

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., DR. REDDY'S LABORATORIES, INC.
and DR. REDDY'S LABORATORIES, LTD.

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00724¹

Patent No. 10,335,462

REPLY DECLARATION OF WILLIAM J. JUSKO, PH.D.

¹ IPR2024-00009 (Dr. Reddy's Laboratories) has been joined with this proceeding.

TABLE OF CONTENTS

	Page
I. SUMMARY OF OPINIONS	13
II. LEGAL STANDARDS	15
III. PERSON OF ORDINARY SKILL IN THE ART	19
IV. CLAIM CONSTRUCTION	21
V. THE '462 PATENT	23
VI. REFERENCES IN THE ART	24
A. SCOPE OF THE PRIOR ART	24
1. WO421 (EX1011)	25
2. Lovshin (EX1012)	28
3. NCT657 (EX1013)	30
4. NCT773 (EX1014)	31
5. WO537 (EX1015)	32
6. Lund (EX1035)	33
7. Seino (EX1038)	36
8. Tamimi (EX1047)	38
9. FDA Exposure Response 2003 (EX1048)	40
B. ADDITIONAL REFERENCES RELIED UPON BY DR. ROSENSTOCK	41
1. Knight (EX2005)	41
2. Arrowsmith (EX2006)	46
3. Novo Nordisk Annual Report 2010 (EX2065)	52
4. Report on the Deliberation Results (EX2067)	59
5. Kim (EX2066)	62
6. Rosenstock 2009 (EX2062)	63
7. Madsbad 2004 (EX2075)	66
8. Nordqvist (EX2061)	73
VII. PURPORTED FAILED AND WITHDRAWN GLP-1 RECEPTOR AGONISTS	76

TABLE OF CONTENTS
(continued)

	Page
VIII. UNPATENTABILITY OF THE '462 PATENT	84
A. GROUND 1: WO421 ANTICIPATED CLAIMS 1-3 OF THE '462 PATENT.....	84
1. WO421 anticipated claim 1	84
a. A skilled artisan would have understood that the 0.1 – 1.6 mg range in WO421 discloses the 1.0 mg dose and would have immediately envisaged the 1.0 mg dose	85
b. The 1.0 mg dose is not critical.....	96
(i) The claims do not require any particular level of efficacy	98
(ii) The claims do not require any particular level of tolerability	102
2. WO421 anticipated claims 2 and 3.....	105
B. GROUND 2: LOVSHIN ANTICIPATED CLAIMS 1-3 OF THE '462 PATENT.....	107
1. Lovshin anticipated claim 1	107
a. A skilled artisan would have understood that the 0.1 – 1.6 mg range in Lovshin discloses the 1.0 mg dose and would have immediately envisaged the 1.0 mg dose	107
b. The 1 mg dose is not critical	112
2. Lovshin anticipated claims 2 and 3.....	112
C. GROUND 3-5: CLAIMS 1-10 OF THE '462 PATENT WOULD HAVE BEEN OBVIOUS.....	114
1. A skilled artisan would have been motivated to pursue a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide	114
2. A skilled artisan would have had a reasonable expectation of success pursuing a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide	124

TABLE OF CONTENTS

(continued)

	Page
a. A skilled artisan would have had a reasonable expectation of success in optimizing to reach a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide	126
b. The claims do not require that the once-weekly 1.0 mg dose of semaglutide have a particular level of efficacy or tolerability	135
(i) A skilled artisan would not have needed to have reported results from a semaglutide clinical trial to have had a reasonable expectation of success	138
(ii) A skilled artisan would not have needed to know the specific shape of the semaglutide dose response curve to have had a reasonable expectation of success	144
(iii) That the semaglutide phase III trial was “on hold” would not have dissuaded a skilled artisan from pursuing the claimed method	150
3. Ground 3: Claims 1-10 of the ’462 Patent Would Have Been Obvious Over WO421	151
a. Claim 1 would have been obvious over WO ’421 considering the ’424 publication	151
b. Claims 2-3 would have been obvious over WO ’421 considering the ’424 publication	152
c. Claims 4-10 would have been obvious over WO ’421 considering the ’424 publication	152
4. Ground 4: Claims 1-10 of the ’462 Patent Would Have Been Obvious Over WO537 Considering Lovshin	152
a. Claim 1 would have been obvious over WO537 considering Lovshin	153
b. Claims 2 and 3 would have been obvious over WO537 considering Lovshin	154
c. Claims 4-10 would have been obvious over WO537 considering Lovshin	155

TABLE OF CONTENTS
(continued)

	Page
5. Ground 5: Claims 1-10 of the '462 Patent Would Have Been Obvious Over NCT657 and NCT773.....	155
a. Claim 1 would have been obvious over NCT657 and NCT773	156
b. Claim 2 and 3 would have been obvious over NCT657 and NCT773	161
c. Claims 4-10 would have been obvious over NCT657, NCT773, and the '424 publication	161
IX. CONCLUSION.....	162

TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation
U.S. Patent App. Pub. No. US2007/0010424	'424 publication (EX1016)
U.S. Patent No. 10,335,462	'462 patent (EX1001)
Arrowsmith, J., <i>Phase II failures: 2008–2010</i> , Nature Reviews, Drug Discovery, Vol. 10 (May 2011)	Arrowsmith (EX2006)
Declaration of John Bantle, MD	Bantle Decl. (EX1003)
Transcript of December 29, 2023 Deposition of John Bantle, M.D.	Bantle Tr. (EX2018)
Bhansali et al., <i>Historical Overview of Incretin Based Therapies</i> , 58 SUPPL. TO JAPI 10 (2010)	Bhansali (EX1137)
Blüher, M. et al., <i>Dose-response effects on HbA1c and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomized clinical trial</i> , Diabetologia (2023), available at https://link.springer.com/content/pdf/10.1007/s00125-023-06053-9.pdf	Blüher (EX2078)
Califf, <i>Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010</i> , 307 J. AM. MED. ASS'N 1838 (2012)	Califf (EX1279)
Chatzigeorgiou et al., <i>The Use of Animal Models in the Study of Diabetes Mellitus</i> , 23 IN VIVO 245 (2009)	Chatzigeorgiou (EX1290)
NCT03144271, <i>Dose Escalation of Single Subcutaneous Doses of NNC 0113-0217 to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics in Healthy Male Subjects</i> , available at https://clinicaltrials.gov/study/NCT03144271 (last visited December 28, 2023)	Dose Escalation Trial (EX2070)
Drab, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects</i> , 30 PHARMACOTHERAPY 609 (2010)	Drab (EX1022)

