any of the asserted claims of the '710, '032, and '781 Patents, you will need to understand the patent claims. As I mentioned at the beginning of the case, the patent claims are the numbered sentences at the end of the patent that describe the boundaries of the patent's protection. It is my job as judge to explain to you the meaning of any language in the claims that needs interpretation.

I have interpreted the meaning of some of the language in the patent claims involved in this case. I handed out a document earlier in this case reflecting those meanings and instructed you to place it in your juror notebook. It should be located at Tab 9 of your juror notebook. You must accept those interpretations as correct.

Those terms and their definitions are as follows:

The Tanner Graph diagram that is claimed in Claims 11 and 18 of the '032 Patent has been construed as "a graph representing an IRA code as a set of parity checks where every message bit is repeated, at least two different subsets of message bits are repeated a different number of times, and check nodes, randomly connected to the repeated message bits, enforce constraints that determine the parity bits."

The term "random permutation" as it appears in the Tanner Graph in Claims 11 and 18 of the '032 Patent has been construed as "changing the order of data elements by a purely random or pseudo random process."

The term "repeat" as it appears in Claim 15 of the '710 Patent, which is incorporated into Claims 20 and 22 of the '710 Patent, and as it appears in the Court's construction of the Tanner Graph in Claims 11 and 18 of the '032 Patent has been construed as "generation of additional bits, where generation can include, for example, duplication or reuse of bits."

The term "low-density generator matrix coder" as it appears in Claim 20 of the '710 Patent has been construed as "coder that generates output bits, where process of generating output bits comprises multiplying a low-density matrix by input bits, and the output bits outputted by the coder can be less than, equal to, or more than the number of input bits."

The term "irregularly" as it appears in Claim 15 of the '710 Patent, which is incorporated into Claims 20 and 22 of the '710 Patent, has been construed as "a different number of times."

The term "scramble" as it appears in Claim 15 of the '710 Patent, which is incorporated into Claims 20 and 22 of the '710 Patent, and the term "permute" as it appears in Claims 11 and 18 of the '032 Patent, have each been construed as "changing the order of data elements."

The term "sums of bits in subsets of the information bits" as it appears in Claim 13 of the '781 Patent has been construed as "the result(s) of adding together two or more information bits from a subset of information bits."

My interpretation of the language should not be taken as an indication that I have a view regarding the issue of infringement. The decisions regarding infringement are yours to make.

For a claim term for which I have not provided a definition, you should apply the ordinary and customary meaning as understood by a person of ordinary skill in the art at the time of the invention when read in the context of the specification and prosecution history.

In these instructions, when there is a reference to a "person of ordinary skill in the art," the reference is to a person who is working in the technology of the asserted invention at the time of the filing date of the patent. In deciding the level of ordinary skill, you should consider all the evidence introduced at trial, including:

(1) the levels of education and experience of persons working in the field;
(2) the types of problems encountered in the field; and
(3) the sophistication of the technology.

V. Caltech's Infringement Claims

I will now instruct you concerning patent infringement. Infringement is assessed on a claim-by-claim basis. Therefore, there may be infringement as to one claim but no infringement as to another.

In this case, Caltech has asserted two types of infringement: (1) direct infringement which includes both "literal infringement" and infringement under the "doctrine of equivalents," and (2) active inducement of a third party to infringe the patent(s), sometimes referred to as "indirect infringement." Additionally, Caltech has asserted that certain of the acts of infringement were

"willful."

Caltech asserts that Broadcom and Apple have directly infringed Claims 20 and 22 of its '710 Patent, Claims 11 and 18 of its '032 Patent, and Claim 13 of its '781 Patent by making, importing, using selling and/or offering for sale certain products within the United States. As to Apple, the alleged infringing products are Apple's devices which support Wi-Fi (including its iPhones, iPads, iMacs, MacBooks, AppleTV, and Airport Routers) and which incorporate Broadcom's chips (that support Wi-Fi). As to Broadcom, the alleged infringing products are those purportedly infringing chips that support WI-Fi.

Caltech also contends that Broadcom and Apple have actively induced infringement of these claims of Caltech's asserted patents by others.

Broadcom and Apple deny that they have infringed the asserted claims of Caltech's patents.

Your job is to decide whether Caltech has proved by a preponderance of the evidence any of the alleged acts of infringement.

If you decide that any claim(s) of the patent(s) has been infringed, you will then need to decide any money damages to be awarded to Caltech to compensate it for the infringement. You will also need to make a finding as to whether the infringement was "willful." If you decide that any infringement was willful, that decision should not affect any damage award you make. I will take willfulness into account later.

I will now instruct you on the rules you must follow in deciding whether Caltech has proven that either Broadcom or Apple has infringed one or more of the asserted claims of the '710, '032 and/or '781 Patents. To prove infringement of any claim, Caltech must persuade you that it is more likely than not that Apple and/or Broadcom has infringed a particular claim.

A. Direct Infringement

A patent's claims define what is covered by the patent. A party directly infringes a patent if its product or method is covered by at least one claim of the patent.

Deciding whether a claim has been directly infringed is a two-step process. The first step is to decide the meaning of the patent claim. I have already instructed you as to the meaning of certain words and terms in the asserted patent claims.

The second step is to decide whether Apple and/or Broadcom have made, used, sold, offered for sale, or imported within the United States a product covered by Claims 20 or 22 of the '710 Patent, or Claims 11 or 18 of the '032 Patent, or whether Apple and/or Broadcom practice within the United States Claim 13 of the '781 patent.

You, the jury, are to make these decisions. With one exception, you must consider each

of the asserted claims of each of the three Patents separately and individually, and decide whether the accused Apple and/or Broadcom products and/or methods infringe that claim.

The one exception to considering claims individually concerns dependent claims. A dependent claim includes all the requirements of the particular independent claim it depends from, plus additional requirements of its own. As a result, if you find that an independent claim is not infringed, you must also find that its dependent claims are not infringed. On the other hand, if you find that an independent claim has been infringed, you must still separately decide whether the additional requirements of its dependent claims have also been infringed.

Whether or not Broadcom or Apple knew its product(s) infringed or even knew of the Caltech's patents does not matter in determining direct infringement. A defendant can directly infringe a patent even though it is unaware that what it is doing amounts to infringement. Further, you heard evidence that the accused products may have been developed through independent research. This is not relevant to the question of whether an accused product infringes. An independently developed product or process that falls within the scope of the asserted patent claims nevertheless infringes. However, independent development can be considered in your determination of whether an infringement was willful.

There are two ways in which a patent claim may be directly infringed. A claim may be "literally" infringed, or it may be infringed under the "doctrine of equivalents." The following instructions will provide more detail on these two types of direct infringement.

1) Literal Infringement

To decide whether Apple's and/or Broadcom's products and/or methods literally infringe Claims 20 and 22 of the '710 Patent, Claims 11 and 18 of the'032 Patent, and/or Claim 13 of the '781 Patent, you must compare the products and methods with the patent claims and determine whether every requirement of the claim is included in the product or method. If so, that product or method literally infringes that claim. If, however, the product or method does not have every requirement in the patent claim, that product or method does not literally infringe the claim. You must decide literal infringement for each asserted claim separately.

In this case, the asserted patent claims use the term "comprising." If the patent claim uses the term "comprising," that patent claim is to be understood as an "open" claim. An open claim may be infringed as long as every requirement in the claim is present in Broadcom's or Apple's product or method. The fact that Broadcom's or Apple's product or method also includes other parts or steps will not avoid infringement, as long as it has every requirement in the patent claim.

2) Infringement under the Doctrine of Equivalents

If you decide that one of Apple's or Broadcom's products or methods does not literally infringe an asserted patent claim, you must then decide whether that product or method infringes the asserted claim under what is called the "doctrine of equivalents."

Under the doctrine of equivalents, the product or method infringes an asserted patent claim if it includes parts or steps that are identical or equivalent to the requirements of the claim. If the product or method is missing an identical or equivalent part or step to even one requirement of the asserted patent claim, the product or method cannot infringe the claim under the doctrine of equivalents. Thus, in making your decision under the doctrine of equivalents, you must look at each individual requirement of the asserted patent claim and decide whether the product or method has either an identical or equivalent part or step to that individual claim requirement.

A part or step of a product or method is equivalent to a requirement of an asserted claim if a person of ordinary skill in the field would think that the differences between the product or method and the requirement were not substantial as of the time of the alleged infringement.

Changes in technique or improvements made possible by technology developed after the patent application is filed may still be equivalent for the purposes of the doctrine of equivalents if it still meets the other requirements of the doctrine of equivalents set forth in this instruction.

One way to decide whether any difference between a requirement of an asserted claim and a part or step of the product or method is not substantial is to consider whether, as of the time of the alleged infringement, the part or step of the product or method performed substantially the same function, in substantially the same way, to achieve substantially the same result as the requirement in the patent claim.

Caltech contends that Broadcom and/or Apple infringe the following claim requirements under the doctrine of equivalents:

- "repeat" and
- "repeat … irregularly"

You may not use the doctrine of equivalents in analyzing infringement for any other claim elements.

3) Sale or Importation within the United States

An alleged infringer is liable for direct infringement of a claim if the patent holder proves by a preponderance of the evidence that the infringer, without the patent holder's authorization, imports, offers to sell, sells, or uses within the United States.

Broadcom and/or Apple may infringe Caltech's asserted patents by agreeing to sell a product or by using a method within the United States covered by a claim of Caltech's Asserted Patents. Sales may be found to have occurred in the United States where a substantial level of sales activity occurs here, even for products manufactured, delivered, and used entirely abroad.

Whether a sale occurs in the United States may depend on facts including where the legal commitment to buy and sell occurred and where other substantial activities of the sales transactions occurred, such as negotiating and contracting. A sale agreed to in the United States can be completed in the United States even though delivery is to be made outside the United States in the future. Also, a sale can occur in the United States based on the "design win" process. In a design win market, the sales are design wins made in the United States where the design of the products or method occurs in the United States and the buyer selects that design in the United States, not a steady flow of discrete product sales outside the United States. The United States sales cycle leading to design wins could also trigger United States sales.

However, if substantial activities of a sales transaction, including the final formation of a contract for sale encompassing all essential terms as well as the delivery and performance under that sales contract occurs entirely outside the United States, then pricing and contracting negotiations in the United States alone do not constitute or transform those extraterritorial activities into a sale within the United States.

B. Inducing Patent Infringement (Indirect Infringement)

Caltech alleges that Broadcom and Apple are each liable for infringement by actively inducing a third party to directly infringe the asserted claims. As with direct infringement, you must determine whether there has been active inducement on a claim-by-claim basis.

In order to be liable for inducing infringement, Broadcom or Apple must have:
(1) intentionally taken action that actually induced direct infringement in the United States;
(2) been aware of Caltech's Asserted Patents; and
(3) known that the acts it was causing would infringe the patent.

If you find that Broadcom (or Apple) was aware of the patent, but believed that the acts it encouraged did not infringe that patent, it cannot be liable for inducement.

In order to establish active inducement of infringement, it is not sufficient that the third party itself directly infringed the claim. Nor is it sufficient that Broadcom or Apple was aware of the act(s) by the third party that allegedly constitute the direct infringement. Rather, in order to find active inducement of infringement, you must find either that Broadcom or Apple specifically intended the third party to infringe the patent, or that Broadcom or Apple believed that there was a high probability that the third party would infringe the patent, but deliberately avoided learning the infringing nature of the third party's acts. The mere fact, if true, that Broadcom or Apple knew or should have known that there was a substantial risk that the third party acts would infringe the patent would not be sufficient for active inducement of infringement.

C. Willful Infringement

In this case, Caltech argues that Broadcom and Apple willfully infringed Caltech's patents *after* this lawsuit had been filed against them.

To prove willful infringement, Caltech must first persuade you that Broadcom or Apple infringed a claim of Caltech's patents. The requirements for proving infringement were discussed in my prior instructions.

In addition, to prove willful infringement of a claim, Caltech must persuade you that it is more likely true than not true that Broadcom or Apple intentionally ignored or recklessly disregarded that claim. You must base your decision on Apple's and Broadcom's knowledge and actions at the time of any infringement occurring after Caltech filed this lawsuit. Evidence that Broadcom or Apple had knowledge of the patent at the time of infringement by itself is not sufficient to show willfulness. Rather, to show willfulness, you must find that Broadcom or Apple engaged in additional conduct evidencing deliberate or reckless disregard of Caltech's patent rights.

In deciding whether Broadcom or Apple willfully infringed, you should consider all of the facts surrounding the infringement including: whether Broadcom or Apple intentionally copied Caltech's patented technology in developing the accused products or methods; whether Broadcom or Apple knew, or should have known, that its conduct involved an unreasonable risk of infringement; and whether Broadcom or Apple had a reasonable belief that at the time of infringement that its products or methods did not infringe the asserted patent.

VI. Damages

I will instruct you about the measure of damages. By instructing you on damages, I am not suggesting which party should win on any issue. If you find that Apple and/or Broadcom infringed any of the five asserted claims herein (Claims 20 and 22 of the '710 Patent, Claims 11 and 18 of the '032 Patent, and/or Claim 13 of the '781 Patent), you must then determine the amount of money damages to be awarded to Caltech to compensate it for the infringement.

The amount of those damages must be adequate to compensate Caltech for any infringement. A damages award should put the patent holder in approximately the financial position it would have been in had the infringement not occurred, but in no event may the damages award be less than a reasonable royalty. You should keep in mind that the damages you award are meant to compensate the patent holder and not to punish an infringer.

Caltech has the burden to persuade you of the amount of its damages. You should award only those damages that it more likely than not suffered. While Caltech is not required to prove its damages with mathematical precision, it must prove them with reasonable certainty. Caltech is not entitled to damages that are remote or speculative.

In this case, Caltech is seeking a reasonable royalty for all alleged infringement.

A "royalty" is a payment made to a patent holder in exchange for the right to make, use or sell the claimed invention. This right is called a "license." A reasonable royalty is the payment for the license that would have resulted from a hypothetical negotiation between the patent holder and each alleged infringer taking place at the time when the infringing activity first began. In considering the nature of this negotiation, you must assume that both parties would have acted reasonably and would have entered into a license agreement. You must also assume that both parties believed the patent was valid and infringed. Your role is to determine what the result of that negotiation would have been. The test for damages is what royalty would have resulted from the hypothetical negotiation and not simply what either party would have preferred.

A royalty can be calculated in several different ways and it is for you to determine which way is the most appropriate based on the evidence you have heard. You should consider all the facts known and available to the parties at the time the alleged infringement began. Some of the factors you may consider in making your determination are:

(1) The value that the claimed invention contributes to the accused product.

(2) The value that factors other than the claimed invention contribute to the accused product.

(3) The amount that a licensor (such as the patentee) and a licensee (such as the infringer) would have agreed upon (at the time the infringement began) if both had been

reasonably and voluntarily trying to reach an agreement; that is, the amount which a prudent licensee – who desired, as a business proposition, to obtain a license to manufacture and sell a particular article embodying the patented invention – would have been willing to pay as a royalty and yet be able to make a reasonable profit and which amount would have been acceptable by a prudent patentee who was willing to grant a license.

(4) Comparable license agreements, such as those covering the use of the claimed invention or similar technology.

One way to calculate a royalty is to determine what is called an "running royalty." To calculate a running royalty, you must first determine the "base," that is, the quantity of products on which the alleged infringer is to pay royalties. You then need to multiply that base by the royalty rate that you find would have resulted from the hypothetical negotiation.

You may decide that the appropriate royalty that would have resulted from a hypothetical negotiation is a fixed amount per unit sold. If you do, the royalty would be that fixed amount times the number of units sold.

Another way to calculate a royalty is to determine a one-time lump sum payment that the alleged infringer would have paid at the time of the hypothetical negotiation for a license covering all sales of the licensed product, both past and future. This differs from payment of a running royalty because, with a running royalty, the licensee pays based on the number of actual licensed products it sells. When a one-time lump sum is paid, the alleged infringer pays a single price for a license covering both past and future sales.

In this case, the asserted patents are alleged to cover only one component of the product that Broadcom or Apple imports, uses, or sells. It is Caltech's burden to demonstrate what value that component has added to the product as a whole and to separate the value of the patented contribution from the value of other parts of the product that are not attributable to the patented invention. The ultimate combination of royalty base and royalty rate must reflect the value attributable to the allegedly infringing feature of the product, and no more.

It is up to you, based on the evidence, to decide what type of royalty is appropriate in this case.

In determining the amount of damages, you must determine when the damages began. In this case, if you find infringement of either the '710 patent or the '032 patent, damages should be calculated beginning on May 26, 2010. If you find only the '781 patent infringed, damages should be calculated as of the date the patent issued or the date the infringement began, whichever was first.

If you find only induced infringement, damages should be calculated as of the date the lawsuit was filed: May 26, 2016.

IV. Concluding Instructions

Before you begin your deliberations, elect one member of the jury as your presiding juror. The presiding juror will preside over the deliberations and serve as the spokesperson for the jury in court.

You shall diligently strive to reach agreement with all of the other jurors if you can do so. Your verdict must be unanimous.

Each of you must decide the case for yourself, but you should do so only after you have considered all of the evidence, discussed it fully with the other jurors, and listened to their views.

It is important that you attempt to reach a unanimous verdict but, of course, only if each of you can do so after having made your own conscientious decision. Do not be unwilling to change your opinion if the discussion persuades you that you should. But do not come to a decision simply because other jurors think it is right, or change an honest belief about the weight and effect of the evidence simply to reach a verdict.

Because you must base your verdict only on the evidence received in the case and on these instructions, I remind you that you must not be exposed to any other information about the case or to the issues it involves. Except for discussing the case with your fellow jurors during your deliberations:

Do not communicate with anyone in any way and do not let anyone else communicate with you in any way about the merits of the case or anything to do with it. This includes discussing the case in person, in writing, by phone or electronic means, via email, via text messaging, or any internet chat room, blog, website or application, including but not limited to Facebook, YouTube, Twitter, Instagram, LinkedIn, Snapchat, or any other forms of social media. This applies to communicating with your family members, your employer, the media or press, and the people involved in the trial. If you are asked or approached in any way about your jury service or anything about this case, you must respond that you have been ordered not to discuss the matter and to report the contact to the court.

Do not read, watch, or listen to any news or media accounts or commentary about the case or anything to do with it; do not do any research, such as consulting dictionaries, searching the Internet, or using other reference materials; and do not make any investigation or in any other way try to learn about the case on your own. Do not visit or view any place discussed in this case, and do not use Internet programs or other devices to search for or view any place discussed during the trial. Also, do not do any research about this case, the law, or the people involved—including the parties, the witnesses or the lawyers—until you have been excused as jurors. If you happen to read or hear anything touching on this case in the media, turn away and report it to me as soon as possible.

These rules protect each party's right to have this case decided only on evidence that has been presented here in court. Witnesses here in court take an oath to tell the truth, and the accuracy of their testimony is tested through the trial process. If you do any research or investigation outside the courtroom, or gain any information through improper communications, then your verdict may be influenced by inaccurate, incomplete or misleading information that has not been tested by the

trial process. Each of the parties is entitled to a fair trial by an impartial jury, and if you decide the case based on information not presented in court, you will have denied the parties a fair trial. Remember, you have taken an oath to follow the rules, and it is very important that you follow these rules.

A juror who violates these restrictions jeopardizes the fairness of these proceedings. If any juror is exposed to any outside information, please notify the court immediately.

If it becomes necessary during your deliberations to communicate with me, you may send a note through the bailiff, signed by your presiding juror or by one or more members of the jury. No member of the jury should ever attempt to communicate with me except by a signed writing; I will communicate with any member of the jury on anything concerning the case only in writing, or here in open court. If you send out a question, I will consult with the parties before answering it, which may take some time. You may continue your deliberations while waiting for the answer to any question. Remember that you are not to tell anyone – including me – how the jury stands, numerically or otherwise, until after you have reached a unanimous verdict or have been discharged. Do not disclose any vote count in any note to the court.

A verdict form will be prepared for you. Please follow the instructions on the form with care. After you have reached unanimous agreement on a verdict, your foreperson should complete the verdict form according to your deliberations, sign and date it, and advise the clerk or bailiff that you are ready to return to the courtroom.

EXHIBIT 13

The California Institute of Technology v. Broadcom Limited et al.; Case No. 2:16-cv-03714-GW-(AGRx)
Tentative Rulings on:

(1) Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial) (Docket No. 942 - public; Docket No. 957 - sealed; *see also* Docket No. 994 (notice of errata)); Opposition (Docket No. 1070 - public; Docket No. 1104 - sealed); Reply (Docket No. 1153 - public; Docket No. 1180 - sealed)

(2) Defendants' Motion for Summary Judgment as to No Joint Infringement (Docket No. 959 - public; Docket No. 1006 - sealed); Opposition (Docket No. 1055 - public; Docket No. 1095 - sealed); Reply (Docket No. 1137 - public; Docket No. 1183 - sealed)

(3) Plaintiff's Motion to Strike Certain Opinions of Defendants Experts Brendan Frey and Wayne Stark (Docket No. 974 - public; Docket No. 1000 - sealed); Opposition (Docket No. 1059 - public; Docket No. 1102 - sealed); Reply (Docket No. 1141 - public; Docket No. 1175 - sealed)

(4) Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner (Docket No. 964 - public; Docket No. 1007 – sealed); Opposition (Docket No. 1057 - public; Docket No. 1094 - sealed); Reply (Docket No. 1133 - public; Docket No. 1182 - sealed)

(5) Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative (Docket No. 971 - public; Docket No. 996 - sealed); Opposition (Docket No. 1052 - public; Docket No. 1101 - sealed); Reply (Docket No. 1144 - public; Docket No. 1176 - sealed)

(6) Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby (Docket No. 968 - public; Docket No. 998 - sealed); Opposition (Docket No. 1064 - public; Docket No. 1103 - sealed); Reply (Docket No. 1149 - public; Docket No. 1174 - sealed)

(7) Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales (Docket No. 975 - public; Docket No. 1008 - sealed); Opposition (Docket No. 1050 - public; Docket No. 1093 - sealed); Reply (Docket No. 1154 - public; Docket No. 1184 - sealed)

[Portions of the parties' briefing related to the pending motions addressed by this Tentative Ruling were filed under seal. The parties will be expected to state their positions as to whether any material should remain under seal during the hearing on the motions, including the basis for any continued request to seal.]

