

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case PGR2025-00085
U.S. Patent No. 12,168,036

DECLARATION OF ROBERT J. FALCONER

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I, Robert John Falconer, Ph.D., declare as follows:

I. OVERVIEW

1. I have been retained by counsel for Alvotech USA, Inc. and Alvotech hf. (together, “Alvotech”) as a technical expert in connection with the above-identified proceeding.

2. I have been asked to provide my opinions concerning invalidity issues related to claims 1-3 of U.S. Patent No. 2,168,036 “the ‘036 Patent”.

3. The ‘36 Patent is titled “Methods for Treating Angiogenic Eye Disorder with High Doses of VEGF Receptor Fusion Proteins.” I understand that the ‘036 Patent is owned by Regeneron Pharmaceuticals Inc. (“Regeneron”).

4. I understand that this declaration is being submitted in support of Alvotech’s Petition for Post Grant Review of the ‘036 Patent.

5. My opinions in this declaration are based on my review of the ‘036 Patent; the prosecution history of the ‘36 Patent, including the applications to which it claims priority; the relevant prior art, other than that I have identified and art that has been provided to me; the other documents cited or otherwise referred to in this declaration; and my own experience, including, developing, and testing pharmaceutical protein products.

6. I am being compensated for my time at my usual consulting rate of \$645. I am also being reimbursed for reasonable travel expenses related to my

consultation. I have no personal or financial interest in the outcome of this proceeding, and my compensation is in no way affected by its outcome.

II. BACKGROUND AND QUALIFICATIONS

7. My education and experience are described more fully in my curriculum vitae, which is attached as **Exhibit A**. I highlight certain achievements here.

8. I received my Bachelor of Science degree in Biotechnology in 1984 from the University of New South Wales, Australia. I received my Ph.D. in 1998 from the University of Adelaide, Australia, in the field of recombinant protein manufacturing process development.

9. I am currently a Professor in Bioprocess Engineering in the Department of Chemical Engineering, University of Adelaide, South Australia. I have held this position since 2019, and my responsibilities have included teaching and researching. My research applies the expertise gained from the liquid formulation of therapeutic proteins.

10. I have over 30 years of industry and academia research experience in chemistry and biotechnology, which is particularly relevant to the issues disclosed below. I have extensive experience in the expression, purification, and formulation of protein biologics.

11. For example, in 1984 and from 1987 to 1992, I worked as a Protein Chemist and Fermentation Scientist for Biotech Australia Pty Ltd in Sydney, Australia. Biotechnology Australia Pty Ltd developed and manufactured recombinant animal vaccine, diagnostic tests and a portfolio of potential therapeutic proteins. I gained hands-on experience producing a range of proteins for use in diagnostic assays, animal experiments, and animal vaccines. I was able to take biopharmaceutical development projects from earliest stages (newly cloned strains) through the fermentation, purification, and formulation unit operations to a finished product. I gained experience in biopharmaceutical process design and the quality management required for the manufacture of medical products.

12. Over the ensuing years, I held a range of roles at different biotechnology and medical product companies improving operations, quality, and productivity. For example, in 1992-1995, I worked at Gropep Pty Ltd, a spin-off company from the University of Adelaide, which manufactured insulin-like growth factor I and II, and fusion proteins containing IGF-I. I worked on process development which included protein formulation by freeze drying and on applying Good Manufacturing Practice to our manufacturing.

13. In 1998-1999 and 2002-2003, I worked at Diagnostic Systems Laboratories (DSLabs), which manufactured 150 different medical diagnostic kits to measure a range of analytes including steroid and protein hormones, cancer

markers, growth factors and binding proteins. The diagnostic kits included monoclonal antibodies and polyclonal antiserum as active ingredients of the tests which were stored as either lyophilised or liquid formulations. I was initially an operations manager and later a product development manager.

14. From 2003 to 2006, I was a Research Coordinator in Bioscience Engineering in the Department of Chemical Engineering at the University of Cambridge, UK. My responsibilities included managing bioscience engineering laboratories and supervising research. We undertook research into papillomavirus virus-like particle self-assembly and competing aggregation reactions, and protein refolding which also had aggregation reactions. We used dynamic light scattering and static light scattering to study hydrodynamic radius and were familiar with the second virial coefficient and its relationship with attraction and repulsion between proteins.

15. From 2006 to 2011, I was a Senior Research Fellow in the Australian Institute of Bioengineering and Nanotechnology at the University of Queensland, Australia. In this position, I developed analytical techniques to support the Australian biotechnology industry and associated research institutes. I focused on protein formulation and the thermodynamics of protein instability. The proteins included therapeutic monoclonal antibody and a synthetic anti-hemophilic factor. I

also lectured on bioprocess engineering at the University of Queensland and the James Cook University.

16. From 2011 to 2015, I was a lecturer in Biological Engineering in the Department of Chemical & Biological Engineering at the University of Sheffield, UK. My research in this position focused on protein stability and formulation and was aimed at supporting the biopharmaceutical industry in achieving stable therapeutic protein formulations. My project used terahertz spectroscopy, dynamic light scattering (DLS) and calorimetry techniques like differential scanning calorimetry (DSC), isothermal titration calorimetry (ITC) and pressure perturbation calorimetry (PPC) to provide fresh insight into the interaction between water and excipients. The project goal was to create a predictive program called “Rational Design of Aqueous Formulations” for the design of liquid protein formulations with a high probability of achieving a long shelf-life.

17. I have authored and co-authored over 60 papers in leading journals including Biotechnology & Bioengineering, Journal of Physical Chemistry, Physical Chemistry & Chemical Physics, and the Journal of Pharmaceutical Science. My work has been cited over 3,600 times. I have published three book chapters and I am the named inventor on two patents.

18. I have extensive experience in liquid formulation of therapeutic proteins, including the interactions between proteins (including a human serum

albumin fusion protein), excipients, and water. I have at least 50 publications and presentations directed to proteins and protein formulations, which are included in my CV.

19. I have supervised several postgraduate students working on these topics related to protein stability and interaction, such as the the mo

uring expression, difficult to express proteins, phytate-protein interactions, and tannin-protein interactions.

20. I currently teach courses on Pharmaceutical Process Validation and Quality, Good Manufacturing Practice, Validation and Regulation, Quality by Design and Process Analytical Technology, and Advanced Technologies in Biopharmaceutical Processing. From 2015 to 2016, I founded a new Master of Science course on Biochemical Engineering with Industrial Management, which teaches a combination of business management and biological engineering. I have also been active in designing the undergraduate biological engineering and chemical engineering curriculum.

21. I was an external examiner of the BSc course in Viticulture and Oenology, Plumpton College, which was administered by the University of Brighton. I was recently external examiner by the National University of Ireland, Galway for their Biopharmaceutical Chemistry course. I am a former committee

member of the IChemE Biochemical Engineering SIG and Pharma Engineering SIG.

I was a member of the committee that founded the BBSRC BioProNET.

III. SUMMARY OF OPINIONS

22. My opinions are limited to VEGF receptor fusion protein formulations, including aflibercept, as claimed in the '036 Patent. I provide my opinions from the perspective of a person of ordinary skill in the art, which I refer to herein as a “POSA” or a “skilled formulator” and define below in Section VI.

23. I understand that Alvotech’s expert Dr. Donald Joseph D’Amico, M.D., offers the following opinions:

- Ground 1: A POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with a reasonable expectation of success; and these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the '036 patent.

- Ground 2: A POSA would have been motivated to combine Regeneron’s Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with a reasonable expectation of success; and these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the '036 Patent.

- Ground 4: A POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with the 2011 Eylea Clinical Review; these references

teach, or at least make obvious, the methods recited in Claims 2 and 3 of the '036 Patent.

- Ground 5: A POSA would have been motivated to combine Regeneron's Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with the 2011 Eylea Clinical Review; and these references teach, or at least make obvious, the methods recited in Claims 2 and 3 of the '036 Patent.

24. I summarize my opinions as follows:

- Ground 1: In light of Vitti and Larson, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation comprising a VEGF receptor fusion protein, including aflibercept, containing the concentrations of VEGF receptor protein or aflibercept and having the viscosities recited in Claims 1 and 4-38 of the '036 Patent.

- Ground 2: In light of Furfine, Dix, and Fiedler and Larson, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation comprising a VEGF receptor fusion protein, including aflibercept, containing the concentrations of VEGF receptor protein or aflibercept and having the viscosities recited in Claims 1 and 4-38 of the '036 Patent.

- Ground 3: Claims 1-38 are invalid for lack of written description.

- Ground 4: In light of Vitti and Larson, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical

formulation comprising a VEGF receptor fusion protein, including aflibercept, containing the concentrations of VEGF receptor protein or aflibercept and having the viscosities recited in Claims 2 and 3 of the '036 Patent.

- Ground 5: In light of Furfine, Dix, and Fiedler and Larson, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation comprising a VEGF receptor fusion protein, including aflibercept, containing the concentrations of VEGF receptor protein and having the viscosities recited in Claims 2 and 3 of the '036 Patent.

IV. MATERIALS CONSIDERED

25. In forming my opinions in this declaration, I relied on my knowledge and professional experience as described above. I have also considered in whole or in part the materials listed below:

Exhibit Number	Citation
EX1001	U.S. Patent No. 12,168,036 to Graham et al.
EX1002	Prosecution History of U.S. Patent No. 12,168,036
EX1005	U.S. Patent No. 7,608,261 to Furfine et al.
EX1006	U.S. Patent No. 8,921,316 to Dix et al.
EX1007	U.S. Patent App. Pub. No. 2016/0144025 to Vitti et al.
EX1010	U.S. Patent App. Pub. No. 2015/0071920 to Larson et al.
EX1011	U.S. Patent App. Pub. No. 2017/0232199 to Fiedler
EX1012	WO 2016/154288 to Ingber et al.
EX1013	Regeneron Application for Extension of Patent Term for U.S. Patent No. 7,374,758, dated Dec. 22, 2011
EX1021	Barton J. Dear et al., <i>Contrasting the Influence of Cationic Amino Acids on the Viscosity and Stability of a Highly</i>

	<i>Concentrated Monoclonal Antibody</i> , 34 PHARM. RES. 193 (2017)
EX1025	Feng He et al., <i>Effect of Sugar Molecules on the Viscosity of High Concentration Monoclonal Antibody Solutions</i> , 28 PHARM. RES. 1552 (2011)
EX1027	Taehun Hong et al., <i>Viscosity Control of Protein Solution by Small Solutes: A Review</i> , 19 CURRENT PROTEIN & PEPTIDE SCI. 746 (2018)
EX1028	Naoto Inoue et al., <i>Arginine and Lysine Reduce the Viscosity of Serum Albumin Solutions for Pharmaceutical Injection</i> , 117 J. BIOSCIENCE & BIOENGINEERING 539 (2014)
EX1032	Chakravarthy Narasimhan et al., <i>High-Dose Monoclonal Antibodies Via the Subcutaneous Route: Challenges and Technical Solutions, an Industry Perspective</i> , 3 THERAPEUTIC DELIVERY 889 (2012)
EX1033	Martin S. Neergaard et al., <i>Viscosity of High Concentration Protein Formulations of Monoclonal Antibodies of the IgG1 and IgG4 Subclass – Prediction of Viscosity Through Protein-Protein Interaction Measurements</i> , 49 EUROPEAN J. PHARM. SCI. 400 (2013)
EX1038	Branden A. Salinas et al., <i>Understanding and Modulating Opalescence and Viscosity in a Monoclonal Antibody Formulation</i> , 99 J. PHARM. SCI. 82 (2010)
EX1043	DABIR S. VISWANATH ET AL., <i>Correlations and Estimation of Pure Liquid Viscosity</i> , in VISCOSITY OF LIQUIDS: THEORY, ESTIMATION, EXPERIMENT, AND DATA (2007)
EX1044	Shujing Wang et al., <i>Viscosity-Lowering Effect of Amino Acids and Salts on Highly Concentrated Solutions of Two IgG1 Monoclonal Antibodies</i> , 12 MOLECULAR PHARMACEUTICS 4478 (2015)
EX1045	Shawn Shouye Wang et al., <i>US FDA-Approved Therapeutic Antibodies with High-Concentration Formulation: Summaries and Perspectives</i> , 4 ANTIBODY THERAPEUTICS 262 (2021)

26. In addition, I considered a conversation with Dr. Donald J. D’Amico, M.D. on September 16, 2025, which I will refer to herein as “D’Amico Conversation.”

V. LEGAL STANDARDS

27. In expressing opinions on what I understand may be considered legal issues, I have applied the following legal standards conveyed to me by counsel.

28. I understand that the analysis of the validity of patent claims is done from the perspective of a person having ordinary skill in the art at the time of the alleged invention in view of the patent's disclosure and prosecution history. For the purposes of my analysis of the '036 Patent, I have used the earliest priority date for the '036 Patent of May 10, 2018.

A. Obviousness

29. I understand that a patent claim is invalid as obvious if the differences between the claimed subject matter and what is taught by the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art at the time that the invention was made. I understand that four factual inquiries guide this determination: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) relevant secondary considerations (or objective criteria), such as unexpected results, commercial success, long-felt but unsolved need, failure of others, copying by others, and simultaneous invention by others.

30. I understand that the hypothetical person having ordinary skill in the art is presumed to have knowledge of the relevant prior art at the time of the claimed

invention, and that the scope of the prior art comprises any prior art that was reasonably pertinent to the particular problems the inventor faced.

31. I understand that a claimed invention may be found obvious based on a combination of prior art references. Further, I understand that there need not be an explicit teaching, suggestion, or motivation to combine those references in order to determine that an invention is obvious. Nonetheless, I understand it is important that a person having ordinary skill in the art have a reason to combine the elements found in the prior art in the way the claimed new invention does. It is my understanding that, in assessing obviousness, one can consider factors such as interrelated teachings of multiple patents, the effects of demands known to the design community or present in the marketplace, and the background knowledge possessed by one of ordinary skill in the art to determine whether there was an apparent reason to have combined the known elements in the fashion claimed by the patent at issue. It is also my understanding that a reason to combine or modify prior art references can come from the prior art itself; can be something that would have been generally known to a person having ordinary skill in the art, including common sense; or can be something derived from the nature of the problem to be solved.

32. I understand that when there is a design need or market pressure to solve a problem, and there are a finite number of identified, predictable solutions, a person having ordinary skill in the art would have had good reason to pursue the known

options within their technical grasp. If this leads to the anticipated success, it is likely the product of ordinary skill and common sense, and therefore obvious. I also understand that obviousness does not require absolute predictability of success. Rather, it is my understanding that a patent claim is obvious so long as there was a reasonable expectation of success.

33. I further understand that the fact that a particular combination of prior art elements was obvious to try may indicate that the combination was obvious.

34. I understand that discovering and claiming a new benefit of an old process cannot make that old process non-obvious, and that recognition of latent properties in the prior art does not render non-obvious an otherwise known invention. I further understand that where a claim limitation necessarily must be present in the prior art reference or a combination of elements disclosed in the prior art, or is the natural result of the composition that is present in the prior art of that is obvious over the prior art, it is obvious by inherency.

B. Written Description

35. I understand that, for each claim, the specification must contain a “written description” of the claimed invention sufficient to convey to a person of ordinary skill in the art that the inventor invented the full scope of what is claimed as of the priority date. I understand that the written description analysis focuses on

what the four corners of the priority document's specification conveys to one of ordinary skill in the art.

36. I understand that the level of detail required to satisfy the written description requirement depends on the nature and scope of the claims and on the complexity and predictability of the technology. I understand that factors used to evaluate the sufficiency of a disclosure include: 1) the existing knowledge in the particular field; 2) the extent and content of the prior art; 3) the maturity of the science or technology; and 4) the predictability of the claimed method or invention.

37. I further understand that, just because a disclosure may be enough to make the claims obvious to a person of ordinary skill in the art, that does not necessarily mean that the disclosure provides adequate written description support.

VI. PERSON OF ORDINARY SKILL IN THE ART

38. I have been informed that the claims of a patent are judged from the perspective of a hypothetical "person of ordinary skill in the art," which I will refer to herein as a "POSA" or a "skilled formulator." I also understand that "the art" is the field of technology to which the patent is related. The purpose of a POSA is to provide an objective viewpoint, and it is my understanding that the question of patent validity is viewed from the perspective of a POSA, and not from the perspective of a lay person, an inventor, or a person of extraordinary skill in the art.

