DECLARATION OF GLENN D. PRESTWICH, Ph.D.

I, Glenn D. Prestwich, Ph. D., residing at 143 First Avenue, Apt. 305, Salt Lake City, UT 84103, do hereby declare as follows:

1. I have been asked by Shumaker, Loop & Kendrick, LLP LLP to provide my opinion concerning the validity of U.S. Patent No. 8,450,475 (the '475 patent) in connection with their petition for inter partes U H Y L H Z , 3 5 patent (IPR Petition). I am being compensated for my time at the rate of $750 per hour for consulting, $400 per hour for travel, and $1000 per hour for oral testimony. My opinion is not influenced in any way by the compensation that I receive, and my compensation will not be affected by the outcome of this matter.

Education, Experience, Publications and Awards

2. I am Presidential Professor of Medicinal Chemistry and Special Presidential Assistant for Faculty Entrepreneurism at the University of Utah in Salt Lake City, UT. I also currently hold the titles of Research Professor of Biochemistry, Adjunct Professor of Chemistry, Adjunct Professor of Bioengineering, and Adjunct Professor of Surgery at the University of Utah. At : D V K L Q J W R Q 6 W D W H 8 Q L Y H U V L W \ , K D Y H E H H Q G Distinguished Visiting Professor. I have set out my background experience below, further particulars of which are set out in my curriculum vitae, which is attached to this Declaration. A complete list of my educational experience, work history, honors/awards, lectures and publications can be found in my curriculum vitae.

3. I obtained a Bachelor of Science Degree (Honors) in Chemistry from the California Institute of Technology in Pasadena, California (1970) and a Ph.D. degree in Organic Chemistry from Stanford University in Palo Alto, California (1974).

4. After obtaining my Ph.D., I worked for two and one-half years as a research scientist in Nairobi, Kenya on insect chemical communication, with the goal of identifying compounds in termites, ticks, tsetse flies, mosquitoes, and armyworms that would be useful for control of insect agricultural pests and insect disease vectors.

5. From 1977 to 1996, I was appointed first as an Assistant Professor and, subsequently, Associate Professor, and then Full Professor of Chemistry at the State University of New York at Stony Brook, NY. From 1992-1996, I was also appointed as Professor of Biochemistry and Cellular Biology, and I was the Director of the New York State Center for Advanced Technology in Biotechnology, also called the Center for Biotechnology, at SUNY Stony Brook.

6. From 1996-2002, I was the Chair of the Department of Medicinal Chemistry at the University of Utah. In addition, from 1997-2002, I directed the Center for Cell Signaling, a Utah Center of Excellence dedicated to launching new start-up companies based on faculty technologies in cell signal research; three new companies were formed. From 2002-2006, I directed a second Utah Center of Excellence, the Center for Therapeutic Biomaterials, from which I helped launch five new companies,

each of which involved technology created in my laboratories.

7. My academic duties have included teaching undergraduate and graduate courses in bioorganic chemistry, structural organic chemistry, medicinal chemistry, chemical ecologyand site-targeted drug delivery. I have also been active in research directing graduate students, technicians, postdoctoral fellows and visiting faculty members. My university research and other scholarly duties have resulted in the publication of over 580 original scientific papers and over 60 book chapters and books. Of these, about 22% of the refereed publications and 28% of the books/book chapters are related to hyaluronic acid or hyaluronan. I am also a named inventor on some 69 patents and patent applications in many areas, including the control of insect pests, cholesterol lowering agents, labeled phospholipids and phosphoinositides in drug discovery assays, anti-cancer and anti-angiogenic agents, signal transduction modifiers, mercury sensing chemicals, and the compositions and uses for a wide variety of chemically modified hyaluronan (HA) derivatives. About half of my patent and patent application portfolio covers compositions of matter, methods of making, and methods for using chemically-modified HA derivatives as biomaterials for wound repair, adhesion prevention, drug delivery, tissue engineering, 3-D cell culture, and cell therapy or as anti-inflammatory compounds for treatment of inflammatory diseases of the eye, skin, bladder, gingiva, kidney, and other tissues.

8. Since 1980, I have been a consultant for a wide variety of pharmaceutical and companies specializing in the development of lipid kinase inhibitors, squalene epoxidase and

oxidosqualene cyclase inhibitors, insect juvenile hormone antagonists, insect pheromone analogs, and hyaluronan-derived biomaterials. My research activities in HA began in approximately 1989, and my first company, Clear Solutions Biotech, was launched with Jim Hayward, President of Collaborative Laboratories, in 1994 based on the hydrazide modification technology discovered in my laboratories. Since moving to Utah in 1996, I have co-founded and held management positions with several biotechnology start-up companies, as well as serving as a consultant for others. I founded and served as a Director, Chief Scientific Officer (CSO), Chief Scientific Adviser, or Chief Executive Officer (CEO) for a number of these start-up companies.

9. These companies include: Clear Solutions Biotech (Stony Brook, NY) (1994-2001); Echelon Biosciences, Inc. (CSO, 1997-2003; Science Advisor 2004 -current); Sentrx Surgical, Inc. (Salt Lake City, UT)(CSO, 2004-2005); Carbylan Biosurgery, Inc. (Palo Alto, CA)(Science Advisor, 2005-2009); Sentrx Animal Care, Inc. (Salt Lake City, UT)(Science Advisor, 2006-current); Glycosan BioSystems, Inc. (Salt Lake City, UT) (CSO, 2006-2011); GlycoMira Therapeutics (Salt Lake City) (CSO, 2008-current); Metallosensors (Salt Lake City) (CEO, 2011-2014); Brickell Biotech (Ft. Lauderdale, FL) (Director, 2011-2013); OncoCyte/BioTime (Alameda, CA)(Scientific Advisor, 2011-2014); Organovo (San Diego, CA)(Scientific Advisory Board (SAB), 2008 - 2014); Modern Meadow (Columbia, MO, now Brooklyn, NY)(SAB, 2012-current); Jade Therapeutics (Salt Lake City, UT)(Scientific Advisor, 2012-2015); Symic Biomedical (San Francisco, CA)(SAB, 2013-2017); Deuteria Agrochemicals LLC (Manager, 2014-current); Deuteria Biomaterials LLC (Manager, 2014-current). Of

these, the technologies for Clear Solutions Biotech, Sentrx Surgical, Carbylan Biosurgery, Sentrx Animal Care, Glycosan, GlycoMira, Brickell Biotech, and BioTime all involve technology for the chemical modification of HA that was licensed from my university laboratories and is the subject of pending, published or issued patents. Deuteria Biomaterials also involves a patented isotopically-modified version of HA.

10. I have received peer and community recognition and numerous awards for my work, including the Alfred P. Sloan Research Award (1981-85) and Camille and Henry Dreyfus Teacher-Scholar Award (1981-86). I received both the 1998 Paul Dawson Biotechnology Award and the 2008 Volwiler Research Award of the American Association of Colleges of Pharmacy. I am a Fellow of the American Institute for Medical and Biological Engineering (2005-current), one of vSpring's Top 100 Entrepreneurs (2005, 2006), recipient of a TIAA-CREF "Greater Good" award (2006), a Utah Business Magazine "Health Care Hero" for 2006, and was awarded the Governor's Medal for Science and Technology for 2006. I received the Utah Governor's Medal for Science and Technology for 2006. In 2010, I received the University of Utah Distinguished Scholarly and Creative Research. Award, as well as the 2010 "Rooster Prize" of the International Society for Hyaluronan Science for outstanding contributions to HA-derived products. I was inducted as a 2013 Fellow of the National Academy of Inventors, and I am the recipient of the 2014 Distinguished Innovation and Impact Award of the University of Utah.

11. During my 40 years as a faculty member, I have trained over 126 graduate and

postdoctoral scientists, many undergraduate students, and mentored 22 adjunct and visiting faculty members. During this time, I have served on 16 editorial boards for prominent journals; my current editorial responsibilities that are relevant to HA science include: BioMatter, Macromolecular Biosciences, Current Opinion in Chemical Biology, Perspectives in Medicinal Chemistry, and Science Translational Medicine. My university research programs for four decades have focused on (i) chemistry and biochemistry of insect defensive compounds, pheromones, and hormones, including natural product structure determinations using x-ray crystallography; (ii) discovery of cholesterol-lowering drugs by inhibition of key biosynthetic enzymes; (iii) developing chemical and photochemical cross-linking reagents and protocols for modification and purification of macromolecules, including proteins and glycosaminoglycans; (iv) chemical synthesis and uses of affinity reagents for biological studies of phosphoinositides; (v) new reagents for lipid signaling in cell biology and cancer treatment; (vi) crosslinked hyaluronan and other glycosaminoglycan and protein-based biomaterials for wound repair, cartilage repair, tissue engineering, cell therapy, scar-free healing, and toxicology and tumor xenograft models; and (vii) sulfated glycosaminoglycan analogues as inflammation modulators for clinical use.

Level of Ordinary Skill in the Art of the '475 Patent

12. I have been asked to opine on the level of ordinary skill in the art in relation to U.S. Pat. No. 8,450,475 (Exhibit 1001, "the '475 patent") as of the earliest effective filing date, August 4, 2008. The '475 patent is directed to hyaluronic acid (HA)-based gels including lidocaine, and more specifically, soft tissue fillers containing HA crosslinked with 1,4-butanediol diglycidyl ether (HA-BDDE), uncrosslinked HA, and lidocaine. I understand

that a person of ordinary skill in the art (POSITA) would have been one who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

13. In my opinion and with respect to the '475 patent, a POSITA would have education and experience concerning preparation and/or use of crosslinked HA, such as that used in soft tissue fillers, as of 2008, with varying levels of education and experience. Such a person would have a B.S. or M.S. in the fields of biochemistry, polymer chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, with several years of practical clinical, academic or industrial experience within these fields, or a Ph.D. in those fields but with reduced practical experience. Alternately, the POSITA could have an M.D. in dermatology, plastic surgery, and/or a related specialty appropriate to the clinical use of dermal fillers.

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14. I understand that the '475 patent purports to provide a soft tissue filler containing HA-BDDE and lidocaine having enhanced stability relative to conventional HA-based compositions "when subjected to sterilization techniques such as autoclaving, and/or when stored for long periods at ambient temperature. Methods for preparing such HA-based compositions are also provided as well as products made by such methods."

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15. I agree with the '475 patent that since the first HA-based filler was approved by the U.S. Food and Drug Administration (FDA) in December 2003, "this was rapidly followed by the development of other HA-based fillers" ('475 patent, 1:63-65).

16. I agree with the '475 patent that before August 2008, "methods of preparing HA based soft tissue fillers including both crosslinked and free HA are well known" ('475 patent, 2:18-19).

17. I also agree with the '475 patent that "It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions" ('475 patent, 2:20-22).

18. I disagree with the assertion that either before or after August 4, 2008:

> HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.
>
> ('475 patent, 2:22-27)

In my opinion, this assertion fails to acknowledge relevant prior art and the expectations of the POSITA based on this prior art.

19. As explained further below, before August 4, 2008 it was known to a POSITA and would have been obvious to a POSITA that the addition of lidocaine to a soft tissue filler containing HA-BDDE would not have caused degradation of the filler, either during high

temperature sterilization steps (autoclaving) and/or when placed in storage for any significant length of time. The '475 patent claims an earliest priority date of August 4, 2008.

Technical Background and State of the Art

HA based soft tissue fillers were known and under rapid development

20. For decades, injectable soft tissue fillers have been used to augment and/or restore fullness of soft tissues (e.g., as wrinkle fillers) to fill in facial wrinkles creating a smoother appearance. In the U.S, wrinkle fillers are medical device implants approved for use by the FDA, based on the FDA's evaluation of safety and effectiveness of the wrinkle fillers when injected into specified areas of facial tissue, in view of the data collected from controlled clinical studies. A list of Wrinkle Fillers Approved by the Center for Devices and Radiological Health can be found at the FDA website: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CosmeticDevices/WrinkleFillers/ucm227749.htm (see FDA Dermal Filler List).

21. In the 1980s, numerous animal-derived injectable collagen fillers, such as Zyderm®/Zyplast® and Fibrel®, were approved by the FDA. Zyderm/®Zyplast® included lidocaine to ease pain associated with injection of the collagen filler. Following development of these animal derived collagen fillers, development of HA-based soft tissue fillers quickly ensued and were subsequently marketed in Europe. In the U.S., the FDA approved the first HA based dermal filler, Restylane®, in December 2003. Compared to the conventional collagen-based fillers, HA-based fillers have better

stability, lasting longer *in vivo*, and having lower immunogenic potential, requiring no skin testing before treatment. Before August 4, 2008, the FDA approved numerous HA-based dermal fillers, such as products of the Restylane®/Perlane®, Hylaform®/Captique®/Prevelle®, Juvederm®, and Elevess® families. (see Juvederm FDA Briefing). Other HA-based dermal fillers, such as the Puragen® family of products, were also approved in other countries, such as Canada (Puragen Plus, Kinney). Similar to the injectable collagen fillers, many of the above mentioned HA fillers included lidocaine to reduce and/or ease pain associated with injection of cross linked HA compositions. Examples of cross linked HA-based dermal fillers available before August 4, 2008 are provided in the following table:

Commercial Name of HA Fillers	Crosslinkers	Anesthetic Included?	HA Gel (Conc.)	% soluble HA
Elevess® by Anika therapeutics FDA approval; December 20, 2006	BCDI (biscarbodiimide or p-phenylene bis(ethyl) carbodiimide)	Yes; 0.3% (lidocaine HCl)	28 mg/mL	None
Puragen® Plus by Mentor in conjunction with Genzyme; Canadian Approval December 19, 2005	DEO (1, 2, 7, 8 diepoxyoctane)	Yes; 0.3% (lidocaine HCl)	20 mg/mL	6%
Prevelle® Silk by Mentor in conjunction with Genzyme; FDA Approval February 26, 2008	DVS (vinyl sulfone)	Yes; 0.3% (lidocaine HCl)	5.5 mg/mL	2%

Methods of preparing HA based soft tissue fillers were well known

22. All of the FDA approved HA-based soft tissue fillers contain crosslinked HA, in which the crosslinking functions to provide stability and longevity *in vivo*. This is discussed in great detail below.

23. HA, or hyaluronan, is a naturally occurring linear polysaccharide with a repeating G L V D F F K-1,4-D-glucuronic acid] ->-1,3-N-acetyl-D-glucosamine], i.e., it is a chain comprised of many (poly) sugar units (disaccharides), often abbreviated as (G1cUA-GlcNAc-)$_n$ (Fig. 1).

The repeating HA disaccharide unit, (G1cUA-G1cNAc-), has a molecular mass of 401 daltons (Da). Each disaccharide (repeating two sugar unit) contains one carboxyl group and thus HA has many negatively charged groups (i.e,HA is a polyanion) at neutral pH. HA naturally occurs as a mixture of physiological salt forms, and has molecular weights ranging from approximately 100,000 up to 8,000,000 Da (100-8000 kilodaltons (kDa)).

24. HA having a molecular weight exceeding approximately 500 kDa has a large hydrodynamic volume and non-Newtonian viscoelastic properties due primarily to the presence of multiple dynamic hydrogen bonds among and within the disaccharide units. This restricts movement at the glycosidic bonds and creates a stiffened, yet mobile polymer chain.

25. HA is widely distributed in connective, epithelial and neural tissues. It is an essential component of the extracellular matrix, which is the molecular support structure for all cells and tissues. Half of the HA in the human body is present in skin. In all tissues, the major function of HA is to maintain hydration and proper homeostasis of moisture. HA has excellent biocompatibility and is well suited for biomedical applications.

26. Native HA and its chemically-modified derivatives have been clinically used as medical and veterinary products for almost four decades, for example in wound repair, prevention of post-surgical adhesions, ophthalmic surgery, dermal fillers, treatment of vocal cords, and treatment of osteoarthritis by intra-articular injection.

27. Native HA has several major limitations for this spectrum of applications. These include its relatively short residence time *in vivo* (i.e., with a half-life of only 0.5 -1.5 days depending on location in the body) and its lack of suitable biomechanical properties. To remedy these limitations, more durable and stronger HA biomaterials have been developed using chemical modification. The rate of degradation and mechanical

properties of these modified HA derivatives are determined by the particular chemical modifications and the physical forms of the derivatives.

28. Most chemical modifications of HA alter its chemical, physical, and biological properties by modification of one of two functional groups that occur at multiple locations along the HA chain: the carboxylic acid and/or hydroxyl groups. As a result, there are only a limited number of ways to crosslink based solely on reactive groups. As discussed below, thH PDMRU ³FRQYHQWLRQDO´ FURVVOLQNHUV XVHG V products before August 4, 2008 included bisepoxide crosslinking agents (e.g., BDDE), sulfone crosslinking agents (e.g., divinyl sulfone), and/or biscarbodiimide crosslinking agents (e.g., BCDI). To understand the differences between native (unmodified) HA, modified but uncrosslinked HA, partially or "lightly" crosslinked HA, and crosslinked HA in a water-insoluble hydrogel, one must understand how crosslinking occurs. When chemical modifications result in crosslinking of HA chains, this can happen in two different ways, and both processes occur simultaneously in any reaction that is intended to crosslink HA. In one type of crosslinking, called intramolecular crosslinking, different regions within one HA chain become covalently linked to other regions of the same chain. In a second type of crosslinking, one HA chain is covalently linked to another HA chain by an intermolecular crosslink. Figure 2 illustrates these two types of crosslinking, as well as the presence of pendant groups that fail to form crosslinks within or between HA chains. This concept is conveyed clearly also by Kablik p 304: "Bifunctional crosslinkers do not necessarily react at both ends to connect two different strands of HA. Often the crosslinker will bond only at one end, leaving the other end pendant."

29. However, to reach the crosslinked state, several steps must occur. In the first step of any chemical crosslinking reaction, one HA disaccharide unit, which is inaccurately referred to as an "HA monomer" in the '475 patent, undergoes a reaction with a crosslinking agent containing two or more reactive moieties (e.g., a carboxylic acid group and/or a hydroxyl group).

30. In the first step, the (GlcUA-G1cNAc)-HA disaccharide unit becomes covalently attached at either the carboxylic acid (of the GlcUA moiety) or one of the primary or secondary hydroxyl groups (of either the GlcUA or GlcNAc moiety) of HA. For BDDE crosslinking, hydroxyl groups are most relevant, and the most reactive of these hydroxyl groups is the primary 6-OH of the GlcNAc moiety. For all chemical crosslinking reactions, the first step produces a pendant group on one HA molecule and this must occur prior to any crosslinking. Typically, a modified HA with a pendant group is still water-soluble but, importantly, no crosslinking has occurred.