I. Introduction

Plaintiff The California Institute of Technology currently alleges patent infringement against Defendants Broadcom Limited, Broadcom Corporation, Avago Technologies Limited, and Apple Inc. *See* First Amended Complaint ("FAC"), Docket No. 36; *see also* Docket No. 1. Plaintiff asserts that Defendants infringe fifteen claims from three of its patents: (1) U.S. Patent No. 7,116,710 ("the '710 Patent"); (2) U.S. Patent No. 7,421,032 ("the '032 Patent"); and (3) U.S. Patent No. 7,916,781 ("the '781 Patent") (collectively, the "Asserted Patents").[1] *See* Docket No. 409 (Plaintiff's Amended Notice of Withdrawal of Certain Asserted Claims of Asserted Patents); *see also* Docket No. 953 (Joint Report Regarding Pending Disputed Issues).

The parties have filed this first "round" of motions for summary judgment and motions to exclude.[2] Those motions have been fully briefed.

For the reasons stated in this Order, the Court would rule as follows:

- Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales (Docket No. 975) would be **GRANTED-IN-PART** and **DENIED-IN-PART** as stated herein.
- Defendants' Motion for Summary Judgment as to No Joint Infringement (Docket No. 959) would be **GRANTED**.
- The Court would **DENY-IN-PART**, **GRANT-IN-PART**, and **DEFER-IN-PART**

[1] The fifteen remaining claims in this case are: Claims 20, 22, and 23 of the '710 Patent; Claims 3, 11, 13, 17, and 18 of the '032 Patent; and Claims 5, 6, 9, 10, 13, 19, and 22 of the '781 Patent. Docket No. 409. Of those claims, eleven were selected as representative claims for purposes of adjudication in this lawsuit: Claims 20, 22, and 23 of the '710 Patent; Claims 3, 11, 17, and 18 of the '032 Patent; and Claims 6, 9, 13, and 22 of the '781 Patent. *See id.*; *see also* Docket No. 487, 488. On March 22, 2019, in a joint report filed by the parties, Plaintiff stated that it intended to file a "formal notice of withdrawal" on the basis that it has "withdrawn its infringement allegations with respect to claims 5, 6, 9, and 10 of the '781 patent and claim 13 of the '032 patent." Docket No. 953 at 2; *see also* Docket No. 998 at 2 (Plaintiff's memorandum in support of motion to exclude improper claim construction opinions, stating that it alleges that Defendants infringe Claims 20, 22, and 23 of the '710 Patent, Claims 3, 11, 17, and 18 of the '032 Patent, and Claims 9, 13 and 22 of the '781 Patent). Plaintiff has not yet filed such a notice, which, once filed, will be understood to remove those five claims from the case entirely given that Plaintiff does not represent that any of the claims "[s]elected for adjudication" are representative of any of the withdrawn claims.

[2] Specifically, the following seven motions have been filed: (1) Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial) (Docket No. 942); (2) Defendants' Motion for Summary Judgment as to No Joint Infringement (Docket No. 959); (3) Plaintiff's Motion to Strike Certain Opinions of Defendants' Experts Brendan Frey and Wayne Stark (Docket No. 974); (4) Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner (Docket No. 964); (5) Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative (Docket No. 971); (6) Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby (Docket No. 968); (7) Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales (Docket No. 975).

Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby (Docket No. 968) as stated herein.

- As stated herein, Plaintiff's Motion to Strike Certain Opinions of Defendants' Experts Brendan Frey and Wayne Stark (Docket No. 974) would be **GRANTED-IN-PART** and **DEFERRED-IN-PART** pending discussion at the hearing.
- Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative (Docket No. 971) would be **DENIED**.
- The Court would **GRANT-IN-PART** and **DENY-IN-PART** Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner (Docket No. 964) as stated herein.
- Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial) (Docket No. 942) would be **GRANTED**.

II. Legal Standard

A. Summary Judgment

Under Federal Rule of Civil Procedure ("Rule") 56, a party may move for summary judgment, identifying each claim or defense − or the part of each claim or defense − on which summary judgment is sought, and the court shall grant it when the pleadings, the discovery and disclosure materials on file, and any affidavits show that "there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *see also Miranda v. City of Cornelius*, 429 F.3d 858, 860 n.1 (9th Cir. 2005). As to materiality, "[o]nly disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). A dispute as to a material fact is "genuine" if there is sufficient evidence for a reasonable jury to return a verdict for the nonmoving party. *Id.*

To satisfy its burden at summary judgment, a moving party with the burden of persuasion must establish "beyond controversy every essential element of its [claim or defense]." *S. Cal. Gas Co. v. City of Santa Ana*, 336 F.3d 885, 888 (9th Cir. 2003); O'Connell & Stevenson, *Rutter Group Prac. Guide: Fed. Civ. Proc. Before Trial* ("*Federal Practice Guide*") § 14:126 (2016). By contrast, a moving party without the burden of persuasion "must either produce evidence negating an essential element of the nonmoving party's claim or defense or show that the nonmoving party does not have enough evidence of an essential element to carry its ultimate burden of persuasion

at trial." *Nissan Fire & Marine Ins. Co., Ltd. v. Fritz Cos.*, Inc., 210 F.3d 1099, 1102 (9th Cir. 2000); *see also Devereaux v. Abbey*, 263 F.3d 1070, 1076 (9th Cir. 2001) (en banc) ("When the nonmoving party has the burden of proof at trial, the moving party need only point out 'that there is an absence of evidence to support the nonmoving party's case.'") (quoting *Celotex Corp. v. Catrett,* 477 U.S. 317, 325 (1986), and citing *Fairbank v. Wunderman Cato Johnson,* 212 F.3d 528, 532 (9th Cir. 2000) (holding that the *Celotex* "showing" can be made by "pointing out through argument . . . the absence of evidence to support plaintiff's claim")).

> If the party moving for summary judgment meets its initial burden of identifying for the court the portions of the materials on file that it believes demonstrate the absence of any genuine issue of material fact, the nonmoving party may not rely on the mere allegations in the pleadings in order to preclude summary judgment[, but instead] must set forth, by affidavit or as otherwise provided in Rule 56, specific facts showing that there is a genuine issue for trial.

T.W. Elec. Serv., Inc., v. Pac. Elec. Contractors Ass'n, 809 F.2d 626, 630 (9th Cir. 1987) (internal citations and quotation marks omitted) (citing, among other cases, *Celotex*, 477 U.S. at 323). "A non-movant's bald assertions or a mere scintilla of evidence in his favor are both insufficient to withstand summary judgment." *See FTC v. Stefanchik*, 559 F.3d 924, 929 (9th Cir. 2009). In addition, the evidence presented by the parties must be admissible. *See* Fed. R. Civ. P. 56(e). Conclusory, speculative testimony in affidavits and moving papers is insufficient to raise genuine issues of fact and defeat summary judgment. *See Thornhill Publ'g Co., Inc. v. GTE Corp.*, 594 F.2d 730, 738 (9th Cir. 1979). Relatedly, "[a]ny objections to declarations or other evidence must be made at or (preferably) before the hearing, and should be ruled upon by the court before ruling on the motion itself." *Federal Practice Guide* § 14:333 (citing *Hollingsworth Solderless Terminal Co. v. Turley*, 622 F.2d 1324, 1335 n.9 (9th Cir. 1980); *Sigler v. American Honda Motor Co.*, 532 F3d 469, 480 (6th Cir. 2008)). In judging evidence at the summary judgment stage, however, courts do not make credibility determinations or weigh conflicting evidence at the summary judgment stage, and must view all evidence and draw all inferences in the light most favorable to the non-moving party. *See T.W. Elec.*, 809 F.2d at 630-31 (citing *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574 (1986)); *Anderson*, 477 U.S. at 255 ("The evidence of the non-movant is to be believed and all justifiable inferences are to be drawn in [the non-movant's] favor.").

"If the court does not grant all the relief requested by the motion, it may enter an order

stating any material fact – including an item of damages or other relief – that is not genuinely in dispute and treating the fact as established in the case." Fed. R. Civ. P. 56(g); *see also* Federal Practice Guide § 14:352 ("A partial summary judgment may be granted on motion of either party for adjudication of particular claims or defenses.") (citing *id.* § 14:33).

B. Motions to Exclude/Strike

1. Rule 37(c) and Timely Disclosure of Information

Under Rule 37(c)(1), "[i]f a party fails to provide information or identify a witness as required by Rule 26(a) or (e), the party is not allowed to use that information or witness to supply evidence on a motion, at a hearing, or at a trial, unless the failure was substantially justified or is harmless." Fed. R. Civ. P. 37(c)(1). The burden is on the party facing the sanction to show that the failure to disclose is substantially justified or harmless. *Yeti by Molly, Ltd. v. Deckers Outdoor Corp.*, 259 F.3d 1101, 1107 (9th Cir. 2001). "Among the factors that ***may*** properly guide a district court in determining whether a violation of a discovery deadline is justified or harmless are: (1) prejudice or surprise to the party against whom the evidence is offered; (2) the ability of that party to cure the prejudice; (3) the likelihood of disruption of the trial; and (4) bad faith or willfulness involved in not timely disclosing the evidence." *Lanard Toys Ltd. v. Novelty, Inc.*, 375 Fed. App'x. 705, 713 (9th Cir. 2010) (citing *David v. Caterpillar, Inc.*, 324 F.3d 851, 857 (7th Cir. 2003)) (emphasis added).

Generally, "the district court's discretion to issue sanctions under Rule 37(c)(1)" is given "particularly wide latitude." *Yeti by Molly*, 259 F.3d at 1107. However, discretion may be limited when the sanction amounts to dismissal of a claim. *R & R Sails, Inc. v. Ins. Co. of Pa.*, 673 F.3d 1240, 1247 (9th Cir. 2012). In such a case, the district court is "required to consider whether the claimed noncompliance involved willfulness, fault, or bad faith, and also to consider the availability of lesser sanctions." *Id.*

2. Experts and *Daubert*

Daubert's "gatekeeping obligation" requires "that all admitted expert testimony is both relevant and reliable." *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1232 (9th Cir. 2017). In addition, expert testimony must "relate to scientific, technical, or other specialized knowledge, which does not include unsupported speculation and subjective beliefs." *Guidroz-Brault v. Missouri Pac. R.R. Co.*, 254 F.3d 825, 829 (9th Cir. 2001). "The test for reliability, however, is not the correctness of the expert's conclusions but the soundness of his methodology." *Stilwell v.*

Smith & Nephew, Inc., 482 F.3d 1187, 1192 (9th Cir. 2007).

That being said, "far from requiring trial judges to mechanically apply the *Daubert* factors - or something like them - to both scientific and non-scientific testimony, *Kumho Tire* heavily emphasizes that judges are entitled to broad discretion when discharging their gatekeeping function." *Hangarter v. Provident Life & Accident Ins. Co.*, 373 F.3d 998, 1017 (9th Cir. 2004). Exclusion of expert testimony is proper only when such testimony is irrelevant or unreliable because "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1993) (citing *Rock v. Arkansas*, 483 U.S. 44, 61 (1987)).

III. Analysis

A. Summary Judgment Motion Regarding Extraterritorial Sales

Defendant Broadcom moves for a summary judgment determination that acts relating to a certain subset of the accused products in this case cannot constitute acts of infringement in the United States as a matter of law.[3] Docket No. 975. Specifically, Broadcom argues that "almost [redacted] of the accused Broadcom chips – the vast majority of the accused Broadcom chips in this case – were made, sold, and delivered outside the United States pursuant to contracts formed outside the United States." Docket No. 1008-1 at 1.

Section 271(a) of the Patent Act states, "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a).

The core disputes between the parties relate to: (1) what constitutes a "sale" or "offer for sale" under 35 U.S.C. § 271(a), and (2) whether, in this case, there are facts to support the conclusion that sales or offers for sale occurred within the United States.

1. Offer for Sale

Regarding an "offer for sale," the Federal Circuit has stated:

> "the location of the contemplated sale controls whether there is an offer to sell *within the United States*." [*Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1309 (Fed. Cir. 2010)]

[3] *See* Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales, Docket No. 975 (public), Docket No. 1008 (sealed); Plaintiff's Opposition, Docket No. 1050 (public), Docket No. 1093 (sealed); Broadcom's Reply, Docket No. 1154 (public), Docket No. 1184 (sealed).

> (emphasis added). "In order for an offer to sell to constitute infringement, the offer must be to sell a patented invention within the United States." *Id.* In *Transocean*, contract negotiations occurred outside the United States for delivery and performance in the United States. This court held that the location of the contemplated sale controlled and that the offer to sell infringed the patent at issue.
>
> The case now before us involves the opposite situation, where the negotiations occurred in the United States, but the contemplated sale occurred outside the United States. We adopt the reasoning of *Transocean* and conclude here that Pulse did not directly infringe the Halo patents under the "offer to sell" provision by offering to sell in the United States the products at issue, because the locations of the contemplated sales were outside the United States. Cisco outsourced all of its manufacturing activities to foreign countries, and it is undisputed that the locations of the contemplated sales were outside the United States. Likewise, with respect to other Pulse customers, there is no evidence that the products at issue were contemplated to be sold within the United States.
>
> An offer to sell, in order to be an infringement, must be an offer contemplating sale in the United States. Otherwise, the presumption against extraterritoriality would be breached. If a sale outside the United States is not an infringement of a U.S. patent, an offer to sell, even if made in the United States, when the sale would occur outside the United States, similarly would not be an infringement of a U.S. patent. We therefore hold that Pulse did not offer to sell the products at issue within the United States for purposes of § 271(a).

Halo Elecs., Inc. v. Pulse Elecs., Inc., 831 F.3d 1369, 1380 (Fed. Cir. 2016).[4]

Plaintiff states that *Halo's* holding relating to offers for sale should be rejected as abrogated by the Supreme Court's determination in a recent case, *WesternGeco LLC v. ION Geophysical Corp.*, 138 S. Ct. 2129 (2018). In *WesternGeco*, the Court considered whether Section 284 of the Patent Act permitted a patent owner to recover lost foreign profits for infringement pursuant to

[4] The Federal Circuit originally reached the same determination, relying on the same analysis, in *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 769 F.3d 1371, 1377 (Fed. Cir. 2014). The Supreme Court subsequently vacated and remanded with respect to the proper test for evaluating enhanced damages under 35 U.S.C. § 284. *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923 (2016). On remand, the Federal Circuit reinstated the portion of its opinion that was not addressed by the Supreme Court, which included this excerpt. *Halo*, 831 F.3d at 1373 ("Because the Supreme Court's review was limited to the issue of enhanced damages and left undisturbed the judgments on other issues, we reaffirm the summary judgment of no direct infringement of the Halo patents by the accused products that Pulse manufactured, shipped, and delivered outside the United States, and we also reaffirm all aspects of the cross-appeal. On those issues, we restate herein the reasoning stated in our earlier opinion."). This Order refers to the remanded opinion, *Halo*, 831 F.3d 1369, unless otherwise noted.

Section 271(f)(2). *See* 35 U.S.C. § 271(f)(2).[5] The Court found that "Section 271(f)(2) focuses on domestic conduct . . . . The conduct that § 271(f)(2) regulates - *i.e.*, its focus - is the domestic act of 'suppl[ying] in or from the United States.'" *WesternGeco*, 138 S. Ct. at 2137-38. The Court went on to state:

> [Defendant] ION is mistaken to assert that this case involves an extraterritorial application of § 284 simply because "lost-profits damages occurred extraterritorially, and foreign conduct subsequent to [ION's] infringement was necessary to give rise to the injury." Those overseas events were merely incidental to the infringement. In other words, they do not have "primacy" for purposes of the extraterritoriality analysis. [*Morrison v. Nat'l Australia Bank Ltd.*, 561 U.S. 247, 267 (2010)].

Id. at 2138 (citation omitted).

Plaintiff's argument regarding *WesternGeco's* impact on the Federal Circuit's ruling relating to offers for sale in *Halo* is unpersuasive. *WesternGeco* was limited to considering whether the case involved a domestic application of the provisions in Sections 284 and 271(f)(2) of the Patent Act. *WesternGeco* did not consider the focus of Section 271(a). It is not this Court's place to say that *WesternGeco* abrogated *Halo's* holding under these circumstances. This is particularly true when, since the time *WesternGeco* was issued, the Federal Circuit has referred to and appeared to cite with approval the determinations in *Halo*. *See Texas Advanced Optoelectronic Sols., Inc. v. Renesas Elecs. Am., Inc.*, 895 F.3d 1304, 1330 (Fed. Cir. 2018) ("*TAOS*") *petition for cert. docketed*, No. 18-600 (Nov. 7, 2018) (describing facts presented in *Halo* and stating, "[u]nder those undisputed facts, this court affirmed the district court's conclusion on summary judgment that there was no sale or offer to sell in the United States.").[6]

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[5] Section 271(f)(2) states,

> Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

35 U.S.C. § 271(f)(2).

[6] In a footnote of its opposition, Plaintiff states:

> Summary judgment is all the more inappropriate at this time because the Supreme Court is considering whether to grant certiorari in *TAOS* on whether, under 35 U.S.C. § 271(a), "an 'offer[ ] to sell' occurs where the offer is actually made or where the offer contemplates that

It is undisputed that the accused products that are the subject of Broadcom's motion are manufactured outside of the United States and shipped to other entities outside of the United States.[7] *See* Defendants' Statement of Undisputed Facts Regarding Summary Judgment as to Non-Infringement as to Extraterritorial Sales, Docket No. 1184-1 § I, ¶¶ 1-10. Under controlling Federal Circuit authority, Plaintiff cannot show that these chips are offered for sale within the United States.

2. Sale

Federal Circuit authority is not so clear-cut insofar as what constitutes a sale in the United States under Section 271(a). The issue was also addressed in *Halo*, where the Federal Circuit found that "the district court did not err in granting summary judgment of no direct infringement with respect to those products that Pulse manufactured, shipped, and delivered outside the United States" because the products were not sold (or offered for sale) in the United States. *Halo*, 831 F.3d at 1376. The Federal Circuit found that:

> [a]lthough Pulse and Cisco had a general business agreement, that agreement did not refer to, and was not a contract to sell, any specific product. While Pulse and Cisco engaged in quarterly pricing negotiations for specific products, the negotiated price and projected demand did not constitute a firm agreement to buy and sell, binding on both Cisco and Pulse. Instead, Pulse received purchase orders from Cisco's foreign contract manufacturers, which then firmly established the essential terms including price and quantity of

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> the proposed sale will take place." Supreme Court Docket 18-600, Petition for a writ of certiorari, "Question Presented" (Nov. 5, 2018). The Supreme Court recently invited the Solicitor General to weigh in with the views of the US. Docket 18-600 (Jan. 7, 2019).

Docket No. 1093 at 22-23 n.9. Unless and until the petition for a writ of certiorari is granted in *TAOS*, this Court declines to consider waiting to make its determinations based on currently-applicable Federal Circuit precedent. The Court expects that the parties will keep it apprised of developments with the *TAOS* petition.

[7] Some underlying "undisputed" facts referenced in this Order, including this one, are technically disputed by Plaintiff or Defendants. The Court has reviewed said disputes and identifies a fact as "undisputed" when supported by the cited evidence, altering the proffered facts if necessary to accurately reflect the uncontroverted evidence. To the extent that the cited underlying "undisputed" facts have been disputed, the Court finds that the stated disputes: (1) fail to controvert the proffered "undisputed" facts, (2) dispute the facts on grounds not germane to the below statements, and/or (3) fail to cite evidence in support of the disputing party's position. As such, the Court treats such facts as undisputed. Any proffered facts not included in this tentative ruling were found to be: (1) improper opinions or conclusions rather than facts, (2) were unsupported by admissible evidence, (3) were deemed irrelevant to the Court's present analysis, or (4) some combination thereof. To the extent the Court uses any facts in this tentative ruling, and does not note that they are disputed, it has determined that they are undisputed.

Although certain documents are listed on the electronic docket as "Objection/Opposition" to particular pending motions (*see, e.g.*, Docket No. 1104), based on the Court's review of such entries, it does not appear that either party has submitted evidentiary objections to the other side's proffered evidence.

> binding contracts to buy and sell. Moreover, Pulse was paid abroad by those contract manufacturers, not by Cisco, upon fulfillment of the purchase orders. Thus, substantial activities of the sales transactions at issue, in addition to manufacturing and delivery, occurred outside the United States. Although Halo did present evidence that pricing negotiations and certain contracting and marketing activities took place in the United States, which purportedly resulted in the purchase orders and sales overseas, as indicated, such pricing and contracting negotiations alone are insufficient to constitute a "sale" within the United States.

Halo, 831 F.3d at 1378.

In comparison, in another decision, the Federal Circuit vacated a portion a jury's damages award, finding that although the defendant had not met its burden of showing that judgment as a matter of law was warranted as to certain of its accused semiconductor microchips, a new trial was necessary on the issue of whether the chips that were not made or used in, or imported into, the United States could be considered "sold" in the United States under the particular facts of the case. *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1311 (Fed. Cir. 2015) ("*CMU*"). The Federal Circuit stated:

> [t]he standards for determining where a sale may be said to occur do not pinpoint a single, universally applicable fact that determines the answer, and it is not even settled whether a sale can have more than one location. *See Halo,* 769 F.3d at 1378-79 (collecting cases; relying in part on *N. Am. Philips Corp. v. Am. Vending Sales, Inc.,* 35 F.3d 1576, 1579 (Fed. Cir. 1994)). Places of seeming relevance include a place of inking the legal commitment to buy and sell and a place of delivery, *see id.; Transocean,* 617 F.3d at 1311; *cf. Norfolk & W. Ry. Co. v. Sims,* 191 U.S. 441, 447, 24 S.Ct. 151, 48 L.Ed. 254 (1903), and perhaps also a place where other "substantial activities of the sales transactions" occurred, *Halo,* 769 F.3d at 1379 & n. 1 (focusing on where "substantial activities of the sales transactions" occurred, but declining to decide whether the location of contract formation on the facts of that case would have established a sales location). At this point, we do not settle on a legal definition or even to say whether any sale has a unique location. The governing legal standards have not been the subject of meaningful briefing here. Identifying those standards, along with relevant factual development, is better undertaken in the remand we order, in part because further factual development may narrow the legal issues actually requiring decision. At present, we do not have a full understanding of, among other things, what a "design win" meant legally and practically, how such a "design win" in the United States in this case compares with the activities that occurred in the United States in *Halo* (which were insufficient), and where specific chip orders were negotiated and made final. Until fuller exploration of factual and legal issues occurs on remand, it is premature to rule on whether sales

occurred in the United States for the chips at issue.