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Declaration of William J. Jusko, Ph.D., in Support of Petition for <i>Inter Partes</i> Review of U.S. Patent No. 10,335,462	First Declaration or First Decl. (EX1005)
FDA Guidance for Industry, <i>Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications</i> (Apr. 2003)	FDA Exposure Response 2003 (EX1048)
<i>International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability</i> , 59 Fed. Reg. 55972 (Nov. 9, 1994)	ICH 1994 (EX1049)
Transcript of January 5, 2024 Deposition of William J. Jusko, Ph.D.	Jusko Tr. (EX2019)
Kendall, <i>Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients with Type 2 Diabetes Treated with Metformin and a Sulfonylurea</i> , 28 DIABETES CARE 1083 (2005)	Kendall (EX1287)
Kim, K., et al., <i>Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms</i> , J Clin Pharmacol, Vol.44, 1083-1105 (2004)	Kim (EX2066)
Knight, A., <i>Systematic Reviews of Animal Experiments Demonstrate Poor Contributions Toward Human Healthcare</i> , Reviews on Recent Clinical Trials, Vol.3, Issue 2, 89-96 (2008)	Knight (EX2005)
Knight, <i>The Beginning of the End for Chimpanzee Experiments?</i> , 3 PHILOSOPHY, ETHICS, & HUMANITIES IN MED. 1 (2008)	Knight 2008 (EX1280)
Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26 DRUGS OF THE FUTURE 677 (2001)	Knudsen 2001 (EX1031)
Knudsen, <i>Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47 J. MED. CHEMISTRY 4128 (2004)	Knudsen 2004 (EX1032)
Knudsen, <i>Liraglutide: The Therapeutic Promise from Animal Models</i> , 64(suppl 167) INT J CLIN PRACT 4 (2010)	Knudsen 2010b (EX1066)
Lovshin, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus</i> , 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)	Lovshin (EX1012)

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Lund, <i>Emerging GLP-1 Receptor Agonists</i> , 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)	Lund (EX1035)
Madsbad, <i>An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists - Available Efficacy and Safety Data and Perspectives for the Future</i> , 13 DIABETES, OBESITY & METABOLISM 394 (2011)	Madsbad (EX1052)
Madsbad, S. et al., <i>Improved Glycemic Control With No Weight Increase in Patients With Type 2 Diabetes After Once-Daily Treatment With the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)</i> , Diabetes Care, Vol.27, Issue 6, 1335-1342 (June 2004)	Madsbad 2004 (EX2075)
Marre, <i>GLP-1 Receptor Agonists Today</i> , 93 DIABETES RSCH & CLIN. PRACTICE 317 (2011)	Marre (EX1284)
Miller, M., et al., <i>Low Viscosity Highly Concentrated Injectable Nonaqueous Suspensions of Lysozyme Microparticles</i> , Langmuir, Author Manuscript (2011), PMC 2011 (Feb 17)	Miller (EX2004)
Mueller, C., <i>University of South Carolina Upstate, CHEM U109 Chemistry of Living Things</i> , 9.1:Solutions, available at https://chem.libretexts.org/Courses/University_of_South_Carolina_Upstate//USC_Upstate%3A_CHEM_U109__Chemistry_of_Living_Things_(Mueller)/09%3A_Solutions/9.1%3A_Solutions (last visited January 16, 2024)	Mueller (EX2077)
Clinical Trial No. NCT00696657	NCT657 (EX1013)
Clinical Trial No. NCT00851773	NCT773 (EX1014)
Novo Nordisk, "Annual Report 2010" (February 1, 2011)	Novo Nordisk, Annual Report 2010 (EX2065)

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Novo Nordisk Annual Report 2011	Novo Nordisk Annual Report 2011 (EX1130)
Novo Nordisk Earnings Call (Feb. 2, 2012)	Novo Nordisk Earnings Call (Feb. 2, 2012) (EX1285)
Novo Nordisk Form 6-K (May 1, 2009)	Novo Nordisk Form 6-K (May 1, 2009) (EX1282)
Novo Nordisk Form 6-K (Feb. 2, 2011)	Novo Nordisk SEC Filing (2011) (EX1131)
Novo Nordisk 2010-2011 Pipeline	Novo Nordisk Pipeline (EX1283)
Nordqvist, C., <i>Experimental Diabetes Drug Taspoglutide Late-Stage Trials Suspended</i> , available at https://www.medicalnewstoday.com/articles/200893#1 (September 13, 2010)	Norqvist (EX2061)
Ozempic® Prescribing Information (September 2023)	Ozempic® Prescribing Label (EX2069)
Synapse, <i>Pegylated GLP-1 analogue (LY2428757) – (Eli Lilly & Co.)</i> , available at https://synapse.patsnap.com/drug/482a547adeba4170ab23efa225fb966d (last updated December 27, 2023)	Pegylated GLP-1 Analogue (LY2428757) EX2064

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Rees, <i>Animal Models of Diabetes Mellitus</i> , 22 DIABET. MED. 359 (2005)	Rees (EX1289)
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, <i>Report on the Deliberation Results</i> , available at https://www.pmda.go.jp/files/000153180.pdf (December 3, 2009)	Report on the Deliberation Results (EX2067)
Declaration of Julio Rosenstock, M.D.	Rosenstock Declaration or Rosenstock Decl. (EX2010)
Rosenstock, <i>Early Diabetic Nephropathy: Assessment and Potential Therapeutic Interventions</i> , 9 DIABETES CARE 529 (1986)	Rosenstock 1986 (EX1291)
Rosenstock, J., et al., <i>Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes</i> , Diabetes Care, Vol.32, Issue 10, 1880-1886 (October 2009)	Rosenstock 2009 (EX2062)
Rosenstock, J., et al., <i>The Fate of Taspoglutide, a Weekly GLP-1 Receptor Agonist, Versus Twice-Daily Exenatide for Type 2 Diabetes</i> , Diabetes Care, Vol.36, 498-504 (March 2013)	Rosenstock 2013 (EX2060)
Seino, <i>Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes</i> , 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)	Seino (EX1038)
Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)	Shargel (EX1045)
Tamimi, <i>Drug Development: From Concept to Marketing!</i> , 113 NEPHRON CLIN PRACT C125 (2009)	Tamimi (EX1047)

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
OPTUMRx, <i>Tanzeum® (albiglutide) – Drug Discontinuation</i> , available at https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_tanzeum_2017-0801.pdf (2017)	Tanzeum® (albiglutide) – Drug Discontinuation EX2063
<i>Victoza</i> , PHYSICIANS’ DESK REFERENCE (65th ed. 2010)	Victoza label (EX1039)
Victoza® Prescribing Information (January 2010)	Victoza® Prescribing Information (January 2010) (EX2068)
International Patent App. Pub. No. WO 2011/138421	WO421 (EX1011)
International Patent App. Pub. No. WO 2006/097537	WO537 (EX1015)

1. I am the same William J. Jusko, Ph.D. who previously submitted a declaration (“First Declaration” or “First Decl.,” EX1005) in this proceeding dated March 15, 2023 on behalf of Petitioner Mylan Pharmaceuticals Inc. (“Mylan” or “Petitioner”) in support of Mylan’s petition for *inter partes* review (“IPR”) of U.S. Patent No. 10,335,462 (“’462 patent,” EX1001). I understand that the Patent Trial and Appeal Board (“Board”) instituted IPR of the ’462 patent. Paper No. 10. I submit this declaration on behalf of Petitioner in support of Petitioner’s Reply. In particular, I respond to opinions expressed in the expert declaration of Julio Rosenstock, M.D. (“Rosenstock Declaration” or “Rosenstock Decl.,” EX2010) dated January 17, 2024, which was submitted in support of Patent Owner Novo Nordisk A/S’s (“Novo Nordisk” or “Patent Owner”) Response to the Petition.