39. I have been informed that the claims of the '036 Patent are to be interpreted as a POSA would have understood them at the relevant time, which I have been asked to assume is May 10, 2018.

40. A POSA at the time of the invention would have been a multidisciplinary team that included (1) a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders, including treatments and dosing regimens of drugs for intravitreal injection including anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and familiarity with the pharmacological properties of anti-VEGF treatments; and (2) a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including for example, fusion proteins or antibodies.

41. The POSA in the field of the '036 Patent would have also had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs.

42. As a Ph.D. in the field of recombinant protein manufacturing process development, with over 30 years of industry and academia research experience in chemistry and biotechnology, including extensive experience in the expression,

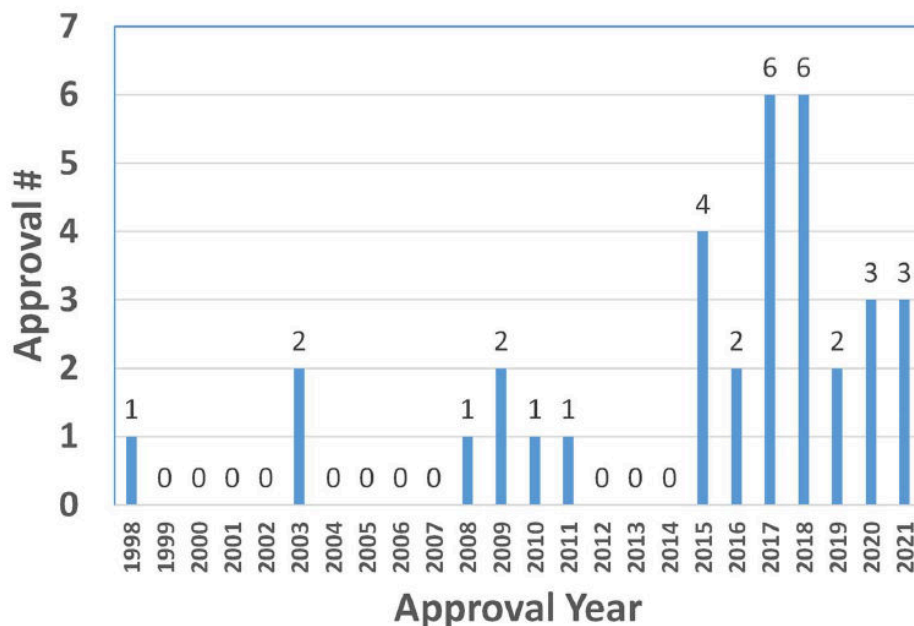
purification, and formulation of protein biologics, I consider myself to have at least the qualifications of a person of ordinary skill in the art at the time of the alleged invention.

VII. BACKGROUND OF THE TECHNOLOGY

A. Overview of Commercial High Concentration Liquid Protein Formulations

43. As the need for protein-based therapeutics has grown, high concentration protein formulations have become increasingly important in the pharmaceutical industry. EX1032 (Narasimhan) at 889 (“All the marketed sc. mAbs are high-concentration products and the new ones currently under development are expected to be the same for maximum patient benefits. Efforts are currently being made to convert the existing low-concentration iv. mAb products for high-concentration sc. products.”). Specifically, the pharmaceutical industry has recognized a need to formulate therapeutic proteins at high concentrations in order to deliver the required high dose in as small a volume as possible. EX1032 (Narasimhan) at 889 (“For the sc. route, a high-concentration product must be developed to deliver a high dose as administration volume is limited.”). Over the last three decades, the United States Food & Drug Administration (FDA) has approved more and more high-concentration protein formulations with at least 100

mg/mL protein concentration, with a significant increase in approvals starting in 2015. EX1045 (Wang 2021) at 263, Table 1, Fig. 1.



The number of approved high-concentration protein formulations (18) from 2015 to 2018 accounted for nearly 70% of the total number (26) of approved high-concentration protein formulations with ≥ 100 mg/mL through the end of 2018, “suggesting the increasing demand of high-concentration formulation in recent years from the biopharmaceutical industry.” EX1045 (Wang 2021) at 263.

B. Formulation Considerations and Solutions Related to High Concentration Liquid Protein Formulations

44. Two important considerations in formulating therapeutic proteins, such as antibodies and fusion proteins, at high concentrations are physical stability and viscosity. EX1010 (Larson) at [0015] (“Many pharmaceutically important high-

molecular weight proteins, such as mAbs, are currently administered via IV infusions in order to deliver therapeutically effective amounts of protein due to problems with high viscosity and other properties of concentrated solutions of large proteins.”). As the industry has continued to shift toward high-concentration protein formulations, several formulation strategies and techniques have emerged that address these considerations and have enabled the development of such formulations.

1. Physical Stability

45. Physical stability refers to the ability of protein in a formulation to maintain its physical structure.

46. A major form of physical instability for therapeutic proteins is aggregation, whereby proteins lose their native structure, self-associate, and form particulates, ultimately resulting in a reduction of efficacy and increased risk of immunogenicity. EX1010 (Larson) at [0005]-[0006]; EX1021 (Dear) at 194; EX1032 (Narasimhan) at 891. Concentrated proteins are particularly prone to aggregation. EX1021 (Dear) at 194; EX1010 (Larson) at [0006].

47. Although aggregation was known to be associated with formulations containing higher concentrations of protein, as of 2018, formulation techniques for minimizing aggregation and enhancing physical stability of protein formulations were available, and as Regeneron’s own prior art patents and publications taught,

had been successfully applied to develop high-concentration protein formulations containing aflibercept. EX1007 (Vitti) at [0094] (“[T]he pharmaceutical formulations are liquid formulations that may contain 5 ± 0.75 mg/mL to 100 ± 15 mg/mL of a VEGF antagonist.”), [0085]-[0086] (identifying aflibercept as a VEGF antagonist), [0108] (“The pharmaceutical formulations of the present invention typically exhibit high levels of stability.”), [0100]-[0101] (describing exemplary thermal stabilizers such as sucrose, sorbitol, glycerol, trehalose, and mannitol, for minimizing aggregation); EX1005 (Furfine) at 2:4-9 (describing “a stable ophthalmic formulation . . . that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist”), 2:49-54 (similar); EX1006 (Dix) at 2:20-24 (describing “high concentration stable liquid formulation[s] of a VEGF antagonist”), 10:17-12:10 (disclosing stable formulations containing 100 mg/mL VEGF trap), cls. 1-2 (similar).

2. Viscosity

48. Viscosity refers to the resistance of liquid to flow under the action of external force. Liquids with higher viscosity require greater force to get a satisfactory flow, whereas those with lower viscosity require less force to get a satisfactory flow.

49. For liquid therapeutic protein formulations administered via injection, viscosity has an impact on ease of delivery from syringes. EX1032 (Narasimhan) at

890 (“The high-solution viscosity causes serious delivery problems from syringes and other dosing devices even when high concentration is achieved.”).

50. The viscosity of a liquid protein formulation can be affected by protein concentration, temperature, formulation excipients, and pH. Among these factors, by far the greatest contributor to viscosity is protein concentration. EX1021 (Dear) at 194 (“The viscosities of protein solutions increase exponentially with concentration due to increased protein-protein interactions (PPI) as surface separation decreases.”); EX1027 (Hong) at 746 (“With increasing concentration of the protein, the viscosity of the protein also increases.”); EX1032 (Narasimhan) at 890 (“The increased protein concentration associated with the limited volume of sc. doses for monoclonal antibodies inevitably leads to elevated viscosity.”).

51. Viscosity in a liquid protein formulation is generally the result of intermolecular protein-protein interactions (PPIs) present in the protein solution. EX1027 (Hong) at 746; EX1038 (Salinas) at 82 (“[H]igh viscosities . . . result from protein-protein intermolecular interactions that can be modulated with solution ionic strength.”); EX1021 (Dear) at 194 (“The viscosities of protein solutions increase exponentially with concentration due to increased protein-protein interactions (PPI) as surface separation decreases”). At low concentrations, where the intermolecular distance is large, long-range repulsive PPIs generally contribute the most to flow behaviour. EX1033 (Neergaard) at 401; EX1032 (Narasimhan) at 890. At high

concentrations, protein solutions tend to experience crowded environments in solution in which the intermolecular distance is reduced and short range PPIs tend to dominate flow behaviour, leading to increased viscosity of the solution. EX1033 (Neergaard) at 401; EX1021 (Dear) at 194.

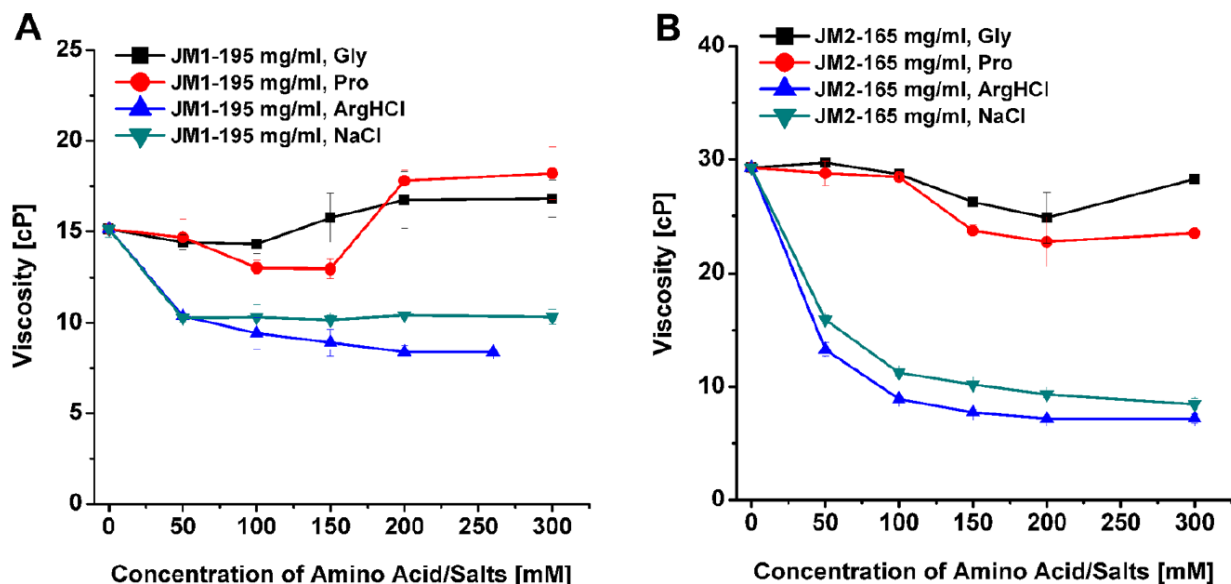
52. With the trend toward higher concentration liquid protein formulations, a number of formulation strategies and techniques have emerged for reducing viscosity, which in turn have enabled highly concentrated protein formulations. I discuss below several exemplary formulation strategies and techniques for reducing viscosity below, including: (a) adding amino acids; (b) adding salts; (c) minimizing the use of sugars or sugar alcohols; (d) adjusting pH relative to pI of the protein; (e) adding viscosity-lowering water soluble dyes; and (f) emulsification.

53. **Adding amino acids that interact with residues on the protein surface.** Viscosity in a high concentration liquid protein formulation may be reduced through the addition of amino acids such as arginine, histidine, and lysine that interact with residues on the protein surface. EX1021 (Dear) at 194 (“An increasingly common strategy for manipulating PPI is to add co-solutes that indirectly or directly interact with residues on the mAb surface.”).

54. For example, in a study from the University of Texas at Austin investigating the effect of charge on the viscosity of monoclonal antibody mAb1 in solution, Dear et al. reported that solutions containing ≥ 200 mg/mL monoclonal

antibody exhibited a “large viscosity reductions” with the addition the basic amino acids arginine and histidine, as well as imidazole when protonated in the cationic state, and anionic camphorsulfonic acid. EX1021 (Dear) at 199-205.

55. As another example, Wang et al. reported that solutions containing 195 mg/mL JM1 and 165 mg/mL JM2 (IgG monoclonal antibodies) exhibited a reduction of viscosity with the addition of amino acids. EX1044 (Wang 2015) at 4480, Fig. 2.



EX1044 (Wang 2015) at Fig. 2. Of the four representative amino acids and salts tested, arginine and sodium chloride provided a “significant viscosity-lowering effect.” EX1044 (Wang 2015) at 4480.

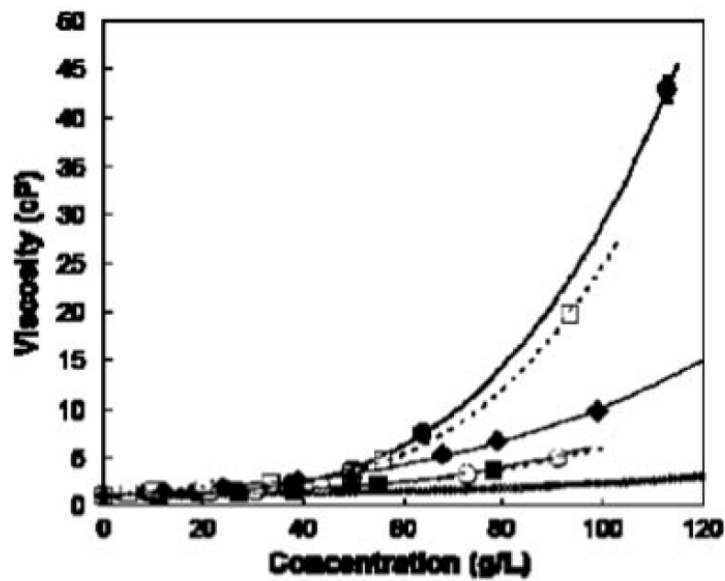
56. In another study, Inoue et al. reported that arginine and lysine may be used to reduce the viscosity of protein solutions for pharmaceutical injection.

EX1028 (Inoue) at 542. Specifically, the study showed that at pH 7.4, the addition of either 200 mM LysHCl or 200 mM ArgHCl resulted in significant (approximately 1.6- to 2-fold) reductions in viscosity for high-concentration protein solutions containing 275 mg/mL bovine serum albumin (BSA) and 305 mg/mL human serum albumin (HSA), respectively. EX1028 (Inoue) at 540, Figs. 3, 6.

57. Adding salts that interact with residues on the protein surface.

Viscosity in a high concentration liquid protein formulation may also be reduced through the addition of salts that interact with residues on the protein surface. EX1021 (Dear) at 194 (“An increasingly common strategy for manipulating PPI is to add co-solutes that indirectly or directly interact with residues on the mAb surface.”).

58. For example, as shown in a study from the University of Colorado involving monoclonal antibodies in solution at concentrations of up to 100 mg/mL subjected to “low” ionic strength (approximately 4 mM) and “high” ionic strength conditions (approximately 154 mM), Salinas et al. observed that addition of 150 mM NaCl resulted in a significant decrease in viscosity in solutions with monoclonal antibodies at concentrations of 80 mg/mL or more (denoted below as a white circle). EX1038 (Salinas) at 86, Fig. 1.



EX1038 (Salinas) at Fig. 1.

59. In addition, Inoue et al. demonstrated that at pH 7.4, the addition of 200 mM NaCl or 200 mM GdnHCl resulted in significant (approximately 1.5- to 2-fold) reductions in viscosity for high-concentration protein solutions containing 275 mg/mL BSA and 305 mg/mL HSA. EX1028 (Inoue) at 540, Figs. 3, 6.

60. Further, Wang et al. reported that solutions containing high concentrations of monoclonal antibodies, 195 mg/L J1 and 165 g/L JM2, exhibited a reduction of viscosity with the addition of NaCl. EX1044 (Wang 2015) at 4480, Fig. 2.

61. **Minimizing the use of sugars or sugar alcohols.** Viscosity in a high concentration liquid protein formulation may be reduced by minimizing the use of

sugars or sugar alcohols, which were known to increase the viscosity of protein solutions. EX1025 (He) at 1554, 1559; EX1021 (Dear) at 194, 198-199.