*   *   *

> Chip designers like [Defendant] Marvell sell customized chips with designs specifically tailored for incorporating into customers' products. J.A. 42,123-24 (Marvell VP of sales: "[E]very chip that Marvell designs for a customer is specifically aimed for that particular customer. It's not, cannot be sold to the, you know, in the general market."). Because of the customized nature of the chips, designers and potential customers put themselves through a lengthy "sales cycle," involving extensive joint work over several years, before any sale is made and chips enter mass production. Only at the end of that sales cycle, if the chip designer is successful, does it secure a "design win," but that win generally results in a customer's exclusive use of that designer's customized chip for a certain period, amounting to tens or hundreds of millions of chips over several years. J.A. 43,654-55 (parties' joint stipulation on the sales cycle); *see* J.A. 44,426 (executive at Western Digital testifying that when he "recommend[ed] that Marvell be selected as the read chip channel supplier," Marvell would become "the exclusive read chip channel supplier"). One executive from a now-defunct chip maker called the industry a "winner takes all business." J.A. 42,121.
>
> Marvell's facilities are in northern California, and CMU's industry expert, Dr. Bajorek, showed that "with the exception of the chip making . . . all the activities related to designing, simulating, testing, evaluating, qualifying the chips by Marvell as well as by its customers occur[ ] in the United States." J.A. 42,159; *see also* J.A. 35,075-77 (charts showing relevant activity and where it occurred); J.A. 43,650-55 (parties' joint stipulation). He also used Marvell's records to show that Marvell, from California, provided potential customers with samples and simulations incorporating its designs. *E.g.,* J.A. 42,147-48; J.A. 53,570, 53,572, 53,612, 53,613. Marvell itself stipulated that "[d]uring [its] sales cycle, [its] engineers assist [its] customers in implementing [its] solutions into their product." J.A. 43,654. And there was some evidence suggesting that specific contractual commitments for specific volumes of chips were made in the United States . . . . Marvell points us to no evidence to the contrary.

Id. at 1308-09.

The parties' primary dispute is whether *Halo* or *CMU* should govern the outcome of Broadcom's motion on the facts presented. Broadcom argues that the facts in this case are similar to those presented in *Halo* and summary judgment is appropriate. Plaintiff argues that the reasoning of *Halo*, and particularly its emphasis on the presumption against extraterritoriality, *see Halo*, 831 F.3d at 1378, is undercut by the Supreme Court's analysis in *WesternGeco*. Plaintiff argues that *CMU* should control for that reason as well as based on an argument that the facts in

this case are similar to those at issue in *CMU* compared to *Halo*.

The Court has already rejected Plaintiff's position that *WesternGeco* abrogates or otherwise undercuts the Federal Circuit's reasoning in *Halo* related to Section 271(a). *See also TAOS*, 895 F.3d at 1330. *TAOS* is also instructive in its analysis of *Halo* and *CMU*. In *TAOS*, in drawing a distinction between *Halo* and *CMU*, the Federal Circuit observed that in *CMU*, "there was some evidence suggesting that specific contractual commitments for specific volumes of chips [(*i.e.*, the accused products)] were made in the United States." *TAOS*, 895 F.3d at 1330 (citing *CMU*, 807 F.3d at 1309). *TAOS* also noted that in the circumstances presented in *CMU*, the defendant "had the opportunity to present evidence at trial that the sales took place only abroad and simply failed to do so," such that the Federal Circuit panel "repeatedly stressed" that judgment as a matter of law in favor of the defendant was not warranted.[8] *Id.*

Importantly, as *CMU* noted, "[t]he standards for determining where a sale may be said to occur do not pinpoint a single, universally applicable fact that determines the answer, and it is not even settled whether a sale can have more than one location." *CMU*, 807 F.3d at 1308; *see also Asia Vital Components Co. v. Asetek Danmark A/S*, Case No. 16-cv-07160-JST, 2019 WL 1369908, *21 (N.D. Cal. Mar. 26, 2019). In other words, the inquiry is extremely fact-intensive and fact-specific. Plaintiff attempts to distinguish the circumstances of this case from *Halo* by mustering evidence of various activities that allegedly occur on United States soil relating to the Apple-Broadcom relationship and the selling and buying of Broadcom's accused chips. A review of most of the facts discussed by the parties supports the conclusion that they sync up with the facts at issue in *Halo*. [redacted][9] A few areas where the parties focus

[8] A new trial was permitted in *CMU* on the basis that the jury instructions were missing "an instruction that required the jury to find a domestic location of sale as to those chips not made or used in, or imported into, the United States." *CMU*, 807 F.3d at 1310. The Federal Circuit in *CMU* found that the defendant "did not properly object to the omission of an instruction focusing on the place of sale for those chips which were not made or used in, or imported into, the United States," but that in exercising a discretionary right of plain error review, the "fundamental importance of the extraterritoriality principle" and other considerations were "enough for a 'miscarriage of justice' under a rule whose function is to produce only a new trial, not a judgment as a matter of law for the objecting party." *Id.* at 1310-11.

[9] The Magistrate Judge similarly found that these documents and activities related to them matched with some of the unsuccessful evidence raised by the plaintiff in *Halo*. *See* Docket No. 273 at 5. The Magistrate Judge ultimately concluded that on the record before her, Defendants had failed to show that sales of Broadcom chips

their dispute, including the facts surrounding purchase orders and "design wins," deserve further discussion.

One of the areas of factual and legal dispute between the parties relates to purchase orders. Plaintiff argues that purchase orders are [redacted] *See, e.g.*, Plaintiff's Statement of Additional Material Facts, Docket No. 1184-1 § II, ¶¶ 58, 61, 67; *see also id.* at § II, ¶¶ 59, 60. Most of Plaintiff's cited evidence does not support the claim [redacted] *See, e.g.*, Docket No. 1093-112. However, [redacted] Docket No. 1093-118. This lone purchase order, if tied to the accused products in this case, would appear to support the conclusion [redacted] *CMU*, 807 F.3d at 1308-09. However, more information is necessary regarding the particular purchase order and accused products to confirm this.

Plaintiff also submits evidence that supports the argument that Apple [redacted] Docket No. 1184-1 § II, ¶¶ 58, 60, 61 (citing, *e.g.* Docket Nos. 1093-50; 1093-54; 1093-76). For this second point, Broadcom argues that similar facts were considered and rejected in *Halo*. *Id.* ¶ 61 ("Halo argued in its opening appellate brief that '[o]nce the quarterly contracting process is complete, Cisco communicates the final price and allocation it sets with Pulse (and the other suppliers) to Cisco's contract manufacturers . . .'"). Contrary to Broadcom's position, Plaintiff's cited evidence [redacted] such that it is the entity that is "firmly establish[ing] the essential terms including price and quantity of binding contracts to buy and sell." *Halo*, 831 F.3d at 1378.

Plaintiff argues that some purchase orders may [redacted] and [redacted] with [redacted] Docket No.

occurred in the United States "to render discovery of the remaining worldwide revenue numbers proportional to the needs of the case." *Id.*at 3.

1093 at 6; Docket No. 1184-1 § II, ¶¶ 43-46; *see also* Docket No. 1093-140 (Exhibit with title [redacted] Although Broadcom refers to this [redacted] in the introduction section of its reply brief, it does not mention it again when later discussing purchase order activities. *See* Docket No. 1184 at 2. In responding to Plaintiff's additional material facts, Broadcom does not dispute that [redacted] nor that [redacted] but instead argues that it is both immaterial and comparable to activities that were deemed insufficient in Halo. *See, e.g.*, Docket No. 1184-1 § II, ¶ 43 at 256 (quoting excerpt of the plaintiff's appellate brief in *Halo* and arguing, "[t]he Federal Circuit rejected a similar argument in *Halo*, where it had been shown that Pulse and Cisco agreed on a final price, negotiated in the U.S., and that ***"Cisco then reimburse[d] the contract manufacture" for the price that had been agreed upon with Pulse.***" (emphasis in original)). The Court is not persuaded that comparable activities, at least at the level of evidentiary detail presented here, are described in *Halo*, *CMU*, or other Federal Circuit cases. Apple's practice [redacted][10]

Aside from the contours of purchase order practice,[11] the parties spend substantial time disputing whether Broadcom's [redacted] makes this matter more comparable to *CMU* than *Halo*. Particularly when considered alongside the other evidence presented, including some of the evidence related [redacted] the Court finds that Broadcom's [redacted] further supports the conclusion that questions of fact preclude summary judgment as a matter of law at this time. Broadcom argues that the design win process in *CMU* is distinguishable

[10] The Magistrate Judge found that this practice was "merely a variation of the agreed upon price that was found insufficient in *Halo*." Docket No. 273 at 5.

[11] Plaintiff also [redacted] *See* Docket No. 1093 at 7; Docket No. 1184-1 § II, ¶¶ 73-76. Broadcom challenges the underlying evidence used to support Plaintiff's assertion about the location [redacted] Docket No. 1184 at 8. Indeed, Plaintiff's cited testimony includes the statement that Broadcom's customer service team [redacted] *See, e.g.* Docket No. 1093-10 at 191:11-23; *see also* Docket No. 1184-4 (Purchase Order addressed to Broadcom in Dublin, Ireland). The same testimony states that [redacted] *See id.* at 191:24-194:21; 196:11-13. Plaintiff's argument on this issue is not particularly persuasive on its own, but perhaps could be considered alongside the other evidence presented.

from Broadcom's [redacted] and that *Halo* effectively considered circumstances involving a sales cycle just as extensive and intimate as the sales cycles Broadcom employs. At least at this stage, more factual information is necessary to support Broadcom's arguments distinguishing *CMU* on these grounds. In particular, more information about the nature of Broadcom's market and, for instance, [redacted], is required. *See, e.g.*, Docket No. 1184-1 § II, ¶¶ 112, 113, 131.

3. Induced Infringement

The parties spend minimal briefing on the issue of induced infringement. Induced infringement requires a showing that direct infringement has occurred. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 923 (2014). Here, for chips that are never imported into the United States, "whether inside an Apple product or otherwise," (*see* Docket No. 1184 at 12), the only dispute raised by the parties is whether ***Broadcom*** directly infringes through sales or offers for sale of those chips in the United States. Plaintiff has not presented evidence or argument to support the conclusion that for the non-imported chips, Broadcom induces a third party to perform acts of infringement. Summary judgment of no induced infringement as to that particular collection of chips is appropriate.

However, for chips that are inside Apple products and are eventually imported into the United States, there is insufficient basis to warrant summary judgment. In its opening brief, Broadcom argues that it does not possess the requisite "specific intent to induce infringement" because it [redacted] Docket No. 1184 at 19-20. However, "requisite intent to induce infringement may be inferred from all of the circumstances." *Warsaw Orthopedic, Inc. v. NuVasive, Inc.*, 824 F.3d 1344, 1347 (Fed. Cir. 2016) (quoting *Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 699 (Fed. Cir. 2008)). Indeed, the Federal Circuit has also found that "willful blindness can satisfy the knowledge requirement for active inducement under § 271(b) (and for contributory infringement under § 271(c)), even in the absence of actual knowledge." *Id.*

Plaintiff argues that [redacted] Docket No. 1093 at 24; *see also* Docket No. 1184-1 § II, ¶¶ 85-87 (*see also* Broadcom's response to ¶ 87, asserting that [redacted]

[redacted]

On the current record, factual questions relating to the exclusive nature of the supply chain and Broadcom's intent preclude summary judgment as to chips that are eventually imported into the United States. *See Largan Precision Co. v. Genius Elec. Optical Co.*, 646 F. App'x 946, 949 n.2 (Fed. Cir. 2016).

4. Conclusion

Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales (Docket Nos. 975, 979) would be **GRANTED-IN-PART** and **DENIED-IN-PART**. Plaintiff cannot show as a matter of law that Broadcom infringes the asserted patents via its accused chips that are never imported into the United States on the basis of *offering to sell* them pursuant to 35 U.S.C. § 271(a) when Broadcom and its customers merely take actions similar to those engaged in by the defendant in *Halo*, and Broadcom's motion would thus be **GRANTED** on that basis. However, questions of fact remain as to whether Broadcom's chips that are never imported into the United States are sold pursuant to 35 U.S.C. § 271(a) (similar to the situation in *CMU*, and Broadcom's motion would thus be **DENIED** on that basis. Plaintiff has failed to present evidence that Broadcom induces others to infringe the asserted patents via its accused chips that are not imported into the United States, and Broadcom's motion would thus be **GRANTED** on that basis. To the extent Broadcom's Motion relates to accused chips that are eventually imported into the United States, fact questions are present regarding whether Broadcom induces infringement of the asserted patents through those chips, and the Motion would be **DENIED** on that basis.

B. Summary Judgment Motion Regarding Joint Infringement

Defendants move for a summary judgment determination that they have not jointly infringed the asserted patents on the basis that Plaintiff has "offered no evidence, opinions, or contentions" to support such a theory.[12] Docket No. 959 at 1.

Plaintiff argues that it timely disclosed a joint infringement theory because its infringement contentions alleged that "***Defendants directly infringe*** the Asserted Claims by ***making*** [and/or] ***using*** . . . the Accused Products" and "***Defendants*** further directly infringe each method claim of

[12] *See* Defendants' Motion for Summary Judgment as to No Joint Infringement, Docket No. 959 (public), Docket No. 1006 (sealed); Opposition, Docket No. 1055 (public), Docket No. 1095 (sealed); Reply, Docket No. 1137 (public), Docket No. 1183 (sealed).

the Asserted Claims because ***Defendants*** have performed each and ever step of the Asserted Claims at least through ***testing*** and/or ***use*** by their employees, among other ways." Docket No. 1095 at 6 (quoting Docket No. 961-2 at 10) (emphasis in original). Plaintiff also identifies a sentence in its contentions where it stated Apple infringes "by requiring the LDPC coding functionality in the Broadcom Accused Products to be enabled." *Id.* (quoting Docket No. 961-2 at 11). Plaintiff argues that similar references to "***Defendants***" plural in some of its expert reports supports the conclusion that it timely disclosed a joint infringement theory. *Id.* at 7. Plaintiff also for the first time in this litigation suggests that it did not have an obligation to disclose all of its litigation theories in a timely fashion because "neither the scheduling order in this case nor any local rule required Caltech to present further details in its infringement contentions." *Id.* at 6-7.

Plaintiff's arguments are not persuasive. The parties have gone through multiple rounds of disputes in this case regarding the sufficiency of Plaintiff's infringement contentions. *See* Docket No. 673 at 2 (September 10, 2018 Order regarding motions, stating, "[t]he parties have been raising disputes about the adequacy of Plaintiff's infringement contentions for about a year now."). Arguing that using the word "Defendants" plural in infringement contentions supports a basis for understanding a joint infringement theory is both troubling and insufficient to put Defendants on notice of a specific joint infringement theory. As Defendants note, Plaintiff also takes other statements in its infringement contentions out of context. Docket No. 961-2 at 2 ("Apple incorporates Broadcom Accused Products into Apple Accused Products in an infringing manner by requiring the LDPC coding functionality in the Broadcom Accused Products to be enabled." (emphasis added).). Because Plaintiff failed to timely disclose any cognizable theory of joint infringement liability to support its affirmative case against Defendants, summary judgment is warranted. Defendants' Motion for Summary Judgment as to No Joint Infringement (Docket No. 959) would be **GRANTED**.

C. Motion to Exclude Improper Claim Construction Opinions

Plaintiff moves to exclude certain opinions of Dr. Wayne Stark and Dr. Andrew Blanksby on the basis that they rely on improper claim construction interpretations.[13] Docket No. 968. Before turning to the nine separate disputes that Plaintiff raises in its motion, the Court notes that

[13] *See* Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby, Docket No. 968 (public), Docket No. 998 (sealed); Opposition, Docket No. 1064 (public), Docket No. 1103 (sealed); Reply, Docket No. 1149 (public), Docket No. 1174 (sealed).

the brief snippets of technologically-complex argument that are directed to each of these disputes appear likely interrelated with much larger, possibly dispositive issues in this case. The Court provides some tentative determinations on the limited record before it, but expects additional information from the parties at the hearing regarding how (hypothetically) granting or denying Plaintiff's motion as to some or all of these disputes would impact dispositive issues in this case, including infringement and invalidity. The Court may reserve a final determination on some or all of the disputes raised herein until after the parties have fully briefed their "second round" of dispositive motions.

1. "Repeat" (all asserted claims)

During claim construction, Defendants argued that the term "repeat" should be construed as "[c]reating a new bit that corresponds to the value of an original bit (*i.e.*, a new copy) by storing the new copied bit in memory. A reuse of a bit is not a repeat of a bit." *See* Docket No. 213 at 8. The Court found that the claim language itself "makes clear that 'repeated bits' are a construct distinct from the original bits from which they are created, as Defendants contend repeatedly." *Id.* at 9; *see also id.* at Cover, 14. The Court went on to state, "nowhere in the claims is the term 'repeat' defined or used in a manner that specifies how the repeated bits are stored in their transitional state," and rejected Defendants' proposal that the term "repeat" be construed to require "storing the new copied bit in memory." *Id.* The Court referred to certain examples, including the low-density generator matrix ("LDGM") in the specification, before explaining, "storage of redundant copies of bits in new memory locations is not a predicate to duplication or reuse of bits to create IRA codes or parity bits, especially not when the repeated bits are merely transitory to generation of parity bits."[14] *Id.*

Plaintiff argues that Defendants' experts improperly submit opinions that would limit the

[14] The claim construction order later stated:

> Defendants also assert that Plaintiff's attempt to re-write the claim to cover mere 'reuse' of bits would render limitations of the asserted claims superfluous. *See* Defs.' Motion at 14; Defs.' Opposition at 4. But Plaintiff is not asking this Court to construe the claims so. Rather, Plaintiff only proposes that the Court adopts the plain and ordinary meaning of the term.

Docket No. 213 at 10. However, in adopting the claim construction ruling as the final ruling of the Court, the cover page included the statement that "while 'repeat' may encompass duplication ***and reuse***, it surely is not limited to . . . specific implementation techniques." *Id.* at Cover (emphasis added); *see also id.* (stating term encompasses "generation of additional bits by means of duplicating the original bits.").

meaning of "repeat" to require "storing new copied bit[s] in memory."[15] *See, e.g.* Docket No. 1174 at 1-2. Plaintiff states:

> [i]nstead of explicitly stating that "repeating" requires "storing the new copied bit in memory," Defendants' experts claim that an information bit cannot be repeated by distributing it to multiple components connected to a wire because (in that context) the value of the original information bit cannot be changed without resulting in a corresponding change to the repeated bit. However, the only way the original bit can change its value without resulting changing the repeated bit is if the repeated bit is stored in memory (*e.g.*, registers, RAM, cache, latches, CD-ROMs, capacitors, etc.). Indeed, even though Defendants claim that bits can be "repeat[ed]" without storing new bits in memory, ***they yet have to identify a single scenario*** that meets Defendants' interpretation of "repeat" and does ***not*** use memory.

Id. (citations omitted) (emphasis added).

The Court agrees with Plaintiff that Defendants appear to hang on the word "distinct" in a sentence of the claim construction order in a way that leads to an interpretation of the word "repeat" that is narrower than its plain and ordinary meaning. Docket No. 213 at 9 ("'repeated bits' are a construct ***distinct*** from the original bits from which they are created, as Defendants contend repeatedly."). As the Court explained elsewhere in the claim construction order, "'repeats' indicates generation of additional bits." *Id.* at 14. A relationship between the generated repeat bits and the original bit (for instance, in the context of memory "pointers," *see id.* at 9) is not precluded by the claim construction order. In other words, to the extent Defendants would argue, for instance, that by saying repeated bits are "distinct" from the original bits, the Court somehow required difference or independence between the repeated and original bits, Defendants have not provided a basis for that position.

The Court agrees with Defendants, however, that on the current record, whether a branched wire meets the limitation of the claims, including a requirement for repeated bits, presents a question of fact. Whether the different points on the wire constitute the "exact same single bit" because "a wire, no matter the number of branches, settles to the exact same voltage at all points," (Docket No. 1103 at 3) or whether the different points on the wire represent repeat bits consistent with the "connections" shown in Figure 3 of the asserted patents because "[a] wire is just a connection from A to B" (Docket No. 1174 at 2-3) presents fact questions that cannot be resolved

[15] Plaintiff specifically requests that paragraphs 414-415, 432, 437, 449, 532-556, 558-562, and 566-569 of the Stark Report and paragraphs 159-170 and 172-179 of the Blanksby Report be excluded. Docket No. 998 at 7.

at this time.

2. "Low-Density Generator Matrix" ('710 Patent, Claim 20; '781 Patent, Claim 5) and "First Coder" ('710 Patent, all asserted claims; '781 Patent, Claim 9)[16]

Claim 15 of the '710 Patent requires, *inter alia*, a "first coder operative to repeat said stream of bits regularly." Claim 20 of the '710 Patent requires that "the first coder comprises a low-density generator matrix coder." During claim construction, Defendants argued that the term "generator matrix" should be construed as "a matrix that, when multiplied by a block of input bits, produced a number of output bits that is greater than or equal to the number of input bits." Docket No. 213 at 13. The Court found that the term should be understood by its plain and ordinary meaning. *Id.* at 16. The term "first coder" was not briefed during claim construction.

Although the Court could attempt summarize the parties' current dispute at a high level, Plaintiff's arguments about Defendants' experts' opinions relating to the "first coder" term in particular have shifted over the course of its briefs.[17] For instance, in its opening brief, Plaintiff argues that Defendants' experts have impermissibly required that the first coder *must* output a codeword or parity bits. Docket No. 998 at 12. In its reply brief, Plaintiff argues that Defendants' experts have impermissibly required that the first coder *must* output more bits than were input, because, Plaintiff argues, this fails to take into account that the first coder could be creating parity bits. Docket No. 1174 at 4. As Defendants also observe, the paragraphs of Defendants' expert reports that Plaintiff requests stricken, particularly for the term "low-density generator matrix," do not on their face all appear to provide opinions relating to that particular term.