2. A copy of my *curriculum vitae* was submitted as EX1006.

3. In providing my opinions in this declaration, in addition to my experience, education, and training, and the materials identified in Exhibit A to my First Declaration (EX1005), I have also considered the materials cited in the Rosenstock Declaration (EX2010), the materials identified in Exhibit A attached to this declaration, as well as any materials cited herein not otherwise identified in Exhibit A.

4. I reaffirm that my scope of work and compensation has not changed since I submitted my First Declaration in this proceeding. I have been retained by

Mylan as a technical expert in this matter to provide various opinions regarding the '462 patent. EX1001. I receive my standard consulting rate of \$800 per hour for my services. No part of my compensation is dependent upon my opinions given or the outcome of this proceeding.

I. SUMMARY OF OPINIONS

5. For the reasons stated in my First Declaration and in this declaration, I conclude that International Patent Application Publication No. WO 2011/138421 ("WO421"), which was published on November 10, 2011, anticipates claims 1-3 of the '462 patent (Ground 1).

6. For the reasons stated in my First Declaration and in this declaration, I conclude that a review article titled "Incretin-Based Therapies for Type 2 Diabetes Mellitus" ("Lovshin") authored by Julie A. Lovshin and Daniel J. Drucker, which was published in May 2009, anticipates claims 1-3 of the '462 patent (Ground 2).

7. For the reasons stated in my First Declaration and in this declaration, I conclude that claims 1-10 of the '462 patent would have been obvious over WO421 considering U.S. Patent Application Publication No. 2007/0010424 A1 ("'424 Publication") (Ground 3). I understand that Dr. Dalby offered an opinion that claims 4-10 would have been obvious over WO421 considering the '424 Publication, and I defer to his opinion for claims 4-10.

8. For the reasons stated in my First Declaration and in this declaration, I conclude that claims 1-10 of the '462 patent would have been obvious over International Patent Application Publication No. WO 2006/097537 A2 ("WO537") considering Lovshin (Ground 4). I understand that Dr. Dalby offered an opinion that claims 4-10 would have been obvious over WO537 considering Lovshin, and I defer to his opinion for claims 4-10.

9. For the reasons stated in my First Declaration and in this declaration, I conclude that claims 1-10 of the '462 patent would have been obvious over Clinical Trial No. NCT00696657 ("NCT657"), Clinical Trial No. NCT00851773 ("NCT773"), and the '424 Publication (Ground 5). I understand that Dr. Dalby offered an opinion that claims 4-10 would have been obvious over NCT657, NCT773, and the '424 Publication, and I defer to his opinion for claims 4-10.

10. I understand that Patent Owner Novo Nordisk has asserted that evidence of secondary considerations, including purported commercial success, unexpected results, long-felt need, industry praise, and skepticism, overcomes any showing of a *prima facie* case of obviousness for Grounds 3-5. I have reviewed the following declarations of Novo Nordisk's experts in support of purported secondary considerations of nonobviousness:

- George Bakris, M.D. regarding purported unexpected results related to kidney protective effects (EX2011);

- Robin S. Goland, M.D. regarding purported unexpected results, long felt but unmet need, industry praise, and skepticism (EX2054);
- Michael Blaha, M.D. M.P.H. regarding purported unexpected results related to cardiovascular benefits (EX2055); and
- Christopher A. Vellturo, Ph.D. regarding purported commercial success of Ozempic® (EX2300).

11. I have also reviewed the following reply declarations of Petitioner Mylan's experts:

- Steven G. Coca, D.O., M.S. responding to Dr. Bakris (EX1306);
- Allen Spiegel, M.D. responding to Dr. Goland (EX1302),
- Arthur Z. Schwartzbard, M.D., F.A.C.C. responding to Dr. Blaha (EX1304); and
- DeForest McDuff, Ph.D. responding to Dr. Vellturo (EX1308).

12. After considering Novo Nordisk's experts' declarations regarding secondary considerations of nonobviousness and Mylan's experts' reply declarations, it remains my opinion that the claims of the '462 patent would have been obvious under each of Grounds 3-5.

II. LEGAL STANDARDS

13. I continue to rely on the legal standards outlined in my First Declaration. EX1005 (First Decl.) ¶¶ 22-27.

14. In particular, I understand that my opinions regarding unpatentability are presented from the viewpoint of a person of ordinary skill in the art ("POSA" or

“skilled artisan”²) in the field of technology of the patent at the time of the invention. It is my understanding that Patent Owner has asserted that claims 1-3 of the ’462 patent are entitled to an earlier invention date of March 17, 2010 or May 28, 2010, but no later than July 1, 2012 for claims 1-3 and July 1, 2012 as to claims 4-10. EX2010 (Rosenstock Decl.) ¶ 22. My opinions for this proceeding would not change regardless of which of these dates is adopted by the Board.

15. I have been informed that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. I am informed that this “preponderance-of-the-evidence” standard means that the Patent Trial and Appeal Board must find it more likely than not that the claims are unpatentable.

16. I understand that for a patent claim to be unpatentable as anticipated, a prior art reference must disclose each element of the claim expressly and/or inherently as arranged in the claim. I have been further informed that a reference can anticipate a claim, even without expressly arranging or combining the components as claimed, so long as a POSA would at once envisage the claimed arrangement or combination upon reviewing the prior art reference.

² Dr. Rosenstock uses the term “POSITA” to refer to the person of ordinary skill in the art.

17. It is my understanding for a claimed feature to be considered “critical,” such that it is not anticipated by a prior art disclosure, the question is whether that difference is “critical to the operability of the claimed invention.” I understand that the criticality question is not just whether the claimed feature creates any difference relative to a broader prior art disclosure.

18. Counsel has informed me that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

19. It is my understanding from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. It is my understanding that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason for combining prior art elements to arrive at the claimed subject matter. I understand the obviousness of an invention, rendering it unpatentable, does not require absolute predictability of outcome but that all that is required is a reasonable expectation of success.

20. I understand that the secondary considerations that can be used to determine the obviousness of claimed subject matter may include evidence of such things as commercial success, unexpected results over the closest prior art, long-felt but unsolved needs, skepticism, and industry praise.