31. Moreover, both the pendant group and the still unreacted crosslinking agents are subjected to chemical reaction with water in the aqueous reaction medium, leading to hydrolysis of one or more reactive moieties. This hydrolysis renders the reactive moieties unreactive, and thus unable to make a crosslink or to undergo any further reaction with an HA disaccharide unit. These processes are depicted graphically below in Figure 3.

32. The next step, for crosslinking to occur, is for a pendant group that still has a reactive moiety present (i.e., the reactive moiety that has not be rendered inactive by hydrolysis), to react with the carboxylic acid or hydroxyl unit of another HA disaccharide unit in the same or different HA molecule. Only when the reactive moiety encounters the appropriate HA reactive group by collision on a molecular level can this reaction actually occur. Then, and only then, does a chemical crosslink form. Figure 3 illustrates the fate of crosslinker reactive moieties during HA modification. In Figure 3, the "star" represents a

reactive moiety capable of crosslinking HA; the "rectangle" represents a hydrolyzed or otherwise inactivated moiety of the crosslinker, incapable of crosslinking HA; and the "circle" represents a chemical reaction that has occurred in which one end of the crosslinker is covalently linked to HA. Specifically, in Figure 3, this linkage is shown to be one of the hydroxyl groups, preferably one of the 6-hydroxyl group, of HA. As emphasized by Kablik "pendant modification is a result of the reaction conditions and is not specific to a bifunctional crosslinker" (Kablik, p310). Moreover, Kablik notes:

> the degree of cross-linking is used interchangeably with the degree of total modification when describing HA dermal fillers. We need to remember that total modification includes the percentage of cross-link plus the percentage of pendant. The crosslink ratio can be defined as the ratio of percentage of cross-linking to the percentage of total modification, and can be used as a way of characterizing a particular gel.

Kablik, p.310).

These concepts will be important in comparing dermal fillers later in this declaration.

33. A POSITA will understand that the rate of a bimolecular chemical reaction (i.e., a reaction between two molecules) depends at a minimum on temperature, concentration, and viscosity. Higher temperatures and higher concentrations generally increase reaction rates, while higher viscosity decreases reaction rates. This is important in the context of the chemical crosslinking of HA, because (i) solutions of HA having a molecular weight of 500 kDa or higher have intrinsically high viscosity, and (ii) as crosslinking

occurs, the viscosity increases further until gels begin to form. Thus, the rates of crosslinking decrease to near zero as the gels form, because pendant reactive moieties on the crosslinking agent can no longer move freely, collide with, and react with reactive carboxylic acid or hydroxyl groups of an HA disaccharide unit.

34. The result of the processes described above is that a preparation resulting from an HA crosslinking reaction contains a mixture of four species of HA. The first species is chemically modified HA with one or more pendant groups and in which the pendant reactive moiety was hydrolyzed and never formed a crosslink; this species is generally water-soluble. The second species is partially or lightly crosslinked HA, in which the pendant reactive moieties formed one or more intra- or intermolecular crosslinks, but then failed to be incorporated into an insoluble network; this partially crosslinked HA may have a larger effective molecular size than the first species, but is still generally water soluble. The third species is the crosslinked HA hydrogel, a water-insoluble network with multiple intra- and intermolecular crosslinks. Finally, the fourth species will be unmodified HA, i.e., HA molecules that failed to be modified by even one reactive crosslinker moiety. These unmodified HA molecules are also intrinsically water soluble. Accordingly, the preparation resulting from an HA crosslinking reaction contains HA as the water insoluble crosslinked hydrogel (the third species), and the water soluble first, second and fourth species. Depending on the manufacturing process, the preparation may also contain unreacted or residual crosslinker.

35. The preparation is then processed and used in a soft tissue filler product. Depending on the manufacturing process, steps may be required to remove the unreacted or residual crosslinker, which can be toxic at high concentrations. The water soluble HA species within the preparation may or may not be removed, depending on the processing that occurs after crosslinking, such as whether the preparation resulting from an HA crosslinking reaction is directly washed or by membrane dialysis, the pore sizes of dialysis tubing if the preparation is dialyzed before being used in an HA filler composition, etc. Insoluble crosslinked HA, with or without any soluble species of HA, is then buffered to a pH and an osmolarity compatible with the human body, because the HA filler composition is generally intended for injection into a human body. Finally, the soft tissue filler product must be sterilized prior to sale or use.

36. To better understand the various HA-based wrinkle fillers, I will discuss the chemical modifications relevant to the HA derivatives used in products of the Hylaform® /Captique® /Prevelle® family, Juvéderm® family, the Restylane® /Perlane® family, the Puragen® family, and the Elevess® family, in more detail below. Four different crosslinkers are used in these chemical modifications.

Chemical modification of HA in the Hylaform ®/ Captique ®/Prevelk Silk® products

37. Reaction of HA with divinylsulfone ("DVS") under basic conditions is used to produce the crosslinked hylan B hydrogel used in the Hylaform® products. To make hylan B, one first prepares a soluble HA derivative known as hylan A by the reaction of HA in a rooster comb extract with formaldehyde. The formaldehyde treatment maintains the

water solubility of the HA, but increases its apparent molecular weight. Hylan B is then produced by the reaction of DVS, under basic conditions, with hydroxyl groups of the HA chains present in hylan A. The chemical reaction for DVS crosslinking of HA chains are illustrated in Fig. 4, where "HA-CH_2OH" is the shorthand for an HA chain and the 6-hydroxyl group of a GlcNAc residue:

The carboxylic acid groups of the GlcUA moieties of HA remain largely unaffected after this reaction, although ester formation and ester hydrolysis can occur during the reaction process.

38. Hylan B is a water insoluble hydrogel consisting of a three-dimensional network of crosslinked HA chains in which water is dispersed (i.e. the gel is "swollen" with water). It is my understanding that Hylaform® contains hylan B. It is also my understanding that Hylagel® also contains hylan B. It is also my understanding that the production of Hylagel® was described in U.S. Pat. Nos. 4,713,448 and 4,605,691 (Reinmuller I, 3:52-54).

39. I understand that Prevelle Silk® and its lidocaine-free version Captique® contain HA crosslinked with DVS manufactured in a similar manner as hylan B in Hylaform , except

that the HA is derived from a bacterial source rather than from the avian source. Moreover, I understand that the bacterial HA is not chemically modified with formaldehyde prior to DVS crosslinking.

Chemical modification of HA in the Restylane®/Perlane® and Juvéderm® products

40. Reaction of HA with diepoxide crosslinker, i.e., 1,4-butanediol diglycidyl ether ("BDDE"), under basic conditions, is used to produce the crosslinked HA in the Restylane® /Perlane® and Juvéderm® products. These products contain HA derived from bacterial fermentation. The bacterial-derived HA is crosslinked by BDDE under somewhat different reaction conditions for the Restylane®/Perlane® and Juvederm® products. The chemical reaction for BDDE crosslinking of HA is illustrated in Fig. 5:

41. In general, the BDDE crosslinking reaction is initiated by dissolving the HA in a basic solution, where the base can be, for example, sodium hydroxide or sodium carbonate. The basic conditions, preferably pH 10-12, facilitate a reaction between the Hydroxy groups of the HA, of which the 6-hydroxyl group of the GlcNAc moiety is the most reactive considering steric effects and the acidity (pKa) of the hydroxyl groups, with the

epoxy groups of one of the two glycidyl ether moieties of BDDE. This reaction leads to a new carbon-oxygen, or ether, linkage. This first step gives an HA molecule with a pendant BDDE glycidyl ether, which can connect to another HA hydroxyl group via the remaining epoxy moiety, affording a crosslink. In competition with the crosslinking is the hydrolysis of the glycidyl ether epoxide moieties to give a derivative with a pendant glyceryl ether, i.e., an unreactive pendant group with two alcohol groups (i.e., a diol). In addition, the epoxides of BDDE can also react with the nucleophilic carboxylate residues under basic conditions. However, the ester bonds formed can be hydrolyzed under the basic reaction conditions, yielding a diol terminus on the crosslinker moiety that is no longer able to form crosslinks.

42. Continued reaction at ambient or elevated temperatures results in the formation of additional modified HA with one or more pendant groups, partially BDDE crosslinked HA that is water soluble, and more completely BDDE crosslinked HA, which forms an insoluble hydrogel network. Partially crosslinked HA molecules increase the viscosity, slowing reaction rates. The insoluble gel network will form fewer new crosslinks since reaction cross-sections become effectively nil.

43. I understand that the Juvederm® products are produced by a proprietary manufacturing process, the Hylacross technology, which involves breaking down the, large gel mass of crosslinked HA by homogenization (Allemann, p630, see also Hylacross). It was reported by Allergan:

> An alternative way to size a large gel mass is to break it down by a homogenization process. The result is a gel

> formulation that displays a smooth consistency and looks like thick egg white when compared with the more granular consistency gel particle formulations mentioned above. Presumably the smooth consistency results from a much broader distribution of gel particle sizes than in products obtained by sieving. Tezel, p40.

44. It is my understanding that Lebreton, which issued as U.S. 7,741,476, describes a process that is used in the preparation of Juvederm® Voluma XC (Allergan Patent Notices), which has a product specification identical to Juvederm® Voluma (without lidocaine) with the exception that Voluma XC contains 0.3% w/w lidocaine hydrochloride (Juvederm FDA Briefing, p20-21). According to Lebreton, after crosslinking HA with BDDE in a basic medium, the crosslinked product is buffered to a pH compatible with the human body, i.e., "between 6.5 and 7.5, advantageously between 7 and 7.4 and very advantageously between 7.1 and 7.3" (Lebreton, para. [0048]). Specifically, the crosslinked product is neutralized to pH 7.2 in a phosphate buffer solution and then dialyzed (Id, para. [0070]). The concentration of the resulting hydrogel is then adjusted and the hydrogel is mechanically homogenized before being packed into syringes and sterilized in an autoclave by means of moist heat (Id.). See also Examples 3 and 4 of Lebreton.

45. It is my understanding that all products in the Juvederm family contain insoluble HA-BDDE. It was reported that some of the Juvederm® products also contain soluble uncrosslinked HA (Juvederm® Ultra, Ultra Plus and Voluma)(see, e.g., Beasley, Table 1, Voluma XC Summary, p2).

Chemical modification of HA in the Puragen® products

46. The reaction of HA with 1,2,7,8-diepoxyoctane ("DEO") is used in the crosslinking of HA in the Puragen® family of products, which also contain HA derived from bacterial fermentation. In contrast to the Restylane® and Juvéderm® families, Puragen® is prepared by a so-called double-crosslinking process. The chemical reactions proposed for DEO crosslinking of HA are illustrated in Fig. 6:

47. The first crosslinking step of HA with DEO follows a similar chemical pathway as that described above for BDDE, modifying primarily the 6-hydroxyl groups of GlcNAc residues in the HA chain. In contrast to BDDE, which is 12 atoms in length and is hydrophilic due to the presence of two oxygen atoms in the chain, DEO is eight atoms in length, and is more hydrophobic, lacking any oxygen atoms in the chain. In addition, the

epoxide groups of DEO are of somewhat lower reactivity than the glycidyl ethers of BDDE.

48. In the first crosslinking step, the basic conditions, preferably pH 10-12, facilitate a reaction between the hydroxyl groups of the HA, primarily the 6-hydroxyl groups of the GlcNAc groups, with the epoxy groups of one of the two epoxide ends of DEO, leading to a new carbon-oxygen, or ether, linkage. This gives an HA molecule with a pendant DEO ether that contains one remaining reactive epoxide moiety. Under the basic conditions, this reactive epoxide can connect to another HA hydroxyl group, affording a crosslink, or be hydrolyzed leading to an unreactive pendant diol moiety.

49. Once the first crosslinking step to give the multiple ether bond crosslinks is completed, the pH of the reaction mixture is adjusted to pH 2-4 and additional DEO may be added. In this case, the second set of crosslinks are more labile ester crosslinks between the crosslinker moiety, either as the alcohol form or as the epoxide form, and two carboxylate groups of GlcUA units in the same or different HA polymer chain. The result is a so-called double crosslinked HA.

50. It is my understanding that products in Puragen® family contain both soluble HA and insoluble crosslinked HA.

Chemical modification of HA in the Elevess® Products

51. Finally, I describe a fourth method of chemically modifying HA using electrophilic carbodiimide moieties to activate the carboxylic acid of the GlcUA moiety of the

HA chain. One such carbodiimide is p-phenylene bis(ethyl)carbodiimide ("BCDI"), a bifunctional electrophilic crosslinker, which is employed to produce the Elevess® family of products, which also contain HA derived from bacterial fermentation. The chemical reaction for BCDI crosslinking of HA is illustrated in Fig. 7:

52. In this case, the first carbodiimide activates a GlcUA carboxylate, but the reactive O-acyl intermediate is not long-lived and undergoes an O-acyl to N acyl migration, affording a stable N-acyl urea linkage between one of the reactive carbodiimide moieties and a GlcUA carboxylate moiety. As with other crosslinking reactions, the pendant N-acyl phenylene carbodiimide can be hydrolyzed or it can undergo a second crosslinking reaction with a GlcUA carboxylate in the same or different HA molecule to produce a bis-N-acyl urea crosslinked HA hydrogel.

53. It is my understanding that the Elevess® products do not contain soluble HA.

Soft tissue fillers containing water insoluble crosslinked HA with or without water soluble HA were commonly known.

54. In general, an insoluble crosslinked HA gel has increased stability and durability compared to soluble uncrosslinked HA after injection into the body. However, the crosslinked HA gel also requires more extrusion force to be injected into the skin through the fine needle of a syringe. HA in its uncrosslinked or soluble form is an excellent lubricant, and is included in many soft tissue fillers containing crosslinked HA in order to decrease extrusion force and make injection of the filler easier. Besides being a lubricant, the uncrosslinked HA may provide other benefits, such as reducing inflammatory side effect of crosslinked HA (see e.g., Reinmuller II). However, because the uncrosslinked HA will be metabolized rather quickly *in vivo*, it will not contribute to the long-term clinical outcome sought by most patients.

55. Depending on the manufacturing process, the uncrosslinked HA can be soluble HA (modified and/or unmodified by the crosslinker) that is added separately to a preparation containing insoluble crosslinked HA. The uncrosslinked HA can also be soluble HA species (modified and unmodified by the crosslinker) present intrinsically in the manufacturing process, such as those resulting from a crosslinking reaction described above, or those resulting from HA degradation during autoclaving or other manufacturing procedures.

56. It is my understanding that many of the products approved before August 2008 contain soluble HA. For example, both Juvederm® Ultra (also known as Juvederm® 24HV) and

Juvederm® Ultra Plus (also known as Juvederm® 30HV) contain uncrosslinked HA (Beasley, Table 1). Based on measurements performed by Kablik, Juvederm® Ultra Plus (30HV) contains 40% of the total HA in the soluble portion of the filler product and 60% of the total HA in the gel phase (Kablik Table 1). It was also reported that, based on data provided by the manufacturer (Allergan), each of Juvederm® Ultra and Juvederm® Ultra Plus contains 10% soluble HA and 90% insoluble crosslinked HA gels (Beasley Table 1). Prevelle® Silk and Puragen® were also reported to contain 2% and 6% soluble HA, respectively, with the remainder as insoluble gel-phase HA (Beasley Table 1, p92).

57. Other publications also described HA fillers containing soluble HA and uncrosslinked HA before August 4, 2008. For example, Debacker describes a dermal filler containing HA-BDDE in an insoluble dispersed phase and uncrosslinked HA in an aqueous solution continuous phase, mixed at a ratio of 2:1 (Debacker, Example 2). Debacker teaches that crosslinked HA is "much more stable in the body than the hyaluronic acid molecule, and also more resistant to autoclave sterilization." (Debacker, 2 :9-11). Debacker also teaches that the aqueous solution continuous phase "serves as injection vehicle for the fragments of the dispersed phase" (Debacker, 3 :34-36), and that after injection, "it protects the dispersed phase, and slows down its degradation." (Debacker, 4 :30-34)

58. Reinmuller II discloses the use of a preparation containing crosslinked and noncrosslinked HA for cosmetic or pharmaceutical use, such as for treating wrinkles of the skin (Reinmuller II, 5: 1-5, referencing to the counterpart US 7,902,171 in this IPR). Reinmuller II teaches that adding noncrosslinked HA to the preparations of exclusively

crosslinked HA suppressed the inflammatory side effects caused by the crosslinked HA (Reinmuller II, 5: 6-15).

59. Piron discloses an implant that is injectable by a sub-cutaneous or intradermal route in the form of a monophasic hydrogel. The hydrogel contains HA-BDDE and free HA (Piron, Example 2), and that the free-HA can be 5% to 50%, preferably 10% to 30% even more preferably 15% by weight of the HA component (Piron, claim 1).

Soft tissue fillers containing crosslinked HA having a mixture of high molecular weight HA and low molecular weight HA were known

60. Lebreton describes a process for crosslinking a mixture containing low-molecular weight HA and high-molecular weight HA with BDDE. According to Lebreton, using the mixture of high- and low-molecular weight HA makes it possible to obtain a monophasic hydrogel (Lebreton, ¶¶ [0021] to [0025], [0045], Examples 3&4). The prepared monophasic hydrogel contains a mixture of high- and low-molecular weight HA in BDDE crosslinked form (Lebreton, Claim 16), which can be used as a filling material in plastic and cosmetic surgery (Lebreton, ¶ [0005]).

61. Juvederm® Voluma, also named Voluma Colneal® (Hoffmann, p3), was described in the prior art publications (Expert Anti-Aging, p5-6). Juvederm® Voluma was used as Sample 6 in Example 3 of the priority documents for the '475 patent (see 1st Prov APP, Example 3). The data presented in Example 3 of the priority documents are identical to the data presented in Example 4 in the '795 patent, which also claims priority from the same priority documents. Accordingly, the two examples describe the same experiments

conducted with the same samples, even though the '795 patent no longer describes the samples by their trade names. According to Example 4 in the '795 patent, Sample 6 (Juvederm® Voluma) has a high molecular weight to low molecular weight ratio from about 10% to 90% (`795 patent, 15:42-48).

