Paper No. ___
Filed: December 21, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00739
Patent No. 9,364,435

PATENT OWNER'S RESPONSE PURSUANT TO 37 C.F.R. § 42.120

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I. STATEMENT OF PRECISE RELIEF REQUESTED

Moderna Therapeutics, Inc. ("Petitioner") filed a petition for *inter partes* review of claims 1-20 of U.S. Patent No. 9,364,435 (the "'435 patent," EX1001). The Board issued its decision instituting trial (Paper 15) on all grounds set forth in the petition. Protiva Biotherapeutics, Inc. ("Patent Owner") hereby requests that the Board now issue a final written decision confirming that claims 1-20 are not unpatentable.

II. INTRODUCTION

The nucleic acid-lipid particles claimed by the '435 patent have achieved tremendous recognition in the field of genetic therapy. The '435 patent is now listed in FDA's Orange Book as protecting the patisiran—tradename "Onpattro"—commercial product. EX2027. Patisiran received regulatory approval in the U.S. and Europe and has been designated by the FDA as a "first-in-class" drug. EX2024.

The therapeutic potential of genetic therapy has been appreciated for over 25 years, but effectively delivering nucleic acids to target cells without eliciting vehicle-related toxicity has prevented realization of this potential. *See e.g.*, EX2011 at 38, 42; EX2014 at 11. By 2008, the industry-wide failure to identify a solution to the delivery problem resulted in waning confidence. EX2015 at 2, 10. Dr. Phillip Sharp, Nobel Laureate and co-founder of Alnylam Pharmaceuticals, was asked about the challenges that lie ahead for RNAi drugs he answered "Delivery, delivery,

delivery." EX2014 at 11; *see also* EX2016, Title of Article ("Merck's Alan Sachs, on RNAi's Big Challenge: Delivery, Delivery, Delivery"); EX2011 at 42 ("Delivery, delivery, delivery.").

The nucleic acid-lipid particle formulations of the '435 patent solved a long-felt need for compositions that could safely and effectively deliver nucleic acids to target cells of patients. Skilled artisans were skeptical that compositions having high levels of cationic lipid (i.e., 50 mol % to 85 mol %) and low levels of conjugated lipid (i.e., 0.5 mol % to 2 mol %) would be effective, let alone well-tolerated when administered *in vivo*. The combination of effectiveness and low toxicity that characterizes the claimed compositions surprised many in the field, and finally solved the delivery problem that hindered the field for decades.

Given the innovation protected by the '435 patent, the petition is a poorly conceived challenge. It seeks troubling shortcuts rather than providing any *bona fide* obviousness analysis addressing motivation to combine and reasonable expectation of success in view of the state of the art at the time. In numerous instances, the petition fails to coherently identify the specific invalidity theories on which its challenge is based.

The obviousness challenges of Grounds 1 and 3 argue for a *prima facie* case of obviousness on a per-limitation basis for what it contends are overlapping ranges of individual claim elements. Petitioner then rests on its putative "*prima facie*" case

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