21. I understand that commercial success is premised on the concept that if a product is economically successful, it may provide objective evidence of nonobviousness. I further understand that the commercial success of the product must be attributable to the alleged novel features of the claimed invention. I understand this to mean that, to support a finding of nonobviousness, any alleged commercial success must be driven by and attributable to the purported merits of the patented invention, and not by other factors unrelated to the allegedly novel features of the claimed invention. In other words, there must be a causal correlation, or “nexus,” between the unique merit of the claimed invention and the success of the product. I also understand that if purported commercial success is due to an element in the prior art, no nexus exists. In essence, I understand that if the feature that creates the purported success was known in the prior art, such success is not pertinent.

22. I understand that for Novo Nordisk to establish unexpected results, it must demonstrate that there is a difference between the results produced by the claimed invention and those produced by the closest prior art, and that the results would have been unexpected by a POSA considering the prior art at the time of the

invention. I also understand that for unexpected results to be persuasive, the new and unexpected results produced by the claimed invention must be different in kind, and not merely in degree, from the results produced by the prior art. I understand that a difference in kind can be the presence of a new property dissimilar to the known property from the prior art. I also understand that Patent Owner, relying on unexpected results to rebut a case of obviousness, must compare the claimed invention to the closest prior art.

23. I understand that evidence of long-felt yet unmet need in the industry for the product covered by the invention may support the invention was not obvious.

24. I understand that for industry praise to weigh against obviousness, it must be specifically directed at the claimed invention. However, when praise is linked to claim elements already known in the prior art or is unconnected to the elements, this secondary consideration is given little weight.

III. PERSON OF ORDINARY SKILL IN THE ART

25. I continue to believe that a person of ordinary skill in the art would have had (1) an M.D., a Pharm. D., or a Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and (3) experience with the development, design, manufacture,

formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

26. Alternatively, the POSA would be (1) a highly skilled scientist lacking an M.D., Pharm. D., or Ph.D., but would have (2) more than five years of experience in the area of protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and/or (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

27. A POSA would have understood the prior art references referred to herein and would have the capability to draw inferences. It is understood that, to the extent necessary, a POSA may collaborate with one or more other POSAs for one or more aspects with which the other POSA may have expertise, experience, and/or knowledge. Additionally, a POSA could have had a lower level of formal education than what I describe here if the person has a higher degree of experience.

28. It is my understanding that the Board adopted the above proposed definition of a skilled artisan for purposes of their Institution Decision. Paper No. 10 at 20-21.

29. I understand that Dr. Rosenstock proposed that “a person of ordinary skill in the art to which the ’462 patent pertains would have an M.D. or, alternatively, a Ph.D. or equivalent degree in Pharmacology, Pharmaceutics, Biopharmaceutics,

or a related field. The M.D. or Ph.D. would have 3-5 years of experience conducting clinical research in the field of diabetes treatments, including in the design of dosing regimens and dosage forms for type 2 diabetes treatments, or would have 3-5 years of research or industry experience relating to developing pharmaceutical formulations and/or dosing regimens. Alternatively, the individual would be a highly skilled scientist lacking a Ph.D. or M.D., but would have more than 5 years of experience conducting clinical research in the field of diabetes treatments. The person of ordinary skill would consult, as appropriate with others having specific expertise in pharmaceutical development, formulation, and manufacturing.” EX2010 (Rosenstock Decl.) ¶ 23.

30. As shown by my qualifications provided in my CV and as explained in my First Declaration, I met the qualifications of a POSA for purposes of the ’462 patent under either party’s definition. My opinions expressed here would not change regardless of which party’s POSA definition is adopted.

IV. CLAIM CONSTRUCTION

31. For the reasons stated in my First Declaration, it remains my opinion that the plain and ordinary meaning of the preamble of claim 1 of the ’462 patent, “[a] method of treating type 2 diabetes,” would have been understood by a skilled artisan to broadly encompass administration of semaglutide for the purpose of alleviating or reducing the symptoms and complications associated with type 2

diabetes or otherwise managing the disease without requiring any specified treatment effect. EX1005 (First Decl.) ¶¶ 58-60.

32. This plain and ordinary meaning is supported by the specification of the '462 patent, which confirms this meaning of the term “treating” and states:

the term “treatment” or “treating” is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition.

See EX1001 ('462 patent) at 5:20-31.

33. I understand that the Board found in their Institution Decision that the preamble of claim 1 is limiting. Paper No. 10 at 23. I also understand that the Board agreed with Novo Nordisk and Mylan that the preamble does not require any particular level of efficacy. *Id.* It is my understanding that the Board found that the terms “treatment” or “treating” as used in the specification of the '462 patent “include the ‘full spectrum’ of treatments for a condition.” *Id.* (citing EX1001 ('462 patent) at 5:16-27). I applied this claim construction when reaching my opinions.

34. Even though under the Board’s construction of the preamble (with which I agree) the claims do not require any particular degree of efficacy, as I stated

in my First Declaration, in my opinion, in light of the prior art a skilled artisan would have expected a 1.0 mg once weekly dose of semaglutide to be effective to treat type 2 diabetes, which establishes even more efficacy than is required by the Board's construction.

V. THE '462 PATENT

35. As I discussed in my First Declaration, I have read the '462 patent and relevant portions of the prosecution history of the '462 patent (EX1002). EX1005 (First Decl.) ¶¶ 40-55.

36. The '462 patent has one independent claim and nine dependent claims.

37. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.”

38. Claim 2 recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.”

39. Claim 3 recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

40. Claim 4 recites, “[t]he method according to claim 1, wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.”

41. Claim 5 recites, “[t]he method according to claim 4, wherein the solution further comprises propylene glycol and phenol.”

42. Claim 6 recites, “[t]he method according to claim 4, wherein the pH is 7.4.”

43. Claim 7 recites, “[t]he method according to claim 6, wherein the solution further comprises propylene glycol and phenol.”

44. Claim 8 recites, “[t]he method according to claim 4, wherein the phosphate buffer is a sodium dihydrogen phosphate buffer.”

45. Claim 9 recites, “[t]he method according to claim 1, wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.”

46. Claim 10 recites, “[t]he method according to claim 9, wherein the pH is 7.4.”

VI. REFERENCES IN THE ART

A. SCOPE OF THE PRIOR ART

47. Dr. Rosenstock addresses many of the references that I rely upon in my First Declaration (EX2010 (Rosenstock Decl.) ¶¶ 66-113, 157-177), which I respond to below and throughout this declaration.

1. WO421 (EX1011)

48. I provided a summary of the WO421 disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 106-111. I disagree with many of Dr. Rosenstock's opinions regarding WO421. EX2010 (Rosenstock Decl.) ¶¶ 66-78.