62. Indeed, as evidenced by Juvederm FDA Briefing, "in 2005, Juvederm® Voluma (without lidocaine) was CE marked and then introduced into the European market (including over 30 countries)" (Juvederm FDA Briefing, p20). "VOLUMA contains a mix of low (90%) and high (10%) molecular weight HA, "(Id, Appendix 3, page 3), and that "the product specifications of Juvéderm® VOLUMA and VOLUMA™ XC are identical with the exception of lidocaine (VOLUMA™ XC contains 0.3% w/w lidocaine hydrochloride)" (Id., p20-21).

HA based soft tissue fillers containing lidocaine were known

63. One drawback to the injection of wrinkle fillers is the pain associated with injection. Upon injection, the filler quickly fills lines and wrinkles to give a more youthful look. However, even with crosslinked HA, the filler will be slowly degraded in vivo and the lines and wrinkles will reappear. Depending on the products, a new injection is needed to refill the lines and wrinkles several months to a year or so after the initial injection. Patients who have had painful experience with a filler may not continue the rejuvenation process with the filler in the future (see Beasley, p92).

64. Lidocaine, as the most widely used local anesthetic since its introduction in 1940s, has well characterized pharmacokinetic and pharmacodynamic properties and limited risk of potential adverse events. It has been pre-included in collagen-based wrinkle fillers, such as Zyderm®, Zyplast®, CosmoDerm , and Cosmoplast , to decrease pain or discomfort related to the injection.

65. It is my understanding that doctors routinely add lidocaine with epinephrine into any HA composition that does not come premixed with lidocaine via a two-sided sterile connector (see Beasley p92).

66. Lidocaine has also been pre-included in fillers containing crosslinked HA. In fact, prior to August 2008, filler products containing lidocaine and HA crosslinked with three out of the four crosslinkers had already been approved. These products are Puragen® Plus, which contains HA crosslinked with DEO and 6% soluble HA; Prevelle® Silk, which contains HA crosslinked with DVS and 2% soluble HA; and Elevess®, which contains HA crosslinked with BCDI and no soluble HA (See Puragen Plus, Kinney, FDA Dermal Filler List, Juvederm FDA Briefing, p2, Prevelle Announcement, Beasley Table 1 & p92).

67. All of these approved lidocaine-containing fillers (collagen or HA-based) contain the same final concentration of lidocaine hydrochloride, 0.3% (w/w) (Juvederm FDA Briefing, p25; Kinney, p742), which is about 11.1 mM, considering that the molecular weight of lidocaine hydrochloride (anhydrous) is 270.80 Da. I understand that from the regulatory point of view, it is advantageous for a later applicant to use the same local

anesthetic (lidocaine hydrochloride) at the same concentration (0.3% w/w) so that the applicant may rely on safety data of the local anesthetic from previous filler applications.

68. Table 1 lists the various lidocaine-containing HA-based wrinkle fillers approved before and after August 2008:

69. In fact, an injectable gel containing Hylagel® and 2% (w/w) lidocaine was described in a PCT application filed as early as Dec 24, 1992 (Reinmuller I, Example 1), more than 15 years before the earliest priority date of the '475 patent. It is my understanding that Hylagel® contains HA gel crosslinked with DVS (Hylan B).

70. Prior to August 4, 2008, preclinical and clinical studies had demonstrated that dermal fillers containing crosslinked HA and lidocaine were stable, effective and durable (see, e.g., Toth and Hanke). In addition, multiple references had taught or suggested dermal

fillers containing lidocaine, HA-BDDE and uncrosslinked HA (see, e.g., Levy, Reinmuller II, Wortzman, Wang and Hunter).

Heat Sterilization of HA Preparations

71. As a medical device to be injected into a human body, an HA filler must be sterile. Heat sterilization or autoclaving has been commonly used to sterilize HA-based soft tissue fillers. Although other methods for rendering fillers sterile can also be used, they can be costly or have limited applications. For example, sterile filtration is not an option for gel products consisting of particles in suspension; aseptic processing may be costly; and irradiation may cause excessive depolymerization of the HA product.

72. For moist heat sterilization, usually, the HA filler composition is packaged into a syringe at a volume of about 1-5 mL, and the filled syringe is then autoclaved using a validated sterilization cycle, i.e., at a defined temperature, typically between about 120 °C and about 130 °C, for a set time, usually from a few minutes to a half hour. HA is hydrated, either at or below equilibrium hydration, in the syringe before autoclaving. During autoclaving, the microorganisms are exposed to moist heat, which irreversibly denature enzymes and proteins of the microorganism, thus killing the microorganisms. After the effective heat sterilization, the filler, packaged within a container or closure system whose integrity has been verified, remains sterile for an extended period of time, e.g., at least as long as the shelf life of the filler.

73. I understand that heat sterilization or autoclaving had been used to sterilize almost any type of HA preparations before 2008. For example, an aqueous formulation containing uncrosslinked sodium HA was sterilized in an autoclave at a temperature of 121°C for 30 minutes (Drizen 7:19-25). A hydrogel containing HA-BDDE with unreacted crosslinking agent and NaHA removed was sterilized in an autoclave (Piron 5: 19-24, Wang p7, ln 7, 24), as were hydrogels containing HA-BDDE having a mixture of high-and low-molecular weight HA (Lebreton, Examples 3-4). In addition, heat sterilization has also been used to sterilize soft tissue fillers containing uncrosslinked HA and HA-BDDE, such as Juvederm® Ultra, Ultra Plus, Voluma, the filler described in Example 2 of Debacker, and the filler described in Example 2 of Piron, all of which were published before 2008 (See Lupo in view of Ultra Label and Ultra Plus Label; Expert Anti-Aging in view of Voluma Label; Piron, Example 2; Debacker at page 14, lines 22-24, Example 2).

74. Furthermore, heat sterilization had also been used to sterilize HA preparations containing lidocaine before 2008. For example, the injectable gel containing Hylagel® and 2% (w/w) lidocaine of Reinmuller I was heat sterilized (Reinmuller I, Example 1). In addition, HA preparations containing BCDI crosslinked HA and 0.2% (w/w) or 0.3% (w/w) lidocaine, respectively, were also autoclave sterilized (Sadozai, Example 12). It was further taught to use autoclaving to sterilize compositions containing lidocaine and HA-BDDE (Wang, p7, ln 7, 24), lidocaine and HA-DVS (Calias, 3:42-43, 4:22-26), or lidocaine and HA crosslinked with polyethylene oxide (Perez, para [0025]).

Stability of HA based soft tissue fillers

75. As a polysaccharide, HA can be cleaved by both enzymatic and non-enzymatic reactions. The enzymatic reactions are catalyzed by the hyaluronidases, a family of endo- and exoglycosidase enzymes. A variety of non-enzymatic reactions can result in HA chain depolymerization, or chain cleavage. These non-enzymatic conditions include, e.g., thermal degradation, degradation on freeze drying, acidic or alkaline hydrolysis, ultrasonic degradation, degradation by oxidants, photodegradation involving microwave, UV or gamma (γ)-irradiation (Kuo, p3443).

76. Thermal degradation of HA occurs via a random-scission mechanism. Random scission involves the cleavage of the glycosidic linkage at an unspecified point on the backbone, producing fragments usually differing in chain length. The fragments break again into smaller fragments. During thermal treatment of a solution, there is often an increased formation and/or activity of reactive oxygen species, such as hydroxyl radical (see Bruskov). These reactive oxygen species are known to be involved in degradation of HA in vivo and in vitro (see e.g., Soltes and Kuo).

77. During autoclaving, thermal degradation of HA may occur. For example, the viscosity of an aqueous solution of uncrosslinked sodium HA decreased exponentially with the increase of temperature (see Lowry, Figures 1-6). Under the test conditions described in Cui, the dynamic viscosity of some crosslinked HA gels, including HA-BDDE gel, also decreased significantly after heat sterilization as compared to that before the sterilization, although the decrease was smaller than that of the unmodified HA (see Cui, Figures

5&6). For example, according to Cui, the dynamic viscosity of HA-BDDE gel was 90.01 (x 10^4 mPa.S) before heat sterilization, but was 58.53 (x 10^4 mPa.S) after heat sterilization, while the dynamic viscosity for unmodified HA (natural HA) gel was 50.39 (x 10^4 mPa.S) before and 20.43 (x 10^4 mPa.S) after the heat sterilization. (Note that mPa.S and mPa*s are equivalent notations for millipascal-seconds, a unit of dynamic viscosity.)

78. The rate of thermal degradation of HA fillers depends on multiple factors, such as the autoclaving conditions (e.g., temperature, processing time and pressure), the solution properties (e.g., pH and ionic strength), the HA molecular properties (e.g., molecular weight, crosslinking agent, degree of crosslinking), the physical properties of the filler (e.g., particle size of crosslinked HA, concentrations of crosslinked and uncrosslinked HA, intended level of hydration), properties of other chemicals in the filler, etc.

79. It was known that, in general, crosslinked HA is much more resistant to heat degradation than unmodified HA (See e.g., Debacker, 2 :9-11, also Cui Figures 5 and 6).

80. It must be noted that even though some HA degradation may occur during the manufacturing process, such as autoclaving, the finished HA filler product can be very stable. The HA filler products, many (if not all) of them have been sterilized by autoclaving and commonly have a shelf-life of 1 to 3 years, as in the approved HA filler products.

Lidocaine was known to stabilize HA

81. I am not aware of any teaching from the scientific literature, nor have I had any personal experience that lidocaine would destabilize crosslinked HA or uncrosslinked HA, either during autoclaving or when stored at room temperature. Indeed, the notion that lidocaine would destabilize HA products is counterintuitive to the skilled person familiar with HA products.

82. Lidocaine is a prototypical amide local anesthetic having the chemical structures shown in Figure 8, with the free base form (non-ionized) shown at left and the protonated ammonium form (ionized) shown at right:

The non-ionized free base form of lidocaine is nearly insoluble in water, whereas the protonated ammonium form is highly soluble in water. The pKa of lidocaine is about 7.9 at room temperature (Powell, Table 2). The pKa expresses the relationship between the two forms of lidocaine: at a pH equal to the pKa, the base and protonated forms of lidocaine are present at equilibrium in equal amounts. At a pH higher than the pKa, the protonated form becomes de-protonated, resulting in a greater proportion of the free base form (a); and at a pH lower than the pKa, the base form becomes protonated (b), resulting in a greater proportion of the protonated form. It was reported that at 25 °C, the

pH of maximum stability for lidocaine is 3-6 (Powell, p44). Thus, for better solubility and stability, lidocaine is usually provided as the protonated form in an acidic solution, most commonly as a lidocaine HC1 solution. Lidocaine HCl powder is commercially available. Dissolving lidocaine HCl powder in water results in an acidic solution. For example, a 0.5% (w/w) solution of lidocaine HCl has a pH of 4-5.5 (See Ph. Eur. monograph 0227).

83. The pKa of lidocaine is known to be temperature dependent, with a pKa of about 7.9 at room temperature, and a pKa of about 6.6 at 100°C (Powell, Table 2). This indicates that upon an increase in temperature, the pH of a lidocaine-containing solution would be expected to decrease. For example, a solution of lidocaine HC1 will become even more acidic at an elevated temperature for autoclaving.

84. Lidocaine is very stable at room temperature and degrades slowly at higher temperature (Powell, p42). It is my understanding that the loss of lidocaine during autoclaving under the conditions for HA heat sterilization or during storage in an HA filler composition at room temperature, if any, would be very minor and negligible.

85. Lidocaine was known to have antioxidant properties, and it functions as a potent hydroxyl radical scavenger and singlet oxygen quencher (see Das). Das teaches that lidocaine was a more potent hydroxyl radical scavenger than thiourea and mannitol, and a P R U H S R W H Q W T X H Q F K H U R I V-carotene in the reaction W K D Q D] L systems (Das, p183). For example, Das showed that in a Fenton type reaction, lidocaine

at 80 μM was able to cause 50% inhibition of hydroxyl radical formation, and virtually eliminated the hydroxyl radical formation at 300 μM (Das, p183). These lidocaine concentrations are at least 30-fold lower than the 0.3% lidocaine (11 mM) used in dermal fillers. In view of Das, 0.3% lidocaine would be expected to be highly effective as a hydroxyl radical scavenger.

86. It was known that lidocaine inhibits the degradation of HA by hydroxyl radicals by acting as a scavenger of said hydroxyl radicals (see Lindvall, p9). Lindvall reports that myeloperoxidase (MPO), in the presence of hydrogen peroxide, degrades HA (Lindvall, Abstract) via a mechanism involving hydroxyl radicals. This degradation was inhibited by mannitol, lidocaine, and other compounds (Lindvall, p5, Table 2). For example, Lindvall teaches that lidocaine, at the tested concentrations of 50 to 500 μM, was able to inhibit the depolymerization of HA similarly to that of mannitol, and indicates that this (hydroxyl radical scavenger) property of lidocaine may explain its protective effect on the dermal response to high-energy irradiation (see Lindvall, p9). These lidocaine concentrations are at least 20-fold lower than the 0.3% lidocaine (11 mM) used in dermal fillers. In view of Lindvall, 0.3% lidocaine would be expected to be very effective in protecting HA against the degradative effect of hydroxyl radicals.

87. It was taught that in addition to acid hydrolysis and high temperature, oxidative degradation also contributes to loss of viscosity in a hydrogel, which can be an HA gel (Ji, para. [0046]), and that adding free radical scavenging moieties to the hydrogel, before or after autoclaving, decreases viscosity loss due to heat and/or storage (Ji, paras.

[0061]-[0064]). Consistent with Das, Lindvall and Ji, it was taught that an HA composition is stabilized by the inclusion of lidocaine compared to an otherwise identical composition that does not include lidocaine (Sadozai, paras. [0068] and [107] and FIGs. 5 and 7).

Understanding the Claim Terms of the '475 patent

88. I have been asked to opine on the following claim terms/phrases in the '475 patent: "stable, sterile soft tissue filler," "uncrosslinked HA," "free HA," "crosslinked HA," "% free (or uncrosslinked) HA by volume," and "degree of crosslinking."

89. I was informed and understand that in *inter partes* review (IPR), claim terms are given their broadest reasonable interpretation (BRI) in light of the specification of the patent in which they appear as understood by a POSITA.

"stable, sterile soft tissue filler"

90. In my opinion, consistent with the specification of the '475 patent, the BRI claim construction for "stable, sterile soft tissue filler" should be

> a soft tissue filler that is free of viable microorganisms as determined by a sterility test recognized by a regulatory authority, the filler can be sterilized by any method known in the art, and is resistant to degradation such that the soft tissue filler maintains one or more of the following aspects:
> transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration, after effective sterilization and being stored at a temperature of at least about 25°C for at least about two months.

91. The specification of the '475 patent does not provide a definition of "stable, sterile soft tissue filler." It defines "autoclave stable or stable to autoclaving" as following:

> Autoclave stable or stable to autoclaving as used herein describes a product or composition that is resistant to degradation such that the product or composition maintains at least one, and preferably all, of the following aspects after effective autoclave sterilization: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration. ('475 patent, 4:41-48)

According to the above definition, an "autoclave stable" composition or a composition that is "stable to autoclaving," maintains at least one of the listed aspects, but does not require all of the listed aspects to remain unchanged. The definition requires the composition to maintain the at least one aspect after effective autoclave sterilization, but does not require all of the listed aspects to remain unchanged from before to after effective autoclave sterilization. Indeed, because the filler composition only becomes sterile after the effective autoclave sterilization, it is impossible for any filler to maintain all of the aspects, which include sterility, before and after effective autoclave sterilization. The specification or the prosecution history of the '475 patent does not provide any data to show that any filler composition maintains the same one or more aspects of transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration viscosity before and after autoclaving.

92. The "autoclave stable" definition provided by the '475 patent does not specify for how long after the effective autoclave sterilization and under what condition the composition

must maintain the one or more aspects. According to the following disclosure in the specification, the composition remains "stable" during storage at temperatures of at least about 25° C for at least about two months:

> The present products and compositions also remain stable when stored for long periods of time at room temperature. Preferably, the present compositions remain stable for a period of at least about two months, or at least about six months, or at least about 9 months, or at least about 12 months, or at least about 36 months, at temperatures of at least about 25° C. In a specific embodiment, the compositions are stable at a temperature up to about 45° C. for a period of at least two months. ('475 patent, 8:4-13)

93. The specification of the '475 patent does not limit the sterilization technique to autoclaving or heat sterilization as shown by the following:

> Sterilization, as used herein comprises any method known in the art to effectively kill or eliminate transmissible agents, preferably without substantially altering of degrading the HA/lidocaine F R P S R V L W L R Q ('475 patent, 11:4-7)

The specification of the '475 patent describes several sterilization techniques including autoclaving ('475 patent, 11:18-28), the use of a gaseous species (S D W 11:29-33) and the use of an irradiation source ('475 patent, 11:34-44).

94. In view of the specification, the BRI construction for "sterile soft tissue filler" should read on a soft tissue filler that is effectively sterilized by any method, not limited to heat sterilization (autoclaving). The BRI construction for "stable, sterile soft tissue filler" does not require the sterile soft tissue filler to be free of HA degradation during sterilization, so long as the filler maintains one, not necessarily all, of the following aspects: transparent

appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration, after the effective sterilization and being stored at a temperature of about 25°C for a period of about two months.

95. Accordingly, under the BRI construction, a soft tissue filler composition that physicians routinely make immediately before injection by mixing a sterile lidocaine solution with a sterile and stable HA filler that does not come premixed with lidocaine (Beasley p92), such as Juvederm® Ultra Plus, would read on a "stable, sterile soft tissue filler," because such a combination product would be sterile, and would maintain at least the sterility after being stored at temperatures of at least about 25° C for a period of at least about two months.

96. It must be noted that although crosslinked or uncrosslinked HA may be subjected to degradation, even significant degradation, during autoclaving, the heat sterilized HA filler product can remain stable and have a shelf-life of 2 months or more at room temperature after autoclaving. For example, after being sterilized in an autoclave at a temperature of 121°C for thirty minutes, a preparation containing uncrosslinked HA is "extremely storage stable over a wide range of temperatures, including temperatures as high as 86°F (30 °C), for at least three years" (Drizen, 7:44-46). Also, it was reported that at 25 °C, a 10% decrease in viscosity of an uncrosslinked HA preparation requires many thousands of hours (Lowry, p1244), i.e., a few months. Furthermore, all of the Juvederm® products Ultra, Ultra Plus and Voluma, have a shelf life of about 2 years even

though they are sterilized by moist heat, i.e., autoclaving (Ultra Label, Ultra Plus Label and Voluma Label).