More information is required, particularly Defendants' responses to arguments in Plaintiff's reply brief, to understand the nature of the parties' dispute.

3. "Random" ('032 Patent, all asserted claims)

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[16] In its opening brief, Plaintiff argued that Defendants' experts' opinions regarding the "first coder" recited in Claim 15 of the '710 Patent are improper because Defendants' experts interpret the term to require that it must output parity bits. Docket No. 998 at 12. Defendants respond by stating, "Drs. Stark and Blanksby do not contend the claimed 'first coder' must output 'parity bits.'" Docket No. 1103 at 19. In reply, Plaintiff argues that the parties' dispute regarding "first coder" is the same as their dispute regarding "low-density generator matrix." *See, e.g.* Docket No. 1174 at 6. Thus, the two disputes are considered together.

[17] Plaintiff requests that paragraphs 414-415, 432, 437, 449, 532-556, 558-562, and 566-569 of the Stark Report and paragraphs 159-170 and 172-179 of the Blanksby Report be excluded with respect to the "low-density generator matrix" term and that paragraphs 566-569 of the Stark Report and paragraphs 172-179 of the Blanksby Report be excluded with respect to the "first coder" term. *See* Docket No. 998 at 7, 13.

During claim construction, Defendants proposed the terms "random" / "randomly" should mean "non-deterministic." Docket No. 213 at 23. The Court rejected Defendants' position, stating, "the intrinsic evidence supports the inference that the named inventors did not attach any specialized meaning to 'random' (or its variations), specifically not 'non-deterministic' . . . , and intended only its plain and ordinary meaning." *Id.* at 24.

Plaintiff argues that Stark, in deposition testimony, improperly equated the claim term "random" to "non-deterministic." Docket No. 998 at 7 (citing Excerpt of Deposition Transcript of Wayne Stark, Docket No. 998-3 at 106:8-9, 107:10-17). On this basis, Plaintiff argues that any of Stark's opinions relating to the term "random" should be excluded.[18]

Defendants argue that "Stark's report never says 'random' is limited to 'non-deterministic,' and instead expressly rejects this (baseless) criticism." Docket No. 1103 (citing Declaration of Dr. Wayne Stark in support of Defendants' Opposition to Motion to Exclude, Docket No. 1103-2, Ex. S-2 ("Stark Report," ECF36-ECF222) ¶¶ 519-20). Defendants similarly argue that at his deposition, Stark "rejected the suggestion that 'random' is limited to 'nondeterministic.'" Docket No. 1103 at 10.

During his deposition, Stark and Defendants' counsel had the following colloquy:

> Q. So in claim construction the defendants argued that "random" meant nondeterministic; right?
>
> A. Right. Right.
>
> Q. And the Court didn't agree with the defendants' construction; right?
>
> A. I'm not sure I would characterize it that way.
>
> Q. How would you characterize it?
>
> A. I -- the way I understood the Court's opinion was that 'nondeterministic' wasn't more helpful than "random" in terms of the term.
>
> Q. Okay. So -- so what definition did you use for "random" in your report?
>
> A. Plain and ordinary meaning.
>
> Q. And what's the plain and ordinary meaning of "random"?
>
> A. Something that has some chance involved.

[18] Plaintiff specifically requests exclusion of paragraphs 252, 254, and 494-528 of the Stark Report. Docket No. 998 at 8. Plaintiff does not seek exclusion of Blanksby's opinions relating to this limitation. *Id.* 8 n.4.

Q. And does that mean that it has to be nondeterministic?

[objection omitted]

A. I think "random" and "nondeterministic" are, kind of, equivalent in terms for the same thing.

So, I mean, you could use the word "nondeterministic," but I don't think it conveys any better meaning than "random"; and probably for ordinary people, they would understand more what random means than "nondeterministic."

Q. So in forming your noninfringement opinions on the "random" limitation, you were essentially treating the term "random" as meaning nondeterministic; right?

[objection omitted]

A. No, I was -- I was treating the term "random" to mean random.

Q. And in your view "random" means nondeterministic; right?

A. Well, that's one interpretation that you could apply to "random." If it's not deterministic, that means there's some randomness in it. But I think the -- as I said earlier, the Court basically said that the word "random" is most likely better understood by a person than "nondeterministic." And my understanding -- I -- I would agree with that; that "random" is a better word to use for an ordinary person, than "nondeterministic."

Q. Can something that's random be deterministic?

A. No, I --

[objection omitted]

-- think if it's random it can't be deterministic.

Q. Okay. So in your view "random" cannot mean deterministic. It must mean nondeterministic.

[objection omitted]

A. I think "random" means that there's some – some chance, some unstructruedness associated with something, something that can't be predicted.

That's, kind of, how "random" should be interpreted.

You can't predict something from another thing if it's random.

Docket No. 998-3 at 105:12-108:4. Stark's testimony suggests that the claim construction order

simply found that "random" was a "better word" than "nondeterministic." In other words, Stark testifies that the claim construction order did not necessarily reject Defendants' claim construction proposal. This interpretation of the claim construction order is not supported by the record. *See, e.g.*, Docket No. 213 at 24 ("A holistic review of the claim language and the specification indicates that Defendants' proposed construction runs contrary to the intrinsic evidence."). Stark otherwise testifies that "if it's random it can't be deterministic." *See supra*. Stark also testifies that "random" and "nondeterministic" can be considered "equivalent" terms.

Plaintiff argues, without citation, that "[i]f you can't predict something from another thing, then it is non-deterministic." Docket No. 1174 at 5. It appears that Plaintiff's position, inversely, is that it is possible to predict something from another thing, but still have it be random.

More context is required to understand the parties' dispute and its impact on dispositive issues in the case. The Court expects the parties to explain their interpretations of the plain and ordinary meaning of "random" consistent with the claim construction order (and, in comparison, their interpretations of both "nondeterministic" and "not deterministic") so that the Court can determine whether those interpretations actually differ or whether the parties instead have a factual dispute rooted in the application of the claims to the accused products.

4. "Repeat . . . Irregularly" (all asserted claims)

The asserted claims require irregular repetition of information bits.[19] For instance, Claim 15 of the '710 Patent states, *inter alia*, "a first coder having an input configured to receive a stream of bits, said first coder operative to repeat said stream of bits irregularly and scramble the repeated bits."[20] Plaintiff argues that Defendants' experts provide expert opinions that rely on an improperly narrow interpretation of this claim language.[21]

[redacted] *Compare* Docket No. 998 at 9 *with* Docket No. 1103 at 13. [redacted]

[19] The asserted claims of the '710 and '032 Patents include an "irregular" limitation. The asserted claims of the '781 Patent require that bits appear in a "variable number of subsets," supporting a requirement for irregular repetition of bits. *See* Docket No. 849 at 22.

[20] Claim 15 of the '710 Patent is not itself an asserted claim, but asserted Claims 20, 22, and 23 depend from Claim 15.

[21] Plaintiff specifically requests that Defendants' expert opinions in paragraphs 410-413, 420-425, 430-431, and 436 of the Stark Report and paragraph 109 of the Blanksby Report be excluded. *See* Docket No. 998 at 10.

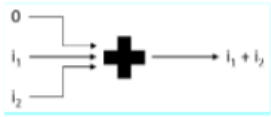
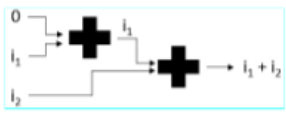
[redacted] *See, e.g.*, Docket No. 1174 at 5-6 [redacted] Docket No. 1103 at 13 [redacted] (Dkt. 213 at 9), [redacted].”). Because, according to Defendants, the step of repeating bits itself does not lead to irregular repetition (this only occurs after the puncturing step), the claim language is not satisfied. *Id.*; *see also id.* at 12.

The parties have presented a factual dispute regarding whether the accused products infringe the “repeat . . . irregularly” limitations of the asserted claims. Whether to characterize the accused products’ process as a single overall repetition “implementation” step or separate repetition and puncturing steps will depend on how a person of ordinary skill in the art would apply the claim language to the accused products. Plaintiff’s arguments relating to Defendants’ experts’ application of the term “repeat . . . irregularly” are rejected.

5. “Sums” (’781 Patent, all asserted claims)

During claim construction, the parties agreed that “sums of bits in subsets of information bits” (and variations thereof) should be construed as “the result(s) of adding together two or more information bits from a subset of information bits.” Dkt. 125 at 1-2. In essence, the parties now dispute whether summing bits by “accumulation” satisfies the parties’ agreed construction. Plaintiff characterizes the parties’ dispute in its opening brief:

> As shown in the table below, according to Defendants’ experts, summing 0+i1+i2 to yield the result i1+i2 in a single operation would be a sum of subsets of information bits, but summing 0+i1 to yield the result i1 and then summing i1+12 to yield i1+i2 [*i.e.*, “accumulation”] would not be a sum of subsets of information bits[:]

Admittedly a Sum of Information Bits	Allegedly Not a Sum of Information Bits
	

Docket No. 998 at 13.

Plaintiff argues that Defendants’ experts have taken an improperly narrow view of the term

"sum."[22] Plaintiff argues that "accumulation is a form of summation," and thus the example in the chart on the right should be covered by the claim term "sums of bits." Among other arguments, Plaintiff also argues that Defendants' experts have themselves admitted that "the claimed 'sums' cover the result of accumulation." *Id.* at 15; *see also id.* at 16 ("Both experts subsequently tried to retract their admissions by submitting errata, but this should not detract from their prior admissions."). Defendants argue that the '781 Patent claims use both the terms "accumulation" and "sums," supporting a presumption that the two terms have different meanings. Docket No. 1103 at 14. Defendants note that in the *Hughes* case, Judge Pfaelzer found, in denying Plaintiff's motion for summary judgment of infringement, that adding a parity bit and an information bit in a similar recursive fashion does not satisfy the claim language "sums of bits." *Id.* at 15.

In her summary judgment order, Judge Pfaelzer specifically stated:

> [t]he accumulator never adds together, for example, i1 and i2. Instead, the accumulator sums i1 and p0 to generate p1. The accumulator then sums p1 and i2. But p1 is not an "information bit from the subset of information bits." Instead, p1 is a newly created bit that does not appear in the original subset of information bits (i1, i2, and i3). Given these facts, the procedure performed by DVB-S2 technology does not "[accumulate] mod-2 or exclusive-OR sums of bits in subsets of the information bits."

California Inst. of Tech. v. Hughes Commc'ns Inc., LACV13-07245-MRP-(JEMx), Docket No. 370 (C.D. Cal. May 5, 2015).[23] Plaintiff argues that Judge Pfaelzer's interpretation of the "sums" limitation is "non-binding" and "does not compel a different outcome" because she was addressing whether products not at issue in this case infringe the asserted patents. Docket No. 1174 at 7 n.8. Plaintiff alternatively argues, "to the extent that opinion addresses claim construction, it is contrary to the plain meaning of sums, the specification, and Defendants' experts' sworn statements." *Id.*

Plaintiff agreed to the same construction of the phrase "sums of bits in subsets of information bits" in this case that the parties in the *Hughes* case had agreed to, despite the fact that, approximately two years earlier, Judge Pfaelzer had effectively interpreted the "sums of bits" term (and the parties' same agreed construction for that term) in her summary judgment order. Having reviewed the parties' agreed construction, which requires "adding ***together*** two or more ***information*** bits," the Court agrees with Judge Pfaelzer that adding an outputted bit and an

[22] Plaintiff asks that paragraphs 653-670 and 672-699 of the Stark Report and paragraphs 212-234 of the Blanksby Report be excluded. Docket No. 998 at 16.

[23] Judge Pfaelzer's summary judgment order is also available at Docket No. 127-7 in this case.

information bit would not satisfy this construction.

The Court has also reviewed Plaintiff's citations to the intrinsic and extrinsic record and is not persuaded that they warrant a different outcome. Plaintiff's request to exclude Defendants' experts' opinions related to the "sums" claim terms is rejected.

6. "Stream" ('710 Patent, all asserted claims; '032 Patent, Claim 3)

The parties dispute whether a "stream" of bits can be made up of "blocks" of bits. Plaintiff argues that Defendants' experts take an improperly narrow view of the scope of the term "stream" because they treat "streams of bits" and "blocks" of data as mutually exclusive.[24] Docket No. 1174 at 7. Plaintiff argues, "[t]here is no support whatsoever for this false dichotomy in the intrinsic or extrinsic evidence." *Id.* Plaintiff cites to portions of the patent specification and argues that it discloses receiving a "stream of bits" "partitioned into blocks of fixed size." *Id.* (citing '710 Patent at 2:35-38). Defendants argue that language in the claims and statements that Plaintiff made in IPR proceedings "demonstrate that 'streams of bits' are different from 'blocks.'" Docket No. 1103. Defendants, however, do not directly explain why a person of ordinary skill in the art would find that a stream of bits - as that phrase is used in the asserted patents - cannot include bits that are streamed as part of a collection of data blocks.

The Court agrees with Plaintiff that to the extent Defendants' experts have submitted opinions relying on an interpretation of "stream of bits" that wholly excludes bits streamed in the form of blocks, Defendants' experts' opinions would be taking a narrow view of the term "stream of bits" that is not consistent with its plain and ordinary meaning. As Plaintiff observes, in describing Figure 2, the '710 Patent states:

> FIG. 2 illustrates a coder 200 according to an embodiment. The coder 200 may include an outer coder 202, an interleaver 204, and inner coder 206. The coder may be used to ***format blocks of data for transmission***, introducing redundancy ***into the stream of data*** to protect the data from loss due to transmission errors. The encoded data may then be decoded at a destination in linear time at rates that may approach the channel capacity.

'710 Patent at 2:33-40. Defendants have not explained how their position would be consistent with this passage of the specification, even though Plaintiff identified it in its opening brief. *See, e.g.*, Docket No. 998 at 16-17. The portions of Defendants' experts' opinions relying on a

[24] Plaintiff specifically requests that the Court strike paragraphs 579-593 and 596-598 of the Stark Report and paragraphs 182-187 of the Blanksby Report. Docket No. 998 at 17.

narrowed interpretation of this claim term would thus be excluded.

7. "Tanner Graph" ('032 Patent, Claims 11, 17, and 18)

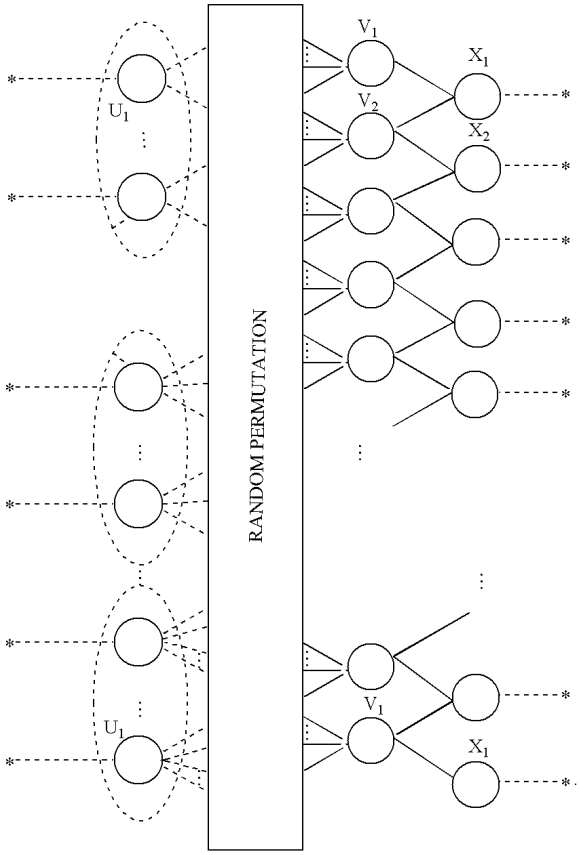
The Court construed the term "Tanner Graph" as "a graph representing an IRA code as a set of parity checks where every message bit is repeated, at least two different subsets of message bits are repeated a different number of times, and check nodes, randomly connected to the repeated message bits, enforce constraints that determine the parity bits." Docket No. 213 at 32. Both parties' proposed construction had included this language, and Defendants' proposed construction also included additional language. The Court found that "[t]he part of the proposed constructions over which the parties agree . . . sufficiently describes the edges that connect check nodes with parity nodes, especially in light of the embodiment and related description provided in the specification, and accurately conveys the scope of the claimed invention." *Id.* at 17.

Plaintiff argues that Defendants' experts have taken an improperly narrow view of the claim term, opining that "claims 11, 17, and 18 of the '032 Patent literally require an accused device to have 'check nodes.'"[25] Docket No. 1174 at 8. Plaintiff argues that the claims simply require an encoder configured "in accordance with" a Tanner graph, not that it physically include a Tanner graph. *Id.* Defendants argue that Plaintiff's reliance on the phrase "in accordance with" in the claims would "vitiate" the Tanner Graph claim requirement altogether. Docket No. 1103 at 11. Defendants focus on the claims' requirement of an encoder "configured to" encode. *Id.* ("In construing the Tanner graph's requirements, the Court defined how an 'encoder' must be 'configured' in order to practice these claims - including that it must be 'configured to' use 'check nodes [that] enforce constraints that determine the parity bits.'").

Claim 11 of the '032 Patent states:

> 11. A device comprising:
> an encoder configured to receive a collection of message bits and encode the message bits to generate a collection of parity bits in accordance with the following Tanner graph:

[25] Plaintiff requests that paragraphs 614-622 and 624 of the Stark Report and paragraphs 196-204 of the Blanksby Report be excluded. Docket No. 998 at 18.

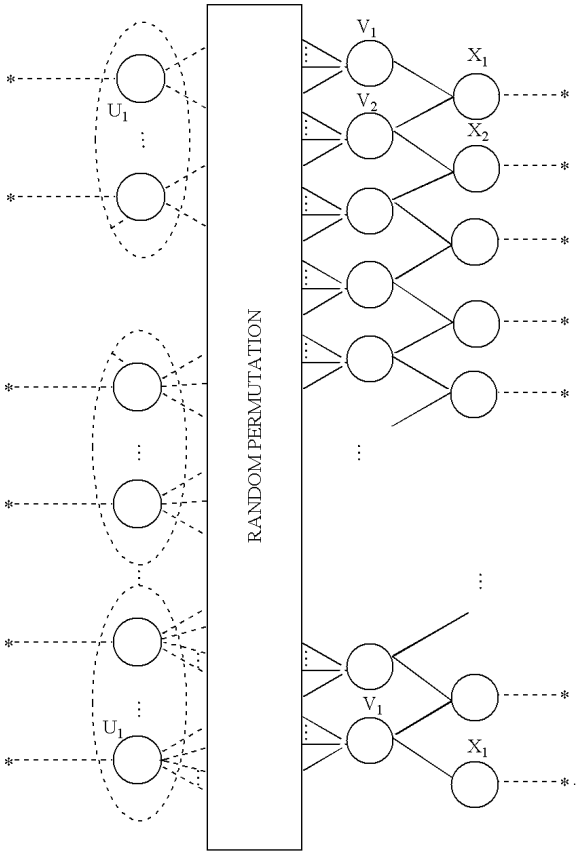


As construed during claim construction, Claim 11 effectively reads:

> 11. A device comprising:
>
> an encoder configured to receive a collection of message bits and encode the message bits to generate a collection of parity bits in accordance with [a graph representing an IRA code as a set of parity checks where every message bit is repeated, at least two different subsets of message bits are repeated a different number of times, and check nodes, randomly connected to the repeated message bits, enforce constraints that determine the parity bits.]

Claim 18 of the ’032 Patent states:

> 18. A device comprising:
>
> a message passing decoder configured to decode a received data stream that includes a collection of parity bits, the message passing decoder comprising two or more check/variable nodes operating in parallel to receive messages from neighboring check/variable nodes and send updated messages to the neighboring variable/check nodes, wherein the message passing decoder is configured to decode the received data stream that has been encoded in accordance with the following Tanner graph:



As construed during claim construction, Claim 18 effectively reads:

> 18. A device comprising:
>
> a message passing decoder configured to decode a received data stream that includes a collection of parity bits, the message passing decoder comprising two or more check/variable nodes operating in parallel to receive messages from neighboring check/variable nodes and send updated messages to the neighboring variable/check nodes, wherein the message passing decoder is configured to decode the received data stream that has been encoded in accordance with [a graph representing an IRA code as a set of parity checks where every message bit is repeated, at least two different subsets of message bits are repeated a different number of times, and check nodes, randomly connected to the repeated message bits, enforce constraints that determine the parity bits.]

Plaintiff has not shown that Defendants' experts' application of the claim term "Tanner Graph," based on the position that an accused encoder must employ check nodes in order to "enforce constraints that determine the parity bits," is inconsistent with how that term was construed by the Court and how it is used in the context of the claim language, particularly when considering Claim

18.[26] Plaintiff's argument is thus rejected.

8. "Scrambled" / "Permutation" ('710 Patent, all asserted claims; '032 Patent, Claims 11, 17, and 18)

Plaintiff argues that Defendants' experts rely on an impermissibly narrow meaning of the claim terms "scrambled" and "permutation" for separate reasons with respect to the '710 Patent asserted claims and '032 Patent asserted claims.[27] *See* Docket No. 1174 at 8-9. Plaintiff characterizes the issues in dispute as "(1) whether claims 11, 17, and 18 of the '032 patent require a two-step process of irregular repetition followed by scrambling; and (2) whether claim 15 of the '710 patent requires that same two-step process." *Id.* Plaintiff argues that repetition and scrambling can occur simultaneously, while Defendants argue that they must occur serially. *Id.*

The parties appear to agree that although Claims 11, 17, and 18 of the '032 Patent do not use the words "scrambled" or "permutation," irregular repetition and permutation are depicted in the claimed Tanner Graph. The parties' dispute relates to whether, in reading a Tanner Graph, "events" like repeating bits and scrambling bits, which admittedly occur in different places in the visual Tanner Graph representation, must also occur at different times or in a particular sequence. The parties' arguments support the conclusion that in the context of these claims, the parties have presented factual disputes about the application of the asserted claims to the accused products, including factual disputes that may be similar to those for the term "repeat . . . irregularly."