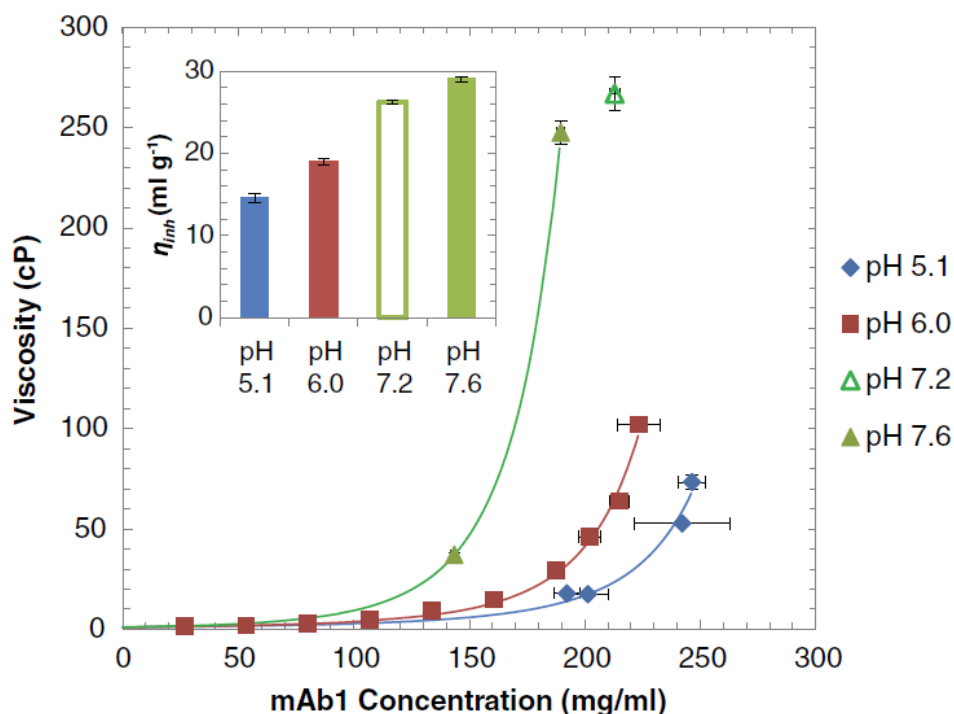
62. For example, in a study from Amgen investigating the effect of different sugar molecules on the viscosity of high concentration solutions containing up to 177 mg/mL monoclonal antibody, He et al. determined that “[t]he addition of sugars increased the solution viscosity at all protein concentrations studied with a greater increase observed as the protein concentration increased.” EX1025 (He) at 1554.

63. **Adjusting pH relative to pI.** Viscosity in a high concentration liquid protein formulation may also be reduced by adjusting pH relative to the pI of the protein (the specific pH at which the protein carries no net charge). EX1032 (Narasimhan) at 890.

64. In particular, it was known that at relatively high concentrations of protein (> 100 mg/mL), viscosity is highest at pH values at or near pI of the protein and lower at pH values that are farther away from the pI. EX1032 (Narasimhan) at 890. At or near the pI, the protein molecules in the solution have neutral or near-neutral charge and thus have no or minimal electrostatic repulsive forces between one another. EX1033 (Neergaard) at 400. With the absence of repulsive forces, local attractive PPIs dominate and can result in an increase in the viscosity of the solution. EX1021 (Dear) at 196-197.

65. By contrast, when the pH of the solution is away from the pI, the protein molecules gain a net positive or negative charge, depending on whether the pH is higher or lower than the pI, respectively. EX1021 (Dear) at 196-197. The presence of a net charge creates electrostatic repulsive PPIs between the protein molecules and keeps the proteins dispersed from one another, which in turn results in lower viscosity of the solution. EX1021 (Dear) at 196-197.

66. For example, Dear et al. determined in experiments on solutions containing between 25 mg/mL and 250 mg/mL of antibodies that “[t]he viscosity for a given concentration decreases markedly with pH from 7.6 to 5.1 at each mAb concentration” as the solution moved away from the pI of mAb1, 9.3, with greater pH-related effects on viscosity being observed at higher concentrations. EX1021 (Dear) at 196, Fig. 1.



EX1021 (Dear) at Fig. 1. As the study reports, “[u]pon reducing the pH below the pI . . . the increase in the net positive charge of the mAb increases the global long-ranged charge repulsion” and “lowering the pH will neutralize some negative charges on the mAb surface weakening anisotropic local electrostatic attraction between opposite charges and dipoles.” EX1021 (Dear) at 196. In the case of mAb1, “as the pH is lowered starting at the pI of 9.3, the local attractive protein-protein interactions (PPI) become weaker and the repulsive PPI become stronger, both of which would be expected to decrease net attraction and therefore reduce the viscosity.” EX1021 (Dear) at 197.

67. **Adding viscosity-lowering water soluble dyes.** Viscosity in high concentration liquid protein formulations may also be reduced by including viscosity-lowering water soluble dyes.

68. For example, as taught in Larson, viscosity of high-concentration formulations containing “preferably from about 100 mg/mL to about 2,000 mg/mL” therapeutic protein may be “reduced by the presence of one or more viscosity-lowering water soluble dyes” to a viscosity of “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 (Larson) at [0022]-[0023], [0075], [0077].

69. **Emulsification.** Viscosity in a high concentration liquid protein formulation may also be reduced through emulsification.

70. For example, as taught in International Publication No. WO 2016/154288 A1 to Ingber et al., which I refer to herein as Ingber, viscosity of high-concentration formulations containing “100 mg/ml or higher” of a therapeutic protein may be reduced by forming an emulsion wherein droplets of the protein can be formed into liquid droplets and dispersed in a carrier liquid of lower viscosity to obtain an emulsion that has a viscosity of “no more than 15 cP.” EX1012 (Ingber) at [0054] (“Examples of an active agent suitable to be administered using various aspects described herein include, but are not limited to, a protein, a peptide, an antibody . . .”), [0061] (“Injection of a high-concentration therapeutics (*e.g.*, . . . at a

concentration of 100 mg/mL or higher) can interfere with the plunging action of syringes, as the high-concentration therapeutics generally tend to be viscous. To overcome such problem, high-concentration and/or high-viscosity therapeutic solutions can be formed into liquid droplets, which are then dispersed in a carrier liquid of a lower viscosity.”), [0062] (“the viscosity of the carrier liquid can be selected such that it can be injected properly (*e.g.*, using a syringe with a small needle).”), [0064] (“The compositions . . . can have a viscosity of . . . no more than 15 cP.”). Additionally, Ingber states that the emulsion may be “designed to allow for the administration into particular compartments of the body, *e.g.*, the eye.” EX1012 (Ingber) at [0054].

VIII. THE '036 PATENT

71. U.S. Application No. 17,384,070, now U.S. Patent No. 12,168,036 (“the '036 Patent,” EX1001), titled “Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins,” was filed on July 23, 2021. The '036 Patent issued on December 17, 2024. EX1001 ('036 Patent). The '036 Patent states that it is a continuation of U.S. Patent Application No. 16/409,631, now U.S. Patent No. 11,103,552. EX1001 ('036 Patent). The '036 Patent also states that it claims priority to earlier filings, including U.S. Provisional Application No. 62/813,882, filed on March 5, 2019, U.S. Provisional Application No. 62/769,876, filed on November 20, 2018, U.S. Provisional Application No.

62/752,127, filed on October 29, 2018, and U.S. Provisional Application No. 62/669,506, filed on May 10, 2018. EX1001 ('036 Patent).

72. The '036 Patent generally relates to “ophthalmic formulations having high concentrations of vascular endothelial growth factor (VEGF) receptor fusion protein and high stability during storage” and “[m]ethods for treating angiogenic eye disorders using the high concentration formulations.” EX1001 ('036 Patent) at Abstract.

73. The '036 Patent has two independent claims, claims 1 and 35.

74. Independent claim 1 recites:

A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 micro liters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

EX1001 ('036 Patent) at Claim 1.

75. Independent claim 35 recites:

A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation

comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.

EX1001 ('036 Patent) at Claim 35.

76. The '036 Patent specification lists 89 “[i]llustrative high concentration VEGF receptor fusion protein containing formulations,” identified as formulations A-KKKK. EX1001 ('036 Patent) at 23:22-28:20. Each of the “illustrative” formulations A-KKKK includes either aflibercept, conbercept, or a generic “VEGF receptor fusion protein.” EX1001 ('036 Patent) at 23:22-28:20. Each of the listed formulations A-KKKK also includes one of a histidine-based buffer, a phosphate-based buffer, or a citrate-based buffer. EX1001 ('036 Patent) at 23:22-28:20. The '036 Patent specification, however, only provides data regarding viscosity testing for certain formulations containing aflibercept and either a histidine-based buffer or a phosphate-based buffer. EX1001 ('036 Patent) at 38:27-40:10 (Example 3), 42:14-22 (Example 5), Figs. 3A-C, 5.

77. Example 3 describes “[a] number of VEGF Trap (aflibercept) containing formulations . . . tested for their viscosity behavior.” EX1001 ('036 Patent) at 38:32-33. As explained in Example 3, “[f]ormulations having from between 10 mg/ml to 160 mg/ml VEGF Trap were tested in the presence and absence of various viscosity reducing agents,” including for example arginine, lysine, sodium chloride, and magnesium chloride. EX1001 ('036 Patent) at 38:33-36, Figs. 3A-3C.

78. As shown in Figure 3A, reproduced below, “formulations having 155 mg/ml VEGF trap in 10 mM sodium phosphate buffer, 5% sucrose and a pH of 6.2 in combination with no inorganic salt, arginine, lysine, sodium chloride and magnesium chloride showed little difference in viscosity,” as measured at 20° C. EX1001 ('036 Patent) at 38:37-43, Fig. 3A.

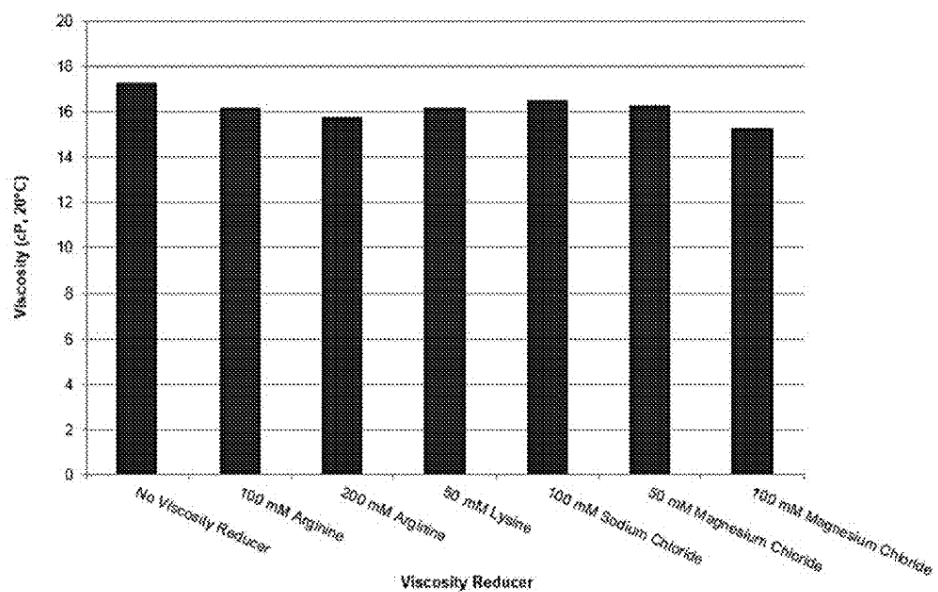


FIG. 3A

According to the '036 Patent specification, “[a] range of viscosity between about 17 cP (no inorganic salt) and 15 cP (100 mM magnesium chloride) was observed, with little variation between which viscosity reducing agent was used, or with the presence of a viscosity reducing agent at all.” EX1001 ('036 Patent) at 38:43-47, Fig. 3A.

79. Figure 3B describes “a similar series of formulations” as those described in Figure 3A, “except that the base buffer is 10 mM histidine and pH 5.8”

instead of 10 mM sodium phosphate buffer and pH 6.2. EX1001 ('036 Patent) at 38:47-49, Fig. 3B.

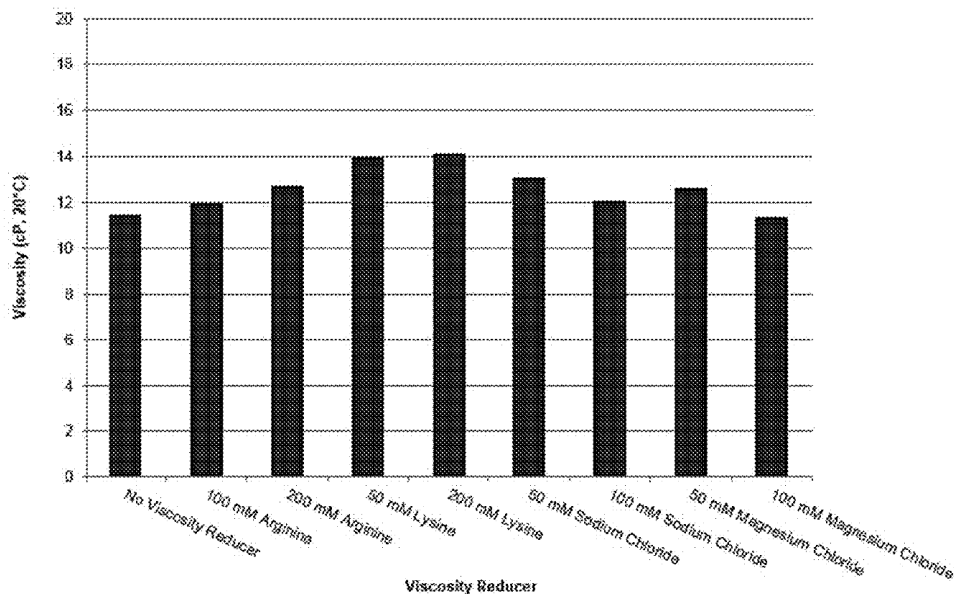


FIG. 3B

According to the '036 Patent specification, “the histidine containing buffer provided excellent viscosity, one in line with other low-concentration biologic injectables.”

EX1001 ('036 Patent) at 38:52-54, Fig. 3B.

80. Regarding Figures 3A and 3B, the '036 Patent specification notes:

As shown in FIGS. 3A and 3B, the viscosity reducing agent had little positive effect on the formulation viscosity, even at higher protein concentrations. This is a surprising result, as arginine and other viscosity reducing agents have previously been shown to have beneficial properties on high concentration protein viscosity.

EX1001 ('036 Patent) at 38:60-67.

81. Figure 3C describes “viscosity of VEGF Trap between the concentrations of 10 mg/ml and 160 mg/ml, with 10 mM sodium phosphate, 5% sucrose at a pH of 6.2 in the absence of arginine, and in 50 mM of arginine hydrochloride.” EX1001 ('036 Patent) at 38:55-58, Fig. 3C.

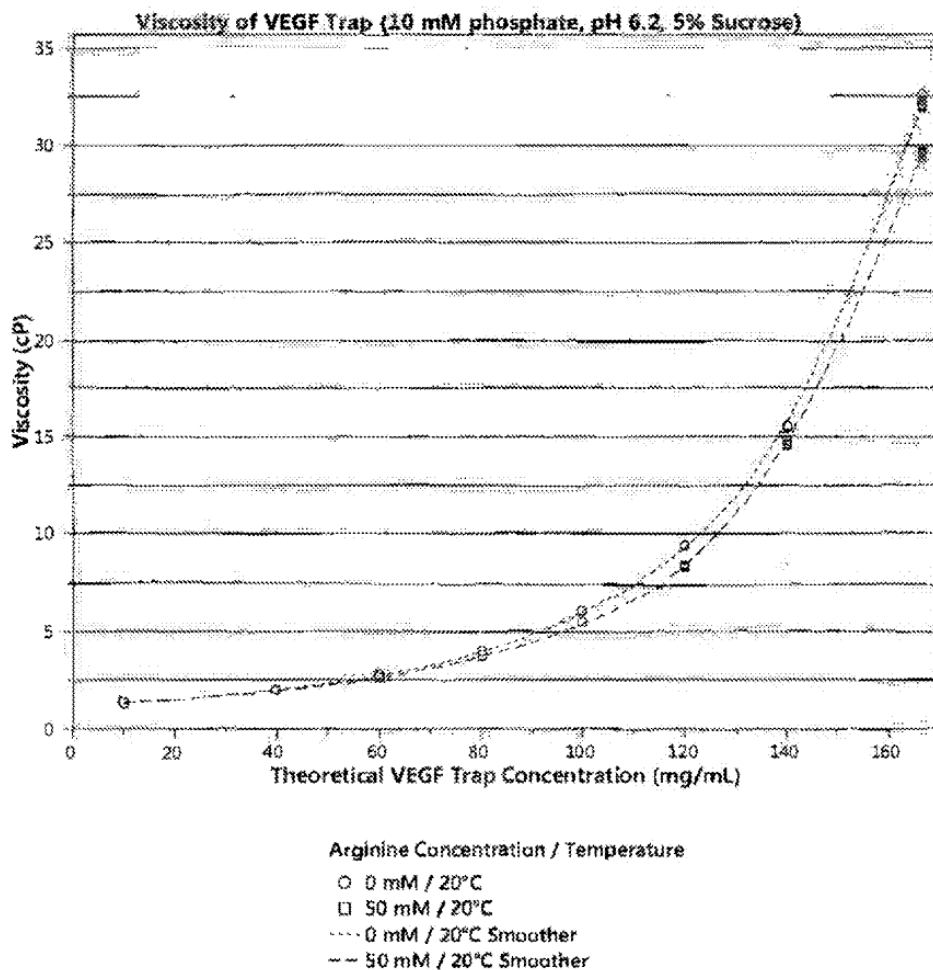


FIG. 3C

According to the '036 Patent specification, “[i]nclusion of the viscosity reducing agent resulted in similar viscosities for all VEGF Trap concentrations tested.” EX1001 ('036 Patent) at 38:58-60.