97. In fact, under the BRI construction, any effectively sterilized soft tissue filler composition containing HA and lidocaine would read on "stable, sterile soft tissue filler," because such composition would maintain at least its sterility for a period of at least about two months after being stored at temperatures of at least about 25° C. The filler composition would also maintain at least the lidocaine concentration after being stored at temperatures of at least about 25° C for a period of at least about two months, because lidocaine is very stable at room temperature (Powell, p42). The filler would further maintain properties related to HA, such as the extrusion force, rheological characteristics and HA concentration after being stored at temperatures of at least about 25° C for a period of at least about two months, in view of the known stability of sterilized HA at room temperature (see Drizen, 7:44-46, and Lowry, p1244). After effective sterilization, crosslinked HA, if it is not more stable, would be at least as stable as uncrosslinked HA, at room temperature.

98. Because an HA filler is intended for injection into a human body, it must be sterile, i.e., free of viable microbes as determined by a sterility test acceptable by the regulatory agency and sterilized using a validated sterilization cycle. It is my understanding that in order to obtain regulatory approval, the sterile HA filler must be stable during its shelf life, which can be months to years at the recommended storage temperature. A filler composition with less than 2 months shelf life would be unlikely to

produce a long-lasting cosmetic effect sought by the patients. The stability of an HA gel is based on tests for sterility, visual appearance, endotoxin, viscoelastic properties of crosslinked gel, UV absorbance, pH, osmolality, HA concentration, extrusion force, HA fragments and lidocaine concentration (see Elevess Summary, p6). The tests are conducted on an HA filler after it has been effectively sterilized, regardless of whether any or all of the above aspects stay the same before and after sterilization. It is my understanding that Elevess® has an expiration date of 15 months (Elevess Summary, p6). Each of Juvederm® Ultra, Ultra Plus and Voluma has a shelf life of 2 years when stored from 2 to 25 °C (Ultra Label, Ultra Plus Label and Voluma Label). Therefore, any of the regulatory approved HA filler products, such as those in the Restylane®/Perlane®, Juvederm®, Elevess®, Puragen® and Hylaform®/Captique /Prevelle® families, would by necessity be a "stable, sterile soft tissue filler."

³XQFURVVOLQNHG +$

99. In my opinion and consistent with the specification of the '475 patent, the BRI claim construction for "uncrosslinked HA" and "free HA" should be the same, i.e., "HA chains and fragments within the water soluble or fluid portion of the filler."

100. The specification of the '475 patent defines "free HA" as following:

> Free HA as used herein refers to individual HA polymer molecules that are not crosslinked to, or very lightly crosslinked to (very low degree of crosslinking) the highly crosslinked (higher degree of crosslinking) macromolecular structure making up the soft tissue filler composition. Free HA generally remains water soluble. Free HA can alternatively be defined as the "uncrosslinked," or lightly

> crosslinked component of the macromolecular structure making up the soft tissue filler composition disclosed herein. (`475 patent, 5:5-13).

101. According to the '475 patent:

> For purposes of this disclosure, free HA includes truly uncrosslinked HA as well as lightly crosslinked HA chains and fragments, all L Q V R O X E O H I R U P L Q Z D W H U µ patent, 3:10-13).

102. The specification of the '475 patent does not explain what distinguishes "free HA" from "uncrosslinked HA," or "truly uncrosslinked HA" from "uncrosslinked HA." Nor does the specification teach how one may make a soft tissue filler with certain desired amount of "free HA" or "uncrosslinked HA," or how one may measure the amount of "free HA" or "uncrosslinked HA" in a soft tissue filler.

103. In view of the specification and in my opinion, "uncrosslinked HA" and "free HA" should have the same BRI construction, i.e., "HA chains and fragments within the water soluble or fluid portion of the filler." The "uncrosslinked HA" or "free HA" includes any water soluble HA species in the filler regardless of whether the soluble HA is chemically modified or not, or whether the soluble HA is added separately to the crosslinked HA (defined below), present intrinsically with the crosslinked HA from a crosslinking reaction, or produced intrinsically during other manufacturing procedures, such as autoclaving.

104. The BRI construction of "uncrosslinked HA" or "free HA" can include one or more of the following three water soluble species of HA in a filler: chemically modified HA with one or more pendant groups and in which the pendant reactive moiety was hydrolyzed and never formed a crosslink; partially or lightly crosslinked HA, in which the pendant reactive moiety formed one or more intra-intermolecular crosslinks, but failed to be incorporated into the insoluble gel network in the filler; and unmodified HA.

³+$ FURVVOLQNHG ZLWK %''(´ RU ³%''(FURVVOLQNHG +$´

105. In my opinion and consistent with the specification of the '475 patent, the BRI claim construction for "HA crosslinked with BDDE" or "BDDE crosslinked HA" should be the same, i.e., "HA chains and fragments within the water insoluble portion of the filler composition, which are formed by crosslinking with BDDE."

106. The specification of the '475 patent does not contain a definition of "HA crosslinked with BDDE" or "BDDE crosslinked HA." However, these terms were clearly meant to read on HA species that are not covered by "uncrosslinked HA" or "free HA." In view of the BRI claim construction for "uncrosslinked HA" or "free HA," the terms "HA crosslinked with BDDE" or "BDDE crosslinked HA" have the same meaning, and should read on HA chains and fragments within the water insoluble portion of the filler, or the water insoluble gel portion of the filler composition, which is formed by crosslinking with BDDE.

"% free (or uncrosslinked) HA by volume"

107. In my opinion, consistent with the specification of the '475 patent and the common knowledge, the BRI claim construction for "% free (or uncrosslinked) HA by volume" should be:

the weight ratio percentage of uncrosslinked HA in a filler composition, which can be calculated by:

$$\frac{\text{(the mass of uncrosslinked HA in the composition)}}{\text{(the mass of total HA in the composition)}} \times 100$$

108. The specification of the '475 patent does not explicitly define "% free (or uncrosslinked) HA by volume." It may appear that "% free (or uncrosslinked) HA by volume" means the volume ratio percentage (v/v%) of free (or uncrosslinked) HA in a filler composition, which should be calculated by [the volume of free (or uncrosslinked) HA in the composition/the volume of total HA in the composition] x 100. However, it is unclear to me how the volume of free (or uncrosslinked) HA and the volume of total HA would be measured. For example, should they be the volumes of the respective dry form of HA before being mixed with other ingredients of the filler composition, or the volumes of the respective HA forms in hydrated form after being mixed with other ingredients of the filler composition? Either way, the specification fails to fully explain how one would measure the volumes of the dry or wet forms of the respective HA components. The specification contains no disclosure on how to measure the respective volumes, and therefore no disclosure on how to calculate the "% uncrosslinked HA by volume."

109. Accordingly, in view of the specification, the claims, and the common knowledge, the reasonable BRI construction that a POSITA may have for "% free (or uncrosslinked) HA by volume" would be the weight ratio percentage of free (or uncrosslinked) HA in the filler composition, which can be determined by [the mass of free (or uncrosslinked) HA in the composition/the mass of total HA in the composition] x 100.

"degree of crosslinking"

110. In my opinion, consistent with the specification of the '475 patent, the BRI claim construction for "degree of crosslinking" should be:

> the weight ratio percentage of the total mass of crosslinking agents to the total mass of HA-disaccharide units within the water insoluble crosslinked portion of the HA based composition.

111. The specification of the '475 patent defines "degree of crosslinking" as follows:

> Degree of Crosslinking as used herein refers to the intermolecular junctions joining the individual HA polymer molecules, or monomer chains, into a permanent structure, or as disclosed herein the soft tissue filler composition. Moreover, degree of crosslinking for purposes of the present disclosure is further defined as the percent weight ratio of the crosslinking agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of HA monomers to crosslinker (HA monomers:crosslinker). µ(patent, 4:2 ±5:4)

I found the aboY H G H I L Q L W L R Q R I G H J U H H R I '475 patent V O L Q N L Q J confusing, particularly in light of the conventional definition below as given by Tezel. As explained in detail above in this Declaration, a chemically crosslinked HA contains crosslinking agents in three forms: an intramolecular junction that covalently connects different regions within one HA chain together; an intermolecular junction that

covalently connects one HA chain to another HA chain; and a pendant group that fails to form crosslinks within or between HA chains. The first sentence of the definition refers to the "degree of crosslinking" as the "intermolecular junctions joining the individual HA polymer molecules, or monomer chains, into a permanent structure." This definition would exclude crosslinking agents in the intramolecular junctions and pendant groups within the insoluble crosslinked gel. The second sentence of the definition further defines the "degree of crosslinking" as the "percent weight ratio of the crosslinking agent to HA-monomeric units within the crosslinked portion of the HA based composition." This definition would include all forms of crosslinking agents within the insoluble crosslinked gel, including those in the intermolecular junctions, intramolecular junctions and pendant groups. The third sentence in the definition describes that the "degree of crosslinking" "is measured by the weight ratio of HA monomers to crosslinker HA monomers:crosslinker)." The last two sentences in the definition appear to describe two different weight ratios, one of which (the last sentence) does not make sense to a trained chemist. For example, if in a given sample, there were 10 mg of crosslinker and 100 mg of HA disaccharide units, then the weight ratio by the last sentence would be 100 mg/10 mg = 1000%. In contrast, the penultimate sentence would give a weight ratio of 10 mg/100 mg, or 10%. For this example, the only reasonable construction for the POSITA would be 10%.

112. Accordingly, in view of the specification and the claims, the reasonable BRI construction that a POSITA may have for "degree of crosslinking" should be "the weight ratio percentage of the total mass of crosslinking agents to the total mass of HA-disaccharide

units within the water insoluble crosslinked portion of the HA based composition." This BRI construction of "degree of crosslinking" involves the total mass of crosslinking agents in the insoluble crosslinked HA gel, regardless of whether the crosslinking agents are in the intramolecular junctions, intermolecular junctions, or pendants. Thus, the BRI construction of "degree of crosslinking" is in fact the same as the degree of modification of the insoluble crosslinked HA gel, regardless of whether the modification forms an intermolecular linkage or not.

113. I note that this weight ratio percentage (wt%) BRI construction of "degree of crosslinking" is unusual and non-standard, and can lead to confusion when one compares the degree of crosslinking used in the '475 patent with the published degree of crosslinking in dermal fillers. A conventional definition of degree of crosslinking can be found at page 38 of Tezel:

> The degree of crosslinking indicates the percentage of HA disaccharide monomer units that are bound to a crosslinker molecule. Thus, to say that a dermal filler has a degree of crosslinking of 4% means that, on average, there are four crosslinker molecules for every 100 disaccharide monomeric units of HA.

Accordingly, the conventional degree of crosslinking is defined by the percentage of the number of HA disaccharide units modified by the number of crosslinker. It is calculated as a mole ratio percentage (mol%) of the total moles of crosslinkers versus the total moles of the HA-disaccharide units within the water insoluble crosslinked portion of the HA based composition.

114. Because the molecular weight (MW) of BDDE (202.25 Da) is about half of the MW of the HA-disaccharide units (401.30 Da), the conventional mole ratio percentage (mol%) degree of crosslinking is about 2x the weight ratio percentage (wt%) "degree of crosslinking" as used in the '475 patent in view of the following calculation:

degree of crosslinking (wt%)= BDDE (wt)/HA disaccharide units (wt)
degree of crosslinking (mol%) = BDDE (mol)/HA disaccharide units (mol)
BDDE (mol) = BDDE (wt)/BDDE MW (202.25 Da)
HA disaccharide units (mol) = HA disaccharide units (wt)/
HA disaccharide unit MW(401.30 Da)
Therefore,
degree of crosslinking mol% = [BDDE (wt)/202.25 Da)]/
[HA disaccharide units (wt)/401.30 Da)]
~2 x[BDDE(wt)/HA disaccharide units (wt)]

~2x Degree of crosslinking (wt%) (BRI)

For example, the dermal filler illustrated in Tezel that has 4% degree of crosslinking would have 2% degree of crosslinking under the BRI of the '475 patent.

<u>Opinions on the Validity of the Challenged Claims</u>

115. I have been asked to give my opinions on whether as of August 4, 2008, a POSITA would have considered a soft tissue filler composition containing lidocaine, HA-BDDE and uncrosslinked HA as recited in claims 1-9,and 18-37 of the '475 patent to be known or obvious over the disclosures in the prior art.

116. In my opinion, as of August 4, 2008, the soft tissue filler compositions recited in claims 1-9 and 18-37 of the '475 patent were well known and/or would have been obvious to a POSITA. In forming my opinion, I have relied on the '475 patent claims and disclosure,

WKH SULRU DUW H[SHULPHQWDO GDWD DWWDFKHG LQ exhibits to the IPR Petition, and my own experience and expertise of the knowledge of the POSITA in the relevant time frame (before August 4, 2008). I understand that the meaning of the terms in the claims of the '475 patent will be determined by the USPTO Patent Trial and Appeal Board (Board). For purposes of this Declaration, I will use the BRI claim construction presented above and in the IPR. I reserve the right to amend my opinions in light of the Board's claim construction.

Stable dermal fillers containing lidocaine, uncrosslinked HA and HA-BDDE had been disclosed in the prior art

117. I have reviewed the arguments presented in Ground 1 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 1-9 of the '475 patent are anticipated by Hunter, evidenced by Beasley.

118. I have also reviewed the arguments presented in Ground 3 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 1, 4, 5, 8, 9 and 27-29 of the '475 patent are anticipated by Levy, evidenced by Prager, Hylacross Technology, Beasley, µ patent, 1st Prov App, and Kablik.

119. I noticed that Wortzman also teaches that any dermal fillers, such as Juvéderm™ and Restylane®, can further include an anesthetic material, such as lidocaine (Wortzman, para. [0033]-[0034]). The same disclosure was included in its priority document, U.S. Prov. Appl. No. 60/953,661, which was filed Aug. 2, 2007, more than 1 year before the earliest priority claimed by the '475 patent. In my opinion, Wortzman anticipates claims

1-7 and 9 of the '475 patent for at least the same reasons as those discussed in Ground 1 in the IPR Petition based on Hunter. In my opinion, Wortzman also anticipates, or in the alternative, renders claims 1, 4, 5, 8, 9 and 27-R I W K H µ S D W H Q W R E Y L R X the same reasons as those discussed in Ground 3 in the IPR Petition based on Levy.

A POSITA would have been highly motivated to add 0.3% (w/w) lidocaine to a preexisting filler product with a reasonable expectation of success to obtain the filler compositions of claims 1-9 and 18-37

120. In my opinion, a POSITA would have considered the stable, sterile soft tissue filler as claimed in claims 1-9 and 18-37 of the '475 patent obvious. A POSITA would have been highly motivated to make a stable, sterile soft tissue filler containing HA-BDDE, uncrosslinked HA, and lidocaine as claimed in the '475 patent, and would have had a reasonable expectation of success to obtain such soft tissue filler by using well-established prior art procedures before August 4, 2008. In addition, no unexpected superior results are achieved by the claimed fillers over the prior art.

121. As discussed in detail in the Technical Background and State of the Art, HA-based soft tissue fillers were under rapid development before August 2008. HA crosslinked with each of four crosslinkers, i.e., BDDE, DVS, DEO and BCDI, had been used in approved filler products for increased stability and durability. Uncrosslinked HA had been used together with crosslinked HA as a lubricant to reduce the extrusion force and ease the injection. More specifically, wrinkle fillers containing HA-BDDE and uncrosslinked HA had been approved and disclosed in the prior art, such as Restylane® (Hunter), Juvederm® J24HV and J30HV (Lupo), and Voluma Corneal® Expert Anti-Aging (

122. I understand that J24HV is also named Juvederm® Ultra and J30HV is also named Juvederm® Ultra Plus (Allemann, p630), and that Voluma Corneal® is the same as Juvederm® Voluma (Hoffmann, p3). I further understand that Juvederm® Ultra and Juvederm® Ultra Plus each contain HA-BDDE and at least 10% fluid HA (Beasley Table 1), which reads on uncrosslinked HA under the BRI construction. Juvederm® Voluma also contains HA-BDDE (Voluma Label) and some remaining lightly crosslinked and uncrosslinked HA" (Voluma XC Summary, p2), which in my opinion either inherently reads on the claimed "at least 10%" uncrosslinked or free HA or renders this claim element obvious.

123. Also, as discussed above in the Technical Background and State of the Art, pain is a major barrier to cosmetic treatment. To reduce the pain, 0.3% (w/w) lidocaine had been included in wrinkle fillers. An injectable gel containing HA-DVS (Hylan B) and lidocaine prepared by heat sterilization was described in a PCT application filed as early as Dec 24, 1992 (Reinmuller I, Example 1). Preclinical and clinical studies had demonstrated that dermal fillers containing crosslinked HA and lidocaine were stable, effective and durable (see, e.g., Toth, Hanke and Sadozai). In fact, before August 2008, dermal fillers containing lidocaine and HA crosslinked with three out of the four crosslinkers, i.e., DEO, BCDI and DVS, had already obtained regulatory approval as Puragen® Plus, Elevess®, and Prevelle® Silk, respectively. See Kinney, Elevess Summary, and Prevelle® Announcement.

124. There was a need for a wrinkle filler containing lidocaine and HA crosslinked with the fourth crosslinker, BDDE, for patients who prefer BDDE than the other crosslinkers. In addition, because patients who have had painful experience with a filler may not continue the so-called rejuvenation process with the filler in the future (see Beasley, p. 92 and Kinney p. 746), there was also a strong commercial need for manufacturers of HA-BDDE wrinkle fillers to add lidocaine to their products in order to remain competitive in the filler market. Accordingly, a POSITA would have been highly motivated to add lidocaine (Toth, Reinmuller II, Kinney, etc) to an existing stable and sterile wrinkle filler containing HA-BDDE and uncrosslinked HA, such as J24HV and J30HV (Lupo), Voluma Corneal® (Expert Anti-Aging), in an effort to obtain a stable, sterile soft tissue filler that can be injected with less pain.