49. Dr. Rosenstock points to the statement in WO421 that discloses “[a]vailable data support the conclusion that in most patients with type 2 diabetes current monotherapy will fail and treatment with multiple drugs will be required.” EX2010 (Rosenstock Decl.) ¶ 70 (quoting EX1011 (WO421), 5:20-21³). In my opinion, this disclosure does not mean that skilled artisans would have thought that monotherapy with semaglutide would not have been successful in treating type 2 diabetes. In my opinion, skilled artisans would have understood that WO421 describes monotherapy failure as a general fact of long-term diabetes control, noting that as diabetes is a progressive disease, even patients with good initial control will need further interventions as it progresses. EX1011 (WO421) at 5. Indeed, skilled artisans would have been aware of many GLP-1 monotherapies that would have not

³ Dr. Rosenstock's citations of WO421 in his declaration are to the original page numbers of WO421 and not the branded page numbers. In this declaration I cite to the branded page number of WO421 unless I am quoting Dr. Rosenstock's citation of WO421.

been considered failures, such as liraglutide and exenatide. *See* EX1032 (Knudsen 2004) (discussing the completed phase 2 trials of liraglutide); EX1012 (Lovshin) at 3 (disclosing that “the success of exenatide has accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration.”).

50. Dr. Rosenstock states “WO421’s specification discloses only the outer bounds of a broad ‘range’ of potential semaglutide doses (which POSITA would have understood are for use in combination with a DPP-4 inhibitor, EX1011 (WO421, 1:4-9)) with endpoints at 0.1 and 1.6 mg once weekly (EX1011 (WO421), 43:13)—and does not even attempt to link even that range to any of the dozens of conditions identified throughout WO421.” EX2010 (Rosenstock Decl.) ¶ 71 (discussing EX1011 (WO421) 2:4-9 and 44:13).

51. As I discussed in my First Declaration and in more detail below, skilled artisans would have known that once weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk’s phase II clinical study and would have understood the 0.1-1.6 mg semaglutide range disclosed in WO421 was the range of doses being used for treating type 2 diabetes. EX1013 (NCT657) at 15-16); EX1005 (First Decl.) ¶¶ 189-190. Dr. Rosenstock agrees with me that skilled artisans would have looked to Novo Nordisk’s NCT657 study testing weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg for treating

type 2 diabetes. EX2010 (Rosenstock Decl.) ¶¶ 210-217. Thus, skilled artisans would have understood the disclosure of the 0.1-1.6 mg semaglutide range in WO421 to be directed to treating type 2 diabetes.

52. Dr. Rosenstock states that WO421 “does not disclose or even mention at all administering 1.0 mg semaglutide (once-weekly or otherwise) for any condition,” does not provide data, and “does not provide any guidance regarding the selection of any specific semaglutide dose.” EX2010 (Rosenstock Decl.) ¶¶ 73, 74. I disagree with Dr. Rosenstock’s opinion. As I discuss below and throughout my First Declaration, WO421 disclosed the once weekly 1.0 mg semaglutide dose for treating type 2 diabetes, which anticipated and rendered obvious the claimed method. See EX1005 (First Decl.) at Sections IX.A, IX.C; *see also* Sections VIII.A, VIII.C below.

53. Dr. Rosenstock also states that WO421 “provide[s] ‘specific dosage strengths’ for every other GLP-1 analogue it lists alongside semaglutide” and that “doses of certain of those compounds ... in increments as small as five micrograms.” EX2010 (Rosenstock Decl.) ¶¶ 75, 76; *see also id.* ¶ 77. As I discuss below, skilled artisans would not have looked beyond certain GLP-1 analogues, such as liraglutide for guidance on semaglutide dosing. See, Section VIII.A.1 below. Moreover, Dr. Rosenstock acknowledges that skilled artisans reading WO421 would have looked to Novo Nordisk’s NCT657 clinical trial to understand WO421’s 0.1-1.6 mg range.

EX2010 (Rosenstock Decl.) ¶ 210. In my opinion, skilled artisans would have known that semaglutide was being dosed once weekly in 0.1 mg increments. See Section VIII.A.1 below.

54. I disagree with Dr. Rosenstock's opinion that claim 17 of WO421 "is directed to a combination therapy." EX2010 (Rosenstock Decl.) ¶ 78. Claim 17 of WO421 recited "semaglutide ... for use in a method of treating type 2 diabetes ... said method comprising administration (e.g., *separate*, sequential or simultaneous administration) of the [semaglutide] and a DPP-4 inhibitor." EX1011 (WO421) at 65:26-31 (emphasis added). Thus, administration of semaglutide may be "separate" from administration of the DPP-4 inhibitor. And although dose amount or frequency is not recited in claim 17, WO421 discloses that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." EX1011 (WO421) at 44:13.

2. Lovshin (EX1012)

55. I provided a summary of Lovshin's disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 112-115. I disagree with many of Dr. Rosenstock's opinions regarding Lovshin. EX2010 (Rosenstock Decl.) ¶¶ 79-93.

56. Although Dr. Rosenstock states that "semaglutide" is not mentioned in Lovshin (EX2010 (Rosenstock Decl.) ¶ 82), as I discussed in my First Declaration, skilled artisans would have known that "NN9535" disclosed in Table 1 of Lovshin was semaglutide. EX1005 (First Decl.) ¶ 114, fn 4.

57. Moreover, although no data were provided for semaglutide in Lovshin (EX2010 (Rosenstock Decl.) ¶ 86), as I discussed in my First Declaration, skilled artisans would have been aware of the structure of semaglutide and that Novo Nordisk was actively investigating once weekly doses of semaglutide to treat type 2 diabetes. EX1005 (First Decl.) ¶¶ 89-102.

58. Dr. Rosenstock refers to Lovshin's Table 1 stating that it "discloses multiple GLP-1 receptor agonists that were then 'being investigated' but were either never approved (*e.g.*, taspoglutide, CJC-1134-PC, LY2428757), or were withdrawn from the market after approval (albiglutide)." EX2010 (Rosenstock Decl.) ¶ 87 (citing EX2061, EX2063; EX2064); *see also id.* ¶¶ 88-93. I disagree with Dr. Rosenstock's opinions regarding the disclosures of Table 1 of Lovshin.

59. First, I discuss Dr. Rosenstock's assertions regarding these GLP-1 receptor agonists in more detail below. *See* Section VII below. As I discuss below, I disagree with Dr. Rosenstock's opinion regarding taspoglutide and albiglutide. *Id.* Further, as of the asserted priority dates, skilled artisans would not have been aware that the listed GLP-1 receptor agonists were never approved or withdrawn from the market. *Id.*

60. Second, many of the drugs listed in Table 1 of Lovshin were ultimately FDA approved, including liraglutide, AVA0010 (lixisenatide, discussed as

“AVE0010” in the text of Lovshin), exenatide once weekly, NN9535 (semaglutide), and LY2189265 (dulaglutide).

61. Third, the claims of the '462 patent do not require any particular degree of efficacy, much less FDA approval. *See* Section IV (Claim Construction) above.

3. NCT657 (EX1013)

62. I provided a summary of NCT657's disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 121-125. I disagree with many of Dr. Rosenstock's opinions regarding NCT657. EX2010 (Rosenstock Decl.) ¶¶ 94-98.