82. Example 5 describes the viscosity of certain aflibercept formulations, measured at 20° C, with 10 mg/mL to 170 mg/mL VEGF Trap (aflibercept) and either (a) 10 mM phosphate buffer, pH 6.2, and 5% sucrose; or (b) 10 mM histidine buffer, pH 6.0, and 5% sucrose. EX1001 ('036 Patent) at 42:14-22.

83. As shown in Figure 5, reproduced below, “[a]t higher VEGF Trap concentrations, the histidine buffer showed an improvement in viscosity (relative to phosphate).” EX1001 ('036 Patent) at 42:14-22, Fig. 5.

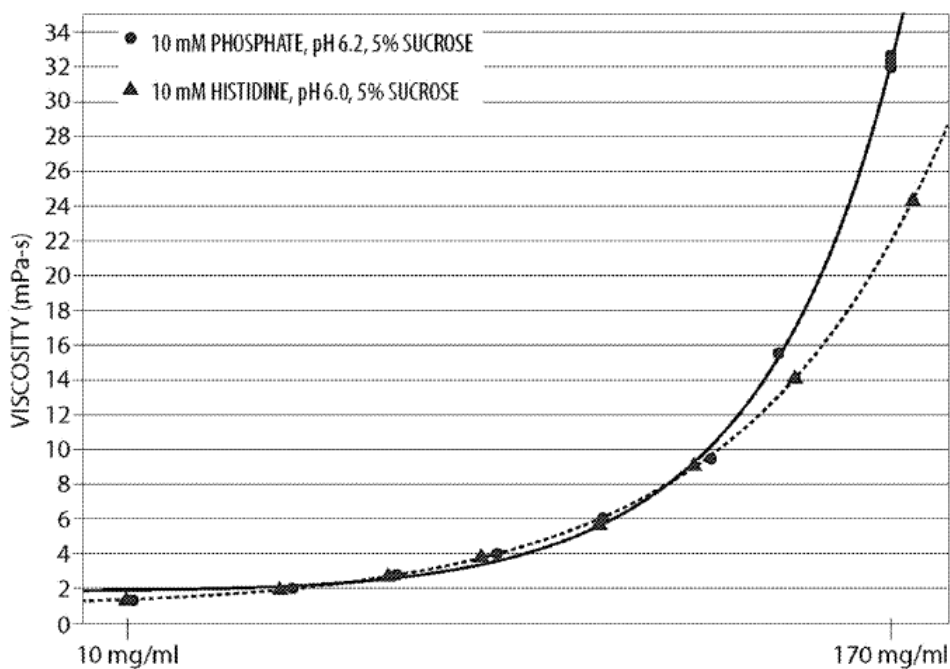


FIG. 5

84. Example 9 describes “the effect of various counterions and other excipients on stability.” EX1001 ('036 Patent) at 46:29-51:13. Viscosity testing on various formulations (Formulations GGG, HHH, III, JJJ, KKK, LLL, MMM, NNN,

OOO, PPP, QQQ, and RRR) was performed and reported in Figure 9, shown below.

EX1001 ('036 Patent) at Table 9-3, Table A, Fig. 9.

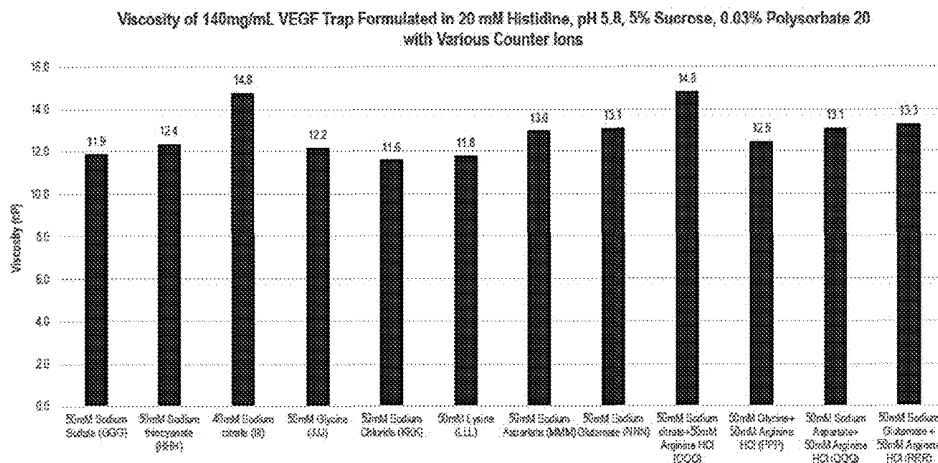


FIG. 9

IX. THE PRIOR ART

A. U.S. Patent App. Pub. No. 2016/0144025 (“Vitti”)

85. U.S. Patent Application Publication No. 2016/0144025, which I refer to herein as Vitti, is entitled “Methods and Formulations for Treating Vascular Eye Diseases.” I understand that Vitti was published on May 26, 2016, and identifies Regeneron as the applicant.

86. Vitti relates to methods for treating vascular eye diseases. EX1007 (Vitti) at [0002].

87. Vitti notes potential “synergistic activity to treat” certain eye disorders using a VEGF antagonist such as aflibercept and a different compound referred to as angiopoietin-2 (Ang-2) inhibitor. EX1007 (Vitti) at [0002], [0022], [0088], [0090]. Vitti teaches that the pharmaceutical formulations that may be administered

as a “co-formulation” comprising both the VEGF antagonist and Ang-2 inhibitor, or as separate formulations wherein the VEGF antagonist is “administered before, after or concurrently with the Ang-2 inhibitor.” EX1007 (Vitti) at [0050], [0091].

88. Vitti teaches that the liquid pharmaceutical composition may be provided in a pre-filled syringe or vial in a volume of approximately up to 100 μ L. EX1007 (Vitti) at [0040], [0041], [0127]. Vitti also teaches that the protein concentration of the VEGF antagonist, aflibercept, is between “5 mg/mL $\pm$ 0.75 mg/mL to about 100 mg/mL $\pm$ 15 mg/mL.” EX1007 (Vitti) at [0027]. Vitti further teaches that its pharmaceutical formulations can include “0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept).” EX1007 (Vitti) at [0139]. Vitti also teaches that its pharmaceutical formulations “typically exhibit high levels of stability.” EX1007 (Vitti) at [0108].

89. Additionally, Vitti cites U.S. Patent No. 7,608,261, which I refer to herein as Furfine, as disclosing “[e]xemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention.” EX1007 (Vitti) at [0107].

B. U.S. Patent App. Pub. No. 2015/0071920 (“Larson”)

90. U.S. Patent Application Publication No. 2015/0071920, which I refer to herein as Larson, is entitled “Liquid Protein Formulations Containing Water Soluble Organic Dyes.” I understand Larson was published on March 12, 2015.

91. Larson concerns “[c]oncentrated, low-viscosity, low-volume liquid pharmaceutical proteins” that include “low-molecular-weight and/or high-molecular-weight proteins, such as mAbs, and viscosity-lowering water soluble organic dyes.” EX1010 (Larson) at Abstract, [0021].

92. Larson acknowledges that “[m]any pharmaceutically important high-molecular-weight proteins, such as mAbs, are currently administered via IV infusions in order to deliver therapeutically effective amounts of protein due to problems with high viscosity and other properties of concentrated solutions of large proteins.” EX1010 (Larson) at [0015]. Larson states that “[i]t is, therefore, an object of the present invention to provide low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins, such as mAbs,” that can “improve injectability and/or patient compliance, convenience, and comfort.” EX1010 (Larson) at [0016]-[0018].

93. In particular, Larson teaches high-concentration, low-viscosity liquid formulations with protein concentrations “between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.” EX1010 (Larson) at [0022].

94. Larson further teaches that “[t]he viscosity of the protein formulation is reduced by the presence of one or more viscosity-lowering water soluble dyes.” EX1010 (Larson) at [0023]. Specifically, “[t]he use of one or more viscosity-

lowering water soluble dyes permits the preparation of formulations having a viscosity less than or about 100 cP . . . more preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 (Larson) at [0075], [0077].

95. Larson discloses that “[a]ny protein can be formulated,” including a protein that has a molecular weight greater than about 150 kDa. EX1010 (Larson) at [0027], [0089], Abstract. Larson also identifies fusion proteins such as EYLEA (aflibercept), “a recombinant fusion protein . . . formulated as an iso-osmotic solution for intravitreal administration” as a suitable protein for its disclosed formulations. EX1010 (Larson) at [0161], [0167]. Larson further identifies ranibizumab as an “antibody therapeutic that can be formulated with viscosity-lowering water soluble dyes.” EX1010 (Larson) at [0158].

96. Larson discloses that its formulations are administered “using an 18-32 gauge needle” and contemplates administration via “subcutaneous, intramuscular, or other types of injection.” EX1010 (Larson) at [0224], [0234].

C. U.S. Patent No. 7,608,261 (“Furfine”)

97. U.S. Patent No. 7,608,261, or Furfine, is entitled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.” I understand that Furfine issued on October 27, 2009 and identifies Regeneron as the assignee.

98. Furfine concerns “pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF)” and “includes liquid pharmaceutical formulations having increased stability.” EX1005 (Furfine) at 1:17-24.

99. Furfine teaches a “stable liquid ophthalmic formulation” that includes “1-100 mg/ml VEGF-specific fusion protein antagonist.” EX1005 (Furfine) at 2:4-9, 2:49-54. The “VEGF-specific fusion protein antagonist” disclosed in Furfine is the same as the “VEGF receptor fusion protein” recited in the claims of the '036 Patent: “VEGF trap,” also known as aflibercept. EX1001 ('036 Patent) at 15:51-67; EX1005 (Furfine) at 1:32-37, 1:58-2:3.

100. Furfine further teaches that its “ophthalmic formulations” are “provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.” EX1005 (Furfine) at 4:65-67.

D. U.S. Patent No. 8,921,316 (“Dix”)

101. U.S. Patent No. 8,921,316, which I refer to herein as Dix, is entitled “Stable Liquid VEGF Antagonist Formulations.” I understand Dix issued on December 30, 2014, and identifies Regeneron as the assignee.

102. Dix, similar to Furfine, concerns “pharmaceutical formulations comprising agents capable of inhibiting vascular endothelial growth factor (VEGF) and “includes pharmaceutical formulations having increased stability.” EX1006

(Dix) at 1:23-27. Also similar to Furfine, the “VEGF-specific fusion protein antagonist” disclosed in Dix is the same as the “VEGF receptor fusion protein” recited in the claims of the '036 Patent: “VEGF trap” or aflibercept. EX1001 ('036 Patent) at 15:51-67; EX1006 (Dix) at 2:20-34, 10:1-11:1.

103. Dix teaches that an aspect of the invention is a “high concentration stable liquid formulation of a VEGF antagonist.” EX1006 (Dix) at 2:20-34. Dix also claims stable liquid formulations comprising 100 mg/mL of a VEGF antagonist. EX1006 (Dix) at cls. 1-2.

104. Example 4 of Dix discloses a lyophilised formulation including 50 mg/mL VEGF trap protein that is reconstituted to a formulation including 100 mg/mL VEGF trap protein. EX1006 (Dix) at 10:17-28. Specifically, the reconstituted formulation includes 100 mg/mL VEGF trap protein, 20 mM histidine, 3% PEG 3350, 1.5% glycine, 5% sucrose, pH 6.3. EX1006 (Dix) at 10:21-28. Dix states that “[s]tability studies showed no degradation of the VEGF trap was detected after 6 months of storage at 2-8° C.” EX1006 (Dix) at 10:26-28.

105. Example 4 of Dix also discloses a liquid formulation that includes 50-100 mg/ml VEGF trap protein, 10 mM histidine, 50 mM NaCl, 5-20% sucrose, and one of 0.1% polysorbate 20 or 3% PEG 3350. EX1006 (Dix) at 10:29-32. Dix teaches that “[o]ne advantage of this liquid formulation is that it provides a higher concentration of VEGF trap without requiring the manufacture of a lyophilized

product.” EX1006 (Dix) at 10:32-34. Dix also teaches that the liquid formulation “provides ease for subcutaneous delivery, for example, by allowing provision of a liquid pre-filled syringe” EX1006 (Dix) at 10:34-38. Dix also provides stability data for the formulation showing less than 2.6% degradation following incubation at 5° C. for up to 15 months:

TABLE 7

Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap VGFT _{SS101})				
Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	—	0.7
24	50	—	3	1.3
15	75	0.1	—	1.5
15	75	—	3	2.0
15	100	0.1	—	1.9
15	100	—	3	2.6

EX1006 (Dix) at Table 7.

106. Example 5 of Dix discloses a lyophilised formulation including 50 mg/ml VEGF trap protein that is reconstituted to a formulation including 100 mg/ml VEGF trap protein. EX1006 (Dix) at 10:62-11:1. Specifically, the reconstituted formulation includes 100 mg/mL VEGF trap protein, 20 mM histidine, 3% PEG 3350, 5% sucrose, and 1.5% glycine. EX1006 (Dix) at 10:66-11:1. Dix provides stability data for the formulation showing greater than 98% of the VEGF trap protein in “native configuration” following storage at 5° C for up to 6 months:

TABLE 8

Stability of VEGF Trap Lyophilized Formulation Stored at 5° C. (VGT-RS475)				
Months	Bioassay	Binding Assay	% Recovered	% Native Configuration
0	120	126	97.9	98.7
1	117	74	97.9	98.6
1 + 24 hr	126	72	99.0	98.5
1 + 4 hr	94	81	101.5	98.2
3	101	98	98.1	98.6
3 + 24 hr	65	94	98.1	98.2

TABLE 8-continued

Stability of VEGF Trap Lyophilized Formulation Stored at 5° C. (VGT-RS475)				
Months	Bioassay	Binding Assay	% Recovered	% Native Configuration
6 + 4 hr			96.9	98.7
6 + 24 hr			98.8	98.6

EX1006 (Dix) at Table 8.

E. U.S. Patent App. Pub. No. 2017/0232199 (“Fiedler”)

107. U.S. Patent Application Publication No. 2017/0232199, which I refer to herein as Fiedler, is entitled “Pre-Filled Plastic Syringe Containing a VEGF Antagonist.” I understand that Fiedler published on August 17, 2017, and identifies Formycon AG as the applicant.

108. Fiedler teaches a “pre-filled syringe containing a liquid formulation of a VEGF antagonist.” EX1011 (Fiedler) at [0017]. Fiedler states that “[i]n a preferred embodiment, the VEGF antagonist is . . . aflibercept.” EX1011 (Fiedler) at [0018].

109. Fiedler teaches that the VEGF antagonist concentration is “1 to 100 mg/ml.” EX1011 (Fiedler) at [0019].

110. Fiedler teaches “intravitreal injection” of a VEGF antagonist, including aflibercept. EX1011 (Fiedler) at [0083]-[0084], [0071].