Regarding Claim 15 of the '710 Patent,[28] the parties dispute whether the particular language of the claim supports the conclusion that repeating and scrambling are or are not performed simultaneously. Claim 15 states:

> 15. A coder comprising:
> a first coder having an input configured to receive a stream of bits, said first coder operative to repeat said stream of bits irregularly and

[26] The parties have not requested, and the Court does not provide an opinion regarding, whether Plaintiff's expert applies the claim term "Tanner Graph" to the accused products consistent with how it is used in the asserted claims of the '032 Patent. There is too little information in the parties' papers to make such a determination. Although Plaintiff challenges Defendants' experts' application of the claim language and generally states, "[b]its can be encoded 'in accordance with' the Tanner graph even if an encoder does not include the specific circuitry shown in the graph," (Docket No. 1174 at 8) Plaintiff does not fully explain its position or its expert's position regarding this term and, for instance, how it and the requirement of "enforc[ing] constraints that determine the parity bits" can be satisfied by an accused product.

[27] Plaintiff requests that paragraphs 453-479 of the Stark Report and paragraphs 118 and 124-149 of the Blanksby Report be excluded. Docket No. 998 at 20.

[28] All asserted claims of the '710 Patent depend from Claim 15 of the '710 Patent.

scramble the repeated bits; and
a second coder operative to further encode bits output from the first coder at a rate within 10% of one.

Defendants emphasize that because Claim 15 refers to "said first coder operative to repeat said stream of bits irregularly and scramble the ***repeated*** bits," it requires that repeating the bits occur before scrambling the bits. Docket No. 1103 at 16-17 (citing *Tuna Processors, Inc. v. Hawaii Int'l Seafood, Inc.*, 327 F. App'x 204 (Fed. Cir. 2009)). Plaintiff argues that the '710 Patent specification does not support Defendants' interpretation, and moreover that the parties have a grammar dispute. Docket No. 1174 at 9-10. Plaintiff states, "[t]he parties dispute whether 'repeated bits' refers to 'bits' that ***are*** 'repeated' or 'bits' that ***were*** 'repeated.' The intrinsic evidence indicates that it is the former - the bits being 'repeated' are also 'scramble[d].'" *Id.* at 10 (emphasis in original) (citing '710 Patent at Fig. 4, Claim 20).

Plaintiff's interpretation of the phrase "said first coder operative to repeat said stream of bits irregularly and scramble the repeated bits" in Claim 15 is not persuasive insofar as Plaintiff would argue that bits can be repeated before they are scrambled. To the extent Plaintiff's position is simply that the two actions on a large scale can occur simultaneously, this position would likely present fact questions requiring a determination of whether, on a small scale level, repetition of a particular bit has taken place before it is scrambled. For similar reasons, to the extent Defendants would take the position that the large scale processes of repetition and scrambling must take place completely separately and sequentially, such a position is not necessarily supported by the claim language. Beyond these comments, there is not enough information about the nuances of the parties' disputes to make any further determinations about the parties' positions, and any determination about whether certain expert opinions should be excluded based on their interpretations of these claim terms would be deferred.

9. Conclusion

As stated herein, the Court would **DENY-IN-PART**, **GRANT-IN-PART**, and **DEFER-IN-PART** Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby (Docket No. 968). The Court would **DENY** the motion as to the terms "repeat" (but with the clarifications about the scope of the claim term provided herein), "repeat . . . irregularly," "sums" (but with the clarifications about the scope of the claim term provided herein), and "Tanner Graph." The Court would **GRANT** the motion as to the term "stream," **STRIKE** paragraphs 579-

593 and 596-598 of the Stark Report and paragraphs 182-187 of the Blanksby Report, and **EXCLUDE** any testimony regarding a meaning of the claim term "stream" that is inconsistent with this Order. The Court would **DEFER** a ruling on the motion as to the terms "low density generator matrix," "first coder," "random," and "scrambled"/"permutation."

D. Motion to Strike Certain Opinions of Frey and Stark

Plaintiff moves to exclude allegedly "new invalidity theories and supplemental non-infringement" theories disclosed in the certain expert reports of Dr. Wayne Stark and Dr. Brendan Frey.[29, 30] Docket No. 974.

Plaintiff argues that in their rebuttal expert reports, Stark and Frey for the first time disclosed new non-infringement and invalidity theories, respectively, "based on prior art Hamming Codes and SEC-DED codes."[31] Docket No. 1000 at 2. Plaintiff also argues that Defendants served a second supplemental report for Frey less than 24 hours before his December 2018 deposition "raising new § 112 written description invalidity theories and a new obviousness theory based on a source code file titled "RA.c." *Id.* Plaintiff notes that Defendants had included the RA.c reference as a relevant prior art reference in each of the first four iterations of their invalidity contentions, but removed it in their fifth iteration served May 31, 2018. Docket No. 1000 at 6.

Defendants argue that the challenged portions of Stark's and Frey's reports are proper rebuttal opinions to opinions raised by Plaintiff's experts. Docket No. 1102. Defendants also argue that the Stark and Frey opinions relating to Hamming Codes and SEC-DED[32] codes are used to "demonstrate how Dr. Shoemake and Caltech have misapplied the Court's construction of the term 'repeat' in a way that covers matrices that pre-date Caltech's alleged invention by decades." *Id.* at 10. Defendants alternatively argue that even if not proper rebuttal, Plaintiff is not prejudiced by the timing of the disclosure of these new opinions.

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[29] *See* Plaintiff's Motion to Strike Certain Opinions of Defendants Experts Brendan Frey and Wayne Stark, Docket No. 974 (public), Docket No. 1000 (sealed); Opposition, Docket No. 1059 (public), Docket No. 1102 (sealed); Reply, Docket No. 1141 (public), Docket No. 1175 (sealed).

[30] Plaintiff specifically requests that the Court "strike Paragraphs 246-72, 305, and 343 of Dr. Stark's Rebuttal Report, Paragraphs 18 and 589-843 of Dr. Frey's Supplemental Report, and the entirety of Dr. Frey's Second Supplemental Report." Docket No. 1000 at 3.

[31] Stark's rebuttal non-infringement report was served August 14, 2018 and Frey's rebuttal invalidity report was served October 12, 2018. *See* Docket No. 1000 at 4-5.

[32] Defendants refer to "SEC-DED" Codes as "Hsiao" Codes. *See, e.g.* Docket No. 1102 at 10.

1. Second Supplemental Frey Report

Defendants have failed to provide a basis for the timing of their disclosure of opinions in Frey's second supplemental report. They do not identify any late discovery as supporting the late disclosure of the opinions, nor do they identify any agreement with Plaintiff to serve a supplemental report shortly before Frey's deposition.

Particularly regarding Frey's opinions for the "RA.c" source code file, the fact that Defendants listed the RA.c reference in four iterations of invalidity contentions before dropping it from their fifth iteration supports the conclusion that Frey should not now be permitted to opine on it in a second supplemental expert report. Even if, as Defendants argue, Frey's opinions were properly limited to considering the RA.c reference as a rebuttal to Plaintiff's arguments regarding secondary considerations of non-obviousness, this record and the timing of Frey's disclosure of those opinions support exclusion. [33] As Defendants note, Plaintiff served its expert reports regarding secondary considerations of non-obviousness on August 14, 2018.[34] *See* Docket No. 1102 at 12. Yet, Frey did not disclose his RA.c opinion until a day before his deposition on December 3, 2018. These opinions will not be permitted.

Similar concerns exist for Frey's late-disclosed written description theory. As Plaintiff notes, its infringement theory relating to accumulators operating in parallel was disclosed in infringement contentions on January 17, 2018. Docket No. 1000 at 11. Indeed, Defendants argue that they responded to this position in their May 2018 non-infringement contentions. Docket No. 1102 at 6. Defendants do not explain, however, their failure to disclose an invalidity theory

[33] Frey's second supplemental expert report states, "Caltech's experts mistakenly suggest that if making RA codes irregular was obvious before the alleged invention someone would have done it . . . . Caltech's experts ignore that my colleague and co-author, the late David J.C. MacKay, did make RA codes irregular before the claimed invention of the asserted patent claims." Second Supplemental Report of Dr. Brendan Frey, Docket No. 974-10 ¶¶ 7, 8. Frey goes on to state that a comment in the RA.c file "explicitly teaches irregular repeat-accumulate codes." *Id.* at ¶ 11. Even if Defendants had timely disclosed such a theory as relating to secondary considerations of non-obviousness (Plaintiff presents evidence to support the conclusion that they did not timely disclose it (Docket No. 1175 at 3 (citing Apple's final response to an interrogatory relating to secondary considerations))), the possibility that Frey's opinions would lead to prejudice and jury confusion, effectively allowing Defendants to sweep in RA.c as another prior art invalidity reference, would be high.

[34] Plaintiff argues that its theory regarding secondary considerations was disclosed as early as January 2017 (*see* Docket No. 1175 at 2 n.1) and in its infringement contentions "no later than January 2018" (*id.* at 2). Defendants essentially agree that they were on notice of Plaintiff's theory by October 2017, stating, "Caltech disclosed its contention that the 'failure of others' in the field to arrive at the claimed IRA codes tends to show that the asserted claims are non-obvious in supplemental interrogatory responses served on the last day of fact discovery, October 13, 2017." Docket No. 1102 at 7.

relating to the "second accumulator" concept until Frey's second supplemental expert report in December 2018, particularly when they served a rebuttal report for Frey in October 2018. Defendants' argument that Frey simply provides an "evidentiary example or complementary proof" is unpersuasive. Frey specifically sets forth an opinion for the first time that the asserted claims are invalid under § 112 ¶ 1 if the claim language is applied as Plaintiff and its experts propose. These portions Frey's second supplemental expert report must be excluded as untimely, because there is not a sufficient basis to support their untimeliness.

2. Frey/Stark Opinions Regarding Hamming Codes and SEC-DED Codes

Defendants argue that the challenged opinions in the Frey and Stark reports relating to Hamming Codes and SEC-DED Codes are used to:

> [i]llustrate how Caltech and Dr. Shoemake have stretched the claim term "repeat" beyond its plain and ordinary meaning to argue infringement. Apple and Broadcom timely disclosed that 'the number of ones in each column' of a parity check matrix 'is not a 'repeat'' in their May 17, 2018 Supplemental Non-Infringement Contentions. Dr. Stark and Dr. Frey use Hamming and Hsiao codes as examples to illustrate how matrices in codes that Dr. Shoemake admits are prior art meet the 'repeat' limitation under Caltech's improperly broad application of that term.

Docket No. 1102 at 1.

In the claim construction order, the Court stated:

> [t]he Asserted Patents provision for creation of parity bits by "choos[ing]" other bits, thereby repeatedly selecting the bits for use without necessarily storing them at a specific location in computer memory . . . . The Asserted Patents also set forth such an implementation in the LDGM coder, which performs the repeat of the message bits using matrix multiplication, the output of which is then fed to an inner coder, an accumulator that performs additional operations on the transitory (repeated and interleaved) bits to produce the final IRA codes. *See, e.g.*, '710 Patent at 3:51-57.

Docket No. 213 at 9-10. More information is required at the hearing regarding whether the experts' opinions are consistent with the claim construction order, as well as the Court's comments *supra* in the context of Plaintiff's motion to exclude improper claim construction opinions. To the extent the experts, through their arguments, are advocating an interpretation of the claims that is inconsistent with the claim construction order, exclusion would be appropriate.

Even if improper claim interpretation is not an issue, the Court agrees Frey's opinions relating to Hamming Code and SEC-DED Code cause concern because they would effectively

allow Frey to "backdoor" invalidity arguments regarding prior art references that were not disclosed in invalidity contentions or Frey's opening expert report.[35] Indeed, sections of Frey's supplemental report are titled "Hamming Codes Invalidate the Asserted Claims As Applied By Caltech And Dr. Shoemake" and "The Hsiao (SEC-DED) Code Invalidates the Asserted Claims as Applied By Caltech and Dr. Shoemake." *See* Supplemental Expert Report of Dr. Brendan Frey, Docket No. 974-9 at v. As part of narrowing the scope of this case, Defendants were limited to identifying seven prior art invalidity "grounds" per patent, and Hamming Codes / SEC-DED Code grounds were not on that earlier list. Frey's extensive invalidity opinions (spanning hundreds of paragraphs of his report) seem to provide more than merely an "evidentiary example or complementary proof." The parties may address this issue at the hearing as well.[36]

Claim interpretation issues aside, certain of Stark's rebuttal non-infringement report do not appear to suffer from the same additional concerns as Frey's supplemental report. Indeed, Plaintiff does not challenge every paragraph of Stark's rebuttal report criticizing Shoemake's interpterion of the claim term "repeat." Some of Stark's rebuttal opinions could well be categorized as "evidentiary examples" highlighting the difference between Shoemake's and Stark's understanding of the plain and ordinary meaning of the claims. *See, e.g.* Rebuttal Expert Report of Dr. Wayne Stark, Docket No. 1000-5 ¶ 237. But Stark crosses the line when he begins comparing the claim language at issue to prior art references and explicitly states for instance, that under Shoemake's logic, the claims "embrace the prior art Hamming code." *See, e.g.*, *id.* ¶ 254. Stark is an expert offering opinions related to non-infringement, not invalidity. At the hearing, the

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[35] Defendants make the comment that "[b]ecause Dr. Frey's opinions primarily relate to an issue on which Apple and Broadcom bear the burden of proof (*i.e.*, invalidity), his response to Dr. Shoemake's overly broad interpretation of the claims was appropriately addressed in a supplemental expert report." Docket No. 1102 at 11 n.5. This comment even further begs the question why Defendants, knowing they bore the burden of proof on invalidity and being on notice of Plaintiff's theories by virtue of contentions, did not include such opinions in Frey's opening expert report, particularly when they argue that they *did* disclose an argument that "a parity check matrix is ***not*** a repeat within the meaning of the claims," albeit in May 2018 non-infringement contentions. *See id.* at 9 (emphasis in original).

[36] The Court notes that a litigant is not precluded "from arguing that if a claim term must be broadly interpreted to read on an accused device, then this same broad construction will read on the prior art." *01 Communique Lab., Inc. v. Citrix Sys., Inc.*, 889 F.3d 735, 742 (Fed. Cir. 2018). The problem here is that, even though Defendants were long on notice of Plaintiff's infringement contentions and thus Plaintiff's broad interpretations of the scope of the claims, Defendants did not allocate any of their prior art invalidity theories to alternative theories relying on Plaintiff's claim interpretations until long after invalidity contentions and even opening expert reports were due. Thus, Defendants effectively deprived Plaintiff of the notice it should have been afforded to have time to respond to these alternative theories. The Court expects the parties to address this point at the hearing as well.

Court would like the parties to provide more information regarding whether all of Plaintiff's identified paragraphs in the Stark Rebuttal Report, *i.e.* ¶¶ 246-72, 305, and 343, suffer from these concerns or whether certain of them need not be excluded on these bases. *See, e.g. id.* ¶ 255 (stating, *inter alia*, "[t]he appearance of a code's Tanner graph is also not indicative of whether that code is an IRA code . . . " without necessarily seeming to compare the claim language to particular prior art references.).

3. Conclusion

Plaintiff's Motion to Strike Certain Opinions of Defendants' Experts Brendan Frey and Wayne Stark (Docket No. 974) would be **GRANTED-IN-PART** and **DEFERRED-IN-PART** pending discussion at the hearing. Specifically, the Court would **GRANT** Plaintiff's motion to the extent it seeks exclusion of the opinions disclosed in Frey's second supplemental expert report. The Court would **DEFER RULING** on Plaintiff's motion with respect to Frey's supplemental expert report and Stark's rebuttal expert report for the reasons stated herein.

E. Motion to Strike Late-Disclosed Non-Infringing Alternative

Plaintiff moves to exclude the testimony of Defendants' experts relating to a non-infringing alternative theory as not timely disclosed.[37, 38] Docket No. 971.

On the deadline for the parties to serve rebuttal expert reports, Defendants for the first time served a Disclosure and Declaration for Dr. Andrew Blanksby. Docket No. 1101 at 5. Blanksby is a long-time Broadcom employee. Thus, Defendants attempted to invoke Rule 26(a)(2)(C) when disclosing more limited opinions for him. The August 2018 Disclosure included the statement that Blanksby "expect[s] to testify about the design, development, and operation of the Broadcom accused products, and a Direct Encoder that [he] designed." Docket No. 699-2 ¶ 12. It further stated, "I expect to testify that the Broadcom accused products and the Direct Encoder that I designed do not implement several elements of the claims of the patents-in-suit." *Id.* ¶ 14. Plaintiff argues, and Defendants do not dispute, that the Blanksby Disclosure was the first instance where the Direct Encoder was disclosed as part of a non-infringing alternative theory. On the same day,

[37] *See* Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative, Docket No. 971 (public), Docket No. 996 (sealed); Opposition, Docket No. 1052 (public), Docket No. 1101 (sealed); Reply, Docket No. 1144 (public), Docket No. 1176 (sealed).

[38] Unlike its other motions to exclude/strike, for this motion, Plaintiff does not provide a listing of the specific paragraphs of Defendants' expert reports that it seeks to have excluded.

Defendants also served rebuttal expert reports for Dr. Wayne Stark and Vincent Thomas that referred to the Direct Encoder and presented opinions about it that, according to Stark and Thomas, are based on undocumented discussions with Blanksby.[39]

Soon after Defendants served the Blanksby Disclosure, Plaintiff moved to strike it in full, arguing that it failed to meet the applicable requirements of Rule 26(a)(2). Docket No. 699. In its motion, Plaintiff referred to the Direct Encoder and speculated that it was created for this litigation. *Id.* at 2 ("For instance, he references: . . . a previously-undisclosed "Direct Encoder" he developed (also apparently for this litigation)."); 12-13 ("Dr. Blanksby's opinions regarding his 'Direct Encoder' . . . are also, by all indications, based on work Dr. Blanksby performed solely for purposes of this litigation."). Defendants did not rebut these suppositions in their opposition brief. *See* Docket No. 720 at 12 (referring to Direct Encoder but not rebutting Plaintiff's assertions about its origins).

On October 22, 2018, the Court issued an order striking the Blanksby Disclosure, but permitting Blanksby to submit a more fulsome accounting of his expert opinions. Docket No. 746 at 3. The order further stated that "Defendants must . . . produce all materials related to and/or underlying Blanksby's expert opinions" within seven days. *Id.*

Blanksby served an amended disclosure on November 9, 2018. Docket No. 1101 at 6. Beyond the source code for the Direct Encoder,[40] Defendants do not dispute that they have not produced any other documents relating to the Direct Encoder. Plaintiff did not move to compel the production of additional documents relating to the Direct Encoder.

During his December 2018 expert deposition, Blanksby was asked questions about the Direct Encoder. *See generally* Excerpts of December 14, 2018 Blanksby Deposition Transcript, Docket No. 1101-2. In response to questions from Plaintiff's counsel, Blanksby testified that: (1) he developed the Direct Encoder (*id.* at 280:7-8); (2) he [redacted] (*id.* at 280:9-14); (3) [redacted] (*id.* at 281:15-22); and (4) [redacted] (*id.* at 281:24-282:3). He

[39] Although Plaintiff makes some passing comments about the sufficiency of Defendants' experts' opinions (Docket No. 996 at 5 (referring to Stark's and Thomas's opinions related to the Direct Encoder as "incomplete")), because Plaintiff brings this motion as a Rule 37 motion, these comments are viewed through the lens of Rule 37(c), not *Daubert* or otherwise as a motion *in limine*.

[40] Defendants produced the source code for the Direct Encoder before the Court issued its October 2018 order.

testified [redacted] *Id.* at 281:6-13.

Both before the Court issued its October 2018 order and after Blanksby's deposition, Plaintiff's expert, Shoemake, served expert reports with opinions relating to the Direct Encoder. *See* Docket No. 1103 at 5-6.

Plaintiff's arguments to support its current motion run the gambit. Plaintiff identifies evidence to support an argument that development of the Direct Encoder happened long before June 2018. Docket No. 1176 at 1. Plaintiff argues Defendants have "concoct[ed]" a "carefully crafted" story regarding the timing of development on the one hand, but Plaintiff argues on the other hand that Defendants' claim that development of the Direct Encoder was not motivated by this litigation is "not plausible." Docket No. 1176 at 1, 3, 3-4 n.2. Plaintiff argues that it has been "wholly deprived of fact discovery" because of the late timing of disclosure of Defendants' Direct Encoder non-infringing alternative theory and thus Plaintiff could not test Defendants' experts' assertions about the Direct Encoder. *Id.* at 1-2. Plaintiff also argues that Defendants' experts were unable to answer "basic technical questions about the Direct Encoder," further compromising Plaintiff's ability to take expert discovery. *Id.* at 7.

The Court declines to make a factual determination at this time about the veracity of statements that the Direct Encoder was first developed in June 2018. The Court also declines to make a factual determination at this time about the motivations underlying development of the Direct Encoder. Plaintiff had a full opportunity in December 2018 to depose Blanksby - who testified under oath - regarding the Direct Encoder, including his development of it and his opinions relating to it. Plaintiff also had a full opportunity to explore the opinions of Defendants' other experts (and their purported shortcomings) during their depositions. Indeed, Plaintiff's expert prepared and served his own competing opinions relating to the Direct Encoder. The Court finds the October 2018 timing of Defendants' disclosure of the Direct Encoder non-infringing alternative theory effectively harmless given these efforts. To the extent Defendants did not produce the answers to Plaintiff's questions or the amount of discovery that Plaintiff would have wished, Defendants will similarly be precluded from relying on any of that allegedly missing information at trial.

Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative (Docket No. 971) would be **DENIED**.

F. Motion to Exclude Infringement Opinions of Tanner

Defendants move to exclude the opinions of Dr. Michael Tanner.[41] Docket No. 964. As Plaintiff explains, "Dr. Tanner's renowned achievement is the development of the Tanner graph." Docket No. 1094 at 3.

In his expert report, Tanner provides various opinions, including opinions related to: (1) "the general concept of Tanner graphs and how they are used to graphically represent sparse parity-check matrix codes"; (2) an explanation of how the "claimed Tanner graphs" in the asserted claims of the '032 Patent relate to IRA encoders, and (3) "the relationship between the claimed Tanner graphs and the 802.11 IRA-LDPC codes." Docket No. 1094 at 3.