125. The POSITA would have had a reasonable expectation of success to obtain a stable, sterile soft tissue filler that contains 0.3% (w/w) lidocaine and the HA component from an existing Juvederm® product, even when the soft tissue filler is sterilized by autoclaving. Under the BRI claim construction, a "stable, sterile soft tissue filler" is not required to be completely free of HA degradation during sterilization. Any effectively sterilized soft tissue filler containing HA and lidocaine would read on "stable, sterile soft tissue filler," because such filler would maintain its sterility after being effectively sterilized, and it would also maintain its lidocaine concentration and HA concentration in view of the known stability of lidocaine (Powell, p42) and the known stability of heat sterilized HA (see Drizen, 7:44-46, and Lowry, p1244) at room temperature. In view of the common knowledge on sterility and the known stabilities of lidocaine and HA at

room temperature, a POSITA would have reasonably expected that, although some HA degradation may occur during autoclaving, the effectively sterilized soft tissue filler would maintain most, if not all, of the following aspects: transparent appearance, pH, extrusion force, rheological properties, HA concentration, sterility, osmolarity, and lidocaine concentration, after being stored at room temperature for 2 or more months after the heat sterilization.

126. This reasonable expectation of success is further supported by the various stable and sterile soft tissue fillers that existed before August, 2008. For example, each of Juvederm® Ultra and Ultra Plus and Voluma contains HA-BDDE and uncrosslinked HA, and has a shelf life of about 2 years after being sterilized by moist heat. This clearly demonstrates that a stable and sterile combination of HA-BDDE and uncrosslinked HA could be readily obtained as in the prior art. Each of Puragen® Plus, Elevess® and Prevelle® Silk contains 0.3% (w/w) lidocaine and HA crosslinked with one of three crosslinkers DEO, BCDI and DVS, respectively. In addition, Puragen® Plus and Prevelle Silk also contain uncrosslinked HA, i.e., 6% and 2%, respectively. As discussed under Technical Background and State of the Art, although the HA products crosslinked with DEO, BCDI and DVS are chemically distinct and different from the HA-BDDE products, all produced stable and sterile soft tissue fillers when combined with lidocaine. This indicates or strongly suggests that sterile and stable soft tissue fillers containing lidocaine, crosslinked HA in general regardless of the type of crosslinker, with or without uncrosslinked HA, can be obtained using methods known in the art. I am not aware of any teaching in the prior art that suggests that lidocaine would cause a stable soft tissue

filler containing uncrosslinked HA and HA-BDDE to be unstable, when it was known that the filler containing uncrosslinked HA and HA-BDDE is stable, and it was further known that fillers containing lidocaine and three other types of crosslinked HA, with or without uncrosslinked HA, are also stable.

127. I have reviewed the arguments presented in Ground 2 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 1-9 and 30 27 would have been obvious over *Lupo*, evidenced by *Beasley* '795 patent, 1st Prov App, *Allemann* and *Kablik*, in view of *Toth* or *Kinney*. I also have reviewed the arguments presented in Ground 4 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 18 and 31-37 would have been obvious over *Lupo*, evidenced by *Beasley* and *Allemann*, in view of *Toth* or *Kinney*, and further in view of *Reinmuller I*. I have further reviewed the arguments presented in Ground 7 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 19-26 would have been obvious over *Expert Anti-Aging* in view of *Sadozai* and further in view of *Lebreton*.

A POSITA would have been motivated to add 0.3% (w/w) lidocaine to a composition in Debacker or Piron with a reasonable expectation of success to obtain the claimed filler

128. As discussed above, uncrosslinked HA had been commonly used together with crosslinked HA to serve as a lubricant. For example, the two-phase filler composition described in Example 2 of *Debacker* contains HA-BDDE and 33% uncrosslinked HA. The filler composition according to Example 2 of *Debacker* contains a mixture of 33% uncrosslinked HA (continuous phase) and exclusively crosslinked HA-BDDE (dispersed phase) (*Debacker*, Example 2). According to *Debacker*, its filler composition "has both a

highly gelatinous character, appreciable lubricity, good biocompatibility as well as good behavior in the body" (*Debacker*, p5, lines 15-17). The uncrosslinked or slightly crosslinked HA in the continuous phase "serves as injection vehicle" and "protects the dispersed phase and slows down its degradation." (*Id.* p4, lines 22 and 33-34). When tested *in vivo*, the product prepared according to Example 2 did not cause notable inflammatory reaction and was effective for long-lasting treatment of cutaneous hollows.

129. It was also commonly known that uncrosslinked HA is generally less stable than crosslinked HA, and is more prone to heat degradation (See e.g., *Debacker*, 2 :9-11, also Cui Figures 5 and 6). Thus, there was a need to obtain a more stable and durable soft tissue filler that contains a significant amount, such as 10% or more, of uncrosslinked HA.

130. As discussed under Technical Background and State of the Art, it was taught that lidocaine stabilizes an HA soft tissue filler (*Sadozai*, para. [0068]). It was commonly known that reactive oxygen species are involved in HA degradation *in vivo* and *in vitro* (see *Soltes*, also *Ji* para. [0046])), and that they were generated during thermal treatment of a solution (see *Bruskov*). It was also known that lidocaine is "a potent scavenger of hydroxyl radicals" and a "potent quencher of singlet oxygen," and that lidocaine (300 μM) virtually eliminated the hydroxyl radical formation (*Das*, pp. 182-183). In addition, lidocaine (50 to 500 μM) inhibited the depolymerization of HA by myeloperoxidase (MPO) in the presence of hydrogen peroxide, in a mechanism involving scavenging hydroxyl radicals (*Lindvall*, p5, Table 2). It was further taught that adding free radical

scavenger to a hydrogel decreases viscosity loss due to heat and/or storage (Id., paras. [0061]-[0064]).

131. More specifically, Sadozai teaches a composition containing HA crosslinked with BCDI for use in tissue augmentation (Sadozai, Abstract). According to Sadozai, lidocaine can have a synergistic effect on the rheological properties of crosslinked HA, stabilizing the HA composition during and after autoclaving compared to otherwise identical compositions without the lidocaine (Id., Examples 12&21, Fig. 7, paras. [0068] and [0069]).

132. Accordingly, a POSITA would have been highly motivated to add lidocaine to an HA filler containing HA-BDDE and at least 10% uncrosslinked HA, such as the filler composition described in Example 2 of Debacker, not only to reduce pain associated with injection, but also as a stabilizer (as taught by Sadozai) in an effort to obtain a more stable and sterile soft tissue filler that can be injected with less pain.

133. The POSITA would have had a reasonable expectation of success to obtain a stable, sterile soft tissue filler containing lidocaine, HA-BDDE and uncrosslinked HA. Nothing in the prior art teaches that the addition of lidocaine to an HA filler would cause the filler composition to become unstable. To the contrary, the POSITA would have reasonably expected that, if 0.3% (w/w) (about 11.1 mM) lidocaine were to have any effect, it would make the HA filler more stable and durable, due to reduction of the known degradative effect of reactive oxygen species on HA (See Soltes) and the known antioxidant or protective activity of lidocaine, even at much lower concentrations (Das, Lindvall).

134. I have reviewed the arguments presented in Ground 5 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 1-4, 8, 9, -36 and 34 would have been obvious over Debacker in view of Sadozai I have reviewed the arguments presented in Ground 6 of the IPR Petition, and agree that for at least the reasons stated in the Petition, claims 5-7, 18, 27-33 and 37 would have been obvious over Debacker in view of Sadozai and further in view of Reinmuller.

135. I noticed that similar to Debacker, Piron also discloses an injectable soft tissue filler that contains HA-BDDE and free HA (Piron, Example 2), and the free-HA can be 5% to 50%, preferably 10% to 30%, even more preferably 15% by weight of the HA component (Piron, claim 1). In my opinion, for reasons similar to those discussed above and presented in the IPR petition, claims of the '475 patent would also have been obvious over Piron in combination with any of the references that teaches to add 0.3% lidocaine to an HA composition, such as Lupo or Sadozai

The percentage of uncrosslinked HA does not make the claims patentable

136. Claims of the '475 patent recite a level of uncrosslinked HA that is greater than 10%. For example, claim 1 of the '475 patent recites "greater than about 10% uncrosslinked HA", claim 2 recites "at least about 15% uncrosslinked HA", and claim 3 recites "at least about 20% uncrosslinked HA." I was asked to opine on whether the claimed amount of uncrosslinked HA would have made the claimed fillers patentable over the prior art.

137. In my opinion, the claimed amount of uncrosslinked HA would not have made the claimed filler compositions patentable over the prior art, at least because the claimed amount of uncrosslinked HA was either already used in the prior art or would have been easily obtained by routine experimentation. As I discussed above under Technical Background and State of the Art, uncrosslinked HA is included in the filler mainly as a lubricant to ease the injection of crosslinked HA. It was known to a POSITA that a larger amount of uncrosslinked HA is needed when more extrusion force is required to inject the crosslinked HA, such as crosslinked HA with higher viscosity, higher degree of crosslinking, larger particle sizes, etc. However, when all other relevant parameters are identical, the higher percentage of uncrosslinked HA in an HA gel, the faster the HA gel may be degraded *in vivo*. It is within routine experimentation for a POSITA to choose the appropriate percentage of uncrosslinked HA that achieves the lubricant function without sacrificing the desired persistence of the filler product.

138. Stable, sterile soft tissue fillers containing at least 10% uncrosslinked HA and HA-BDDE were already taught by the prior art. For example, the composition described in Example 2 of Debacker contains HA-BDDE and uncrosslinked HA mixed at a ratio of 2:1 (thus 33% uncrosslinked HA). The hydrogel in Piron contains HA-BDDE and 5% to 50%, preferably 10% to 30%, even more preferably 15% by weight of free HA (Piron, Example 2, claim 1). Juvederm® Ultra (J24HV) and Juvederm® Ultra Plus (J30HV) taught by Lupo contain at least about 10% uncrosslinked HA (Beasley Table 1) or maybe even about 40% uncrosslinked HA according to the measurement by Kablik (Kablik, Table 1). Voluma Corneal® (Juvederm® Voluma) taught by Expert Anti-Aging also

contains some uncrosslinked HA" (Voluma XC Summary, p2).

139. *Lebreton* does not explicitly describe that its compositions contain at least about 10% free HA as recited in claim 19. According to *Lebreton*, after the crosslinking reaction, the reaction product was neutralized and then dialyzed (Examples 3 and 4). As I discussed in paragraph 34 above, the preparation resulting from a crosslinking reaction contains water insoluble crosslinked HA and three water soluble HA species: unmodified HA, modified but not crosslinked HA, and lightly crosslinked HA, and the soluble HA, which reads on the claimed uncrosslinked HA. When the preparation from *Lebreton* was dialyzed, depending on the pore sizes of dialysis tubing, some of the soluble HA species, which are much bigger than the unreacted BDDE, might remain and be sequestered within the insoluble crosslinked HA into syringes as part of the filler composition. Thus, the compositions according to *Lebreton* may intrinsically contain at least about 10% free HA after the crosslinking reaction, particularly since much less BDDE was used in the reaction than HA.

140. *Expert Anti-Aging* also does not explicitly describe that Voluma Comeal® (Juvederm® Voluma) contains at least 10% free HA. However, based on published information, Juvederm® Voluma is "made primarily of crosslinked HA with some remaining lightly crosslinked and uncrosslinked HA" (Voluma XC Summary, p2). The "remaining lightly crosslinked and uncrosslinked HA" either inherently reads on the claimed "at least 10%" uncrosslinked or free HA or renders this claim element obvious. Indeed, according to Borrell, Juvederm® Voluma, a "20-mg/ml smooth, cohesive volumizing gel filler" as

described in Hoffmann (which is reference number 12 in Borrell) has about 10% uncrosslinked HA (Borrell, Table II). In addition, according to Allergan's patent notice, Juvederm® Voluma XC practices at least some claim(s) of the '475 (Allergan Patent Notices). Because Juvederm® Voluma and Juvederm® Voluma XC have identical specifications except that Voluma XC contains 0.3% (w/w) lidocaine (Juvederm FDA Briefing, page 20-21), Allergan's Patent Notices again strongly suggests that Juvederm® Voluma has at least 10% or more uncrosslinked or free HA, as required by all claims of the '475 patent, with the exception of claims 34, 35 and 37.

141. Therefore, claims of the '475 patent are directed to a stable, sterile soft tissue filler containing a combination of lidocaine with a stable, sterile soft tissue filler having the claimed more than 10% uncrosslinked HA that had already been taught by the prior art (see e.g., Lupo, Debacker, Piron, Expert Anti-Aging). Nothing in the intrinsic record of the '475 patent showed that adding lidocaine to the prior art fillers achieved any unexpected superior results when compared to the prior art fillers without lidocaine (see discussion below).

142. In addition, varying the amount of uncrosslinked HA in a dermal filler is routine experimentatioQ 7KH LQWULQVLF UHFRUG RI WKH µ475 patent contains no evidence demonstrating that having greater than 10% uncrosslinked HA is critical to the claimed filler comSRVLWLRQ 7R WKH µ475 patent describes that "in other embodiments, the precursor composition comprises no greater than about 1% to about 10% of free HA E\ YROXPH µ475 patent, 7:1-3).

143. $V GLVFXVVHG DERYH DW WKH WLPH RI ILOLQJ WKH µ against adding lidocaine to an HA composition containing HA-BDDE and/or uncrosslinked HA. If anything, in view of the known stabilization effect of lidocaine to HA, the common knowledge that uncrosslinked HA is less stable than crosslinked HA, and the desire to reduce injection pain, a POSITA would have been even more motivated to add lidocaine to a composition containing greater than 10% uncrosslinked HA, with a reasonable expectation of success to obtain a stable, sterile soft tissue filler as claimed.

The degree of crosslinking does not make the claims patentable

144. Some claims of the '475 patent recite various degree(s) of crosslinking. For example, claim 5 in the '475 patent recites a "degree of crosslinking of less than about 6%," claims 6, 18, 19, 31 and 37 recite a "degree of crosslinking of less than about 5%," and claim 7 recites a "degree of crosslinking of about 2%." I was asked to opine on whether the claimed degree of crosslinking would have made the claimed filler compositions patentable over the prior art.

145. In my opinion, the degree of crosslinking would not have made the claimed filler compositions nonobvious over the prior art at least because the claimed degree of crosslinking was either already used in the prior art fillers or could have been easily obtained by routine experimentation. It is within routine experimentation for a POSITA to choose the appropriate degree of crosslinking that achieves the desired persistence without causing undesired side effects. The degree of crosslinking is only applicable to

the crosslinked HA, because it measures the percentage weight ratio of the total mass of crosslinking agent to the total mass of HA-disaccharide units within the water insoluble crosslinked portion of the HA-based composition. Crosslinked HA with higher degree of crosslinking usually is stiffer or more brittle than one having a lower degree of crosslinking. When all other relevant parameters are identical, a higher degree of crosslinking can result in a longer lasting HA gel. However, if the degree of crosslinking is too high, this may reduce the degree of hydration of the HA product. In addition, gels that are too highly crosslinked may also have poorer biocompatibility, and may induce immune reactions, resulting in adverse reactions *in vivo*. Reinmuller II teaches that the pharmaceutical composition can have a degree of crosslinking in the range from 0.1% to 10% (Reinmuller II, 2: 21-26).

146. Stable, sterile soft tissue fillers containing HA-BDDE with the claimed degree of crosslinking have already been taught by the prior art. For example, J30HV (Juvederm® Ultra Plus) (Lupo) was used as Sample 5 in the priority applications (1st Prov App, p16), which was reported to have about 6% crosslinking according to the '795 patent ('795 patent, 15:44-45). I noticed that the '795 patent also claims priority from the 1st Prov App. The definition of degree of crosslinking in the '795 patent (5: 43-52) is identical to that in the '475 patent (4:62-5:4). Thus, as evidenced by the disclosure in the 1st Prov App and the '795 patent, J30HV (Juvederm® Ultra Plus) has about 6% degree of crosslinking.

147. The '795 patent and the priority applications do not describe the degree of crosslinking for J24HV (Lupo). Allemann describes that J24HV (Juvederm® Ultra) is 9% crosslinked

and J30HV (Juvederm® Ultra Plus) is 11% crosslinked (Allemann, p631, Table 2). The 11% for J30HV in Allemann is about double the 6% for J30HV in the '795 patent, indicating or strongly suggesting that the crosslinking rate in Allemann is calculated by the conventional mole ratio percentage (mol%). As I discussed above, the degree of crosslinking based on the conventional mole ratio percentage is about double the degree of crosslinking based on the weight ratio percentage (wt%) used in the '475 patent, because the molecular weight of BDDE is about half of that of the HA disaccharide unit. Accordingly, based on the 9% crosslinking (mol%) reported in Allemann, J24HV has about 4-5% crosslinking (wt%) as used in the '475 patent.

148. Expert Anti-Aging describes another stable, sterile soft tissue filler containing HA-BDDE, Voluma Corneal® (Juvederm® Voluma), which was used as Sample 6 in the 1st Prov App (1st Prov App, Example 3). According to the '795 patent, Sample 6 (Juvederm® Voluma) K D V D E R X W F U R V V O L Q J -52). μ S D W H Q W

149. In addition, Lebreton teaches crosslinking reactions with a "non-excessive amount of crosslinking agent" to result in a low degree of crosslinking. More specifically, Lebreton teaches a crosslinking reaction conducted with a "non-excessive amount," rather than a large excess, of crosslinking agent. The recommended degree of F U R V V O L Q N L Q J ´ L V defined by the ratio of "total number of reactive groups in said crosslinking agent/total number of disaccharide units of the polymer molecules x 100" of 0.5 to 70%, and "advantageously between 4 and 50%" (Lebreton, para. [0046]). Because each BDDE has W Z R U H D F W L Y H J U R X S V D O V R V H H) L J Lebreton D E R Y H W K H

twice (2x) that of the conventionally used mol% ratio, therefore, four times (4x) that of the wt% ratio as used in the `475 patent. Accordingly, Lebreton teaches a soft tissue filler WKDW KDV D GHJUHH RI FURVVOLQNLQJ RI WR EHWZHHQ WR ´ DQG ZKLFK crosslinking. RQ WKH

150. Therefore, claims of the '475 patent are directed to a stable, sterile soft tissue filler containing a combination of lidocaine with a prior art stable, sterile soft tissue filler having the claimed degree of crosslinking of less than about 5 or 6% (see e.g., Lupo, Expert Anti-Aging, Lebreton).