63. Dr. Rosenstock criticizes NCT657 because it “does not disclose a 1.0 mg dose.” EX2010 (Rosenstock Decl.) ¶ 97. But as I discuss in detail in my First Declaration and in this declaration, the purpose of phase II studies is to investigate a range of doses from suboptimal to maximally effective doses to determine optimal doses, which are doses with an acceptable balance of beneficial effects and undesired effects. *See* EX1005 (First Decl.) ¶¶ 68-73; EX1047 (Tamimi) at 4; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

64. For the NCT657 study, skilled artisans would have reasonably expected that the doses on the lower end of the range (e.g., ~0.1 mg doses) would be suboptimal doses, in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See, e.g.*, EX1005 (First Decl.) ¶¶ 227,

229, 255, 257, 281, 284; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2. Skilled artisans would also have understood that effectiveness of a dose that was not tested in the phase II study, such as once-weekly 1.0 mg semaglutide, could be estimated based on extrapolation from the dose response curve. Further, the NCT657 study disclosed doses of 0.1, 0.2, 0.4, 0.8 and 1.6 mg (EX1013 (NCT657)), and Dr. Rosenstock has not shown that the claimed 1.0 mg dose has any material difference with the disclosed 0.8 mg dose.

4. NCT773 (EX1014)

65. I provided a summary of NCT773's disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 126-130. I disagree with many of Dr. Rosenstock's opinions regarding NCT773. EX2010 (Rosenstock Decl.) ¶¶ 99-105. My ultimate opinions that the claims are unpatentable do not require the disclosure of the version of NCT773 that states "Last Updated on July 15, 2010," which includes disclosure of the 1.2 mg dose in the NCT773 study. EX1014 (NCT773) at 7-8. This disclosure only confirms my opinion that the claims are unpatentable.

66. Although Dr. Rosenstock states that "semaglutide" is not mentioned in NCT773 (EX2010 (Rosenstock Decl.) ¶ 100), as I discussed in my First Declaration, skilled artisans would have known that "NN9535" was semaglutide. EX1005 (First Decl.) ¶ 89.

67. Similar to the NCT657 study, Dr. Rosenstock states that “NCT773 does not disclose a 1.0 mg dose.” EX2010 (Rosenstock Decl.) ¶¶ 103, 104. But the NCT773 study disclosed doses of 0.1, 0.2, 0.4, 0.8, 1.2 and 1.6 mg (EX1014 (NCT773)), and Dr. Rosenstock has not shown that the claimed 1.0 mg dose has any material difference with the disclosed 0.8 mg dose.

5. WO537 (EX1015)

68. I provided a summary of WO537’s disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 116-120. I disagree with many of Dr. Rosenstock’s opinions regarding WO537. EX2010 (Rosenstock Decl.) ¶¶ 106-110.

69. Dr. Rosenstock states that WO537 “does not disclose any dose of semaglutide” and “does not disclose that semaglutide would have been safe, effective, and tolerable if administered once weekly for the treatment of any condition.” EX2010 (Rosenstock Decl.) ¶¶ 108-109. As I discussed above, the claims of the ’462 patent do not require any particular degree of efficacy (*see* Section IV (Claim Construction) above). Further, my reliance on WO537 is not in isolation but in combination with Lovshin’s disclosures, including the once weekly 0.1-1.6 mg semaglutide range. *See* EX1005 (First Decl.) ¶¶ 247-274; Section VIII.C.4 below. In my opinion, skilled artisans would have understood that Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., in vitro and healthy and diseased animal models) related to the pharmacokinetics and

pharmacodynamics of semaglutide to provide a scientific rationale and support for the range of 0.1-1.6 mg doses tested in the semaglutide phase I and II studies being both safe and efficacious in human patients. *See* EX1005 (First Decl.) ¶¶ 228, 256, 260, 283, 287.

6. Lund (EX1035)

70. I provided a summary of Lund’s disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 142-148. I disagree with many of Dr. Rosenstock’s opinions regarding Lund. EX2010 (Rosenstock Decl.) ¶¶ 157-166.

71. Dr. Rosenstock asserts that I “extensively” cite Lund in my First Declaration, but only cites the paragraphs in which I summarized the disclosure of Lund. EX2010 (Rosenstock Decl.) ¶ 160 (citing EX1005 (First Decl.) ¶¶ 142-148). As I stated in my First Declaration: “My opinion that the claims of the ’462 patent are anticipated and obvious does not require the disclosures of Lund (EX1035). Exhibit 1035 merely confirms the other prior art set forth in this declaration.” EX1005 (First Decl.) ¶ 142, fn 6.

72. Dr. Rosenstock states that Table 1 of Lund discloses that “[o]ngoing trials” of semaglutide were “[o]n hold.” EX2010 (Rosenstock Decl.) ¶ 159 (citing EX1035 (Lund) at Table 1). Dr. Rosenstock alleges that this statement “would have affected POSITA’s view of the status of semaglutide clinical development” and “POSITA reading Lund . . . would have questioned the status and prospects of

semaglutide's clinical development (due to e.g., unfavorable trial outcome).” EX2010 (Rosenstock Decl.) ¶¶ 160-161. I disagree with Dr. Rosenstock's assessment of the disclosure of Lund.

73. In my opinion, skilled artisans would have understood that the “Phase II” once-weekly semaglutide trial listed in Table 1 of Lund as being “[o]n hold” was completed in February 2009. *See* EX1013 (NCT657). Skilled artisans would have understood that there could be several reasons for delay of a drug that relate to issues other than the drug itself. Indeed, as I discuss below with respect to the Novo Nordisk Annual Report 2010 (EX2065), skilled artisans would have understood that Novo Nordisk was evaluating their long-acting GLP-1 portfolio in view of other long-acting GLP-1 receptor agonists being pursued by Novo Nordisk. EX2065 (Novo Nordisk Annual Report 2010) at 26; *see* Section VI.B.3 below. Skilled artisans would have also been aware that Novo Nordisk reported that the NCT657 phase II study “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.” *See* EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12 (“Novo Nordisk very recently finalised a phase 2 study investigating safety and efficacy of five doses of semaglutide (NN9535), a once-weekly human GLP-1 analogue, versus placebo and open-label liraglutide add-on therapy in people with type 2 diabetes.... The 12-week multi-centre, multinational, double-blind, placebo-controlled, randomised dose-finding trial, which included a little more than 400

patients, demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.”).

74. Thus, skilled artisans would not have interpreted Lund’s disclosure that the Phase II trial for semaglutide was “[o]n-hold” as “calling its [semaglutide’s] development into serious question” or “suggesting that this was due to unfavorable outcomes of those trials” as stated by Dr. Rosenstock. EX2010 (Rosenstock Decl.) ¶ 160; *see also id.* ¶¶ 162-164.