Defendants appear to be challenging all of Tanner's report,[42] but they focus their arguments on concern with the third category of Tanner's opinions. Docket No. 1182. Defendants argue that Tanner's opinions about the "relationship" between the "*claimed* Tanner Graphs" and the 802.11 standards is a stand-in for an infringement analysis between the claims and Defendants' accused products. *Id.* at 1-4. Defendants argue that such an analysis is not only improper in that it substitutes analysis of the standard for the analysis of the accused products, but is also likely to confuse or mislead the jury. *Id.* at 4-5. Plaintiff, for its part, argues that Tanner was not required to set forth opinions on the ultimate issue of infringement, but that his opinions comparing the claimed Tanner Graphs to the 802.11 standards are "relevant in educating the jury on Tanner graphs and how the 802.11 IRA-LDPC codes are in accordance with the claimed Tanner graphs." Docket No. 1094 at 8-9.

Plaintiff does not adequately explain what admissible purpose is served by Tanner's opinions comparing the claimed Tanner graphs to the codes contemplated by the 802.11 standards. The Court agrees with Defendants that in drawing this comparison, Tanner appears to be undertaking an analysis similar to an infringement analysis, but without the accused products. Doing so holds a high likelihood of confusing or misleading the jury. For instance, if the jury was persuaded by Tanner's opinions comparing the Tanner graphs to the 802.11 standards, and another

[41] *See* Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner, Docket No. 964 (public), Docket No. 1007 (sealed); Opposition, Docket No. 1057 (public), Docket No. 1094 (sealed); Reply, Docket No. 1133 (public), Docket No. 1182 (sealed).

[42] The title of Defendants' motion suggests that it relates only to some of Tanner's opinions. However, the conclusion of Defendants' opening brief appears to request exclusion of Tanner's entire expert report. *See, e.g.*, Docket No. 1007 at 8.

expert simply opined that the accused products also satisfy the 802.11 standards, the jury might think it appropriate to find the accused products infringe the Tanner graph limitations of the asserted '032 Patent claims by simple, and improper, syllogism. Allowing the jury to connect the dots in such a way would be particularly unsupported because in providing his opinions, Tanner simply states he would "expect" encoders built according to the 802.11 standards to be "in accordance with" the claimed Tanner graphs. As Defendants observe, this open-ended opinion is speculative.

Because of the concerns with Tanner's opinions on this topic, permitting him to provide opinions to the jury on such issues would be improper under *Daubert*. Therefore, the Court would **GRANT-IN-PART** and **DENY-IN-PART** Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner. Docket No. 964. Paragraphs 2-3, 69-89 of the Tanner Report (*see* Docket No. 1094-1) would be **STRICKEN** to the extent they include opinions comparing the claimed Tanner graphs to the 802.11 standards. Defendants' motion would be otherwise **DENIED** as it relates to other portions of Tanner's testimony, as Defendants have not provided a sufficient basis for excluding it. Defendants do not dispute, for instance, that Tanner's opinions regarding and explaining the Tanner graphs generally would likely assist the jury.

G. Summary Judgment Motion Regarding Inequitable Conduct

Plaintiff moves for summary judgment of no inequitable conduct.[43] Docket No. 942.

1. Unpled Inequitable Conduct Theories

Defendants' operative Answer and Counterclaims specifically alleged that the patent applicant committed equitable conduct by failing to disclose Luby97, Luby98, and Richardson99 during prosecution of the asserted patents. *See* Docket No. 47 at Answer, Sixth Affirmative Defense; *id.* at Counterclaims, Count IX. Defendants have since identified some inequitable conduct theories that were not pled in their Answer and Counterclaims. Specifically, Defendants argue that they properly disclosed additional inequitable conduct theories relating to Frey and Pfister in a supplemental interrogatory response served on the last day of fact discovery. Docket No. 1104 at 9-10, 24. Defendants frame these new undisclosed prior art theories as relying on undisclosed "known or used" invalidity theories. *Id.*

[43] *See* Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial), Docket No. 942 (public), Docket No. 957 (sealed), *see also* Docket No. 994 (notice of errata); Opposition, Docket No. 1070 (public), Docket No. 1104 (sealed); Reply, Docket No. 1153 (public), Docket No. 1180 (sealed).

Inequitable conduct, however, is a claim for relief that is subject to a Rule 9(b) pleading standard. *Ferguson Beauregard/Logic Controls, Div. of Dover Resources, Inc. v. Mega Sys., LLC*, 350 F.3d 1327, 1344 (Fed. Cir. 2003) ("[I]nequitable conduct, while a broader concept than fraud, must be pled with particularity" under Rule 9(b)."). Unlike notice pleading, an inequitable conduct pleading must identify the "'who, what, when, where and how' of the alleged material misrepresentation, and offer 'sufficient underlying facts from which a court may reasonably infer that a party acted with the requisite state of mind.'" *Parallax Grp. Int'l LLC v. Incstores LLC*, No. SACV 16-00929 AG (DFMx), 2017 WL 3453299, at *3 (C.D. Cal. June 30, 2017) (quoting *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1327 (Fed. Cir. 2009)).

The Court finds that in the particular circumstances of this case, it was not appropriate for Defendants to bypass their pleading obligations under Rule 9(b) by incorporating new inequitable conduct theories into an interrogatory response served on the fact discovery deadline. In these circumstances, there was no opportunity for the parties to conduct additional fact discovery relating to Defendants' new theories.

Other district courts have similarly found inequitable conduct theories waived if not pled. Plaintiff cites *CSB-Sys. Int'l Inc. v. SAP Am., Inc.*, No. CIV.A. 10-2156, 2012 WL 1645582, at *6 (E.D. Pa. May 10, 2012), which itself similarly collected cases:

> As set forth above, "inequitable conduct, while a broader concept that fraud, must be ***pled*** with particularity." *Cent. Admixture Pharm. Servs, Inc. v. Adv. Cardiac Solutions, P.C.*, 482 F.3d 1347, 1356 (Fed. Cir. 2007) (emphasis added) (quoting *Ferguson Beauregard/Logic Controls, Inc. v. Mega Sys., LLC*, 350 F.3d 1327, 1344 (Fed. Cir. 2003)). Defendants' pleadings must "give notice to the other party of the facts on which the defense is premised." *Id.* at 1357. "Without such a pleading, a party may not raise, as an affirmative defense, inequitable conduct in a motion for summary judgment." *Lab. Skin Care, Inc. v. Ltd. Brands, Inc.*, No. Civ.A.06-601, 2009 WL 2524577, at *2 (D. Del. Aug. 17, 2009). Repeatedly, courts have declined to allow a defendant to assert a new theory of inequitable conduct if the answer and counterclaims asserted a different theory of inequitable conduct than that relied upon in summary judgment proceedings. *See, e.g., id.* at *3-4 (declining to consider new theory of inequitable conduct where defendant's answer "does not support the particular theory of inequitable conduct in Defendants' Motion for Summary Judgment"); *ChemFree Corp. v. J. Walter, Inc.*, No. Civ.A.04-3711, 2008 WL 3884365, at *2 (N.D. Ga. June 10, 2008) (finding that "Defendants may not now change their theories of inequitable conduct at the final stages of this litigation in an effort to avoid summary judgment. Therefore, the Court will only consider Defendants' original allegations of inequitable conduct as pleaded in their Amended

> Answer and Counterclaims"); *Inline Connection Corp. v. AOL Time Warner, Inc.*, 237 F.R.D. 361, 367-68 (D. Del. 2006) (finding that, even assuming defendants did not have all necessary information to plead new theory of inequitable conduct when filing Second Amended Answer, the defendants had an obligation to file a Third Amended Answer to include new theory of inequitable conduct as soon as they had that information; even though previous Answer alleged inequitable conduct, their failure to amend their Answer to include new theory precluded their reliance on that theory); *Heraeus Electro-Note Co. v. Midwest Instrument Co., Inc.*, No. Civ.A.06-355, 2006 WL 3004877, at *6 (E.D. Pa. Oct.18, 2006) (finding that the defendant's best mode theory of inequitable conduct, as pled, failed to satisfy Rule 9(b) because none of the assertions contained in the defendant's response to the plaintiff's motion to dismiss were pled in the amended counterclaims).

Id. (emphasis in original).

EMC Corp. v. Storage Tech. Corp., 921 F. Supp. 1261, 1263-64 (D. Del. 1996) presents another example and collection of cases:

> Only a handful of courts have addressed the issue of whether pleadings found to be inadequate under Rule 9(b) may be salvaged by future discovery. The Courts that have examined the issue have held that they cannot. *See, e.g., Nichols Motorcycle Supply, Inc. v. Dunlop Tire Corp.*, No. 93 C 5578, 1994 WL 113108, at *2-3 (N.D. Ill. March 30, 1994) (plaintiff cannot "indirectly amend its complaint to include its responses to interrogatories"); *see also id.*, at *3 (even if interrogatory recites all information, defendant is entitled to reassurance that response is entire basis for fraud claim); *National Union Fire Ins. Co. of Pittsburgh v. Continental Illinois Corp.*, 658 F.Supp. 775, 778 (N.D. Ill 1987) (not deciding issue but pointing out that "how discovery responses can cure threshold pleading defects is another unexplained mystery"). Other courts have held that where the allegations are pled with particularity, the parties may then rely upon interrogatories for specific details. *Union Mutual Life Ins. Co. v. Simon*, 22 F.R.D. 186, 187 (E.D. Pa. 1958) (where pleadings are particular, purpose of interrogatories is to elicit complete and exact details); *Scervini v. Miles Laboratories, Inc.*, 91 U.S.P.Q. 206, 207, 11 F.R.D. 542 (S.D.N.Y. 1951) (where pleadings fulfil particularity requirements, defendants can use interrogatories to obtain additional information). Thus, the Court concludes that EMC may not use its interrogatory responses to fulfill the particularity requirements of Rule 9(b). Accordingly, the Court concludes that Paragraph Seven of EMC's Counterclaim and Answer to STK's Third Counterclaim fails to meet the particularity requirement of Rule 9(b).

EMC Corp. v. Storage Tech. Corp., 921 F. Supp. 1261, 1263-64 (D. Del. 1996).

In the particular circumstances presented here, the Court agrees with these district courts and declines to permit Defendants to rely on an unpled inequitable conduct claim on the basis that

it was disclosed in written discovery. Defendants' Answer and Counterclaims govern in this case, and Defendants should have sought leave to amend their operative pleading consistent with Rule 9(b), to ensure that both the substance of Defendants' proposed new allegations and any procedural concerns relating to their timing could be considered. Moreover, the Court is not persuaded that Defendants, in their interrogatory responses, sufficiently disclosed an inequitable conduct theory relying on the underlying "known or used" invalidity theories they now raise. Although Defendants' supplemental interrogatory response generally referred to the presentations made of Pfister/Pfister Slides and Frey/Frey Slides at the Allerton Conference, the email and testimony Defendants now invoke to support such a theory, and the material information allegedly provided to support such a theory, were not sufficiently disclosed in Defendants' response. Defendants suggest that the timing of their supplemental interrogatory response was based on the late timing of two depositions during the fact discovery period. Defendants also blame Plaintiff for not raising an earlier challenge to the new theories disclosed in Defendants' supplemental response. These arguments are not persuasive. It is still Defendants' responsibility to ensure that the operative pleading governing their case aligns with the arguments and theories they seek to raise in this case. That is not a responsibility that changes based on the late timing of certain discovery or the opposing side's failure to raise the issue, particularly in the context of Rule 9(b) pleading obligations.

Because Defendants failed to take these steps, Defendants' unpled inequitable conduct theories are deemed waived and are not considered on their merits.

2. Pled Inequitable Conduct Theories

As noted, Defendants' operative Answer and Counterclaims allege inequitable conduct theories based on Plaintiff's failure to disclose Luby97, Luby98, and Richardson99 during prosecution of the asserted patents. *See* Docket No. 47.

Although Plaintiff does not dispute that these references were not disclosed to the Patent Office before the asserted patents issued, the Patent Office has had reason to consider at least two of them subsequently. Luby97 and Luby98 were identified as part of one or more obviousness combinations in challenges to some of the asserted claims during *inter partes* review proceedings. After considering the various obviousness combinations that included these references, the Patent Trial and Appeal Board found the challenged claims at issue not unpatentable over them. Plaintiff argues that on this basis, Defendants cannot show that Luby97, Luby98, or Richardson99 satisfy

the but-for materiality standard required to prove inequitable conduct.

Defendants argue that the exact prior art grounds they intend to present at trial were not considered by the PTAB. Defendants also emphasize the claims that were not subject to IPR: Claim 23 of the '710 Patent, Claims 3 and 17 of the '032 Patent, and Claim 9 of the '781 Patent. *See, e.g.* Docket No. 1104 at 23. Defendants argue that if the jury invalidates the claims at trial based on obviousness combinations that include these references, that would support a conclusion of but-for materiality for purposes of an inequitable conduct analysis.

"When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1291 (Fed. Cir. 2011). Importantly, "[i]n making this patentability determination, the court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction." *Id.* at 1291-92 (citing Manual of Patent Examining Procedure ("MPEP") §§ 706, 2111 (8th ed. Rev.8, July 2010)). The Federal Circuit in *Therasense* went on to state, "even if a district court does not invalidate a claim based on a deliberately withheld reference, the reference may be material if it would have blocked patent issuance under the PTO's different evidentiary standards." *Id.* at 1292 (citing MPEP §§ 706 (preponderance of the evidence), 2111 (broadest reasonable construction)).

In their opposition, Defendants mix in their position regarding their pled inequitable conduct theories with arguments relating to their unpled inequitable conduct theories. Indeed, Defendants appear to place much more emphasis on their Frey/Pfister "known or used" invalidity theories than they do emphasizing Luby97, Luby98, and Richardson99.

Defendants' Answer and Counterclaims allege that Luby97, Luby98, and Richardson99 were material to the patentability of the Asserted Patents because they "expressly teach the benefits of making regular codes irregular." Docket No. 47 at ¶ 67. During IPR, Defendants identified Luby97 and Luby98 for the same purpose. Namely, Defendants argued that a person of ordinary skill in the art would modify another prior art reference, Divsalar, to incorporate "irregularity" based on these two references. *See* Docket No. 1180 at 4. The PTAB rejected this argument. Importantly, in reviewing these asserted claims during IPR, the PTAB applied the broadest reasonable interpretation standard to determine the scope of the claims. This is the same claim construction standard *Therasense* states should be applied in considering whether an undisclosed reference is but-for material. Moreover, Defendants relied in Luby97 and Luby98 in the IPR

proceedings for the same concept of making codes irregular that they argue supports theses references' but-for materiality. On this record, the Court finds as a matter of law that Luby97 and Luby98 were not but-for material to the patentability of the asserted claims that were reviewed against these references during IPR.

As to Richardson99, the Answer and Counterclaims allege that Richardson99 "provides a similar disclosure" to Luby98. Docket No. 47 ¶ 65; *see also* Docket No. 944-4 at 30-31 (Apple's Supplemental Interrogatory Response and Objections to Plaintiff's Common Interrogatory No. 7). The Answer and Counterclaims highlight excerpts of Richardson99's disclosure referring to the benefits of irregular low-density parity check codes. *Id.* In their opposition, Defendants similarly state that Richardson99 was "building on [the] work" of Luby97 and Luby98 in its discussion of irregular low-density parity check codes. Docket No. 1104 at 5. Defendants do not provide an independent basis in their pleading or opposition as to how Richardson99 is arguably but-for material in some way that differs from Luby97 and Luby98. The fact that the PTAB considered and rejected obviousness combinations where Luby97 and Luby98 were offered for the same concept that Defendants also would offer Richardson99 similarly supports the conclusion that Richardson99 is not but-for material to the patentability of the asserted claims.

For the four asserted claims that were not examined during IPR, Defendants also have not specifically explained how the application of Luby97, Luby98, or Richardson99 to those claims would have impacted their allowability in a way unique from the asserted claims that were the subject of IPR proceedings. This is particularly the case where Defendants' disclosed inequitable conduct theories against all of the asserted claims simply rely on the fact that Luby97, Luby98, and Richardson99 disclose irregular codes. Defendants did not identify other disclosure in Luby97, Luby98, or Richardson99 that is allegedly but-for material to the patentability of individual asserted claims, whether that claim was subject to IPR proceedings or not. In their opposition, Defendants highlight Claim 9 of the '781 Patent, which was not subject to IPR proceedings, as presenting factual issues because Claims 1 and 2 of the '781 Patent were found anticipated by Divsalar during IPR proceedings. Docket No. 1104 at 20. Defendants state, "[t]he additional limitations of claim 9 are every bit as invalid." *Id.* at 21. Defendants do not further explain their position in their opposition memorandum, and this conclusory assertion is insufficient to create a factual question regarding the but-for materiality of Luby97, Luby98, or Richardson99

with respect to that claim.[44]

3. Conclusion

Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial) (Docket No. 942) would be **GRANTED** for the reasons stated herein.

IV. Conclusion

For the reasons stated in this Order, the Court would rule as follows:

- Broadcom's Motion for Summary Judgment as to Non-Infringement as to Extraterritorial Sales (Docket No. 975) would be **GRANTED-IN-PART** and **DENIED-IN-PART** as stated herein.
- Defendants' Motion for Summary Judgment as to No Joint Infringement (Docket No. 959) would be **GRANTED**.
- The Court would **DENY-IN-PART**, **GRANT-IN-PART**, and **DEFER-IN-PART** Plaintiff's Motion to Exclude Improper Claim Construction Opinions of Dr. Stark and Dr. Blanksby (Docket No. 968) as stated herein.
- As stated herein, Plaintiff's Motion to Strike Certain Opinions of Defendants' Experts Brendan Frey and Wayne Stark (Docket No. 974) would be **GRANTED-IN-PART** and **DEFERRED-IN-PART** pending discussion at the hearing.
- Plaintiff's Motion to Strike Late-Disclosed Non-Infringing Alternative (Docket No. 971) would be **DENIED**.
- The Court would **GRANT-IN-PART** and **DENY-IN-PART** Defendants' Motion to Exclude Infringement Opinions of Dr. Michael Tanner (Docket No. 964) as stated herein.
- Plaintiff's Motion for Summary Judgment as to No Inequitable Conduct (Partial) (Docket No. 942) would be **GRANTED**.

[44] Claim 9 of the '781 Patent recites: "[t]he method of claim 6, wherein the information bits appear in a variable number of subsets." The Court had occasion to consider the scope of the "variable number of subsets" limitation when considering Defendants' challenge to the patentability of these claims under 35 U.S.C. § 101 and found that "the phrase 'variable number of subsets' creates a requirement in the relevant claims for irregular repetition of information bits." *See* Docket No. 849 at 14.

EXHIBIT 14

Haunschild, Philip

From: Li, Yan-Xin <yanxin.li@kirkland.com>
Sent: Wednesday, January 3, 2024 9:32 PM
To: Haunschild, Philip; Genevant Team; Arbutus_MoFo; *jshaw@shawkeller.com; 'kkeller@shawkeller.com'; 'nhoeschen@shawkeller.com'
Cc: #KEModernaSpikevaxService; 'jblumenfeld@morrisnichols.com'; 'began@mnat.com'; 'tmurray@morrisnichols.com'
Subject: RE: Arbutus v. Moderna (22-cv-252) // OUS Discovery

Philip:

That Moderna has not allegedly produced "a single document Plaintiffs have requested" is a direct result of Plaintiffs' ever-changing demands over the last 10 months—a fact you do not (and cannot) dispute. Plaintiffs' conduct has unnecessarily and disproportionately enlarged the scope of this case against Moderna while continuing to stonewall relevant discovery sought by Moderna. Moreover, we wholly disagree that Moderna has not produced documents responsive to Plaintiffs' requests. In fact, Moderna has produced more than 1.35 million pages of information; Plaintiffs on the other hand have produced less than 500 thousand pages. And contrary to your reference to Plaintiffs' May 11, 2023 letter, which misrepresented the parties' discussions, Moderna did ***not*** agree that it is broadly required to "produce information regarding [] foreign activity" as Plaintiffs claim. *See* August 1, 2023 letter (M. McLennan to A. Sheh, S. Dawson) at 7. We further asked you to provide authority supporting how batches made outside the U.S. and never imported into the U.S. can constitute infringement of a U.S. patent. *Id.* To date, Plaintiffs have identified none.

We have also responded to your "extensive caselaw," and as we noted in our prior correspondence, your repeated selective recitation of certain language and the exclusion of others does not change the holding of those cases or the facts at issue here. We will not waste time repeating ourselves or highlighting Plaintiffs' convenient omissions from your cited cases.

Your listing of RFP Nos. 51, 53, 60, 64, 69, 74, 75, 81, 83, 97, and 174 as requests for which Plaintiffs continue to see production only further clouds Moderna's understanding of what exactly Plaintiffs want as to OUS discovery. We flagged in our last email that it appears Plaintiffs were now pivoting to seek foreign sales (after asking for all OUS batch COAs, followed by all OUS contracts), but it is unclear under which RFP you seek this information. Plaintiffs' shifting position makes it impossible for Moderna to negotiate in good faith. We will note as such should Plaintiffs declare impasse and move to compel for OUS discovery.