111. Fiedler teaches that “[f]or intravitreal administration the needle size is typically 30 gauge, although 31-, 32, 33- and 34-gauge needles may also be used.” EX1011 (Fiedler) at [0052].

112. Fiedler teaches that “the volume which is actually administered to the patient is between 0.01 ml and 1 ml . . . and most preferably the volume which is actually administered to the patient is 0.05 ml.” EX1011 (Fiedler) at [0067]. Fiedler also teaches that intravitreally-administered protein formulations, including Lucentis® (ranibizumab), Eylea® (aflibercept), and Avastin® (bevacizumab) are “typically” administered in a volume of 0.05 mL, or 50 µL. EX1011 (Fiedler) at [0068].

X. GROUND 1: CLAIMS 1 AND 4-38 ARE OBVIOUS OVER VITTI, AU EYLEA® LABEL, AND LARSON

A. Claim 1

1. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 micro liters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an

aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

113. In my opinion, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration comprising at least 100 mg/ml of aflibercept, a VEGF receptor fusion protein, that has a viscosity of about 5-15 cP, as required by claim 1.

**1. Vitti Teaches an Aqueous Pharmaceutical Formulation
Comprising at Least 100 mg/mL of a VEGF Receptor
Fusion Protein**

114. Vitti teaches an aqueous pharmaceutical formulation including at least 100 mg/mL of aflibercept, a VEGF receptor fusion protein.

115. Specifically, Vitti teaches high concentration aqueous “pharmaceutical formulations” that contain 85 mg/mL to 115 mg/mL of aflibercept, including specifically, 100 mg/mL of aflibercept. In particular, Vitti discloses “liquid formulations that may contain . . . [up] to 100±15 mg/mL of a VEGF antagonist.” EX1007 (Vitti) at [0094]. Vitti identifies as exemplary VEGF antagonists “VEGF receptor-based chimeric molecules or VEGF-inhibiting fusion proteins (also referred to herein as “VEGF-Traps”). and notes that “[a]n exemplary VEGF receptor-based chimeric molecule” is aflibercept. EX1007 (Vitti) at [0085]-[0086].

116. Although Vitti also discloses administration of an Ang-2 inhibitor in combination with the VEGF antagonist, Vitti contemplates that the VEGF antagonist

may be formulated and administered separately from the Ang-2 inhibitor. EX1007 (Vitti) at [0012] (“the methods comprise administering a single dose of a VEGF antagonist followed by one or more doses of a pharmaceutical composition comprising an Ang-2 inhibitor subject to the subject in need thereof”); [0018] (“In certain embodiments, the Ang-2 inhibitor is administered intravenously or subcutaneously in combination with the VEGF antagonist, wherein the VEGF antagonist is administered intravitreally.”).

117. With respect to aflibercept, Vitti states that the formulation may include up to “100 mg/mL of aflibercept” that is “comprised in a prefilled syringe and is administered intravitreally in a volume of approximately up to 100 μ L.” EX1007 (Vitti) at [0127]. Vitti states that these “pharmaceutical formulations . . . typically exhibit high levels of stability.” EX1007 (Vitti) at [0108].

118. Therefore, Vitti teaches an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept.

2. A Skilled Formulator Would Have Had a Reasonable Expectation of Success in Achieving a Viscosity of About 5-15 cP at 20° C

119. In my opinion, a skilled formulator, in light of Vitti and Larson, would have had a reasonable expectation of success in achieving a viscosity of about 5-15 cP at 20° C with the 100 mg/mL aflibercept formulation taught in Vitti.

120. Vitti teaches that “excipients . . . any non-therapeutic agent added to the formulation to provide a desired . . . viscosity or stabilizing effect” may be included in its formulations. EX1007 (Vitti) at [0096]. Vitti also teaches that its aflibercept formulations, which include up to 115 mg/mL of a VEGF antagonist, including aflibercept, may be administered intravitreally via a syringe fitted with a 30-gauge needle. EX1007 (Vitti) at [0018], [0094], [0115], [0127].

121. Vitti also references Furfine, EX1007 (Vitti) at [0107], which discloses stable, high-concentration aflibercept formulations containing up to 100 mg/mL that were “suitable for intravitreal administration.” EX1005 (Furfine) at 1:17-24, 2:4-9, 2:49-54.

122. Vitti does not expressly specify the level of viscosity that would be desirable, nor does it disclose any specific excipients for obtaining the desired viscosity. EX1007 (Vitti). This is not surprising because a skilled formulator would have understood that the viscosity of a high-concentration formulation is preferably low. A skilled formulator would have looked Larson, which teaches high-concentration pharmaceutical protein formulations, including formulations with aflibercept, having a desired viscosity of about 5-15 cP at 20° C.

123. In particular, Larson teaches aqueous pharmaceutical protein formulations, including high-concentration aflibercept formulations, that have a viscosity of about 5-15 cP at 20° C. Specifically, like Vitti, Larson teaches high-

concentration protein formulations suitable for intravitreal administration that contain up to 100 mg/mL of protein, including specifically aflibercept. EX1010 (Larson) at [0089] (“[a]ny protein can be formulated In certain embodiments, the protein has a molecular weight greater than about 150 kDa.”), [0161] (“The protein can be . . . a fusion protein.”), [0167] (“EYLEA® (aflibercept) is a recombinant fusion protein . . . formulated as an iso-osmotic solution for intravitreal administration.”). Larson also teaches that viscosity-reducing excipients can be used in a formulation with a protein concentration of 100 mg/mL or more to achieve a viscosity of “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 (Larson) at [0022] (“The concentration of proteins is between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.”), [0075] (“[t]he use of one or more viscosity-lowering water soluble dyes permits the preparation of formulations having a viscosity less than or about 100 cP . . . preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.”), [0077] (similar).

124. A skilled formulator would have understood that a protein formulation with a viscosity of 10 cP measured at 25° C would have a viscosity of approximately 11.26 cP measured at 20° C, and a protein formulation with a viscosity of 20 cP measured at 25° C would have a viscosity of approximately 22.52 cP measured at

20° C. As described by the Vogel-Fulcher-Tamman equation, wherein $\ln\mu$ is the natural logarithm of viscosity, the viscosity of liquids is a function of temperature T:

$$\ln\mu = A + \left(\frac{B}{C - T}\right)$$

EX1043 (Viswanath) at 163, 188. As applied to water, wherein A is -0.45318, B is -220.57, and C is 149.39, as shown below, that viscosity decreased as temperature increased:

Temperature (°C)	Viscosity (cP)
10	1.306427
20	1.003528
25	0.891299
30	0.797747
50	0.545675
70	0.403678
90	0.315952

EX1043 (Viswanath) at 176. Thus, the viscosity of a protein-containing aqueous solution at 25° C may be estimated to be approximately 1.126 times greater than the viscosity of the same solution at 20° C. Assuming the temperature-dependent change in viscosity of protein-containing aqueous solution, such as an aflibercept formulation, is similar to water, a viscosity of 10 cP at 25° C may be estimated to approximately 11.26 cP at 20° C, and a viscosity of 20 cP at 25° C may be estimated to approximately 22.52 cP measured at 20° C. A skilled formulator would therefore have understood that Larson’s teaching of “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C,” EX1010

(Larson) at [0075], [0077], is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

125. Moreover, Vitti teaches that its aflibercept formulations are administered intravitreally using a syringe fitted with a 30-gauge needle. EX1007 (Vitti) at [0018], (“the VEGF antagonist is administered intravitreally.”), [0115] (“For the treatment of eye disorders, the pharmaceutical formulations of the invention may be administered, e.g., by . . . intravitreal injection . . .”), [0127] (“[T]he liquid formulation comprising . . . 10 mg/mL of aflibercept is comprised in a pre-filled syringe and is administered intravitreally in a volume of approximately up to 100 µL. . . In one embodiment, the syringe is a 1 mL long glass syringe fitted with a 30-gauge thin wall needle . . .”). A skilled formulator would have understood from Larson that an aflibercept formulation that is administered intravitreally using a syringe with a 30-gauge needle, as taught in Vitti, would have a viscosity of about 5-15 cP at 20° C. EX1010 (Larson) at [0075], [0077], [0224], [0234]. Indeed, Larson teaches formulations administered “using an 18-32 gauge needle” and contemplates administration via “subcutaneous, intramuscular, or other types of injection.” EX1010 (Larson) at [0224], [0234]. A skilled formulator would have understood, in light of Larson’s express disclosures of aflibercept and other intravitreally-administered proteins like ranibizumab, EX1010 (Larson) at [0158], [0167], that “other types of injection” include intravitreal injection. And as

explained above, Larson teaches a viscosity “preferably less than or about 20 cP, or most preferably less than or about 10 cP . . . when measured at 25° C.” EX1010 (Larson) at [0075], [0077].

126. Accordingly, a skilled formulator, in light of Vitti and Larson, would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with a protein concentration of at least 100 mg/mL and having a viscosity within the claimed range of about 5-15 cP at 20° C.

127. Moreover, as discussed above in Section VII.B.2, the relationship between viscosity and concentration was known in the art, and there were several formulation strategies known and available to a skilled formulator at the time that had already been successfully applied to improve the viscosity characteristics of high-concentration protein formulations, including for example by (a) adding amino acids; (b) adding salts; (c) minimizing the use of sugars or sugar alcohols; (d) adjusting pH relative to pI of the protein; (e) adding viscosity-lowering water soluble dyes; and (f) emulsification. While Larson discloses a particular technique for achieving a desired viscosity, a skilled formulator would therefore have understood, with a reasonable expectation of success, that any one of a number of available solutions in the art at the time could have been applied as needed to an aqueous pharmaceutical formulation containing at least 100 mg/mL of aflibercept, as taught in Vitti, to achieve a viscosity of about 5-15 cP at 20° C, as taught in Larson.

128. Therefore, a skilled formulator would have reasonably expected to succeed in obtaining a pharmaceutical formulation with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C.

B. Claim 4

4. The method of claim 1, wherein the viscosity is about 10-13 cP at 20° C.

129. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

130. As discussed above in Section X.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

131. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 10-13 cP at 20° C.

C. Claim 5

5. The method of claim 1, wherein the viscosity is about 11-12 cP at 20° C.

132. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

133. As discussed above in Section X.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

134. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 11-12 cP at 20° C.

D. Claim 6

6. The method of claim 1, wherein the viscosity is about 12-15 cP at 20° C.

135. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

136. As discussed above in Section X.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP . . . when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP at 20° C.

137. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 12-15 cP at 20° C.

E. Claim 7

7. The method of claim 1, wherein the viscosity is about 5 cP at 20° C.

138. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

139. As discussed above in Section X.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

140. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 5 cP at 20° C.

F. Claim 8

8. The method of claim 1, wherein the viscosity is about 6 cP at 20° C.

141. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

142. As discussed above in Section X.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

143. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 6 cP at 20° C.

G. Claim 9

9. The method of claim 1, wherein the formulation comprises a sugar.

144. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

145. I further note that sugars were commonly used excipients in protein formulations. Indeed, Vitti discloses that its pharmaceutical formulations include excipients and specifically identifies "a sugar or sugar alcohol selected from sucrose, sorbitol glycerol, trehalose and mannitol, or any combination thereof" as exemplary excipients that may be included as a thermal stabilizer. EX1007 (Vitti) at [0033],

[0096], [0101]. Vitti also references Furfine for “[e]xemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention.” EX1007 (Vitti) at [0107]. Furfine discloses formulations suitable for intravitreal administration that include as a stabilizing agent, sucrose, a sugar. EX1005 (Furfine) at 2:15-16. Furfine also discloses the use of trehalose, a different sugar, as a stabilizing agent. EX1005 (Furfine) at 2:15-16, 2:63-65, 6:29-40. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and a sugar, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

H. Claim 10

10. The method of claim 1, wherein the formulation comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.

146. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

147. As discussed above in Section X.G, sugars were commonly used excipients in protein formulations. Indeed, Vitti discloses that its pharmaceutical formulations include excipients and specifically identifies “a sugar or sugar alcohol

selected from sucrose, sorbitol, glycerol, trehalose and mannitol, or any combination thereof” as exemplary excipients that may be included as a thermal stabilizer. EX1007 (Vitti) at [0033], [0096], [0101]. Vitti also references Furfine for “[e]xemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention.” EX1007 (Vitti) at [0107]. Furfine discloses formulations suitable for intravitreal administration that include sucrose. EX1005 (Furfine) at 2:15-16. Furfine also discloses the use of “one or more of sucrose, sorbitol, glycerol, trehalose, and mannitol” as a stabilizing agent. EX1005 (Furfine) at 2:15-16, 2:63-65, 6:29-40. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and one or more of sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

I. Claim 11

11. The method of claim 1, wherein the formulation comprises an amino acid.

148. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

149. I further note that amino acids were commonly used excipients in protein formulations. Vitti discloses its pharmaceutical formulations may comprise “excipients” to “provide a desired consistency, viscosity or stabilizing effect.” EX1007 (Vitti) at [0096]. Vitti discloses a “buffer or buffer system” as such an excipient. EX1007 (Vitti) at [0106]. Larson discloses the use of “L-histidine buffer” in commercial therapeutic protein products, which includes L-histidine, an amino acid. EX1010 (Larson) at [0008]. And Dix confirms histidine was suitable for use in a formulation comprising aflibercept. EX1006 (Dix) at 10:14-11:1, cls. 1-2. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and an amino acid, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

J. Claim 12

12. The method of claim 1, wherein the VEGF receptor fusion protein is aflibercept.

150. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

K. Claim 13

13. The method of claim 1, wherein the angiogenic eye disorder is age- related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

151. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

L. Claim 14

14. The method of claim 13, wherein the angiogenic eye disorder is wet age-related macular degeneration.

152. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

M. Claim 15

15. The method of claim 14, wherein the VEGF receptor fusion protein is aflibercept.

153. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

N. Claim 16

16. The method of claim 13, wherein the angiogenic eye disorder is diabetic macular edema.

154. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

O. Claim 17

17. The method of claim 16, wherein the VEGF receptor fusion protein is aflibercept.

155. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

P. Claim 18

18. The method of claim 13, wherein the angiogenic eye disorder is diabetic retinopathy.

156. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

Q. Claim 19

19. The method of claim 18, wherein the VEGF receptor fusion protein is aflibercept.

157. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

R. Claim 20

20. The method of claim 13, wherein the angiogenic eye disorder is non-proliferative diabetic retinopathy.

158. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

S. Claim 21

21. The method of claim 20, wherein the VEGF receptor fusion protein is aflibercept.

159. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

T. Claim 22

22. The method of claim 13, wherein the angiogenic eye disorder is proliferative diabetic retinopathy.

160. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

U. Claim 23

23. The method of claim 22, wherein the VEGF receptor fusion protein is aflibercept.

161. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

V. Claim 24

24. The method of claim 13, wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.

162. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

W. Claim 25

25. The method of claim 24, wherein the VEGF receptor fusion protein is aflibercept.

163. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

X. Claim 26

26. The method of claim 13, wherein the VEGF receptor fusion protein is aflibercept.

164. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

Y. Claim 27

27. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising

at least 100 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.

165. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

Z. Claim 28

28. The method of claim 27, wherein the angiogenic eye disorder is wet age-related macular degeneration.

166. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

AA. Claim 29

29. The method of claim 27, wherein the angiogenic eye disorder is diabetic macular edema.

167. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

BB. Claim 30

30. The method of claim 27, wherein the angiogenic eye disorder is diabetic retinopathy.

168. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

CC. Claim 31

31. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 70 microliters, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.

169. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

170. With respect to concentration, and in contrast to claim 1, which requires an aqueous formulation comprising “at least 100 mg/ml of the VEGF receptor fusion protein,” claim 31 requires an aqueous pharmaceutical formulation comprising “about 114.3 mg/ml of aflibercept.”

171. In my opinion, a skilled formulator, in light of Vitti, would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation with about 114.3 mg/ml of aflibercept.