75. Dr. Rosenstock also takes issue with Lund’s statement that “long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects” because he states that “[t]his turned out not to be correct for many GLP-1 receptor agonists, including albiglutide, which . . . had significant side effects when administered once monthly.” EX2010 (Rosenstock Decl.) ¶ 165 (emphasis omitted) (citing EX1035 (Lund) at 1). But as I discuss below, Rosenstock 2009 disclosed that the highest monthly dose of albiglutide, which was “constrained,” was the 100 mg dose, which was 70 mg higher than the 30 mg once weekly albiglutide dose that had an “acceptable safety and tolerability profile.” EX2062 (Rosenstock 2009) at 6; *see* Section VI.B.6 below. Rosenstock 2009 also stated that one of the weaknesses of the albiglutide trial was that “no escalating doses were tested for biweekly and monthly dosing, which may have attenuated GI [gastrointestinal] adverse events and FPG

[fasting plasma glucose] fluctuations.” EX2062 (Rosenstock 2009) at 6. Therefore, in my opinion, skilled artisans would have understood that escalating doses, such as the titration scheme used in the phase I (NCT773) and phase II (NCT657) studies would help mitigate GI side effects. *See* Section VI.B.6 below.

7. Seino (EX1038)

76. I provided a summary of Seino’s disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 149-151. I disagree with many of Dr. Rosenstock’s opinions regarding Seino. EX2010 (Rosenstock Decl.) ¶¶ 167-171.

77. In my First Declaration, I discuss that Seino disclosed that liraglutide exhibits consistent dose/response profiles for lowering HbA_{1c} as might be expected for any agent that functions as a GLP-1 agonist. EX1005 (First Decl.) ¶ 85. Figure 1 of Seino provided one of the earliest Dose/Response profiles published for liraglutide showing lowering of HbA_{1c} after 14 weeks of once-daily treatment of type 2 diabetic patients. *See* EX1038 (Seino) at 4, Fig. 1. The narrow error bars (representing the standard error) indicate that variability was modest at each dose level and that higher doses produced stronger effects than lower doses, reflecting a clear dose-response relationship for HbA_{1c}. *See id.* at 6 (“A clear dose response relationship for HbA_{1c} was shown in this study.”). As shown in Figure 1 of Seino, liraglutide showed the classic sigmoidal dose/response profile for lowering HbA_{1c}. EX1005 (First Decl.) ¶ 86.

78. As I discuss in my First Declaration, because liraglutide was shown to exhibit the classic sigmoidal dose/response profile for lowering HbA_{1c}, (see EX1038 (Seino) at 4, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have had a strong scientific basis to expect a similar dose response relationship with semaglutide for lowering HbA_{1c}. See, e.g., EX1005 (First Decl.) ¶ 238.

79. Dr. Rosenstock states that “POSITA would have understood that [the] 0.9 mg maximum dose reported by Seino was half of the maximum 1.8 mg FDA-approved liraglutide dose that was approved as of 2010 in the United States” and that the “daily maintenance dose of liraglutide is 0.9 mg in Japan.” EX2010 (Rosenstock Decl.) ¶ 169 (emphasis omitted) (citing EX1039 (Victoza® Prescribing Information), 2 (“Dosage and Administration”) and EX2067 (Report on the Deliberation Results), 19)). Dr. Rosenstock also quotes Seino’s disclosure stating that the pathophysiology and nature of type 2 diabetes differs between Japanese and Caucasian patients. EX2010 (Rosenstock Decl.) ¶¶ 170-171.

80. In my opinion, that the patients in Seino were Japanese does not impact my reliance on the shape of the liraglutide dose response profile disclosed in Seino. Skilled artisans would have understood that the overall classic sigmoidal dose/response profile for lowering HbA_{1c} would not differ between Japanese and Caucasian patients, even if the maintenance dose is lower with Japanese patients.

Whether the patients were Japanese and/or Caucasian, skilled artisans would have expected that, similar to liraglutide, increased doses of semaglutide would result in increased efficacy.

81. Moreover, in my opinion, skilled artisans would have been aware of the drug metabolism variability that may occur between different populations of patients and the need for potential dose adjustment. However, skilled artisans would have still been able to estimate the semaglutide doses in the general patient population. In my opinion, overall trends and results from studies in one particular population (e.g., Japanese or Caucasian) would have been instructive to skilled artisans when considering the general patient population.

82. Further, the '462 patent claims are not limited to any particular population, including race or nationality. In my opinion, it would have been reasonable for skilled artisans to have relied on information from a particular population (e.g., Japanese patients) to pursue a once weekly 1.0 mg semaglutide dose for treating type 2 diabetes.

8. Tamimi (EX1047)

83. I provided a summary of Tamimi's disclosures in my First Declaration. EX1005 (First Decl.) ¶¶ 162-164. I disagree with many of Dr. Rosenstock's opinions regarding Tamimi. EX2010 (Rosenstock Decl.) ¶¶ 172-174.

84. Dr. Rosenstock relies on Tamimi's disclosure that "[e]xperience tells us that approximately only 1 in 10 drugs that start the clinical phase will make it to market" and states that this contradicts my "opinion[] regarding the likelihood of success and the ability for pre-clinical data to predict favorable clinical outcomes." EX2010 (Rosenstock Decl.) ¶¶ 173-174 (quoting EX1047 (Tamimi) at 1).

85. But Tamimi discusses drug development generally, and skilled artisans would have had the underlying knowledge about the success of GLP-receptor agonist phase II clinical trials, for example, those of liraglutide and exenatide. See EX1032 (Knudsen 2004) (discussing the completed phase 2 trials of liraglutide); EX1012 (Lovshin) at 3 (disclosing that "the success of exenatide has accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration.").

86. Moreover, the claims of the '462 patent do not require that the drug "make it to market" as stated in Tamimi and relied upon by Dr. Rosenstock. EX1047 (Tamimi) at 1. As I discuss in detail below, skilled artisans would have been motivated with a reasonable expectation of success in pursuing a once-weekly 1.0 mg semaglutide dose in the claimed "[m]ethod for treating type 2 diabetes." See Section VIII.C below.

9. FDA Exposure Response 2003 (EX1048)

87. I provided a summary of FDA Exposure Response 2003 in my First Declaration. EX1005 (First Decl.) ¶¶ 165-166. I disagree with many of Dr. Rosenstock's opinions regarding FDA Exposure Response 2003. EX2010 (Rosenstock Decl.) ¶¶ 175-177.

88. Dr. Rosenstock relies on statements made in FDA Exposure Response 2003 providing general guidance about phase I and II studies. EX2010 (Rosenstock Decl.) ¶¶ 176-177 (citing EX1048 (FDA Exposure Response 2003) at 6). Dr. Rosenstock states that "POSITA would have understood from FDA Exposure Response 2003 that the purpose of Phase I and Phase II clinical trials (such as NCT773 and NCT657, respectively) is to 'link animal and human findings' (which are not linked before such trials are conducted) and to provide 'proof of concept' for what, at the time of trial design, are merely 'hypothesized.' mechanisms." EX2010 (Rosenstock Decl.) ¶ 177 (EX1048) at 6) (emphasis omitted). I disagree with Dr. Rosenstock's opinions.