Yan-Xin Li

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555 California Street, San Francisco, CA 94104
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yanxin.li@kirkland.com

From: Haunschild, Philip <phaunschild@wc.com>
Sent: Tuesday, January 2, 2024 6:31 PM
To: Li, Yan-Xin <yanxin.li@kirkland.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>
Subject: RE: Arbutus v. Moderna (22-cv-252) // OUS Discovery

Yan-Xin,

Your email simultaneously asserts that the parties are not at an impasse while declaring unequivocally that "Moderna does not agree with Plaintiffs' position that 'discovery about batches manufactured [abroad] and used abroad' is relevant" and refusing to provide a single document Plaintiffs have requested. We have repeatedly explained, including in our correspondence below, that Plaintiffs are seeking this discovery to assess whether Moderna's sales in fact occurred in the U.S., and whether these sales infringed the Patents-in-Suit, a point that Moderna acknowledged was relevant on the parties' meet-and-confers in March and April 2023. *See* May 11, 2023 Letter from L. Cash at 4. Your response to the extensive caselaw we have cited—including binding Federal Circuit caselaw—ignores the uniform conclusion of these cases that information regarding whether a sale occurred in the U.S. is relevant to determining whether there is an infringing sale, regardless of where a product is made or used. And your attempt to distinguish the caselaw on the basis that these cases involve exports and imports to the United States ignores multiple cases cited below and in separate correspondence in which discovery was not limited solely to products that were imported or exported into or from the United States. *See, e.g.*, *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1310 (Fed. Cir. 2015); *Cal. Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 992 (Fed. Cir. 2022); *MLC Intell. Prop., LLC v. Micron Tech., Inc.*, No. 14-CV-03657-SI, 2018 WL 6175982, at *2 (N.D. Cal. Nov. 26, 2018); *McGinley v. Luv N' Care, Ltd.*, No. CV 17-0821, 2018 WL 9814589, at *4 (W.D. La. Sept. 10, 2018) ("to the extent that a sale occurs within the United States, products not made or imported into the United States may be included in determining royalties"); *Polaris Innovations Ltd. v. Kingston Tech. Co.*, No. cv-00300-CJC-RAOX, 2017 WL 3275615, at *5 (C.D. Cal. Feb. 14, 2017). Moderna may disagree on the ultimate merits of whether its sales occurred in the United States, but as the authority we have cited notes, there is no requirement that a plaintiff "essentially has to win before it can have discovery of that which is relevant to the question of whether [the defendant] is an infringer." *Murata Mfg. Co. v. Bel Fuse, Inc.*, 422 F. Supp. 2d 934, 946 (N.D. Ill. 2006). While your most recent email states without support that Moderna's products were "sold to customers abroad," Plaintiffs are entitled to the discovery to assess that fact.

We have been meeting and conferring about these requests for ten months. If Moderna has a good faith offer to make about documents it will produce in response to RFP Nos. 51, 53, 60, 64, 69, 74, 75, 81, 83, 97, and 174, as well as Interrogatories 6 and 11, by COB tomorrow, we will consider your position. Otherwise, the parties are in fact at an impasse, and we will seek the Court's assistance in obtaining this discovery.

Thank you,

Philip N. Haunschild
Associate | Williams and Connolly LLP
680 Maine Avenue SW, Washington, DC 20024
202-434-5979 | phaunschild@wc.com | www.wc.com

From: Li, Yan-Xin <yanxin.li@kirkland.com>
Sent: Friday, December 22, 2023 4:26 PM
To: Haunschild, Philip <phaunschild@wc.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>
Subject: RE: Arbutus v. Moderna (22-cv-252) // OUS Discovery

Philip:

If Plaintiffs actually explained the relevance of the OUS-related materials that you seek, the parties would not be in this present situation. Indeed, Plaintiffs' demand for information concerning Moderna's OUS batches morphed from all testing, analyses, and collection of COAs to an "initial" request for all OUS-related contracts, which Plaintiffs only raised for the first time in the parties' November 17 meet and confer. This is hardly "precise[]" as you allege. Moreover, as Moderna has explained since the onset, collecting all testing, analysis, and COAs for ***every one of the*** OUS batches is incredibly burdensome and not proportionate. Collection and production of all OUS-related contracts would similarly require enormous burden, including addressing third-party confidentiality issues, which is not proportionate to the needs of the case.

Moderna further responded to the "extensive caselaw" that Plaintiffs cited in their November 15 and 20 emails in our December 7 email. Your recitation yet again does not change the fact that Moderna's "substantial activities" of these OUS batches for which Plaintiffs seek discovery are manufactured abroad, sold to customers abroad, and not imported into the United States—a point Plaintiffs continue to ignore because it does not serve their burdensome fishing expedition into information that is not relevant to the parties' claims and defenses. Your newly identified cases overlook the distinguishable facts of this case. *Apeldyn Corp. v. AU Optronics Corp.*, No. 08-568, 2010 WL 11470585, at *1 (D. Del. Apr. 12, 2010) (Court noted defendant's excuse that "it does not know where its products go is not good enough to avoid the production of documents"); *Abiomed, Inc. v. Maquet Cardiovascular LLC*, No. 16-10914, 2019 WL 13089050, at *1 (D. Mass. June 21, 2019) (foreign sales sought were for products whose components were ***exported from the United States***); *Murata Mfg. Co. v. Bel Fuse, Inc.*, 422 F. Supp. 2d 934, 945 (N.D. Ill. 2006) (based on plaintiff's claim that ***defendant was inducing non-party component manufacturers*** to incorporate infringing component into their products ***to import and sell in the United States***); *MLC Intell. Prop., LLC v. Micron Tech., Inc.*, No. 14-3657, 2018 WL 6175982, at *2 (N.D. Cal. Nov. 26, 2018) (Court noting defendant's declarant stated information sought was "readily available").

Moreover, the cases you cite now suggest that Plaintiffs are seeking Moderna's foreign sales—which is different than your November 17 request for Moderna's OUS contracts and different from your prior broad request of all testing, analyses, and collection of COAs for each OUS batch. Even your email below pivots to seeking "executed contracts" ***and*** "documents evidencing their negotiation, execution, individual purchases, or marketing documents." This only emphasizes Plaintiffs' ever-shifting position as to what exactly Plaintiffs seek concerning Moderna's OUS batches. Moderna does not agree with Plaintiffs' position that "discovery about batches manufactured [abroad] and used abroad" is relevant.

For the reasons that Plaintiffs argue Moderna cannot "unilaterally declare a dispute premature," Plaintiffs similarly cannot unilaterally declare impasse where Moderna has attempted in good faith to understand and respond to Plaintiffs' unreasonable and changing demands. Moderna reserves all rights if Plaintiffs move prematurely.

Yan-Xin Li

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Thursday, December 21, 2023 3:58 PM
To: Li, Yan-Xin <yanxin.li@kirkland.com>; Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>
Subject: RE: Arbutus v. Moderna (22-cv-252) // OUS Discovery

Yan-Xin,

We disagree that any motion would be premature. Plaintiffs have repeatedly explained the relevance of the materials we have requested and have cited extensive caselaw, including most recently during the parties' meet and confer on November 17, and in our emails on November 15 and November 20. As we have now explained a number of times,

regardless of whether batches were manufactured and used outside of the United States, Plaintiffs are entitled to discovery about whether sufficient activities surrounding the sale occurred within the United States (for example, from Moderna's headquarters in Massachusetts) to constitute an act of infringement in the United States. *See, e.g.*, 28 U.S.C. 271(a); *Carnegie Mellon Univ. v. Marvell Tech. Grp., Ltd.*, 807 F.3d 1283, 1310 (Fed. Cir. 2015) (products "not made or used in, or imported into, the United States" may infringe if there is a "domestic location of sale"). In your December 7 email, you acknowledged that to determine whether a sale occurred in the United States, "'the key question' is 'whether there were such substantial activities in the United States.'" December 7, 2023 Email from Y. Li (quoting *Cal. Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 992 (Fed. Cir. 2022). That is precisely the question that Plaintiffs are trying to assess, and it is entirely improper for Moderna to insist that its *ipse dixit* should control, rather than providing discovery on this issue. *See, e.g.*, *Apeldyn Corp. v. AU Optronics Corp.*, 2010 WL 11470585, at *1 (D. Del. Apr. 12, 2010); *Abiomed, Inc. v. Maquet Cardiovascular LLC*, No. CV 16-10914-FDS, 2019 WL 13089050, at *1, n.1 (D. Mass. June 21, 2019) (granting discovery into foreign sales where Plaintiff had not even pleaded a theory of infringement under § 271(f)); *Murata Mfg. Co. v. Bel Fuse, Inc.*, 422 F.Supp.2d 934, 946 (N.D. Ill. 2006) (§ 271(f) case emphasizing there is no requirement that a plaintiff "essentially has to win before it can have discovery of that which is relevant to the question of whether [the defendant] is an infringer"); *MLC Intell. Prop., LLC v. Micron Tech., Inc.*, No. 14-CV-03657-SI, 2018 WL 6175982, at *2 (N.D. Cal. Nov. 26, 2018) (compelling discovery of worldwide sales information).

Moderna may disagree with the precedent compelling the discovery that Plaintiffs have sought, but Moderna cannot unilaterally declare a dispute premature by simply asking us to re-explain what we have said multiple times before. Nor can Moderna point to its production of its regulatory files and other documents as resolving the scope of what Plaintiffs have requested concerning Moderna's OUS batches. Moderna has refused to provide its executed contracts for the sale of the Accused Product with entities outside the United States, let alone documents evidencing their negotiation, execution, individual purchases, or marketing documents.

If Moderna agrees that discovery about batches manufactured and used abroad is relevant, and that it will negotiate in good faith over the documents it will provide, we will consider your position. Please confirm that clearly in writing by 4:00 PM tomorrow or we will continue to understand that the parties are at an impasse over this issue and seek the Court's assistance in compelling discovery.

Thank you,

Philip N. Haunschild
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202-434-5979 | phaunschild@wc.com | www.wc.com

From: Li, Yan-Xin <yanxin.li@kirkland.com>
Sent: Wednesday, December 20, 2023 12:11 PM
To: Genevant Team <GenevantTeam@wc.com>; Arbutus_MoFo <Arbutus_MoFo@mofo.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>
Subject: Arbutus v. Moderna (22-cv-252) // OUS Discovery

Dear Counsel:

Footnote 1 of Plaintiffs' December 15, 2023 letter to the Court states "[t]he parties also dispute discovery concerning batches manufactured overseas, which Plaintiffs allege were sold or offered for sale (and thereby infringed) in the U.S. Plaintiffs are filing a separate motion on this dispute, but for clarity, seek samples from all Moderna's batches, including those manufactured overseas."

As an initial matter, any motion Plaintiffs intend to file concerning discovery of Moderna's batches manufactured outside of the United States ("OUS") is premature, as Plaintiffs have not explained the relevance of such information and how it is within the scope of Plaintiffs' claims in this action, i.e., under 35 U.S.C. § 271(a). *See* 12/7/2023 Y. Li Email. Plaintiffs cannot ignore authority that the scope of their infringement claim "appl[ies] only domestically." *Cal. Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 992 (Fed. Cir. 2022). To date, Plaintiffs have not made clear what their theory is for requesting OUS discovery. It appears that Plaintiffs are simply dissatisfied with the fact that Moderna's OUS batches are manufactured OUS, sold to customers OUS, and not imported into the United States—a point the parties' prior correspondence acknowledge and agree—and seek discovery to prove a negative. *See also Kajeet, Inc. v. Qustodio, LLC*, 2019 WL 8060078, at *13 (C.D. Cal. Oct. 22, 2019) (any alleged foreign exploitation of a purported patented invention "is not infringement at all," and noting OUS discovery may be appropriate where a claim for infringement is made under § 271(f)).

Any motion Plaintiffs intend to file is additionally premature given Moderna's rolling productions. Moderna has provided almost a million pages of discovery to date and, per the parties' agreement, will be making another large production this week. Plaintiffs should therefore review the information Moderna has and will produce to identify documents that may arguably support their theory for the relevance of OUS discovery. Should Plaintiffs actually articulate a basis for OUS discovery, Moderna is willing to consider a limited and further targeted collection.

Best regards,
Yan-Xin

Yan-Xin Li

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EXHIBIT 15

Haunschild, Philip

From: Haunschild, Philip
Sent: Friday, January 5, 2024 4:11 PM
To: Harris, Laura Ashley; Afinogenova, Alina; Sheh, Anthony; Elenberg, Falicia; Komis, Jihad; Genevant Team; 'Arbutus_MoFo'; Berl, David; Mahaffy, Shaun; Harber, Adam; Fletcher, Thomas; Ryen, Jessica; 'NTan@mofo.com'; Bolte, Erik; *jshaw@shawkeller.com; 'kkeller@shawkeller.com'; 'nhoeschen@shawkeller.com'; 'EWiener@mofo.com'; shaelyndawson@mofo.com; #KEModernaSpikevaxService; 'began@mnat.com'; 'tmurray@morrisnichols.com'; 'jblumenfeld@morrisnichols.com'; Carson, Patricia A.; Parrado, Alvaro
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Laura,

We have discussed Plaintiffs' RFP No. 130 with Moderna for four months now, and at every step of the way Moderna has shifted its demands of Plaintiffs in what is a plain effort to delay any resolution. In September 2023, we discussed Plaintiffs' RFP No 130 on the parties' meet-and-confer, and Moderna requested that Plaintiffs investigate whether Plaintiffs would agree to produce the same scope of materials in response to this RFP that Plaintiffs have requested of Moderna. *See* Oct. 25, 2023 Letter from M. McLennan at 2. We did so, and we confirmed that Plaintiffs would agree to produce the identical scope of materials requested by RFP No. 130. *See* Nov. 16, 2023 Email from P. Haunschild. After nearly a month's delay, Moderna shifted to the vastly disproportionate demand that Plaintiffs produce all materials relating to essentially every LNP composition Plaintiffs or their predecessors made over their decades of history, in addition to materials mentioning Moderna or the Accused Product. Dec. 8, 2023 Email from A. Afinogenova. In response to new demands by Moderna, we then agreed to provide documents responsive to Moderna's RFP No. 22, requesting Plaintiffs' Board Materials regarding litigation against Moderna, in addition to those we had already agreed to provide. *See* Dec. 21, 2023 Email from P. Haunschild. Then yesterday, we confirmed the precise scope of Plaintiffs centralized repositories—notwithstanding Moderna's refusal to provide the same information—which Moderna indicated it needed to have in order to assess Plaintiffs' agreed scope of discovery. *See* Jan. 4, 2023 Email from P. Haunschild. Only now that Plaintiffs have informed Moderna that Plaintiffs will be producing documents responsive to these RFPs and that Arbutus and Genevant have repositories across the relevant time periods is Moderna shifting to demand materials from non-party *Roivant*—which Moderna has never requested or mentioned in our months-long correspondence. Further, for the first time, Moderna has limited its proposed scope to documents discussing the Asserted Patents and the lipid molar ratio of the Accused Product, which ignores the clear relevance of Moderna's Board's decisionmaking regarding the strategy, sales, and development of the Accused Product to damages. *See* Dec. 11, 2023 Email from P. Haunschild.

Moderna's continually shifting demands make clear that Moderna is not interested in reaching any good faith resolution with respect to these RFPs. We see no other option than to seek the Court's assistance in obtaining this relevant discovery, and intend to do so.

Thank you,

Philip N. Haunschild
Associate | Williams and Connolly LLP
680 Maine Avenue SW, Washington, DC 20024
202-434-5979 | phaunschild@wc.com | www.wc.com

From: Harris, Laura Ashley <lauraashley.harris@kirkland.com>
Sent: Friday, January 5, 2024 10:06 AM
To: Haunschild, Philip <phaunschild@wc.com>; Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony

<ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

Thank you for your confirmation regarding Plaintiffs' document storage and the scope of Board documents Plaintiffs intend to search and produce.

Provided that Genevant, Arbutus, and Roivant are willing to search for and produce non-privileged board materials referring to the Asserted Patents and the lipid molar ratio of the Accused Product, Moderna is willing to search for and produce non-privileged Board documents which reference lipid molar ratios in the Accused Product or refer to the Asserted Patents. We hope this resolves your concerns and avoids any need to burden the Court.

Moderna would also like Plaintiffs' agreement to allow for relevance redactions for the Board materials that are produced (*e.g.*, to redact everything other than references to the scope described above). Due to the sensitivity of Board materials, we hope you can appreciate the need for such a request.

Best,
Laura

Laura Ashley Harris

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lauraashley.harris@kirkland.com

From: Haunschild, Philip <phaunschild@wc.com>
Sent: Thursday, January 4, 2024 11:24 AM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

We continue to be puzzled by Moderna's refusal to answer a simple question about what it will produce. Plaintiffs have agreed to search for and produce the identical scope of documents as what we are seeking from Moderna. How those documents are maintained simply is not relevant to any issue other than Moderna's apparent wish to delay Plaintiffs from seeking relief. Nevertheless, we confirm that Plaintiffs have centralized repositories of Board materials dating back to 2013, which contain final minutes and materials provided to the Board, and will search for and produce non-privileged documents responsive to the scope of Plaintiffs' RFP No. 130 and Moderna's RFP No. 22, from those repositories. If Moderna does not confirm by COB today that it will search for and produce the documents responsive to RFP No. 130, we will be moving the Court.

Thank you,

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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Thursday, January 4, 2024 11:41 AM
To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

The scope of Plaintiffs' repositories is directly relevant to your claims that Plaintiffs will "provide an ***identical*** scope of discovery." Dec. 20 & 21 emails. While we appreciate that "Plaintiffs can confirm that they have documents responsive to these requests," such a vague response to three very specific questions posed in our December 20 email provides little comfort to Moderna. To be clear, Moderna is not refusing to provide any Board of Directors materials (in addition to those incidentally found in custodial files) and continues to believe a compromise is possible. We would appreciate an answer to the questions we posed below so that the parties can productively move forward in reaching that compromise without needlessly burdening the Court.

Thank you,
Alina

Alina Afinogenova

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Wednesday, January 3, 2024 9:18 AM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

We do not see how the scope of Plaintiffs' repositories, or the burden that Plaintiffs have agreed to undertake, has any bearing whatsoever on the relevance of Moderna's documents or the burden to Moderna in producing its own Board materials. Plaintiffs have agreed to produce documents responsive to the scope of Plaintiffs' own RFP No. 130, and Moderna's RFP No. 22, if Moderna agrees to produce documents responsive to Plaintiffs' RFP No. 130. Though Moderna itself has consistently refused to provide information about its own document searches, Plaintiffs can confirm that they have documents responsive to these requests.

We have sought Moderna's simple confirmation that it will search for and produce documents responsive to RFP No. 130 for five months now. Moderna's transparent effort at delay has greatly prejudiced Plaintiffs. Please confirm by noon tomorrow that Moderna will produce its Board materials responsive to Plaintiffs' RFP No. 130, or the parties are in fact at an impasse and we will be forced to raise this dispute with the Court.

Thank you,

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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Friday, December 22, 2023 3:58 PM
To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

Your position is not abundantly clear, which is precisely why we have raised the questions in our December 20 email, to which you continue to refuse to provide a response. Put plainly, we need confirmation that Plaintiffs actually possess the full scope of materials Plaintiffs have purportedly "agreed to provide." Throughout discovery in this case, Plaintiffs have pointed to the fact that Plaintiffs do not maintain centralized non-custodial repositories—including even centralized repositories of regulatory material—as a reason either not to collect certain categories of documents or why a collection of certain materials will be unduly burdensome. You can therefore appreciate why Moderna now needs assurances that both Plaintiffs actually maintain a repository from which they will collect Board of Directors materials and information on the time period during which materials have been maintained in said repositories. Once Moderna receives that confirmation, we hope that the parties can engage in a productive discussion to reach a compromise as to a reasonable scope of materials for collection and production.

We reiterate that we do not believe that the parties are at an impasse and continue to believe there is a path forward without needlessly burdening the Court. Should Plaintiffs nonetheless choose to prematurely move on this issue, Moderna reserves all rights.

Regards,
Alina

Alina Afinogenova

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Thursday, December 21, 2023 11:30 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

Our position is abundantly clear that Plaintiffs are agreeing to provide an identical scope of discovery to that which Plaintiffs have requested Moderna to provide. And your email still does not point to a request where Moderna has sought Plaintiffs' board materials beyond those discussing the current litigation. To the extent there is any confusion, we confirm that we will conduct a reasonable investigation to determine whether Plaintiffs have any non-privileged board materials responsive to Moderna's RFP No. 22, and produce such non-privileged materials to the extent they exist.

We have been asking Moderna for months to confirm that it is producing the documents sought by RFP 130, and your email—yet again—refuses to answer. Moderna cannot prevent Plaintiffs from seeking relief by continually stonewalling

and then using its own obstruction to declare unilaterally that the dispute is not ripe. Please confirm by 4:00 PM tomorrow, December 22, that Moderna will be providing its board materials responsive to the full scope of Plaintiffs' RFP No. 130, otherwise we understand the parties to remain at an impasse based on your email, and Plaintiffs will proceed accordingly.

Thank you,

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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Wednesday, December 20, 2023 4:56 PM
To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

To be clear, we are not avoiding answering questions about your discovery request. We are merely trying to understand the proposal in your November 16 email to determine if there is room for compromise. As you acknowledge in your email, Moderna's position has always been that any agreement to produce Board of Directors materials should be reciprocal. As you've pointed out, it is "typical" for publicly traded companies to maintain a centralized, non-custodial repository of Board of Directors materials. We are therefore trying to confirm that this is true of Arbutus and what the parameters of this repository are. With respect to Genevant, we have gotten no confirmation that Genevant even has a Board of Directors, let alone a repository of the materials being discussed. We have now asked you to fill in these blanks as we try to assess Plaintiffs' position.

While Plaintiffs may have "agreed that Plaintiffs will provide an identical scope of discovery responsive to Plaintiffs' RFP No. 130," Plaintiffs have not been consistent in their representations, which is precisely what prompted our questions earlier today. In Plaintiffs' October 9 letter, Plaintiffs merely stated that they "will investigate whether Plaintiffs have any non-privileged final Board minutes and materials provided to Plaintiffs' Board of Directors, or any committee of such Board." Oct. 9 Sheh letter at 2. Then on November 16, you "confirmed" that Plaintiffs will produce such materials, without ever confirming whether your investigation identified any such materials in Plaintiffs' possession, custody, or control, and if so, whether that is true of both Plaintiffs. Finally, in your December 11 email, you again do not confirm whether such materials exist, stating only that "Plaintiffs have offered to conduct a separate noncustodial collection of board materials." We also note that, as you acknowledge, Moderna has at least one RFP directed to Plaintiffs' Board of Directors materials that may not be fully covered by Plaintiffs' offer, which is narrowly circumscribed to materials relating to the Accused Product. It would be most reasonable to address all of the Requests directed to this set of materials at once, which is precisely what we are trying to do.

We therefore again reiterate our need for additional information to be able to fully assess the parties' respective positions on this issue. We would appreciate an answer to our questions. We do not believe it is proper for Plaintiffs to

rush to the Court on this issue when there might still be room for compromise. We remain hopeful that the parties can reach a resolution without burdening the Court.