172. As discussed above in Section X.A.1, Vitti teaches high concentration aqueous pharmaceutical formulations that contain up to 115 mg/mL of aflibercept and that may be administered intravitreally. EX1007 (Vitti) at [0094], [0127]. And Vitti teaches that its formulations “typically exhibit high levels of stability.” EX1007 (Vitti) at [0108]. In addition, Vitti cites to Furfine as disclosing “[e]xemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention,” EX1007 (Vitti) at [0107], and Furfine teaches stable, high-concentration VEGF antagonist pharmaceutical formulations containing up to 100 mg/mL that were “suitable for intravitreal administration.” EX1005 (Furfine) at 1:17-24, 2:4-9, 2:49-54. Vitti therefore confirms that a skilled formulator would reasonably expect to succeed in obtaining a formulation containing up to 115 mg/mL of aflibercept that is stable and suitable for intravitreal administration.

173. Furthermore, a skilled formulator would have been aware of the trend in the industry towards higher-concentration therapeutic protein formulations and the numerous successfully developed high-concentration therapeutic protein

formulations already FDA-approved and commercially available at the time. EX1045 (Wang 2021) at 263, Table 1, Fig. 1.

174. I understand from Dr. D’Amico that it would have been desirable to obtain an aflibercept dose of at least about 8 mg. D’Amico Conversation. I further understand from Dr. D’Amico that the injection volume for intravitreally administered formulations known in the art ranged from preferably about 50 µL up to a maximum of 100 µL, with 100 µL being the known upper safe volume limit for a liquid formulation for intravitreal injection into the eye, as undesirable increases in intra-ocular pressure were associated with higher injection volumes, particularly volumes exceeding 100 µL. D’Amico Conversation.

175. Assuming an aflibercept dose of about 8 mg and injection volume ranging from 50 µL to 100 µL, a skilled formulator would reasonably expect to succeed in optimizing for and obtaining a concentration of about 114.3 mg/mL in light of Vitti’s teaching of stable, high concentration aqueous pharmaceutical formulations for intravitreal administration that contain up to 115 mg/mL of aflibercept.

176. Concentration is an expression of the amount of the solute (i.e., dose) present per unit of total volume of the solution, as shown below:

$$\frac{Dose}{Volume} = Concentration$$

177. Thus, within the parameters described above—an 8 mg dose of aflibercept provided in an injection volume ranging from 50 μ L to 100 μ L—a skilled formulator would have been able to determine the range of possible concentrations for the aflibercept within the aqueous pharmaceutical formulation is as follows:

Dose (mg)	Injection Volume (μ L)	Concentration (mg/mL)
8	50	160
8	60	133.3
8	70	114.3
8	80	100
8	90	88.9
8	100	80

And, given the teachings in Vitti regarding stable aqueous pharmaceutical formulations for intravitreal injection containing up to 115 mg/mL of aflibercept, EX1007 (Vitti) at [0094], [0108], [0127], as well as Vitti’s reference to Furfine, which relates to liquid “pharmaceutical formulations suitable for intravitreal administration suitable for intravitreal administration . . . having increased stability” that include up to 100 mg/mL VEGF antagonist, EX1007 (Vitti) at [0107], EX1005 (Furfine) at 1:17-24, 2:4-9, a skilled formulator would have reasonably expected that an aqueous pharmaceutical formulation containing about 114.3 mg/mL would likewise be stable and suitable for intravitreal administration.

178. Accordingly, in light of Vitti, a skilled formulator would have reasonably expected to succeed in optimizing for and obtaining an aqueous

pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept.

DD. Claim 32

32. The method of claim 31, wherein the angiogenic eye disorder is wet age-related macular degeneration.

179. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.CC.

EE. Claim 33

33. The method of claim 31, wherein the angiogenic eye disorder is diabetic macular edema.

180. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.CC.

FF. Claim 34

34. The method of claim 31, wherein the angiogenic eye disorder is diabetic retinopathy.

181. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.CC.

GG. Claim 35

35. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.

182. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining a pharmaceutical formulation with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Sections X.A and X.CC.

183. With respect to concentration, and in contrast to claim 1, which requires an aqueous formulation comprising “at least 100 mg/ml of the VEGF receptor fusion protein,” and claim 31, which requires an aqueous pharmaceutical formulation comprising “about 114.3 mg/ml of aflibercept,” claim 35 requires an aqueous pharmaceutical formulation comprising “about 103-126 mg/ml of aflibercept.” I note that the recited concentration in claim 35, “about 103-126 mg/ml of aflibercept” is merely about 10% greater or less than “about 114.3 mg/ml of aflibercept” as recited in claim 31.

184. As discussed above, Vitti teaches high concentration aqueous pharmaceutical formulations that contain 85 mg/mL to 115 mg/mL of aflibercept,

EX1007 (Vitti) at [0094], which includes the range of 103 mg/mL to 115 mg/mL. Vitti also teaches that aqueous pharmaceutical formulations containing up to 115 mg/mL of aflibercept “typically exhibit high levels of stability” and may be administered intravitreally, EX1007 (Vitti) at [0108], [0127], confirming that a skilled formulator would have understood how to make and optimize for, with a reasonable expectation of success, a stable aflibercept formulation for intravitreal administration with a concentration of up to 115 mg/mL and within the claimed range.

185. Accordingly, in light of Vitti, a skilled formulator would have reasonably expected to succeed in optimizing for and obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept.

HH. Claim 36

36. The method of claim 35, wherein the angiogenic eye disorder is wet age-related macular degeneration.

186. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.GG.

II. Claim 37

37. The method of claim 35, wherein the angiogenic eye disorder is diabetic macular edema.

187. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.GG.

JJ. Claim 38

38. The method of claim 35, wherein the angiogenic eye disorder is diabetic retinopathy.

188. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.GG.

XI. GROUND 2: CLAIMS 1 AND 4-38 ARE OBVIOUS OVER FURFINE, DIX, AU EYLEA® LABEL, FIEDLER, AND LARSON

A. Claim 1

1. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 micro liters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

189. In my opinion, a skilled formulator would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration comprising at least 100 mg/ml of aflibercept, a VEGF receptor fusion protein, that has a viscosity of about 5-15 cP, as required by claim 1.

1. Furfine and Dix Teach an Aqueous Pharmaceutical Formulation Comprising at Least 100 mg/mL of a VEGF Receptor Fusion Protein

190. In my opinion, Furfine and Dix teach an aqueous pharmaceutical formulation including 100 mg/mL of aflibercept, a VEGF receptor fusion protein.

191. Furfine teaches stable aflibercept formulations containing at least 100 mg/mL of aflibercept. In particular, Furfine discloses a “stable liquid ophthalmic formulation” that comprises “1-100 mg/ml VEGF-specific fusion protein antagonist.” EX1005 (Furfine) at 2:4-9, 2:49-54, cls. 1, 3. Furfine discloses that the VEGF-specific fusion protein antagonist, is a “fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a “VEGF trap.”). EX1005 (Furfine) at 1:58-64. A skilled formulator would have understood that VEGF trap, as disclosed in Furfine, is aflibercept. Indeed, Regeneron itself has confirmed in statements to the

U.S. Patent and Trademark Office that aflibercept and VEGF trap refer to the same fusion protein:

The name of the approved product is EYLEA™. The name active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flt1 and an Ig domain 3 of a second VEGF receptor that is human Flk1; and (b) an Fc portion of a human IgG1.

EX1013 (Regeneron Application for Extension of Patent Term for U.S. Patent No. 7,374,758, dated Dec. 22, 2011) at 2.

192. Dix teaches “high concentration stable liquid formulation[s] of a VEGF antagonist,” including specifically a stable “liquid formulation” that comprises “50-100 mg/ml VEGF trap,” as well as “pre-lyophilized” and subsequently reconstituted formulations containing “100 mg/ml VEGF trap protein.” EX1006 (Dix) at 2:20-35, 10:1-12:9. And as with the VEGF trap in Furfine discussed above, a skilled formulator would have understood that VEGF trap, as disclosed in Dix, is aflibercept. EX1013 (Regeneron Application for Extension of Patent Term for U.S. Patent No. 7,374,758, dated Dec. 22, 2011) at 2.

193. Therefore, Furfine and Dix teach an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept.

2. A Skilled Formulator Would Have Had a Reasonable Expectation of Success in Achieving a Viscosity of About 5-15 cP at 20° C

194. In my opinion, a skilled formulator, in light of Larson, would have had a reasonable expectation of success in achieving a viscosity of 5-15 cP at 20° C with the 100 mg/mL aflibercept formulations taught in Furfine and Dix.

195. While Furfine and Dix do not expressly specify the level of viscosity that would be desirable or disclose any specific excipients for obtaining the desired viscosity, a skilled formulator would nevertheless have expected that the disclosed 100 mg/mL aflibercept formulations would have an appropriately low viscosity. In particular, Furfine teaches that its formulations, which include up to 100 mg/mL aflibercept, are “suitable for intravitreal administration.” EX1005 (Furfine) at 1:17-24, 2:4-9, 2:49-54, 4:65-67. Similarly, Dix teaches that its formulations advantageously provides “ease for subcutaneous delivery.” EX1006 (Dix) at 10:34-38. Further, Fiedler confirms that formulations including high concentrations of protein, including up to 100 mg/mL of aflibercept, are administered intravitreally, “typically” with a needle size of 30 gauge. EX1011 (Fiedler) at [0043], [0052], [0076], [0083].

196. In addition, a skilled formulator would have looked to Larson, which teaches aqueous pharmaceutical protein formulations, including formulations with aflibercept, having a desired viscosity of about 5-15 cP at 20° C. Specifically, like

Furfine, Dix, and Fiedler, Larson teaches high-concentration protein formulations suitable for intravitreal administration that contain up to 100 mg/mL of protein, including specifically aflibercept. EX1010 (Larson) at [0089] (“[a]ny protein can be formulated In certain embodiments, the protein has a molecular weight greater than about 150 kDa.”), [0161] (“The protein can be . . . a fusion protein.”), [0167] (“EYLEA® (aflibercept) is a recombinant fusion protein . . . formulated as an iso-osmotic solution for intravitreal administration.”). Larson also teaches formulations administered “using an 18-32 gauge needle” and contemplates administration via “subcutaneous, intramuscular, or other types of injection.” EX1010 (Larson) at [0224], [0234]. Larson further teaches that viscosity-reducing excipients can be used to achieve a viscosity of “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 (Larson) at [0022] (“The concentration of proteins is between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.”), [0075] (“[t]he use of one or more viscosity-lowering water soluble dyes permits the preparation of formulations having a viscosity less than or about 100 cP . . . preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.”), [0077] (similar). A POSA would therefore have understood from Larson that an aflibercept formulation that is administered intravitreally would have a desired viscosity of about 5-15 cP at 20° C.

197. As explained above in Section X.A.2, a skilled formulator would have understood that a protein formulation with a viscosity of 10 cP measured at 25° C would have a viscosity of approximately 11.26 cP measured at 20° C, and a protein formulation with a viscosity of 20 cP measured at 25° C would have a viscosity of approximately 22.52 cP measured at 20° C. A skilled formulator would therefore have understood that Larson's teaching of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077], is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

198. Moreover, as discussed above in Section VII.B.2, the relationship between viscosity and concentration was known in the art, and there were several formulation strategies known and available to a skilled formulator at the time that had already been successfully applied to improve the viscosity characteristics of high-concentration protein formulations, including for example by (a) adding amino acids; (b) adding salts; (c) minimizing the use of sugars or sugar alcohols; (d) adjusting pH relative to pI of the protein; (e) adding viscosity-lowering water soluble dyes; and (f) emulsification. A skilled formulator would therefore have understood, with a reasonable expectation of success, that any one of a number of available solutions in the art at the time could have been applied as needed to an aqueous pharmaceutical formulation containing at least 100 mg/mL of aflibercept, as taught

in Furfine, Dix, and Fiedler, to achieve a viscosity of about 5-15 cP at 20° C, as taught in Larson.

199. Therefore, a skilled formulator would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C.

B. Claim 4

4. The method of claim 1, wherein the viscosity is about 10-13 cP at 20° C.

200. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

201. As discussed above in Section XI.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

202. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 10-13 cP at 20° C.

C. Claim 5

5. The method of claim 1, wherein the viscosity is about 11-12 cP at 20° C.

203. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

204. As discussed above in Section XI.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

205. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 11-12 cP at 20° C.

D. Claim 6

6. The method of claim 1, wherein the viscosity is about 12-15 cP at 20° C.

206. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

207. As discussed above in Section XI.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP . . . when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP at 20° C.

208. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 12-15 cP at 20° C.

E. Claim 7

7. The method of claim 1, wherein the viscosity is about 5 cP at 20° C.

209. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

210. As discussed above in Section XI.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

211. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 5 cP at 20° C.

F. Claim 8

8. The method of claim 1, wherein the viscosity is about 6 cP at 20° C.

212. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

213. As discussed above in Section XI.A, a skilled formulator would have understood that Larson's teaching of a viscosity of "preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C," EX1010 (Larson) at [0075], [0077]," is approximately equivalent to less than or about 22.52 cP, or less than or about 11.26 cP at 20° C.

214. Accordingly, a skilled formulator would have understood that Larson teaches a viscosity of about 6 cP at 20° C.

G. Claim 9

9. The method of claim 1, wherein the formulation comprises a sugar.

215. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

216. As discussed above in Section X.G, sugars were commonly used excipients in protein formulations. Furfine discloses formulations suitable for intravitreal administration that include as a stabilizing agent, sucrose, a sugar. EX1005 (Furfine) at 2:15-16. Furfine also discloses the use of trehalose, a different sugar, as a stabilizing agent. EX1005 (Furfine) at 2:15-16, 2:63-65, 6:29-40. Dix discloses formulations that include sucrose. EX1006 (Dix) at 10:1-11:1. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and a sugar, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

H. Claim 10

10. The method of claim 1, wherein the formulation comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.

217. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

218. As discussed above in Section X.G, sugars were commonly used excipients in protein formulations. Furfine discloses formulations suitable for intravitreal administration that include sucrose. EX1005 (Furfine) at 2:15-16.

Additionally, Furfine discloses the use of “one or more of sucrose, sorbitol, glycerol, trehalose, and mannitol” as a stabilizing agent. EX1005 (Furfine) at 2:15-16, 2:63-65, 6:29-40. Dix also discloses formulations that include sucrose. EX1006 (Dix) at 10:1-11:1. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and one or more of sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

I. Claim 11

11. The method of claim 1, wherein the formulation comprises an amino acid.

219. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

220. As discussed above in Section X.I, amino acids were commonly used excipients in protein formulations. Dix discloses formulations that include histidine and/or glycine, which are both amino acids. EX1006 (Dix) at 10:14-11:1, cls. 1-2. A skilled formulator would have understood that an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept

and an amino acid, and having a viscosity of about 5-15 cP at 20° C could be obtained with a reasonable expectation of success.

J. Claim 12

12. The method of claim 1, wherein the VEGF receptor fusion protein is aflibercept.

221. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

K. Claim 13

13. The method of claim 1, wherein the angiogenic eye disorder is age- related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.

222. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

L. Claim 14

14. The method of claim 13, wherein the angiogenic eye disorder is wet age-related macular degeneration.

223. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

M. Claim 15

15. The method of claim 14, wherein the VEGF receptor fusion protein is aflibercept.

224. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

N. Claim 16

16. The method of claim 13, wherein the angiogenic eye disorder is diabetic macular edema.

225. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

O. Claim 17

17. The method of claim 16, wherein the VEGF receptor fusion protein is aflibercept.

226. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

P. Claim 18

18. The method of claim 13, wherein the angiogenic eye disorder is diabetic retinopathy.

227. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

Q. Claim 19

19. The method of claim 18, wherein the VEGF receptor fusion protein is aflibercept.

228. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

R. Claim 20

20. The method of claim 13, wherein the angiogenic eye disorder is non-proliferative diabetic retinopathy.

229. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

S. Claim 21

21. The method of claim 20, wherein the VEGF receptor fusion protein is aflibercept.

230. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

T. Claim 22

22. The method of claim 13, wherein the angiogenic eye disorder is proliferative diabetic retinopathy.

231. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

U. Claim 23

23. The method of claim 22, wherein the VEGF receptor fusion protein is aflibercept.

232. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

V. Claim 24

24. The method of claim 13, wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.

233. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

W. Claim 25

25. The method of claim 24, wherein the VEGF receptor fusion protein is aflibercept.

234. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

X. Claim 26

26. The method of claim 13, wherein the VEGF receptor fusion protein is aflibercept.

235. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

Y. Claim 27

27. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.

236. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

Z. Claim 28

28. The method of claim 27, wherein the angiogenic eye disorder is wet age-related macular degeneration.

237. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

AA. Claim 29

29. The method of claim 27, wherein the angiogenic eye disorder is diabetic macular edema.

238. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

BB. Claim 30

30. The method of claim 27, wherein the angiogenic eye disorder is diabetic retinopathy.

239. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with at least 100 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

CC. Claim 31

31. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 70 microliters, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.

240. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

241. As previously noted, with respect to concentration, and in contrast to claim 1, which requires an aqueous formulation comprising “at least 100 mg/ml of the VEGF receptor fusion protein,” claim 31 requires an aqueous pharmaceutical formulation comprising “about 114.3 mg/ml of aflibercept.”

242. In my opinion, a skilled formulator, in light of Furfine, Dix, and Fiedler, would have reasonably expected to succeed in optimizing the concentration of aflibercept to obtain an aqueous pharmaceutical formulation with about 114.3 mg/mL of aflibercept.

243. As discussed above in Section XI.A, Furfine and Dix teach stable, high concentration aqueous pharmaceutical formulations contain up to 100 mg/mL of aflibercept. EX1005 (Furfine) at 2:4-9, 2:49-54, cl. 1; EX1006 (Dix) at 2:20-35, 10:17-12:9. Fiedler similarly teaches stable, high concentration aqueous pharmaceutical formulations contain up to 100 mg/mL of aflibercept. EX1011 (Fiedler) at [0019], [0043], [0045], [0076], cl. 4. And Furfine and Fiedler further teach that such formulations are suitable for intravitreal administration. EX1005 (Furfine) at 1:17-24, 4:65-67; EX1011 (Fiedler) at [0052], [0083]-[0084].

244. The difference between 114.3 mg/mL, as recited in claim 31, and 100 mg/mL, as taught in Furfine, Dix, and Fiedler, is less than a 15% difference. A skilled formulator would not have expected the relatively minor increase in concentration from 100 mg/mL to 114.3 mg/mL to meaningfully affect the stability and viscosity properties of the formulation.

245. Moreover, if necessary, a skilled formulator would have known how to make any adjustments in the formulation to obtain a stable aflibercept formulation suitable for intravitreal injection. Indeed, Vitti, which teaches stable, liquid pharmaceutical formulations containing up to “100±15 mg/mL of a VEGF antagonist” (or 15% greater or less than 100 mg/mL) for intravitreal administration via a syringe fitted with a 30-gauge needle, EX1007 (Vitti) at [0094], [0108], [0115], [0127], confirms or at least suggests that a formulation with a comparable or lower concentration of aflibercept, such as 114.3 mg/mL, would likewise be stable and suitable for intravitreal administration.

246. Furthermore, a skilled formulator would have been aware of the trend in the industry towards higher-concentration therapeutic protein formulations and the numerous successfully developed high-concentration therapeutic protein formulations already FDA-approved and commercially available at the time. EX1045 (Wang 2021) at 263, Table 1, Fig. 1.

247. Accordingly, given the relatively small increase in concentration from the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler, a skilled formulator would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation with 114.3 mg/mL as claimed.

248. I understand from Dr. D'Amico that it would have been desirable to obtain an aflibercept dose of at least about 8 mg. D'Amico Conversation. I also understand from Dr. D'Amico that the desire to decrease the treatment burden on patients associated with long-term, frequent intravitreal injections has driven a movement in the field toward higher-dose, higher-concentration ophthalmic formulations for intravitreal administration. D'Amico Conversation. Accordingly, it is my understanding from Dr. D'Amico that, to achieve the objective of decreasing patient treatment burden associated with intravitreal administration of an aqueous pharmaceutical formulation of aflibercept, it would have been desirable from a clinical perspective to increase the concentration of the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler. D'Amico Conversation.

249. I further understand from Dr. D'Amico that the injection volume for intravitreally administered formulations known in the art ranged from preferably about 50 μ L up to a maximum of 100 μ L, with 100 μ L being the known upper safe volume limit for a liquid formulation for intravitreal injection. D'Amico Conversation. I understand that while any injection volume between 50 μ L to 100

μL would have been clinically acceptable, a lower injection volume within that range is still preferable to a higher injection volume to the decreased risk of adverse clinical events associated with increased intraocular pressure from higher volume injections. D'Amico Conversation. I understand from Dr. D'Amico that it would have been preferable to deliver the 8mg dose at the 50 μL volume of the existing VEGF antagonists (low dose Eylea, Lucentis, and Avastin) or a volume close to 50 μL. D'Amico Conversation.

250. Assuming an aflibercept dose of about 8 mg and injection volume ranging from 50 μL to 100 μL, a skilled formulator would have been able to determine the range of possible concentrations for the aflibercept in the aqueous pharmaceutical formulation is 80 mg/mL to 160 mg/mL as set forth below:

Dose (mg)	Injection Volume (μL)	Concentration (mg/mL)
8	50	160
8	60	133.3
8	70	114.3
8	80	100
8	90	88.9
8	100	80

After determining the range of possible concentrations based on an aflibercept dose of 8 mg and an injection volume of 50 μL to 100 μL, a skilled formulator would have been able to identify, and reasonably expect to succeed in obtaining, a stable aqueous pharmaceutical formulation for intravitreal administration containing 114.3

mg/mL aflibercept as a matter of routine optimization based on the teachings of Furfine, Dix, and Fiedler.

251. While it may have been possible to obtain an aflibercept formulation with a protein concentration above 115 mg/mL, a skilled formulator would have understood that higher concentration protein formulations carry a greater risk of failure due to increased risk of aggregation and increased viscosity, EX1021 (Dear) at 194; EX1028 (Inoue) at 539; EX1033 (Neergaard) at 401, and thus potentially require additional stabilizing and/or viscosity-reducing excipients, all of which complicate the formulation and increase the risk of a failed formulation.

252. In light of the clinical considerations related to patient treatment burden and adverse clinical events described by Dr. Amico (which favor a higher protein concentration to deliver an 8 mg dose of aflibercept at a lower volume), D'Amico Conversation, that must be balanced with the competing formulation considerations related to aggregation and viscosity (which favor a lower protein concentration to deliver the same 8 mg dose at a higher volume), a skilled formulator working together with a skilled clinician would have recognized that a formulation containing 114.3 mg/mL of aflibercept for providing an 8 mg dose at a volume of 70 μ L would have been a suitable option.

253. A skilled formulator would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation suitable for intravitreal injection

with a protein concentration of 114.3 mg/mL based on Furfine, Dix, and Fiedler as a matter of routine optimization.

DD. Claim 32

32. The method of claim 31, wherein the angiogenic eye disorder is wet age-related macular degeneration.

254. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.CC.

EE. Claim 33

33. The method of claim 31, wherein the angiogenic eye disorder is diabetic macular edema.

255. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.CC.

FF. Claim 34

34. The method of claim 31, wherein the angiogenic eye disorder is diabetic retinopathy.

256. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.CC.

GG. Claim 35

35. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.

257. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining a pharmaceutical formulation with about 114.3 mg/mL of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Sections XI.A and XI.CC.

258. With respect to concentration, and in contrast to claim 1, which requires an aqueous formulation comprising “at least 100 mg/ml of the VEGF receptor fusion protein,” and claim 31, which requires an aqueous pharmaceutical formulation comprising “about 114.3 mg/ml of aflibercept,” claim 35 requires an aqueous pharmaceutical formulation comprising “about 103-126 mg/ml of aflibercept.” I note that the recited concentration in claim 35, “about 103-126 mg/ml of aflibercept” is merely about 10% greater or less than “about 114.3 mg/ml of aflibercept” as recited in claim 31.

259. As discussed above in Section XI.CC, a skilled formulator would not have expected the relatively minor 15% increase in protein concentration from 100

mg/mL, as taught in Furfine, Dix, and Fiedler, up to 115 mg/mL to meaningfully affect the stability and viscosity properties of the formulation. A skilled formulator would therefore have understood how to make, with a reasonable expectation of success, a stable aflibercept formulation for intravitreal administration with a concentration of up to 115 mg/mL and within the claimed range.

260. Accordingly, in light of Furfine, Dix, and Fiedler, a skilled formulator would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept.

HH. Claim 36

36. The method of claim 35, wherein the angiogenic eye disorder is wet age-related macular degeneration.

261. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.GG.

II. Claim 37

37. The method of claim 35, wherein the angiogenic eye disorder is diabetic macular edema.

262. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal

administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.GG.

JJ. Claim 38

38. The method of claim 35, wherein the angiogenic eye disorder is diabetic retinopathy.

263. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.GG.

XII. GROUND 3: CLAIMS 1-38 LACK WRITTEN DESCRIPTION

264. In my opinion, claims 1-38 of the '036 Patent are not supported by sufficient written description because the specification does not show that the inventors possessed formulations reflecting the full scope of the claims to achieve the claimed viscosity levels.

265. As explained in greater detail below, the specification's disclosure of formulations that meet the claimed viscosity levels reflect only a small subset of a large genus of formulations that fall within the scope of the claims. Moreover, although all of the formulations disclosed in the specification contain a buffer, the claims do not require a buffer. Based on these disclosures in the specification, a

skilled formulator would not understand the inventors to have possessed the full scope of the claimed formulations that achieve the required viscosity levels.

1. The Specification Fails to Provide Written Description Support for the Full Scope of the Claims

266. The '036 Patent claims cover a method for treating an angiogenic eye disorder comprising intravitreal administration of a broad genus of potential formulations having a concentration of at least 100 mg/mL of a specified VEGF receptor protein, such that they administer at least 8 mg of that fusion protein in a volume of about 100 μ L or less, and having a viscosity of about 5-15 cP at 20° C.

267. The broadest claims cover a large genus of potential formulations that achieve the claimed viscosity levels but do not specify any specific components of the formulation other than the VEGF fusion protein itself, including whether the formulation contains a buffer, a surfactant, a viscosity reducing agent, or a thermal stabilizer—all components that are discussed in the '036 Patent specification—let alone the identity or concentration of any such component. Even the narrowest claims add only the requirement that the formulation contains a sugar or an amino acid. EX1001 ('036 Patent) at cls. 9-11.

268. I understand that the claim requirement of a viscosity of about 5-15 cP at 20° C is a functional feature because it recites the desired result of the claimed formulation.

269. In contrast to the broad genus of formulations potentially covered by the claim, the '036 Patent specification discloses only a small number of species that actually achieve the required viscosity, and all those species contain a buffer and contain polysorbate. Specifically, while the specification lists approximately 89 potential high-concentration VEGF formulations, it only provides viscosity data for a limited subset of them, all of which include similar excipients.

270. In particular, the specification provides viscosity data in Figures 3A-C, 5, 9, and Table A. EX1001 ('036 Patent) at Figs. 3A-C, 9, Table A. The formulations of Figure 3A contain 155 mg/ml VEGF Trap in 10 mM sodium phosphate buffer, 5% sucrose and a pH of 6.2 in combination with no inorganic salt, arginine, lysine, sodium chloride and magnesium chloride. EX1001 ('036 Patent) at 38:37-47, Fig. 3A. The formulations of Figure 3B contain the same components except that the buffer is 10 mM histidine and the formulations have a pH of 5.8. EX1001 ('036 Patent) at 38:47-54, Fig. 3B. The formulations tested in Figure 3C have concentrations of VEGF Trap between 10 mg/ml and 160 mg/ml, a 10 mM sodium phosphate buffer, 5% sucrose, and a pH of 6.2, some with no arginine and some with 50 mM of arginine hydrochloride. EX1001 ('036 Patent) at 38:55-67, Fig. 3C.

271. The formulations of Figure 5 have the same VEGF concentration range and either phosphate or histidine buffer. EX1001 ('036 Patent) at Fig. 5.

272. The formulations tested in Table A and reflected in Figure 9 all contain a buffer, specifically, a histidine buffer. All of these formulations also include sucrose and polysorbate 20.

TABLE A

Formulations F1-F12.				
Formulation #	VEGF Trap (mg/mL)	Buffer	Other Excipients	Screening Excipients (mM)
F1 (GGG)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium sulfate
F2 (HHH)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium thiocyanate
F3 (III)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	40 mM Sodium citrate
F4 (JJJ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Glycine
F5 (KKK)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium chloride

TABLE A-continued

Formulations F1-F12.				
Formulation #	VEGF Trap (mg/mL)	Buffer	Other Excipients	Screening Excipients (mM)
F6 (LLL)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Lysine
F7 (MMM)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium aspartate
F8 (NNN)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium glutamate
F9 (OOO)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium Citrate + 50 mM Arginine hydrochloride
F10 (PPP)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Glycine + 50 mM Arginine hydrochloride
F11 (QQQ)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium aspartate + 50 mM Arginine hydrochloride
F12 (RRR)	140	20 mM Histidine, pH 5.8	5% Sucrose, 0.03% Polysorbate 20	50 mM Sodium glutamate + 50 mM Arginine hydrochloride

EX1001 ('036 Patent) at Table A.

273. Although the tested formulations represent only a small fraction of the possible formulations that could fall within the scope of the claims, the viscosity data demonstrates that the specific formulation components and percentages matter to achieving the required viscosity levels. For example, all the tested formulations that contain a histidine buffer fall within the claimed viscosity range of 5-15 cP:

TABLE 3-2

Viscosity-Histidine formulations (cP at 20° C.)	
Buffer Composition	10 mM Histidine, pH 5.8
No Viscosity Reducer	11.5
100 mM Arginine	12.0
200 mM Arginine	12.7
50 mM Lysine	14.0

TABLE 3-2-continued

Viscosity-Histidine formulations (cP at 20° C.)	
Buffer Composition	10 mM Histidine, pH 5.8
200 mM Lysine	14.1
50 mM Sodium Chloride	13.1
100 mM Sodium Chloride	12.1
50 mM Chloride	12.6
100 mM Magnesium Chloride	11.4

EX1001 ('036 Patent) at Table 3-2. The tested formulations containing a phosphate buffer, however, fall above the claimed range, showing viscosities of up to 17.3 cP:

TABLE 3-1

Viscosity-Phosphate formulations (cP at 20° C.)	
Buffer Composition	10 mM Sodium Phosphate, 5% Sucrose, pH 6.2
No Viscosity Reducer	17.3
100 mM Arginine	16.2
200 mM Arginine	15.8
50 mM Lysine	16.2
100 mM Sodium Chloride	16.5
50 mM Magnesium Chloride	16.3
100 mM Magnesium Chloride	15.3

EX1001 ('036 Patent) at Table 3-1. As the specification explains, “[a]t higher VEGF Trap concentrations, the histidine buffer showed an improvement in viscosity (relative to phosphate).” EX1001 ('036 Patent) at 42:19-21. Thus, the only formulations that were even tested have a buffer, and the specification demonstrates that even the particular type of formulation components like the specific buffer impact the viscosity of the formulation and, critically, whether it falls within the claimed range or not.

274. Moreover, the claims recite concentrations of at least 100 mg/mL of the VEGF fusion protein, with no stated upper limit. But Figure 5 demonstrates that, above about 160 mg/mL, the viscosity of both phosphate and histidine-containing formulations falls well above the claimed range:

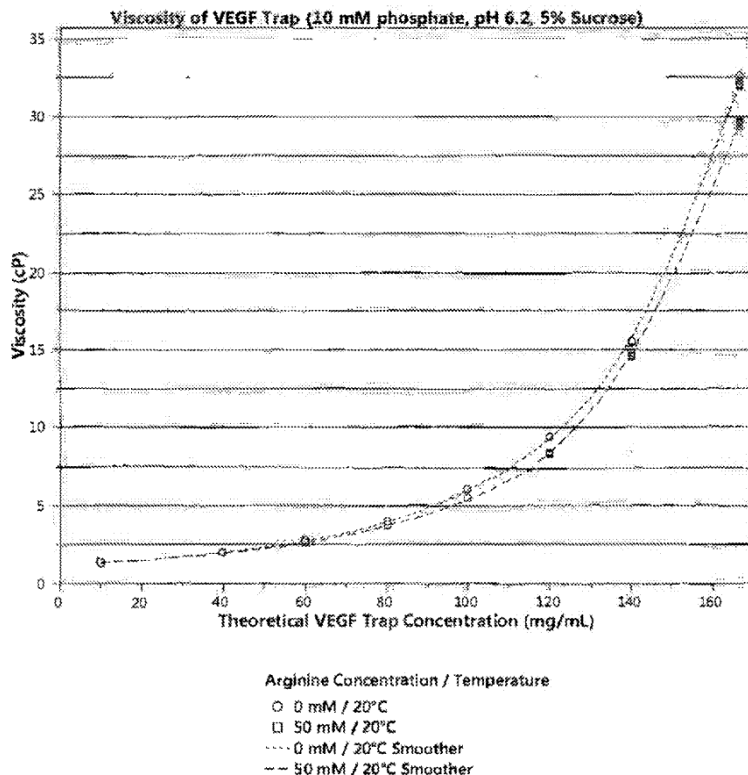


FIG. 3C

EX1001 ('036 Patent) at Fig. 5.