151. I noticed that other publications have reported different degrees of crosslinking for the Juvederm® products. For example, Beasley reported that based on data provided by Allergan, Juvederm® Ultra and Juvederm® Ultra Plus have 6% or 8% crosslinked HA, respectively (Beasley, Table 1), and Kablik reported 2% crosslinked HA and 10% degree of HA modification for Juvederm® 30 HV (Ultra Plus) based on their measurements (Kablik, Table 1). Even assuming that the prior art Juvederm® products each has a degree of crosslinking more than 6%, it would have been routine experimentation for a POSITA to make a filler product having less than 6% or 5%, or about 2% degree of crosslinking in a filler composition as claimed in the '475 patent. The '475 patent does not include any evidence to show that the claimed degree of crosslinking is critical to its filler composition or has achieved unexpected superior results. To the contrary, the '475 patent describes that "the degree of crosslinking in the HA component of the present compositions is at least about 2% and is up to about 20%."

The combination of a high molecular weight HA component and a low molecular weight HA component does not make the claims patentable

152. Claims 19-26 of the '475 patent recite an HA material crosslinked with BDDE that includes "a high molecular weight HA component and a low molecular weight HA component." I was asked to opine on whether the claim recitations on a combination of the high and low molecular weight HA components in the crosslinked HA material would have made the claimed filler compositions patentable over the prior art.

153. In my opinion, the combination of the high and low molecular weight HA components in the crosslinked HA material would not have made the claimed filler compositions patentable over the prior art, because the claimed combination of the high and low molecular weight HA components was either already used in the prior art or would have been easily obtained by routine experimentation.

154. As I discussed above, the prior art teaches a stable and sterile soft tissue filler containing HA crosslinked with BDDE that includes a high molecular weight HA component and a low molecular weight HA component, such as VOLUMA Corneal (Juvederm Voluma) in Expert Anti-Aging (p5-6) as evidenced by Juvederm FDA Briefing, Appendix 3, page 3 of 19, or the composition of Lebreton (see Lebreton claim 16, para. [0048]), Examples 3 and 4).

155. Claims 20-25 depend on claim 19 and recite various molecular weights for the high- or low-molecular weight HA components. In my opinion, these claims are also obvious over

the prior art for at least the reasons discussed above for claim 19, and further because Lebreton, or Expert Anti-Aging teaches or suggests the claimed molecular weights. According to Lebreton, the low molecular weight HA has a molecular weight of 9.9 x 10^5 Da (0.99 MDa) or less, advantageously between 0.01 MDa to 0.99 MDa, and the high molecular weight HA has a molecular weight of 1 MDa or more, advantageously between 1 MDa and 100 MDa, very advantageously between 1.1 MDa and 5 MDa (Lebreton, claim 5). In particular, the composition can have about 90% (w/w) of HA having a molecular weight of about 0.3 MDa and about 10% (w/w) of HA having a molecular weight of about 3 MDa (Lebreton, claim 9). The disclosed low molecular weight HA reads on the "less than about 1.0 MDa" (claim 23), "between about 0.2 MDa and less than 1.0 MDa" (claim 24), and "between about 0.3 MDa and less than 0.75 MDa" (claim 25) recited in the '475 patent. The disclosed higher molecular weight HA reads on the "between about 1.0 MDa and about 4.0 MDa" (claim 20), "about 2.0 MDa" (claim 21), "about 2.8 MDa" (claim 22), and "at least about 1.0 MDa" (claim 23) recited in the '475 patent. In addition, the '475 patent contains no evidence that any of the claimed molecular weights is critical to the claimed composition.

156. Claim 26 would also have been obvious for reasons discussed above for claim 19, and further because Lebreton teaches a composition having a mixture of low (90%) and high (10%) molecular weight HA (Lebreton, Example 4 and claim 26), and Juvederm® VOLUMA also has a mixture of low (90%) and high (10%) molecular weight HA (Juvederm FDA Briefing, Appendix 3, page 3 of 19).

Heat sterilization does not make the claims patentable

157. Some claims in the '475 patent have recitations related to heat sterilization. For example, claim 18 recites "wherein the soft tissue filler has been heat sterilized," claim 31 recites "a heat-sterilized, stable dermal filler," and claim 34 recites "wherein the soft tissue filler is stable after heat sterilization at between about 120 °C and about 130 °C." I was asked to opine on whether the heat sterilization related claim recitations would have made the claimed filler compositions nonobvious over the prior art.

158. In my opinion, the heat sterilization related claim recitations would not have made the claimed filler compositions nonobvious over the prior art. At the outset, "stable to D X W R F O D Y L Q J ³V W D E O H D I W H U K H D W V W H U L O L] D W L R Q a composition to be completely free of HA degradation during autoclaving, i.e., to maintain the same aspects in transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration before and after autoclaving. The intrinsic record of the '475 patent contains no evidence demonstrating that any composition maintains the same aspects before and after autoclaving.

159. HA is known to be subject to degradation during autoclaving. However, a stable soft tissue filler is not required to be completely free of HA degradation during autoclaving, so long as the filler is stable after effective sterilization. It was known that after autoclaving, a heat sterilized HA preparation can be "extremely storage stable over a wide range of temperatures, including temperatures as high as 86°F (30 °C), for at least

three years" (Drizen, 7:44-46). It was further known that lidocaine is very stable at room temperature (Powell, p42). I am not aware of any prior art teaching that combining these two stable ingredients together would have resulted in an unstable composition.

160. As I discussed above, heat sterilization at a temperature between about 120 °C and about 130 °C had been commonly used to sterilize various HA preparations before 2008. For example, Reinmuller I discloses the existence of a heat sterilized injectable gel containing crosslinked HA and lidocaine more than 15 years before the earliest priority date of the '475 patent. Wang, Perez, and Calias teach autoclaving sterilization of a composition containing lidocaine and HA crosslinked with BDDE, polyethylene oxides, and DVS, respectively. Sadozai teaches that the addition of lidocaine to an HA soft tissue filler results in a composition with enhanced stability, and the filler was heat sterilized. Consistent with Sadozai, Ji teaches that adding a free radical scavenger to an HA hydrogel decreases viscosity loss due to heat and/or storage. It was known that lidocaine is a potent hydroxyl radical scavenger and singlet oxygen quencher (Das), and inhibits HA degradation by the mechanism of scavenging hydroxyl radicals (Lindvall).

161. In view of the common knowledge in the prior art that heat sterilization can be used to sterilize almost any type of HA preparation, a POSITA would have been highly motivated to use heat sterilization (e.g., autoclaving) to sterilize a soft tissue filler containing lidocaine, uncrosslinked HA and HA-BDDE. The POSITA would have had a reasonable expectation of success to obtain a stable, sterile, soft tissue filler containing lidocaine, HA-BDDE and uncrosslinked HA after the heat sterilization in view of the

known stability of HA and lidocaine at room temperature.

The concentration of lidocaine does not make the claims patentable

162. Some claims of the '475 patent have recitations related to the concentration of lidocaine. For example, claim 8 recites "wherein the lidocaine is at a concentration of between about 0.1% and about 5% by weight of said soft tissue filler," claim 18 recites "lidocaine having a concentration of about 0.3% by weight of said soft tissue filler," etc. I was asked to opine on whether the recited lidocaine concentration would have made the claimed filler compositions nonobvious over the prior art.

163. In my opinion, the claimed lidocaine concentration would not have made the claimed filler compositions nonobvious over the prior art for at least the following reasons. As I discussed above, all of the approved lidocaine-containing dermal fillers (collagen or HA-based) contain the same final concentration of lidocaine hydrochloride, 0.3% (w/w) (Juvederm FDA Briefing, p25; Kinney, p742). Therefore, a POSITA would have been strongly motivated to include the same concentration of lidocaine in a dermal filler containing HA-BDDE and uncrosslinked HA. The 0.3% (w/w) lidocaine hydrochloride reads on the claimed "about 0.1% and about 5% by weight" or "about 0.3% by weight" lidocaine.

No unexpected superior result over the prior art fillers

164. I understand that the applicant of the '475 patent argued that he had unexpectedly found that the addition of lidocaine to the instant hyaluronic acid soft tissue filler did not result

in instability of the composition as was expected by those of ordinary skill in the art at the time of the instant invention, and the claims were allowed based on the applicant's arguments. However, I found no evidence that supports this argument.

165. As discussed above, I am not aware of any teaching from the scientific literature, nor have I had any personal experience that lidocaine would destabilize crosslinked HA or uncrosslinked HA, either during autoclaving or when stored at room temperature. I therefore disagree with the applicant's statement that those of ordinary skill expected that the addition of lidocaine to the instant hyaluronic acid soft tissue filler would result in instability of the composition. Contrary to the applicant's assertion, the prior art, such as those discussed in this Declaration and the IPR Petition, abundantly taught and demonstrated that the combination of lidocaine with crosslinked HA and uncrosslinked HA is stable, and that if lidocaine has any impact on the stability of an HA filler composition, it would only be expected to stabilize HA due to the known hydroxyl radical scavenging activity of lidocaine and the known ability of reactive oxygen species such as hydroxyl radicals to depolymerize HA. Thus, what the applicant observed, i.e., that the addition of lidocaine to the claimed HA filler composition did not result in instability of the composition, but may in fact have stabilized the composition, is merely a predictable outcome based on the prior art teaching, and is in no way unexpected.

166. Also, Petitioner further conducted experiments (attached in this Declaration as ³$SSHQGL[$´ E\ SUHSDULQJ %'(crosslinked HA gels consistent with a standard

manufacturing process before August 4, 2008. These BDDE-crosslinked HA gels were specifically prepared as discussed in Appendix A and included (i) a BDDE-crosslinked HA gel having a pH 7.0 without lidocaine, (ii) a BDDE-crosslinked gel having a pH 7.0 with lidocaine, (iii) a BDDE-crosslinked HA gel having an adjusted pH of 7.6 before the addition of lidocaine, and (iv) a BDDE-crosslinked HA gel with lidocaine having a pH 7.0 that is subsequently adjusted to pH 7.6 with NaOH.

167. , KDYH HYDOXDWHG WKH H[SHULPHQWV DQG DQDO\VHV substantiate my earlier opinions on the role of lidocaine in crosslinked HA gel products.

168. In my opinion and based on personal experience, the experimental results shown in Figure 1 of Appendix A are fully consistent with the teachings of the prior art before August 4, 2008 and are consistent with the results a POSITA would have expected to obtain before, during, and after heat sterilization (autoclaving) for BDDE-crosslinked HA gels that include lidocaine, and that further include or omit pH adjustment.

169. Similar to Sadozai LQ SDUDJUDSKV > @ DQG > @ GLVFXVVLQ effect on crosslinked HA compositions, the results shown in Appendix A demonstrate that the addition of lidocaine to crosslinked HA compositions (e.g., BDDE crosslinked compositions) and subsequent sterilization by autoclaving does not result in instability/degradation of the crosslinked HA composition when compared to similar crosslinked HA compositions that do not contain added lidocaine that are subjected to identical conditions. Indeed, the results shown in Figure 1 of Appendix A demonstrate

that lidocaine exhibits a slight stabilizing effect resulting in a slightly decreased loss of viscosity during and/or after heat sterilization when compared to similar crosslinked HA compositions that lack lidocaine. These results are consistent with, for example, the teachings of Sadozai as well as the other prior art references discussed above in this Declaration.

170. The results in Figure 1 of Appendix A further demonstrate that pH adjustment of crosslinked HA gels containing or lacking lidocaine exhibit similar viscosity losses during heat sterilization, which would have been a predictable result consistent with the expectations of a POSITA before August 4, 2008.

171. It should be further noted that the crosslinked HA compositions including lidocaine having pH 7.0 (i.e., without pH adjustment) exhibited less viscosity loss during and/or after heat sterilization than the crosslinked HA compositions including lidocaine having an adjusted pH of 7.6. Contrary to the assertions in the ' patent and assertions made during prosecution of the ' patent, these data suggest that pH adjustment may show a trend towards a minor degradative effect on crosslinked HA compositions including lidocaine, rather than a stabilizing effect. Overall, these data suggest that pH adjustment, at best, has negligible effects on crosslinked HA compositions including lidocaine, which, in my opinion, is also completely consistent with the expectations of a POSITA before August 4, 2008.

172. The data in Appendix A demonstrate a trend that shows that (1) the addition of lidocaine to a crosslinked HA composition(s) would not have destabilized/degraded crosslinked HA compositions during or after heat sterilization and (2) pH adjustment of crosslinked HA compositions including lidocaine, at best, has negligible effects on the crosslinked HA compositions, which, in my opinion and based on personal experience, is consistent with the prior art teachings before August 4, 2008. These results further corroborate the results that a POSITA would have expected to obtain before August 4, 2008.

173. The '475 patent and its prosecution history do not contain a single citation to any reference that describes the alleged prior art problem that adding lidocaine to an HA filler composition would cause the filler composition to become unstable. The '475 patent and the prosecution history also do not include any example(s) or data to substantiate the alleged unexpected discovery. The only example that compared various HA filler products including or lacking lidocaine is Example 3 of the priority documents for the '475 patent: App. Nos. 61/085,956, 61/087,934 and 61/096,278. See 1st Prov App and 3rd Prov App (the descriptions for Example 3 in the first two provisional applications are identical). This Example is not included in the '475 patent.

174. Example 3 in each of the three provisional applications describes the same stability study and presents the same data. In the study described in Example 3, each of six HA compositions was subjected to three tests, followed by autoclaving, and the viscosity of the HA composition was measured after the autoclaving. All six lidocaine-free HA samples were taught by the prior art, and they are:

a. Sample 1: Rhexeal, an ophthalmic viscosurgical device used in eye surgery that contains free HA (13.5 mg/g) and hydroxypropyl methylcellulose (5.5 mg/g);

b. Sample 2: Hylaform, a dermal filler that contains about 5.5 mg/ml in total HA crosslinked with DVS and uncrosslinked HA;

c. Sample 3: a non-commercial gel that "is believed to be similar to Restylane," which contains 80% BDDE crosslinked HA particles obtained by disintegrating SKGEL, an implant for glaucoma surgery, and 20% uncrosslinked HA;

d. Sample 4: Juvederm® Refine;

e. Sample 5: Juvederm® Ultra Plus; and

f. Sample 6: Juvederm® Voluma.

Each of the six HA compositions was subjected to the following three tests:

a. Test 1: about 20 g of each of Samples 1-6 was individually mixed with a solution of lidocaine chlorhydrate, then filled into a syringe and autoclaved;

b. Test 2: about 20 g of each of Samples 1-6 was individually mixed with a solution of lidocaine chlorhydrate as in Test 1, except that the pH was adjusted to 7.2 using NaOH solution as described in Example 1, then filled into a syringe and autoclaved;

c. Test 3: about 20 g of each of Samples 1-6 was individually mixed with an equivalent amount of water for injection (WFI) to take into account dilution effect, without adding lidocaine, then filled into a syringe and autoclaved.

Example 3 does not describe how the solution of lidocaine chlorhydrate (lidocaine HCl) was made, nor at what concentration. According to Example 1, a solution of lidocaine chlorhydrate was made by solubilizing lidocaine chlorhydrate powder in WFI and filtered through a 0.2 μm filter, and the final desired concentration of lidocaine HCl is about 0.3% (w/w) (1st Prov App, p13).

175. Data presented in Example 3 showed that, adding a solution of lidocaine chlorhydrate to each of Samples 1-6 without pH adjustment (Test 1) resulted in a decrease in viscosity for Samples 1-4, but no change in viscosity for Samples 5 and 6, compared to that of adding WFI to the same sample (Test 3) (1st Prov, Figs 2-6 & 8). Data in Example 3 also showed that adjusting the pH of each of Samples 1-6 to a slightly alkaline state (pH 7.2) using a suitable amount of sodium hydroxide solution prior to autoclaving (Test 2) resulted in smaller decrease in viscosity for Samples 1 and 2, and no decrease or slight increase in viscosity for Samples 3-6, compared to that of adding WFI to the same sample (Test 3) (1st Prov, Figs 2-6 & 8).

176. The data in Example 3 do not support the alleged prior art problem. All six HA samples are taught by the prior art. A decrease in viscosity was observed in some of the prior art samples, but not the others. Also, the decrease in viscosity was readily reduced or eliminated by a simple pH adjustment, which as discussed in more detail below, is a routine experimentation known very well to those of ordinary skill in the art.

177. The data in Example 3 do not demonstrate that the addition of lidocaine had in fact caused HA degradation in any of the samples tested, because the tests were not done properlywith adequate controls, and Example 3 was incompletely described. Besides lidocaine, the solution of lidocaine HC1 is different from WFI in other aspects, such as pH and ionic strength, which could have independently affected the measured viscosity.

178. For example, it was known that the viscoelasticity of HA in aqueous solution is pH

dependent and affected by the ionic strength of the solution (see Brown, p309). It was known that an increase in ionization can decrease the hydrogen bonding between disaccharides and within disaccharides in the HA molecules, which results in a decrease in the viscosity of an HA sample even without HA degradation. Solutions added to a given HA Sample in Tests 1-3 had different solute concentrations, and could thus affect the ionic strength differently. Adding a lidocaine HC1 solution to an HA sample, as done in Test 1, might have resulted in an increased ionic strength relative to that resulting from the addition of WFI as done in Test 3. It was also known that an HA composition can have a lower viscosity at an acidic pH. For example, it was observed that "when HA was processed at pH 4.75...., the viscosity dropped approximately 10%." (Kuo, p86). Thus, the increase in ionic strength and decrease in pH in Test 1 might have caused a decrease in the sample viscosity as compared to Test 3 even before autoclaving.

179. In contrast to Figure 1 in Appendix A (attached herein), Example 3 contains no information on the viscosity before autoclaving, either prior to or after the addition of the various solutions to the HA samples in Tests 1-3. It also does not compare molecular weights of HA before and after autoclaving to show HA degradation during autoclaving. Thus, a POSITA could not reasonably conclude whether the measured reduction in viscosity after the addition of lidocaine HCl in Test 1 or 2 relative to that with the addition of WFI in Test 3 was in fact due to more HA degradation during autoclaving, or change in ionic strength or pH even before autoclaving, both, or possibly other factors. The experiment simply lacks adequate controls for the number of variables altered.

180. Even assuming that the reduction in viscosity in Test 1 or 2 relative to Test 3 was primarily due to more HA degradation during autoclaving, a POSITA still could not reasonably conclude that the HA degradation was in fact due to the addition of lidocaine, because the HA degradation might have been caused by other factors that are different in Tests 1 or 2 in comparison to the control Test 3.