Thank you,
Alina

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Wednesday, December 20, 2023 12:26 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

If Moderna has an issue with our RFP responses, it is welcome to raise that, though we note that Moderna has not even served a document request for the materials that it is requesting from Plaintiffs. *See* Moderna RFP No. 22 (requesting board materials *related to the institution of this action*). Nevertheless, we have already agreed that Plaintiffs will provide an identical scope of discovery responsive to Plaintiffs' RFP No. 130. *See* Nov. 16 Email below. It is not proper for Moderna repeatedly to avoid answering our questions about a specific discovery request we have served. Plaintiffs are prejudiced by Moderna's refusal to provide this discovery in response to this request that Moderna has had for more than four months. If Moderna does not agree by COB today to produce its Board Materials in response to Plaintiffs RFP No. 130, we intend to raise this deficiency with the Court and note Moderna's refusal to answer our questions about its alleged burden.

Thank you,

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Sent: Wednesday, December 20, 2023 11:06 AM
To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo'

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Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

As stated in our previous email, we are considering Plaintiffs' position. For Moderna to better understand what Plaintiffs are proposing, please confirm (1) that both Arbutus and Genevant each have centralized repositories of Board materials, (2) what types of documents those repositories contain (e.g. whether each entity's centralized repository houses final agendas and/or minutes of its board meetings and the materials that are provided to or reviewed by its Board of Directors), and (3) what time period do the materials contained in each Plaintiffs' centralized repository cover.

We are trying to work with Plaintiffs to arrive at a workable compromise and do not agree that the parties have reached an impasse on this issue.

Thank you,
Alina

Alina Afinogenova

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Tuesday, December 19, 2023 2:20 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

Please confirm by COB Wednesday, December 20, that Moderna will be providing its Board Materials in response to Plaintiffs RFP No. 130, or we understand the parties to be at an impasse.

Thank you,

Philip N. Haunschild
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From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Wednesday, December 13, 2023 5:57 PM
To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Philip,

We are considering your email and will respond in due course.

Thank you,
Alina

Alina Afinogenova

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Sent: Monday, December 11, 2023 9:00 PM
To: Afinogenova, Alina <alina.afinogenova@kirkland.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Plaintiffs' RFP No. 130

Alina,

Moderna's proposal is plainly insufficient.

First, Moderna's limitation to produce only custodial documents is unjustified for a category of documents that is typically maintained in a centralized, non-custodial repository for public companies like Moderna. In addition, none of Moderna's proposed custodians is on the Board of Directors, making this approach doubly insufficient. If Moderna's position is that it does not have a repository or Board Materials, please confirm that in writing. Otherwise, we expect that Moderna will search for responsive documents in its repository of Board Materials and not by picking through whatever documents happen to be in one of its custodian's emails.

Second, Plaintiffs have requested all documents created, prepared, and/or reviewed for or by Moderna's Board of Directors, or any committee of such Board, *related to the Accused Product*. Moderna's limitation to produce only documents that are responsive to the narrowly defined categories that Moderna limited to those documents that Moderna has already agreed to produce would omit plainly relevant documents that are provided to the Board of Directors, including e.g., the damages to which Plaintiffs are entitled, Moderna's willful infringement, and/or Moderna's infringement of the patents. Such documents are routinely ordered to be produced in cases like this one. *See, e.g. Vasudevan Software, Inc. v. MicroStrategy Inc.*, No. 11-CV-06637-RS-PSG, 2013 WL 597655, at *1 (N.D. Cal. Feb. 15, 2013) (finding "board minutes relating to the products VSI accuses as infringing . . . fall within the broad scope of relevancy under Rule 26" and ordering that they must be produced); *Unilin Beheer B.V. v. NSL Trading Corp.*, No. CV 14-2210, 2015 WL 12698382, at *9 (C.D. Cal. Feb. 27, 2015) (ordering defendants to conduct reasonable investigation for board of directors meeting minutes and other financial and corporate structure documents).

Moderna's efforts to condition its own production of Board materials to increasingly broad requests for Plaintiffs' documents are improper, and inconsistent with Moderna's prior statements in its correspondence and on the parties' meet-and-confer. *See* Oct. 25, 2023 Letter from M. McLennan at 2 ("[W]e understand Plaintiffs are still investigating whether to search for and produce non-privileged final Board minutes and materials provided to Plaintiffs' Board of Directors, or any committee of such Board, concerning Moderna's Accused Product."). In any event, Plaintiffs are not withholding non-privileged board materials on the basis that are otherwise responsive to the categories of documents that Plaintiffs have agreed to produce, and Plaintiffs have offered to conduct a separate noncustodial collection of board materials, consistent with the scope of Plaintiffs' RFP No. 130, as Moderna requested on the parties' September 15, 2023 meet-and-confer, provided Moderna agrees to do the same. *See* Oct. 9, 2023 Letter from A. Sheh.

Moderna has had our request for these Board materials for over four months, and the parties met and conferred regarding this RFP on September 15. Please confirm by Wednesday, December 13, that Moderna will be providing documents responsive to the full scope of this RFP, including by agreeing to produce all documents created, prepared, and/or reviewed for or by Moderna's Board of Directors, or any committee of such Board, related to the Accused Product. To the extent that Moderna will not produce documents responsive to the full scope of this RFP, please confirm by December 13 whether Moderna has centralized repositories of final minutes of its board meetings or the materials that are provided to or reviewed by its Board of Directors. Plaintiffs are requesting a discrete set of highly relevant documents, and we will seek the Court's intervention if Moderna continues its refusal to produce them.

Thank you,

Philip N. Haunschild
Associate | Williams and Connolly LLP
680 Maine Avenue SW, Washington, DC 20024
202-434-5979 | phaunschild@wc.com | www.wc.com

From: Afinogenova, Alina <alina.afinogenova@kirkland.com>
Sent: Friday, December 8, 2023 6:26 PM

To: Haunschild, Philip <phaunschild@wc.com>; Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 - Correspondence

Counsel,

Moderna will agree to produce non-privileged Board of Directors materials that are found in Moderna's custodial collections, are otherwise responsive to what Moderna has already agreed to produce (e.g. LNP development of the Accused Product) and hit upon Moderna's search terms, if Plaintiffs will produce Plaintiffs' Board of Directors materials relating to Plaintiffs' own Covered Products, LNP technology or the patents-in-suit, in addition to Moderna and the Accused Product. Plaintiffs' attempt to unduly narrow the scope of their production to Moderna's COVID-19 vaccine improperly excludes highly relevant materials.

Best regards,
Alina

Alina Afinogenova

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From: Haunschild, Philip <phaunschild@wc.com>
Sent: Thursday, November 16, 2023 5:00 PM
To: Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com; #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>; Parrado, Alvaro <alvaro.parrado@kirkland.com>
Subject: RE: Arbutus v. Moderna, 1-22-cv-00252 -Correspondence

Counsel,

Regarding Plaintiffs' RFP No. 130, we understand that Moderna has conditioned its agreement to produce its own board materials responsive to this RFP on Plaintiffs agreeing to provide their own board materials related to the Accused Product. Plaintiffs confirm that they will produce all non-privileged documents and communications created, prepared,

and/or reviewed for or by Plaintiffs' Board of Directors, or any committee of such Board, related to the Accused Product, including final meeting minutes and presentations and other materials provided to the Board, provided that Moderna agrees to provide its own board materials related to the Accused Product, responsive to the full scope of this Request. These documents are plainly relevant to issues in dispute in this case. Please confirm Moderna's agreement by November 20 so that we may promptly resolve this dispute, if necessary.

Thank you,

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From: Parrado, Alvaro <alvaro.parrado@kirkland.com>
Sent: Wednesday, October 25, 2023 2:34 PM
To: Sheh, Anthony <ASheh@wc.com>; Elenberg, Falicia <felenberg@wc.com>; Komis, Jihad <JKomis@wc.com>; Genevant Team <GenevantTeam@wc.com>; 'Arbutus_MoFo' <Arbutus_MoFo@mofo.com>; Berl, David <DBerl@wc.com>; Mahaffy, Shaun <SMahaffy@wc.com>; Harber, Adam <AHarber@wc.com>; Fletcher, Thomas <TFletcher@wc.com>; Ryen, Jessica <JRyen@wc.com>; 'NTan@mofo.com' <NTan@mofo.com>; Bolte, Erik <ebolte@wc.com>; *jshaw@shawkeller.com <jshaw@shawkeller.com>; 'kkeller@shawkeller.com' <kkeller@shawkeller.com>; 'nhoeschen@shawkeller.com' <nhoeschen@shawkeller.com>; 'EWiener@mofo.com' <EWiener@mofo.com>; shaelyndawson@mofo.com
Cc: #KEModernaSpikevaxService <KEModernaSpikevaxService@kirkland.com>; 'began@mnat.com' <began@mnat.com>; 'tmurray@morrisnichols.com' <tmurray@morrisnichols.com>; 'jblumenfeld@morrisnichols.com' <jblumenfeld@morrisnichols.com>; Carson, Patricia A. <patricia.carson@kirkland.com>
Subject: Arbutus v. Moderna, 1-22-cv-00252 -Correspondence

Counsel,

Please see the attached case correspondence.

Thank you,

Alvaro R. Parrado
Senior Paralegal | Intellectual Property

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EXHIBIT 16

Transcript of Hearing

Date: March 22, 2023
Case: Transcription Services

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1

HEARING O THE
SENATE COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS
UNITED STATES SENATE

STEPHANE BANCEL, MODERNA CEO
Testifies on COVID 9 Vaccine Price Increase

Wednesday, March 22, 2023

Job No.: 5 86
Pages: 8
Transcribed by: Esther M. Taylor

2

SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR,
AND PENSIONS

BERNIE SANDERS, Vermont, Chair
BILL CASSIDY, M.D., Louisiana, Ranking
Member
RAND PAUL, M.D., Kentucky
ROBERT P. CASEY, JR., Pennsylvania
MITT ROMNEY, Utah
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MARKWAYNE MULLIN, Oklahoma
MAGGIE HASSAN, New Hampshire
EDWARD MARKEY, Massachusetts
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SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR,
AND PENSIONS

SPEAKERS:
STEPHANE BANCEL, CEO, Moderna
CHRISTOPHER MORTEN, JD, PhD
AMEET SARPATWARI, PhD, JD
CRAIG GARTHWAITE, PhD

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THE CHAIR: The Senate Committee on Health, Education, Labor, and Pensions will come to order.

Let me begin by thanking Mr. Bancel, the CEO of Moderna, for being with us today and all other panelists who will be joining us.

Mr. Bancel very early on agreed to be here voluntarily, and I appreciate that very much.

I also want to take this opportunity, so there is no confusion, to congratulate Moderna, Pfizer, other companies, and the great scientists at the National Institute of Health and other Federal agencies for their extraordinary work in rapidly producing COVID vaccines that have saved millions of lives. We should be grateful to all those in Government and in the private sector who worked so hard to save lives.

This hearing, to my mind, is about several enormously important and interrelated issues that are on the minds of the American

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doesn t, I lose it all.
There are, right now, in our country, hundreds of startup businesses trying to develop drugs that will cure diseases.
I happen to know that because I invested in some in my prior life. I lost my money in every single one. Studied them as well as we could. We lost our money. That s the nature. But we thought, if it works, we re going to really get a huge return for ourselves and for our investors.
So, you know, I don t know how much money is the right amount of money, but the idea that somehow corporate greed has just been invented in America is absurd. It s been there from the beginning of free enterprise. Individuals investing, hoping that if it succeeds, they ll do very well financially, extraordinarily well. So I want to applaud the example we have.
By the way, the socialist countries, China and Russia and Northern Europe, did they

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come up with a vaccine that saved lives? No. No. They didn t.
Pfizer got technology from a German company, free enterprise company -- Moderna -- and saved lives. It is a stark demonstration of the comparison between free enterprise and socialism. And free enterprise works and socialism doesn t when it comes to saving our lives.
Now, I look at the technology which you re proposing to continue to develop in other areas, and I guess I want to ask what are the kinds of things that you re working on now? What are the prospects that you believe for some of these to make a real difference in saving lives or improving lives? Is this a one-off technology -- mRNA, is this something which is really just effective for vaccines or does it have broader application? And what will you do with the money that the company is making?
By the way, I noted that you re a billionaire now. Did the company pay you a

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salary of billions of dollars?
MR. BANCEL: No, Senator.
SEN. ROMNEY: You re a billionaire because the stock that you got when you started the company, you kept some of it, I presume.
MR. BANCEL: Mm-hmm.
SEN. ROMNEY: That stock is now worth a lot of money because your technology has been proven to actually work.
Is it going to work beyond vaccines? And what kinds of things are you working on?
MR. BANCEL: So thank you, Senator.
So we are very excited because this is a platform that we worked on for 10 years. We shared, just before Christmas, exciting data in cancer, which we are very excited because, of course, all of us have been touched or are being touched right now by cancer. And we show 44 percent reduction in recurrence of disease for melanoma cancer or deaths.
We are working very quickly to get this to the FDA, in a Phase 3 study this year.

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We are also working with our partners at Merck to try this -- and we want to explore as many tumor type as we can to see where can we help people because if we -- if that result translates to other tumor type, which we believe should happen, we have to be careful and, of course, wait for the clinical data -- that could help a lot of people.
We are also working on rare genetic disease. One of the reason I got excited about Moderna in the early days is, you know, I have children and --
THE CHAIR: I m sorry, Senator Romney s speech on socialism took up the bulk of the time. We have to go to Senator Murray right now.
SEN. ROMNEY: As did -- as did our Chairman.
SEN. MURRAY: Thank you very much, Mr. Chairman, for holding this hearing.
Mr. Bancel, welcome to the Committee.
You know, I understand that shifting

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from a single Federal contract to a multi-layered payer market is adding complexity to your distribution claims. But we are talking about a vaccine that taxpayers invested $12 billion in, a vaccine that was once $15, and now you re planning, of course, to price it at $130 despite the fact that it just costs about $3 to make. And that -- as we know, that cost is going to get passed on to consumers whether it s through higher premiums or higher administration fees.

So I want to know what is your answer to this Committee and really to the public about the need for such a drastic quadrupling of the cost.

MR. BANCEL: Thank you, Senator, for the question.

So, first, just to precise some numbers. The U.S. Government invested $1.7 billion in the vaccine development. The rest of the amount that you mentioned was actually purchase of product -- not investment

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in the development.

As I said in my oral testimony, we decided -- and this was discussed at our Board. This was not asked of us by the Government.

We, in the letter I wrote to the Government, when we started discussing about procuring the vaccine in September of 2020, we proposed a discount. It was not asked of us.

We discussed with our Board and we said if the vaccine work -- in September 2020, we had no idea. The Phase 3 come in November, the data -- if the vaccine work, we think it s our responsibility to return the capital to tax payers. And we returned, as I mentioned, $2.9 billion in discount versus the -- mRNA vaccine that the Government procured.

So despite our vaccine having three times more mRNA in it -- 100 microgram versus the other one was 30 microgram, we discounted our product to return $2.9 billion to the U.S. taxpayer. We thought it was the right thing to do, to say thank you to the Government.

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In addition, the Government got $5 trillion of economic value, 18 million hospitalization less, impact on humans and the cost of it, and 3 million lives saved.

So in the endemic setting, the challenge that we have is -- as I mentioned in my opening testimony, the wastage we re going to have to take care of.

So, first, we have to make more product than we think we will sell because we cannot have patients going to pharmacies and having no supply. And this is a very hard business, very complex because it s a seasonal product.

The FDA currently plans to tell us they think late May/early June, what they want in the vial. We re going to spend the whole summer making as much as we can. And what we know is the forecast is going to be wrong. The forecast are always wrong.

And so the question to protect people, we need to make more than we think is

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going to be needed. That waste, we re going to have to pay for it.

What happened in the fall of 2022, which I think is an important way to think about it -- the U.S. Government purchased 160 million doses. The last number I got from CDC, around 50 million doses got in arms, but the Government bought everything. So the difference, 110 million doses might go to waste, in the garbage.

So saying that the cost of the vaccine before was $20, I don t think is the right way to do the cost. It s not the cost to the U.S. taxpayer. The U.S. taxpayer paid for everything. If you do the math, it s around $80.

The cost in the fall of 22, still with five product in the vial.

SEN. MURRAY: Okay. Well, I understand that, and I just have a minute here left. I want to ask a couple of questions.

You are talking about having a

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that are making a claim that you had a patent infringement. I m hearing that not only here, but patent tweaking, patent infringements, when it comes to where we spend even more money on biologics and biosimilars.

Point being, whether it s the Government paying for it or the private sector, it s a broken system and you need to get better at it or you re going to get solutions in the long run that you don t like.

Your distribution system -- why is it something that you sound like you gotta recreate it? Where has it been up to this point? How do you distribute your flu vaccines? Why do you need this much money? A 400 percent price increase is preposterous, especially when you ve been given all this Government largess and it s even going to protect you from these lawsuits.

What s the nature of your current distribution system to where you can t just put this into it, and why is this that much different than what you ve done for years in

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distributing a flu vaccine? Because it looks like we re headed more to where this is going to be like the flu than it s going to be something extra normal.

MR. BANCEL: Thank you, Senator, for your question.

So just to clarify, we do not have a flu vaccine on the market yet. We have one in clinical study. We should have a Phase 3 data soon and hopefully --

SEN. BRAUN: You may not have one on the market, but there s a distribution network for them from your competitors. Why wouldn t you be able to get into that? Why do you have to justify creating a new distribution network? No one would ever do that.

MR. BANCEL: So indeed, Senator, we are going to use, but we have to set up the distribution network. I m not saying that we are going to build our own warehouses like other companies do. We are going to work with companies, but we have to set up those

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contracts.

During the pandemic, we only shipped trucks to three warehouses in the U.S. when the CDC was taking the responsibility and the cost of getting the vaccine to hospitals, pharmacies --

SEN. BRAUN: Is Government requiring you to do something different here that would cause you to use a different network?

What do McKesson and Cardinal and the others do? There s a network to get this stuff to pharmacies already and the places they need to go. Why can t you blend it into that, keep the cost down, be a little entrepreneurial in what you re doing?

MR. BANCEL: It s part of the solution we re going to be doing, Senator, is we re going to use existing networks, but we have to set up everything because we never had a commercial product before. We just have to go, which we are doing right now, through all the contracting, negotiating of all those rights and

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so on to set up the distribution capability so that we can get the vaccine to pharmacies.

SEN. BRAUN: I ve run out of time. You cannot, as well as the rest of the industry including hospitals, have the best of both worlds where you want Government to be in there helping you when it s tough and where for the private side, most of us are not happy with the fact that we re lucky if your health insurance plan only goes up 5 to 10 percent, which incorporates hospitals, pharma, and maybe the Darth Vader of it all, the insurance business.

Something s got to give or you re going to get more Government involved in healthcare. Thank you.

THE CHAIR: Senator Hickenlooper.

SEN. HICKENLOOPER: Thank you, Mr. Chair.

Mr. Bancel, thank you for coming in and testifying before us.

It really is a remarkable, if you look at the arc of what happened and you look at

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it -- actually take it all the way back to when Moderna was founded in 2010 and you came on board in 2011. I look at so many moments of risk and how many times -- I don t want to alarm anyone, but the company could be at risk when your margins were so thin, you didn t have sufficient money to invest.

And I think the notion of what the Federal Government did during a time of crisis where we made, I think, the decision baked in wisdom to pursue six different solutions. I m talking about multiple working hypotheses.

And in your case, the Federal Government, BARDA, provided, I think, it was $1.7 billion in your statement, you said. And that was money that really was after the earlier investments, which were largely in research and those are public-private partnerships that have -- that money is invested. We do that -- Government does that in all different levels.

In this case, the $1.7 billion, you actually turned 2.9 billion? 2.8?

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MR. BANCEL: 2.9 billion.

SEN. HICKENLOOPER: $2.9 billion. What was part of your motivation and that?

MR. BANCEL: Thank you, Senator, for the comments and for the question.

It s actually quite simple. As we were starting, so there were two moments during the pandemic in partnership with the Government. First, focus on the vaccine development and accelerate it. That s what BARDA funding provided.

Then we started to discuss with the Government toward the end of the summer 2020 about purchasing vaccine in case the FDA will approve them. And as we started to have those discussions, we started to discuss with our Board. And it became very clear, like, a five-minute discussion at a Board meeting, that we had to find a way to give the money back to the U.S. Government because we all felt very grateful that thanks to that funding, we were able to accelerate the vaccine.

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I believe Moderna would have got the vaccine approved without the funding, but it will not happen by the end of the year, so Americans lives would have been impacted by that delay without the support.

And so when we looked at it, we -- like, if we re going to get, you know, the vaccine to work, we should provide a discount. And the Board decided in five minutes and that s what I put in my letter that I sent to the Government in our first discussions for procurement.

SEN. HICKENLOOPER: And I did an interesting calculation to look at how many lives were saved by accelerating that process with that $1.7 billion that was paid back almost not quite double, but certainly more than just paying it back.

And I am sympathetic to some of the issues as you look at pricing going forward that this is something that has to be kept at a cold temperature, you re going from one customer to

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thousands of customers, you re looking at a 90 percent or 95 percent reduction in what you re producing, so all your manufacturing is going to have to be reconfigured.

MR. BANCEL: Yes.

SEN. HICKENLOOPER: You know, and I m not an expert in pharmaceuticals, so I can t address that, but I think it is a complex issue that we need to spend more time looking at and in these kinds of public-private partnerships, we want to get to the alignment of interest.

And I guess my question is -- you can comment on that, but I would also -- what do you think, going forward, how can we do a better job of creating these public-private partnerships so that both sides feel they know exactly what they re getting and what s -- you know that there s an alignment of that self-interest.

MR. BANCEL: Thank you, Senator.

Actually, the way we think about the price during the pandemic was actually a discount. We are talking here today about an

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I, Esther M. Taylor, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding; that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; and that I am neither counsel for, related to, nor employed by any of the parties to the case and have no interest, financial or otherwise, in its outcome.

Esther M Taylor

ESTHER M. TAYLOR
October 19, 2023
(511186, Moderna, 3-22-2023)