275. There are no examples of VEGF fusion protein concentrations above 155 mg/mL that achieve the required viscosity levels.

276. In summary, the limited number of formulations disclosed in the '036 Patent specification that achieve the claimed viscosity of 5-15 cP at 20° C fails to provide adequate written description support for the full scope of the claims, which cover effectively any high-concentration VEGF fusion protein formulation that achieves that viscosity. The specification does not provide sufficient information to distinguish which potential options for formulations falling within the scope of the

claims will achieve the required viscosity levels and which will not. Likewise, there is no disclosure of a representative number of species in the genus because, as discussed above, the disclosed species are highly similar to one another, including all having a buffer when the claim allows for no buffer, and do not reflect the full scope of the claims. The specification only shows that a narrow, limited group of formulations achieve the required viscosity levels, but the claims recite effectively any high-concentration VEGF fusion protein formulation, regardless of its components, that achieves those levels.

2. The Claims Lack Written Description Support Because They Do Not Recite a Buffer

277. The claims also lack written description support because they do not require a buffer, which the specification makes clear is required.

278. Every single example in the specification contains a buffer, and there is nothing to suggest it is optional. And, as discussed above, the specification also shows that the buffer has a significant impact on the viscosity. Because the specification fails to demonstrate possession of a formulation that achieves the claimed viscosity levels without a buffer, the claims lack written description support.

279. As discussed above, all formulations for which the '036 Patent includes viscosity data contain a buffer. Similarly, all 89 listed “[i]llustrative formulations,” also include buffers. EX1001 ('036 Patent) at 23:22-28:20. The description of many

of these illustrative formulations expressly states when a particular component is not required. EX1001 ('036 Patent) at 23:22-28:20. For example, the description of Formulation G states that the formulation excludes a viscosity reducing agent:

Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, *specifically excluding a viscosity reducing agent*.

EX1001 ('036 Patent) at 23:44-47. Formulations H-L, S-X, EE-JJ, and QQ-VV similarly state that the formulation excludes a viscosity reducing agent. EX1001 ('036 Patent) at 23:48-66 (Formulations H-L), 24:20-43 (Formulations S-X), 24:62-25:19 (Formulations EE-JJ), 25:38-61 (Formulations QQ-VV).

280. Throughout the specification, the buffer, as opposed to other formulation components, is always included in the disclosed formulations. For example, the specification explains that:

Embodiments herein provide formulations having a VEGF receptor fusion protein, *a buffer*, a thermal stabilizer, a viscosity reducing agent, and a surfactant. In other embodiments, the formulations do not include a viscosity reducing agent. Formulations of the present invention have a pH and viscosity suitable for injection, and in particular, for therapeutic ocular injection.

EX1001 ('036 Patent) at 2:34-40 (emphasis added). The specification also states that “[s]uitable formulations included herein comprise a high concentration of VEGF receptor fusion protein, *a buffer*, a thermal stabilizer and a surfactant. *In some*

aspects, a suitable formulation further includes a viscosity reducing agent.” EX1001 (’036 Patent) at 14:65-15:3 (emphases added).

281. By contrast, if a formulation component is optional, the specification specifically so states. For example, the specification expressly states that viscosity reducing agents and thermal stabilizers may “optionally” be included in the pharmaceutical formulation. EX1001 (’036 Patent) at 2:41-50. Similarly, the specification lists the general formulation components but then notes “[i]n other embodiments, the formulations do not include a viscosity reducing agent.” EX1001 (’036 Patent) at 2:36-38. Unlike the viscosity reducing agents and thermal stabilizers, the buffer, however, is never characterized in the specification as optional.

282. This characterization of certain formulation components, but never the buffer, as optional occurs consistently throughout the specification. The ’036 Patent explains that “embodiments herein also include methods for preparing a formulation by combining a histidine-based, citrate-based, acetate-based or phosphate-based buffer, with sucrose, polysorbate 20 and a VEGF receptor fusion protein; and, optionally, one or more additional components, e.g., as discussed herein.” EX1001 (’036 Patent) at 7:61-66.

283. In contrast to the treatment of buffers, when discussing other components, such as viscosity reducing agents, the specification expressly

contemplates formulations without them. For example, the specification identifies concentrations for viscosity reducing agents “when present,” suggesting by negative implication that there may also be formulations that do not have viscosity reducing agents present:

When present herein, viscosity reducing agents can be present at from about 10 mM to about 100 mM, and more typically from about 30 mM to about 75 mM, and even more typically from about 40 mM to about 70 mM.”

EX1001 ('036 Patent) at 20:2-6. As another example, the specification states that suitable formulations include a buffer, and “in some aspects . . . further includes a viscosity reducing agent,” suggesting that a suitable formulation in other aspect may exclude a viscosity reducing agent:

Suitable formulations included herein comprise a high concentration of VEGF receptor fusion protein, *a buffer*, a thermal stabilizer and a surfactant. *In some aspects, a suitable formulation further includes a viscosity reducing agent.*”

EX1001 ('036 Patent) at 14:65-15:3 (emphasis added). And as noted above, the specification notes that excipients like a thermal stabilizer and/or a viscosity reducing agent may “optionally” be included in the formulation, suggesting that those excipients may also optionally be excluded from the formulation. EX1001 ('036 Patent) at 2:41-50.

284. However, nowhere in the specification is it expressly contemplated that the buffer may be excluded. The specification's characterization of other excipients as "optional" is a notable contrast to its characterization of buffers.

285. In light of every formulation in the specification having a buffer, the statements in the specification demonstrating that the buffer is not an optional ingredient, and the data in the specification showing that the presence of a buffer impacts the viscosity of the formulation, claim 1 also lack written description because it does not recite a buffer, which is a key limitation present in the compositions that are shown by the specification to meet the claimed viscosity limitation.

286. The specification demonstrates to a skilled formulator that the inventors did not invent high-concentration VEGF formulations with the specified viscosity levels that do not contain a buffer. Every disclosed formulation that meets the claimed viscosity levels contains a buffer; in fact, every disclosed formulation, even those for which viscosity was not tested contains a buffer. Additionally, the specification never suggests that a buffer could be optional. Because the specification supports only formulations with a buffer that achieve the claimed viscosity levels, yet the claims broadly cover any high-concentration VEGF formulation that would meet those levels, the claims are invalid for lack of written description.

XIII. GROUND 4: CLAIMS 2 AND 3 ARE OBVIOUS OVER VITTI, AU EYLEA® LABEL, LARSON, AND 2011 EYLEA CLINICAL REVIEW

A. Claim 2

2. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.

287. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

B. Claim 3

3. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.

288. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section X.A.

XIV. GROUND 5: CLAIMS 2 AND 3 ARE OBVIOUS OVER FURFINE, DIX, FIEDLER, AU EYLEA® LABEL, LARSON, AND 2011 EYLEA CLINICAL REVIEW

A. Claim 2

2. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.

289. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

B. Claim 3

3. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.

290. I incorporate and refer to my analysis regarding reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with at least 100 mg/mL of aflibercept for intravitreal administration and having a viscosity of about 5-15 cP at 20° C, set forth above in Section XI.A.

XV. ADDITIONAL REMARKS

291. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

292. I currently hold the opinions expressed in this declaration. My analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in additional observations. I reserve the right to offer additional opinions regarding the subject matter set forth in this declaration, including in response to any argument raised by Regeneron, or in response to expert opinions offered on behalf of Regeneron.

Dated: September 17, 2025



ROBERT J. FALCONER

EXHIBIT A

Curriculum Vitae Robert John Falconer

Curriculum Vitae
Robert John Falconer
Professor in Bioprocess Engineering

PERSONAL DETAILS

Name: Robert John Falconer
Nationality: Australian & British
Orcid: 0000-0002-9912-9036

Education

1995-1997 Ph.D., Department of Chemical Engineering, University of Adelaide, Australia
1980-1983 B.Sc., Department of Biotechnology, University of New South Wales, Australia

Current Appointment

2019-Present Professor in Bioprocess Engineering, School of Chemical Engineering, University of Adelaide, South Australia

Previous Appointments

2011-2019 Reader in Biological Engineering, Department of Chemical & Biological Engineering, University of Sheffield, UK
2006-2011 Senior Research Fellow, AIBN, University of Queensland, Australia
2003-2006 Research Coordinator in Bioscience Engineering, Department of Chemical Engineering, University of Cambridge, UK
2002-2003 Project Development Manager, Diagnostic Systems Laboratories Inc., Houston, Texas, USA. (Medical Diagnostics)
2000-2002 Production Manager, Tuta Healthcare Pty Limited, Sydney, Australia. (Medical Devices)
1999-2000 Project Manager, DuPont, Sydney, Australia. (Analytical Technology)
1998-1999 Operations Manager, Diagnostic Systems Laboratories Inc., Houston, Texas, USA.
1992-1995 Senior Production Scientist, GroPep Pty Ltd, Adelaide, Australia. (Biotechnology)
1984,1987-1992 Scientist, Biotech Australia Pty Ltd, Sydney, Australia. (Biotechnology)

Publications

68 peer-reviewed papers
3 book chapters
2 patents

Funding

Total >\$11 million AUD; Australia; CRCP tenth round, \$3,000,000 “mRNA manufacturing and formulation service for late stage clinical trials”; AFW Fame grant \$94,896 and SA Department of Trade and Industry \$218,000, AFW SCALE grant \$239,582; MRFF, \$5,000,000 “Developing enabling technologies for manufacture of precision mRNA vaccines”. Great Britain; Industrial funding: MedImmune & DSM, approx. £440,000; Innovate UK: MedImmune & Teraviva, £69,597; BBSRC Research Grants £322,327, £301,286, £212,892; BBSRC Training Grants £94,126, £93,520; Grantham Foundation £90,000.

Teaching

Current load:

BIOPRENG 7061 Quality by Design and Process Analytical Technology

BIOPRENG 7063 Good Manufacturing Practice, Validation and Regulation

BIOPRENG 7066 Advanced Technologies in Biopharmaceutical Processing

Industrial collaborations

Current collaborations are with Biocina (Jan Bekker, Phillip Elliot). Previous collaborations include DSM (Aaron Cowieson); MedImmune (Ray Field, Jenny Smith, Shahid Uddin and Chris van der Walle); and Fujifilm Diosynth (Tibor Nagy), Teraview Limited (Alessia Portieri and Paddy O'Kelly).

Academic collaborations

Collaborations whilst at TUoS with Prof Mike Williamson (Molecular Biology & Biotechnology), Prof Duncan Cameron (Animal & Plant Science), Dr Colin Freeman (Material Science & Engineering), Prof Roger Lewis (Mechanical Engineering), Dr Axel Zeitler (U. of Cambridge), Ass Prof Vincent Wallace (U. of Western Australia) and Dr Rachel Kilmister (DEPI, Victorian Government); collaborations whilst at UoA, Dr Simon Schmitt, Dr Markus Herderich (AWRI).

Primary PhD student supervision (University of Cambridge, Sheffield and Adelaide)

10 graduated to date; 6 currently engaged in research

Industrial experience

Operations Manager (1998-1999), Project Development Manager (2002-2003), Diagnostic Systems Laboratories, Inc., Houston, Texas.

Diagnostic Systems Laboratories (DSLabs) manufactured 150 different medical diagnostic kits to measure a range of analytes including steroid and protein hormones, cancer markers, growth factors and binding proteins. The company was privately owned, was based in Webster, Texas and was acquired by Beckman Coulter in 2005. I was employed by DSLabs twice, initially as an operations manager and later as a project development manager. As the operations manager I directly supervised 12 staff and undertook the scheduling of the manufacture of over 100 different immunodiagnostic kits. I modelled the manufacturing process and implemented changes that improved productivity by 50% with minimal capital expenditure. I also assisted in product troubleshooting.

Production Manager (2000-2002), Tuta Healthcare Pty Ltd, Sydney, Australia

Tuta Healthcare Pty Ltd is a medical device manufacturer specializing in disposable hospital products. Initially I was employed as the Quality Assurance and Regulatory Affairs Manager to bring the quality system into conformance with the EN46000 Medical Device Quality Management Systems Standard. I reduced customer complaints from 3 per week down to none in three months through rigorous control of incoming goods and investigation of non-conforming product. After nine months I was promoted to Production Manager. In this new role I reduced backorders to a tenth of their previous levels, increased batch sizes and improved efficiency. During this period, I supervised 35 staff, managed two thirds of the company's budget and reported directly to the board. Our key achievement was to turn a company that made a \$2,000,000 AUD loss per year to one that made a healthy annual profit running at approximately 25% of turnover. Most importantly the Tuta Healthcare was well positioned to develop new products in collaboration with surgeons and other medical practitioners, and take advantage of new business opportunities.

Senior Production Scientist (1992-1995), GroPep Ltd, Adelaide, Australia

GroPep was an Australian biotechnology company it was acquired by Novozyme in 2006. As the senior production scientist I helped redesign the IGF manufacturing processes to comply with the code of good manufacturing practice (GMP). I wrote the company's Quality Manual, Validation Master Plan, and wrote a business plan justifying the expenditure required to construct a LONG®R3-IGF-I manufacturing facility. I was a key part of the team that

designed the GMP manufacturing facility. LONG®R3-IGF-I went on to be GroPep's major product as an important component in cell culture media. The commercial success of this product led to the acquisition of GroPep Ltd by Novozyme in 2006 for \$96 million AUD.

Protein Chemist and Fermentation Scientist (1984-1992), Biotechnology Australia Pty Ltd, Sydney Australia

Biotechnology Australia Pty Ltd developed and manufactured recombinant animal vaccine, diagnostic tests and had a portfolio of potential therapeutic proteins. The company was purchased by GroPep Ltd in 2002. I gained hands-on experience producing a range of recombinant proteins for use in diagnostic assays, animal trials and in animal vaccines. I was able to take biopharmaceutical development projects from earliest stages (newly cloned strains) through the fermentation, purification and formulation unit operations to a finished product. I gained experience in biopharmaceutical process design and the quality management required for the manufacture of medical product.

Publication List

Papers – peer reviewed

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67. Akintayo, O.A.; Falconer, R.J.; Lauer, J.C.; Cowley, J.M.; Bozurt, H. (2025) The effect of gelatinisation and enzymatic hydrolysis methods on the starch, sugar, and physicochemical properties of faba bean milk. *International Journal of Biological Macromolecules*. doi.org/10.1016/j.ijbiomac.2025.140898.
66. Wright, L.; Francis, J.; Curtis, R.; Falconer R.J. (2025) Dynamic light scattering analysis of lipid nanoparticles: effect of salts on diffusion interaction parameter and hydrodynamic diameter at infinite dilution. *Analytical Chemistry*, 97, 2437-2442.
65. Capili, M.J.A.; Oerlemans S.K.; Wright L.; Falconer, R.J. (2024) Complexity associated with caprylate binding to bovine serum albumin: Dimerization, allostery, and variance between the change in free energy and enthalpy of binding. *Protein Science* 33, e5224.
64. Toronjo Urquiza, L.; Besford, Q.A.; Falconer, R.J. (2024) Interactions between small organic molecules and water measured using pressure perturbation calorimetry. *Journal of Thermal Analysis and Calorimetry*, 149, 9223-9231.
63. Flint, K.L.; Evans, J.D.; Carraro, F.; Renner, S.; Linder-Patton, O.M.; Amenitsch, H.; Falconer, R.J.; White, N.G.; Sumbly, C.J.; Falcato, P.; Doonan, C.J. (2023) Protein-induced modifications in crystal morphology of a hydrogen-bonded organic framework. *Journal of Materials Chemistry* 11, 23026-23033.
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