181. For example, it was known that acidic or basic pH destabilizes HA. The destabilization effect of acidic or basic pH may be more pronounced at high temperature and pressure during autoclaving, in part due to the decrease in pKa for lidocaine at high temperature during autoclaving. Example 3 contains no information on the pH of the HA samples in Tests 1-3 before autoclaving. It was known that a 0.5% (w/w) solution of lidocaine HC1 has a pH of 4-5.5 (See Ph. Eur. monograph 0227). The solution of lidocaine HC1 used in Example 3 was acidic, because it was made by solubilizing lidocaine HC1 powder in WFI (1st Prov App, p13), without pH adjustment or buffering. This is evident by the disclosure in Example 1 where adding the lidocaine chlorhydrate solution to an HA sample having a pH of 7.58 resulted in an HA sample having a pH of about 7 (1st Prov App, p13). In the solution, lidocaine existed in a protonated ammonium form as shown in Fig. 8b.

182. Adding the acidic lidocaine HCl solution to a pH neutral HA sample without pH adjustment as done in Test 1 may acidify the HA sample. In comparison, adding WFI to a neutral HA composition without pH adjustment as done in Test 3 should not have any significant impact on the pH of the sample. Based on common knowledge and the

disclosure in the provisional application, the six tested HA samples likely have different buffering capacities. Thus, the pH of these samples may be affected differently upon the addition of the solution of lidocaine HC1 in Test 1. For example, a sample with a higher buffering capacity may have no or less change in pH in Test 1, thus resulting in no or smaller degradation during autoclaving than a sample with a lower buffering capacity. Adjusting the HA sample to a slightly alkaline state prior to the addition of the lidocaine chlorhydrate (a.k.a., lidocaine HCl) solution as done in Test 2 would reduce or prevent the acidification, and thus reduce the degradation of viscosity caused by the acidification.

183. Therefore, the HA samples in Tests 1 and 3 may have different pH before autoclaving, i.e., an acidic pH in Test 1 and neutral pH in Test 3. The observed reduction of viscosity can be reasonably explained by the decrease in pH caused by the addition of the lidocaine chlorhydrate solution in Test 1, particularly in view of the known destabilization effect of acidic pH on HA, especially at high temperature. As discussed above, the pKa of lidocaine is temperature dependent, and that an acidic lidocaine-containing composition at room temperature will become even more acidic at the elevated temperature for autoclaving. This may result in more HA degradation during autoclaving, because it was known that low pH conditions and/or high temperature conditions cause degradation of HA (Kuo, p34-43). A POSITA would find this pH-based explanation more plausible than that based on some counterintuitive putative destabilizing effect of lidocaine, particularly in view of the results of Test 2, which demonstrated that adjusting the pH, but maintaining the same lidocaine concentration as that in Test 1, had reduced or completely eliminated the decrease of viscosity relative to that of Test 3.

184. Because the experiments in Example 3 were poorly designed and incompletely described, a POSITA could not have reached any reasonable conclusion on any effect of lidocaine on the stability of an HA soft tissue fillers. Example 3 does not even demonstrate that adding lidocaine to any of the six prior art HA samples had in fact caused HA degradation. Thus, Example 3 could not possibly support the applicant's assertion that the claimed HA soft tissue filler had achieved unexpected superior result by being stable upon addition of the lidocaine HC1 solution to the claimed filler.

185. Furthermore, the data in Example 3 also do not show that any of the lidocaine-containing HA compositions was unstable after autoclaving when placed in storage for any significant length of time. The viscosities of the HA samples were only measured once after autoclaving. A single point measurement provides no information as to whether the compositions were stable or not after being stored for a significant length of time. Solutions of HA are known in the art to be susceptible to degradation by depolymerization during autoclaving, and this property is unrelated to the presence or absence of lidocaine. However, it was also known that after autoclaving, compositions containing HA or modified HA can be stable at room temperature for years. The data in Example 3 do not support the applicant's allegation that lidocaine-containing HA composition is prone to degradation when in storage for a significant length of time ('475 patent, 2: 25-27).

186. Accordingly, it is my opinion that Example 3 does not demonstrate the alleged prior art

problem:

> HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time. ('475 patent, 2:22-27).

It is also my opinion that Example 3 does not show any unexpected superior result of the claimed invention.

187. If anything, the results in Example 3 demonstrated that the claimed lidocaine containing soft tissue filler has achieved no unexpected superior result compared to the prior art lidocaine-free soft tissue filler (and the experimental data in Appendix A). Sample 5 (Juvederm® Ultra Plus) is identical to J30HV described in Lu discussed above. Sample 6 (Juvederm® Voluma) is another prior art dermal filler (Expert Anti-Aging). Example 3 showed that these lidocaine-containing products had substantially the same viscosity as those of the lidocaine free prior art products (1st Prov App, Figs. 5&7), thus achieving no unexpected superior results compared to the prior art.

188. Consistent with the results in Example 3, other evidence published by Allergan also showed that the addition of lidocaine to a Juvederm® composition has no effect on HA concentration or volume, HA degradation, product viscosity or extrusion force, or pH level as compared to the identical Juvederm® composition without the lidocaine (see, e.g., Hylacross Tech). This again demonstrates that the claimed soft tissue filler composition has achieved no unexpected superior results compared to the prior art such as the prior art Juvederm® products without lidocaine. I am not aware of any evidence

demonstrating that claimed soft tissue filler composition has achieved unexpected superior results compared to the prior art dermal fillers containing lidocaine and HA crosslinked with other crosslinking agents, such as Puragen® Plus, Elevess® and Prevelle® Silk.

189. In addition, results in Example 3 have demonstrated that it takes no more than routine experimentation to obtain a stable lidocaine-containing soft tissue filler. With respect to Samples 5 and 6, merely adding a solution of lidocaine HC1 to the prior art lidocaine-free fillers resulted in combination products having rheological properties substantially identical to those of the lidocaine-free products (1st Prov App, Figs.6-9). With respect to Samples 3 and 4, a simple pH adjustment to a slightly alkaline state (7.2) prior to autoclaving resulted in combination products having rheological properties substantially identical to those of the lidocaine-free products (1st Prov App, Figs.4-5). The pH adjustment is a routine optimization, particularly considering that lidocaine is supplied in an acidic solution, and adjusting the pH of the HA composition before autoclaving would ensure the combined filler product to have a physiologically appropriate pH suitable for soft tissue injection and to minimize potential degradation of HA due to acidic pH during autoclaving.

190. For at least the above discussed reasons, even in light of the publicly-available information relating to possible secondary consideration arguments, claims 1-9, 18 and 27-37 of the '475 patent would have been obvious over the prior art teaching(s).

APPENDIX A

APPENDIX A
COMMENTS

According to the specification and the prosecution history RI 86 µthe inventors alleged that DW WKH WLPH RI ILOLQJ 86 LW ZDV WKRXJKW WKDW lidocaine would cause degradation of Hyaluronic Acid (HA)-based gels when subjected to heat sterilization (autoclaving). SOHDVH VHH 86¶ -27, FROXPQ and February 6, 2013 Examiner Interview Summary DQG WKH 0DUFK DQG $SULO 1RWLFHV RI $OO and 86¶ example 4, column 16, lines 28 to 37; 86¶ FROXPQ -27). OLQHV

+RZHYHU LQ YLHZ RI WKH SULRU DUW¶V GLVFORVXUHV OL... was believed to have a stabilizing effect on crosslinked HA-based compositions (please see Das, Lindvall, Ji, Sadozai and Prestwich Declaration paragraphs 81-87).

For overcoming the alleged degradative drawback when incorporating lidocaine in a crosslinked HA composition, Allergan states that LW¶V QHFHVVDU\ WR KDYH FRKHVLYH + (86¶ FROXPQ -41; 86¶ FROXPQ -31) OLQHV preferably with a particular adjusted pH greater than about 7.2, preferentially between about 7.5 and about 8.0, before adding the lidocaine hydrochloride (HCl) in said HA components (86¶ FROXPQ OLQ 6-9; 86¶ FROXPQ -67; 86¶ OLQHV H[DPSOH).

In view of the above, Petitioner (Teoxane) provides experimental data herein contradicting $OOHUJDQ¶V DERYH-PHQWLRQHG DVVHUWLRQV WKDW UHVXOWHG LQ LV... Prestwich has reviewed this data and believes this experimental data to be consistent with the prior art disclosures before August 4, 2008 and representative of what one skilled in the art would have expected to observe when including lidocaine in cross-linked HA compositions (and sterilizing/ adjusting the pH thereof) prior to August 4, 2008.

In this context, Petitioner (Teoxane) performed experimental studies evaluating:

(1) the effective influence of lidocaine on HA-based composition stability subjected to heat sterilization;
(2) the effective influence of a pH adjustment step on HA-based composition stability subjected to heat sterilization; and
(3) the effective influence of the sequence of preparation steps required by $OOHUJDQ LQ 86 on HA-based composition stability subjected to heat sterilization.

The experimental results obtained by Petitioner and discussed herein demonstrate the absence of any observable destabilizing effect of lidocaine when included in a HA-based composition when subjecting these formulations to (i) heat sterilization and/or (ii) pH adjustment. These results are consistent with the disclosures of the prior art before August 4, 2008, as discussed in the Petition and Prestwich Declaration, and further demonstrate that the patentee did not disclose, solve, and/or invent a non-obvious technical solution to any real technical problem.

Experiments on pH adjustment step

1. MATERIALS AND METHODS

1.1. Materials

Preparation of a BDDE-crosslinked HA-based GEL

A BDDE-crosslinked HA-based composition with common characteristics (ordinary HA concentration, crosslinking degree, etc.) was prepared as discussed below according to a standard
PDQXIDFWXULQJ SURFHVV NQRZQ WR RQH VNLOOHG LQ WKH
DQG 86¶ 6SHFLILFDOO\ WKH SURFHVV XVHG WR SUHSDU
discussed herein was disclosed in Example 1 (paragraphs [0068]- @ RI $OOHUJDQ¶V 8
2006/0194758, which published August 31, 2006. The only differences between the process used to prepare the BDDE-crosslinked HA-based composition disclosed herein and the one disclosed in US2006/0194758 were routine adjustment(s) notably those disclosed in WO2005/112888 of Mentor Corporation (please see in particular page 4 lines 8 to 14 and page 4 lines 21-28
UHVSHFWLYHO\ UHJDUGLQJ FKRLFH RI VRGLXP K\DOXURQDV
and crosslinking time.

This gel, called GEL A, has a concentration of HA of 24mg/g and a crosslinking degree of 6% (the crosslinking degree being defined as the ratio of the mass of BDDE related to the mass of {HA + BDDE} to be crosslinked).

10.0g of dry NaHA was added into 73.3g of a 1% NaOH solution and then , about 3.20g of a solution of BDDE diluted 1:5 in a 1% NaOH solution, (i.e. corresponding to about 0.6g of pure
%''(ZDV DGGHG WKHUHE\ \LHOGLQJ D ³UHDFWLRQ PHGLXP´ gently manually homogenized (as described in US2006/0194758 (Lebreton)) for about 1 hour and 30 minutes, until a homogenous HA solution (highly viscous with no agglomerate) was obtained. Afterwards, the homogenous HA solution was heated for 3 hours at 52°C in a water bath.

A solid gel was subsequently obtained. The solid gel was then neutralized and swollen by addition of an acidified phosphate buffer solution, and homogenized during 20 hours, so as to obtain a hydrogel of crosslinked hyaluronic acid, with a pH between 6.8 to 7.8. Said gel was purified by dialysis within a Phosphate Buffered Saline (PBS, pH=7.3) for 48 hours. Upon concluding dialysis, the pH of the composition was rectified by means of a HCl/Water for Injection (WFI) solution to obtain a pH equal to about 7.0. Finally, the gel was passed through a 500µm sieve LQ RUGHU WR REWDLQ D KRPRJHQRXV DQG UHJXODU GEL A.

GEL A was then split into 4 parts of 40 g and was numbered from A1 to A4.

As discussed in greater detail further below, Gels A1 to A4 either included or omitted:

- lidocaine and/or

- NaOH solutions for pH adjustment and/or
- Water for Injection (WFI) for maintaining the same volume between compared gels.

Preparation of a lidocaine solution.
The lidocaine solution was prepared by solubilizing lidocaine hydrochloride powder in WFI to obtain a 30 wt% lidocaine hydrochloride solution.

When added (e.g., in Gels A2, A3, and A4), the solution of lidocaine was incorporated in a proportion such that the final composition included about 0.3% of lidocaine hydrochloride, i.e. the concentration used in collagen-based dermal fillers, and more importantly commercially available crosslinked HA-based dermal fillers, in the prior art (e.g., Prevelle Silk, Elevess and Puragen Plus) before August 4, 2008.

The total volume of lidocaine solution added to the A2, A3, and A4 gels was small compared to the total volume of crosslinked HA gel, and therefore did not substantially alter HA concentration in the final gel.

- A1 was a BDDE-crosslinked HA-based composition without lidocaine that was prepared by adding 465µL of WFI to 40 g of gel A.

- A2 was a BDDE-crosslinked HA-based composition comprising 0.3% of lidocaine that was prepared without any pH adjustment step(s).
  Gel A2 was prepared by adding 405 µL of a 30% lidocaine HCl solution to 40 g of Gel A then adding 60µL of WFI. By adding 405µL of a 30% lidocaine HCl solution and 60 µL of WFI, the overall volume added to the initial gel A was 465 µL, which is an identical volume to that described for Gel A1 when adding WFI.

- A3 was a BDDE-crosslinked HA-based composition comprising 0.3% of lidocaine having an adjusted pH before the addition of lidocaine.
  Gel A3 was prepared by adding 60 µL of NaOH to 40 g of gel A to obtain a pH of 7.6 before adding 405µL of a 30% lidocaine HCl solution. An overall volume of 465µL was added when preparing Gel A3, which is an identical volume to that described for Gels A1 and A2.

- A4 was a BDDE-crosslinked HA-based composition comprising 0.3% lidocaine having an adjusted pH after the addition of lidocaine.
  Gel A4 was prepared by adding the same amount of NaOH as for the preparation of gel A3 (i.e. 60µL of NaOH) but after adding 405 µL of the 30% lidocaine HCl solution to the 40 g of gel A. An overall volume of 465 µL was added when preparing Gel A4, which is an identical volume to that described for Gels A1-A3.

Gels A1-A4 were filled into syringes and subsequently sterilized under moist heat, by autoclaving.

Similar to disclosures LQ 86¶ VSHFLILFDWLRQ ³WHPSHUDWXUHV RI DW OHDVW about 120 °C to about 130 °C and/or pressures of at least about 12 pounds per square inch (PSI) to about 20 PSI during autoclaving for a period of at least about 1 minute to about 15 PLQXWHV´ SOHDVH VHH 86¶ FROXPQ OLQHV

For sake of comparability, all of the studied gels were sterilized in the same autoclave cycle and were thus subjected to the same autoclaving conditions (temperature, pressure and time).

1.2. Methods

1.2.1. pH adjustment step

$FFRUGLQJ WR 86 µ DIWHU SXULILFDWLRQ E\ GLDO\VLV substantially neutral, DQG preferably adjusted to cause the gels to become slightly alkaline such that the gels have a pH of greater than about 7.2, for example, about 7.5 to about 8.0. This step may be accomplished by any suitable means, for example, by adding a suitable amount of dilute NaOH, KOH, NaHCO3 or LiOH, to the gels or any other alkaline molecule, solution and/or buffering composition known by one skilled in the art´ (SOHDVH VHH 86¶ FROXP lines 6-14).

Accordingly, for the present experiments, a suitable amount of a NaOH solution was used to obtain a pH between about 7.5 and about 8.0 (please see gel A3 whose pH is adjusted to 7.6 after dialysis).

In order to compare compositions whose pH was adjusted before versus after the addition of lidocaine HCl, the same amounts of NaOH solution and when applicable, of WFI, were added before or after the addition of lidocaine (please see preparation of gels A3 to A4).

When there was no pH adjustment (gels A1 and A2), an equivalent amount of WFI was added to the composition after dialysis in order to obtain gels with comparable volumes and take into account the dilution effect.

1.2.2. Stability of gels

,Q H[DPSOH RI 86¶ FLWHG IURP 86 µ ZKLFK FODLPV SULRUL In order to determine stability of its studied gels, Allergan compared viscosities of crosslinked HA-based compositions that (i) included or omitted lidocaine (ii) with or without a pH adjustment.

Regarding gel stability and when comparing viscosities of sterilized crosslinked HA FRPSRVLWLRQV WKDW HLWKHU LQFOXGH RU RPLW OLGRFDL states that viscosity decreases up to about 30% (after autoclaving) were not considered to be appreciable decreases (86 µ example 4, column 16, lines 59-63).

Accordingly, a composition including lidocaine that exhibited a viscosity loss of 30%, or less when compared to the viscosity of a composition without lidocaine was considered stable DFFRUGLQJ WR H[DPSOH RI 86 µ. However, this statement required at least the following two suppositions.

First, the person skilled in the art knows that crosslinked HA-based compositions will exhibit viscosity loss after a sterilization step (e.g., autoclaving) due to depolymerization of the crosslinked HA-based composition during sterilization. Based on the above-mentioned disclosures by the patentee, the patentee infers that viscosity losses of, for example, 10%, 20%, and up to 30% are negligible. Even though viscosity loss is expected with crosslinked HA-based compositions, a 10%, 20% or 30% viscosity loss remains significant.
Therefore, when crosslinked HA compositions (one without lidocaine and another with lidocaine and an adjusted pH during the process) exhibit a difference of viscosity of 10%, 20% or 30%, it cannot be inferred that said difference is negligible.

Second, in the specification a ³VWDEOH FRPSRVLWLRQ´ is defined as a composition which ³maintain[s] at least one of, or all of, the following aspects after effective autoclave sterilization and/or prolonged storage: transparent appearance, pH for use in a patient, extrusion force and/or rheological characteristics, HA concentration, sterility, osmolarity, and lidocaine concentration´ (86¶ FROXPQ 6, lines 20-25; 86 µ FROXPQ 6, lines 20-25).

,Q H[DPSOH RI 86 µ only viscosities after sterilization were measured and compared but the observed differences in example 4 could be easily attributed to differing viscosities before sterilization as undefined volumes of solutions having different pH and ionic strength (WFI vs. lidocaine) were addHG WR WKH JHOV DQG 86 µ. It is known that viscoelasticity of a HA aqueous solution is pH dependent and might be affected by its ionic strength (Prestwich Declaration paragraphs 205 and 208 and Brown p309). Accordingly, such a comparison does not allow one to GHILQH ³VWDEOH FRPSRVLWLRQV´ LQ WKH 86 µ. The patentee did not study any other characteristic allowing one to conclude on the stability of the studied samples.

Accordingly, in the present experiments, and as it should have been conducted for experiments in 86 µ 86 µ, the stability of studied gels were evaluated by their loss of viscosity after autoclaving (in %), said viscosity being a rheological characteristic supposed to be maintained after sterilization LQ ³VWDEOH FRPSRVLWLRQV´ LQ W Allergan's patent which is studied by the patentee.

1.2.3. pH measurement

During different stages of the gel preparation process (i.e. at the end of the dialysis, after pH adjustments and at the end of the process), pH values were monitored and controlled by a pH-meter sensitive to hydrogen-ion activity.

1.2.4. Viscoelastic properties measurements

The viscoelastic properties of the gels are characterized in oscillatory rheology with a deformation sweep by P H D V X U L Q J W K H L U U H Y L Q Pa.s) L V F R V L W \ , ,

The measurements were performed at ambient temperature with a frequency sweep between 0.1 Hz and 1Hz and a stress of 5 Pa using a TA instrument DHR2 rheometer with a 1°/40 mm diameter cone-plate geometry

1.2.5. Determination of the cohesivity of gels

, Q 8 6 ¶ 8 6 ¶ , the term cohesive is used I R U G H V F U L E L Q J the ability of a HA-based composition to retain its shape and resist deformation S O H D V H V H H 8 6 ¶ - F R O X P Q D Q G 8 6 ¶ F R O X P Q 6 3) O L Q H V

As such, this concept of cohesivity can thus be related to the gel rheology.
In this way, a gel highly cohesive (or cohesive enough) should have higher rheological properties H J K L J K H U Y L V F R V L W \ K L J K H U H O D V W L F P R G X O X V

The below mentioned experiments studied stability of gels and further demonstrated gel cohesivity as determined by the method described L Q 8 6 ¶ D Q G 8 6 ¶ V S H F L I L F D W L R Q V
"First, 0.2 g or 0.4 g of [the] gel composition to be tested is placed in a glass syringe. Next, 0.2 g or more of phosphate buffer is added to the syringe and the mixture is thoroughly mixed for about 1 hour to obtain a homogenous mixture [first mixing with a vortex at maximum speed during 20 seconds, then with a thermomixer 1 hour, at 1200 rpm, then with the vortex at maximum speed during 20 seconds, again]. Then, the homogenized mixture is centrifuged for 5 min at 2000 tr/min to remove the air bubbles and to allow the decantation of any particles. The syringe is then held in a vertical position and one drop of eosin colorant is deposited at the surface of the gel by means of a syringe and an 18G needle. After 10 min, the dye has slowly diffused through the gel.´ 8 6 ¶ H [D P S O H F R O X P Q O L Q H V and W R F
8 6 ¶ H [D P S O H F R O X P Q O L Q H) W R F R O X P Q O L Q H

³After dilution of the gel, homogenization and decantation, a relatively low cohesivity gel shows a phase separation (an upper diluted less viscous phase without particles and a lower one composed of decanted particles that are visible with the naked eye or under microscope). Under the same conditions, a highly cohesive gel shows substantially no phase separation, and the dye is prevented from diffusing into the cohesive formulation. 8 6 ¶ H [D P S O H F R O X P Q 8-15 D Q G 8 6 ¶ H [D P S O H F R O X P Q). O L Q H W R F R O X P Q

2. Results

2.1. Cohesivity

Cohesivity of Gel A1 was determine and compared with cohesivity of Juvéderm® Ultra XC by D S S O \ L Q J W K H W H V W V D G L V F O R V H G as above (1.2.4. Determination of the cohesivity of gels).

A photo was taken just after (T0min) and 10 minutes after (T10min) eosin deposition on the sample. Data are presented below.

Table 1

	T0min	T10min
Gel A1		
Juvederm Ultra XC		

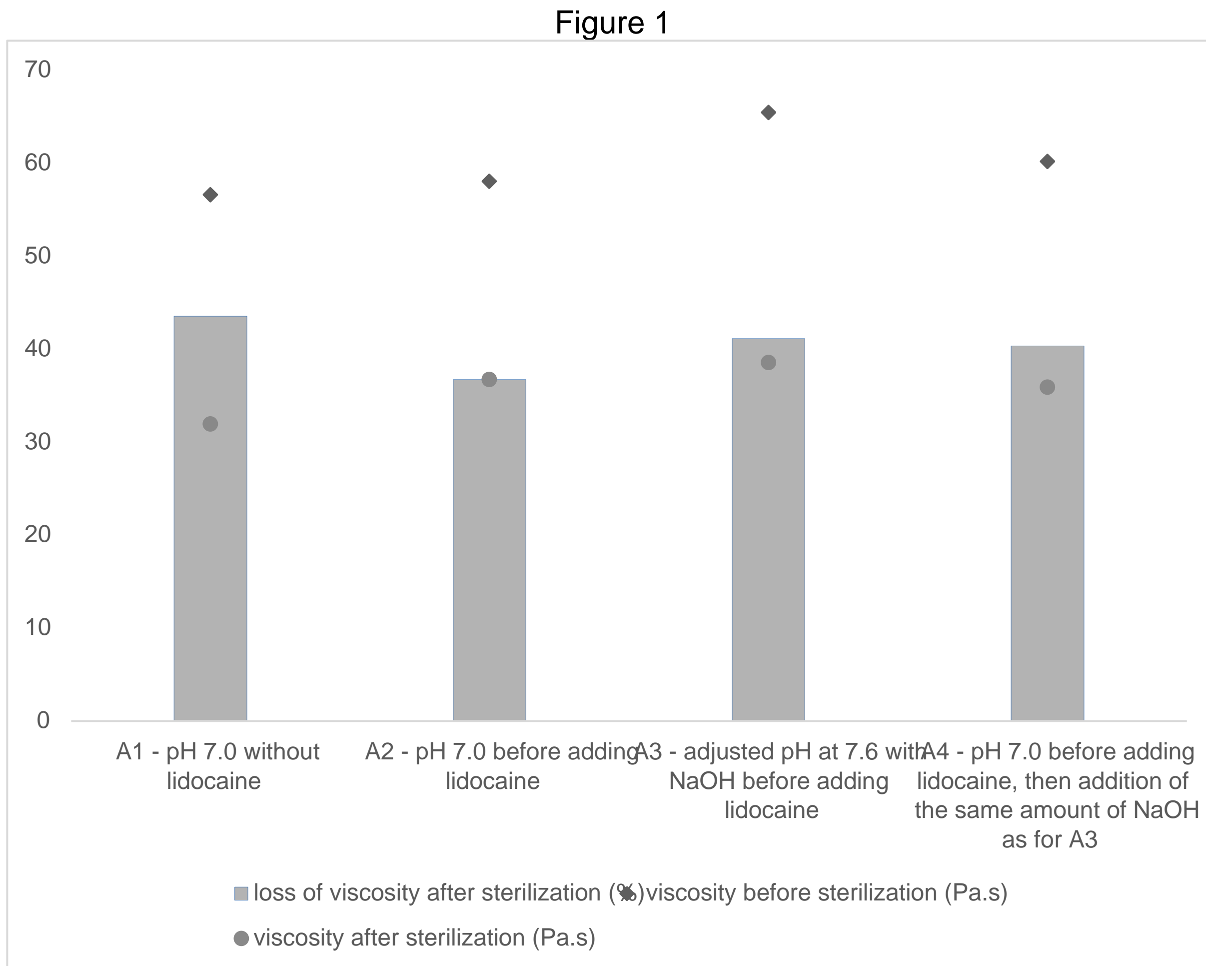
, Q Y L H Z R I W K H D E R Y H S K R W R J U D S K V D Q G D F F R U G L Q J W R \ both gels are cohesive because colorant was prevented from diffusing into the above shown gels.

Further, the result obtained for gel A1 is similar to Juvederm® Ultra XC, which is a cohesive gel DFFRUGLQJ $OOHUJDQ VHH 86¶ it must be concluded that studied VDPSOH W gels A (and Gels A1-A4) are cohesive.

2.2. Viscoelastic properties

Viscosities of Gels A1 to A4 were measured before and after heat sterilization and loss of viscosity was calculated and presented in Figure 1 below.

Figure 1



In view of these results, the studied gels have weak mechanical properties. Indeed, they show

- D ORZ *¶ DERXW 3D LQ WKH DEVHQFH RI OLGRFDLQ shown in Figure 1),
- a relatively low viscosity (about 57 Pa.s in the absence of lidocaine and pH adjustment (A1)) and
- a great loss of viscosity after sterilization even in the absence of lidocaine and pH adjustment (loss greater than 40% (A1)).

Thus, such a gel is logically expected to be more susceptible to a degradation stimulus by the skilled person in the art.

3. Interpretation of the results

3.1. Preliminary remarks on gel cohesivity

Gel A prepared for these experiments has, as explained above, weak mechanical properties. Therefore, it can be concluded that they are poorly cohesive according to the definition given by Allergan, i.e. they barely ³retain their shape and resist deformation´ S O H D V H V H H 8 6 ¶ column 5, lines 14- D Q G 8 6 ¶ F R O X P Q (6B) O L Q H V

Thus, if lidocaine actually had a negative influence on HA-based compositions, it would have been particularly obvious on the studied samples

Furthermore, it has to be noted that the eosin test does not allow a discrimination of weak and stronger gels as the same result is obtain for gel A (a weak gel) and Juvederm® Ultra XC which is a stronger gel (said Juvederm® 8 O W U D ; & S U R G X F W L V H [H P S O L I L H G L Q $ example 4, sample 5, figure 5) disclosing higher viscosity (about 100- D Q G D K L J K H U * ¶ (about 170 Pa).

3.2. Influence of lidocaine on HA-based composition stability under heat

Although Gel A has weak mechanical properties as specified above (2.2. Viscoelastic properties and 3.1 Remarks on gels cohesivity), the above results demonstrate that viscosity losses after sterilization are very similar for crosslinked HA compositions with lidocaine (A2) when compared to crosslinked HA compositions without lidocaine (A1).

Even if the difference between these two values is recognizable (A2 ± 5% in regard to the control sample A1), this difference would not dissuade one from including lidocaine in the crosslinked HA composition. The results further suggest that lidocaine may exhibit a stabilizing effect on the crosslinked HA composition, which is completely consistent with W K H S U L R U D U W ¶ V G L V F O R V X U H V and would have been expected by the person skilled in the art in view of O L G R F D L Q H ¶ V antioxidant properties and hydroxyl radical scavenger and singlet oxygen quencher functions (please see Das, Lindvall, Ji and Prestwich Declaration paragraphs 76-82).

Accordingly, it should be concluded from these data that lidocaine does not cause degradation of HA-based compositions during heat sterilization and this conclusion

remains regardless of whether the absolute value of loss after sterilization is considered significant or not.

Therefore, the alleged prior art problem (i.e., HA-based injectable compositions comprising lidocaine are not achieved because of their partial or almost complete degradation prior to injection, particularly during high temperature sterilization 8 6 ¶ column 2, lines 22-27; US ¶ F R O X P Q -27) is unfounded based on the experimental results shown in Figure 1.

3.3. Influence of the pH adjustment of the HA-based composition before autoclaving on HA-based composition stability under heat

In view of the above results (2.2. Viscoelastic properties; Figure 1), the viscosity losses observed after sterilization are similar for compositions with lidocaine prepared without any pH adjustment step (A2) when compared to compositions whose pH was adjusted either before or after the addition of lidocaine (A3, A4).

Even if the difference in viscosity loss is considered significant, these results do not demonstrate a stabilizing effect related to pH adjustment. To the contrary, the sample prepared with lidocaine without any pH adjustment (A2) exhibited the least amount of viscosity loss after sterilization. Accordingly, these results suggest that pH adjustment may lead to viscosity loss (de-stabilizing effect(s)) and further suggest not adjusting the pH of an HA-based composition that includes lidocaine, or at least the lack of motivation for adjusting pH to stabilize a crosslinked HA gel that includes lidocaine.

The above discussed experimental results demonstrate that pH adjustment step is not relevant for stabilizing HA-based compositions.

3.4. Influence of the sequence of preparation steps on HA-based composition stability under heat

Loss of viscosity after sterilization is similar for compositions whose pH is adjusted after the addition of lidocaine (A4) in comparison with compositions whose pH is adjusted before the D G G L W L R Q R I O L G R F D L Q H L H F R P S R V L W L R Q V K D Y L Q J D Q 8 6 µ when lidocaine is added; please see A3 and 1.2.1. pH adjustment step)

Thus, it can be concluded that the sequence for adjusting pH of HA composition to a pH greater than about 7.2, preferably between about 7.5 and about 8.0 before adding the lidocaine is not relevant for improving the stability under heat sterilization of HA-based compositions.

Furthermore, in order to obtain an injectable composition, one skilled in the art would have used a routine pH adjustment (addition of acid or base) to obtain a crosslinked HA composition at a physiological pH. Accordingly, the pH adjustment step H V F U L E H G L Q 8 6 8 6 µ is just an obvious routine adjustment with no particular technical effect.

Summary of preparation processes of the studied gels

Denomination in our document	Initial prototype	Prototype Name	NaHA concentration before dialysis	NaHA concentration after dialysis	pH after dialysis	Comments	weight of treated gel (g)	Post dialysis conditions 1	pH control	Post dialysis conditions 2	pH control	Post dialysis conditions 3	pH control	final mass of gel (g)
A1	Gel B PFB-170206-C	PFB-170206-C5	24mg/g	22.4mg/g	7.3	Without Lidocaine pH adjusted to 7.0 by addition of HCl	40	V HCl = 6µL	7.08	WFI for adjusting the final total weight WFI = 40.471 - 40.000 - 0.006 = 0.465 g (or V WFI = 465µL)	7.08	NA	NA	40.471
A2	Gel B PFB-170206-C	PFB-170206-C6	24mg/g	22.4mg/g	7.3	1/ pH adjusted to 7.0 by addition of HCl 2/ addition of lidocaine (for obtaining a gel with 0.3% of lidocaine)	40	V HCl = 6µL	7.06	1% Lido (30% solution) = 0.3% of lidocaine within the gel lidocaine solution = (40 + 0.066) x 1/99 = 0.405 g (or V sol Lido = 405µL)	6.70	WFI for adjusting the final total weight WFI = 40.471 - 40.000 - 0.405 0.006 = 0.060 g (or V WFI = 60µL)	6.70	40.471
A3	Gel B PFB-170206-C	PFB-170206-C8	24mg/g	22.4mg/g	7.3	1/ pH adjusted at 7.0 by addition of HCl 2/ pH adjusted at 7.6by addition of NaOH 3/ Addition of lidocaine (for obtaining a gel with 0.3% of lidocaine)	40	V HCl = 6µL	7.03	Y = V NaOH = 6µL	7.60	1% Lido (30% solution) = 0.3 of lidocaine within the gel sol Lido = (40 + 0.066) x 1/99 = 0.405 g (or V Lidocaine solution = 405 µL	6.83	40.471
A4	Gel B PFB-170206-C	PFB-170206-C9	24mg/g	22.4mg/g	7.3	1/ pH adjusted at 7.0 by addition of HCl 2/ Addition of lidocaine (for obtaining a gel with 0.3% of lidocaine) 3/ Addition of NaOH in an amount equal to prototype	40	V HCl = 6µL	7.08	1% Lido (30% solution) = 0.3% de lidocaine within the gel Lidocaine solution = (40 + 0.066) x 1/99 = 0.405 g (or V Lidocaine solution = 405 µL)	6.72	Y = V NaOH = 6µL	6.89	40.471

Other data:

lidocaine solution pH = 4.75
PBS pH = 7.09
WFI pH = 6.90
WFI/HCl solution pH = 4.77

Raw data on rheology

Denomination in our document	Initial prototype		Frequency Sweep Amplitude (Cone / Plan)						pH
			f = 0.1Hz			f = 1Hz			
			G' (Pa)	G(°)	K* (Pa.s)	G' (Pa)	G(°)	K* (Pa.s)	
A1	PFB-170206-C5	before ster 1	33.9	14.5	55.8	49.0	18.5	8.2	7.08
		before ster 2	34.9	14.2	57.4	50.2	18.2	8.4	
		Average NS	34.4	14.4	56.6	49.6	18.3	8.3	
		after ster 1	20.1	21.4	34.3	33.7	23.3	5.8	7.12
		after ster 2	18.4	22.4	31.7	32.0	24.2	5.6	
		after ster 3	17.2	23.1	29.8	30.4	25.0	5.4	
		Average S	18.6	22.3	31.9	32.1	24.2	5.6	
A2	PFB-170206-C6	before ster 1	35.2	15.5	58.2	51.4	18.7	8.6	6.70
		before ster 2	35.1	15.3	57.9	51.1	18.4	8.6	
		Average NS	35.1	15.4	58.0	51.3	18.5	8.6	
		after ster 1	21.6	21.8	37.1	36.8	23.6	6.4	6.90
		after ster 2	21.3	21.1	36.4	35.9	23.4	6.2	
		Average S	21.5	21.4	36.7	36.4	23.5	6.3	
A3	PFB-170206-C8	before ster 1	39.7	16.5	65.9	59.3	18.8	10.0	6.83
		before ster 2	39.2	16.4	65.0	58.6	18.8	9.9	
		Average NS	39.4	16.4	65.4	59.0	18.8	9.9	
		after ster 1	22.5	21.9	38.6	38.8	23.6	6.7	7.01
		after ster 2	22.4	22.3	38.5	38.9	24.0	6.8	
		Average S	22.4	22.1	38.5	38.9	23.8	6.8	
A4	PFB-170206-C9	before ster 1	36.6	16.5	60.9	54.8	19.0	9.2	6.89
		before ster 2	35.7	16.8	59.4	53.9	19.2	9.1	
		Average NS	36.2	16.6	60.2	54.3	19.1	9.2	
		after ster 1	20.6	22.4	35.4	35.9	24.3	6.3	7.05
		after ster 2	21.1	22.4	36.3	36.7	24.0	6.4	
		Average S	20.8	22.4	35.9	36.3	24.1	6.3	

NS means No Sterilization

S means Sterilization

ster means sterilization