89. As I stated in my First Declaration, in my opinion, a skilled artisan would also have understood that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the

pharmacokinetics and pharmacodynamics of semaglutide. *See* EX1047 (Tamimi) at 3; EX1066 (Knudsen 2010b) at 1; *see, e.g.*, EX1005 (First Decl.) ¶¶ 260, 287.

B. ADDITIONAL REFERENCES RELIED UPON BY DR. ROSENSTOCK

90. Dr. Rosenstock relies on additional references in his declaration that he states “provide POSITA with information regarding the state of the art as of ’462’s priority date.” EX2010 (Rosenstock Decl.) ¶¶ 114-156. I address these references below and throughout my declaration.

1. Knight (EX2005)

91. Dr. Rosenstock relies on a review article titled “Systematic Review of Animal Experiments Demonstrate Poor Contributions Toward Human Healthcare” by Andrew Knight (“Knight”), which he states was published in May 2008. *See* EX2010 (Rosenstock Decl.) ¶ 115.

92. Dr. Rosenstock relies on Knight to assert that skilled artisans would not have used animal models to predict outcomes in humans. *See* EX2010 (Rosenstock Decl.) ¶¶ 117-118, 356, 389, 405. I disagree with Dr. Rosenstock’s opinions regarding animal models for the reasons I set forth below. *See* ¶¶ 93-103, 317, 352 below.

93. Next to the author’s name there is an asterisk indicating to address correspondence to “Animal Consultants International.” EX2005 (Knight) at 1. It should be noted that at the time of the asserted priority dates, a POSA would have

known that in addition to being a veterinarian, Andrew Knight had published extensively advocating for animal welfare interests, including questioning the need for animal experimentation. For example, at the end of one of Andrew Knight's publications titled "The beginning of the end for chimpanzee experiments?" from 2008 it states "[a]bout the author":

London-based veterinarian Andrew Knight is the Director of Animal Consultants International [111], which provides multi-disciplinary expertise on animal issues. He founded the organization in 2004 to facilitate increased effectiveness of animal advocacy campaigns worldwide, via international skill-sharing. Andrew is interested in a range of bioethical issues, and has published a series of studies critically assessing the human clinical and toxicological utility of animal experimentation, and reviewing the use of non-animal methodologies, within fundamental research, toxicity testing and biomedical education.

EX1280 (Knight 2008) at 11.

94. Relying on Knight, Dr. Rosenstock opines "that animal models are frequently 'inconsistent with human outcomes' and thus results from animal testing do not indicate to POSITA that a particular medication (such as semaglutide) or dosing would have been expected to be reasonably likely to be safe, efficacious, and tolerable in humans." EX2010 (Rosenstock Decl.) ¶¶ 117-118; *see also id.* ¶¶ 356, 389, 405. I disagree with Dr. Rosenstock's opinion regarding animal models.

95. First, I note that the '462 patent claims do not require any particular level of efficacy or tolerability. *See* Section IV (Claim Construction) above.

96. Second, in my opinion, skilled artisans would have considered that the disclosures of Knight likely included or were influenced by the author's own personal bias due to Andrew Knight's background as a self-described animal advocate who questioned the utility of animal experimentation. In my opinion, skilled artisans would not have relied on Knight to understand how well data from animal models translates to human outcomes.

97. Third, skilled artisans would have known that while Knight addresses some disadvantages of translation of animal model data to humans generally, in the case of type 2 diabetes, type 2 diabetic animal models were regularly employed by skilled artisans for studying the effects of type 2 diabetes drugs in GLP-1 receptor agonist molecules.

98. For example, Knudsen 2010b, authored by Lotte Knudsen, "part of the team that discovered and developed liraglutide" (EX1066 (Knudsen 2010b) at 1), and sponsored by Novo Nordisk (*id.*), discussed the numerous animal models of diabetes and obesity relied on by skilled artisans in the field, including those at Novo Nordisk. *See id.* generally (discussing mouse models, rat models, minipig models used for analyzing the effects of liraglutide). Another example is Knudsen 2001, also sponsored by Novo Nordisk, which stated that "in a broad spectrum of animal

models [liraglutide] has been shown to lower blood glucose and body weight, and to increase or maintain β -cell mass. All the effects are consistent with the known physiological effects of GLP-1.” EX1031 (Knudsen 2001) at 6.

99. Other prior art also discussed the importance of animal models to the study of diabetes in humans. For example, Rees disclosed that “[a]nimal models have been used extensively in diabetes research.” EX1289 (Rees) at 1. Rees further discussed that a variety of new animal models were produced to study diabetes:

Apart from their use in studying the pathogenesis of the disease and its complications, all new treatments for diabetes, including islet cell transplantation and preventative strategies, are initially investigated in animals. In recent years, molecular biological techniques have produced a large number of new animal models for the study of diabetes, including knock-in, generalized knock-out and tissue-specific knockout mice.

Id.

100. Another example, Chatzigeorgiou, disclosed the “enormous” contributions that animal models have provided for the study of diabetes:

Animal models have enormously contributed to the study of diabetes mellitus, a metabolic disease with abnormal glucose homeostasis, due to some defect in the secretion or the action of insulin. They give researchers the opportunity to control in vivo the genetic and environmental factors that may influence the development of the

disease and establishment of its complications, and thus gain new information about its handling and treatment in humans.

EX1290 (Chatzigeorgiou) at 1.

101. In his own publications, Dr. Rosenstock has also relied on animal models of diabetic disease and their predictive information when translated to human disease. See, e.g., EX2062 (Rosenstock 2009) at 1 (“In nonclinical studies, albiglutide stimulated cAMP production through the GLP-1 receptor and induced insulin secretion from INS-1 cells in vitro and in animal models.”); EX1287 (Kendall) at 7 (“In animal models of diabetes and in insulin secretory cell lines, exenatide and GLP-1 reportedly improve β -cell function by increasing the expression of key genes involved in β -cell function, by increasing insulin biosynthesis and processing, and by augmenting β -cell mass through multiple mechanisms (18). Data obtained in animal and human studies also indicate that exenatide and GLP-1 reduce food intake, cause weight loss, and may have an insulin-sensitizing effect (18,27,32,33).”); EX1291 (Rosenstock 1986) at 12 (“In contrast, glomeruli myoinositol content was reduced in diabetic animals, and this fall was completely prevented by the drug. Note that the glomerular accumulation of protein in diabetic rates was also prevented with aldose-reductase inhibition, suggesting a role for this pathway in the genesis of diabetic nephropathy.”).

102. That diabetic animal models were frequently used by skilled artisans as investigative tools for human diabetes is confirmed by the '462 patent. For example, the '462 patent admits that “[t]he diabetic db/db mouse is one example of a suitable animal model, and the blood glucose lowering effect may be determined in such mice in vivo, e.g., as described in Assay (III), or as described in Example 43 of WO09/030738.” EX1001 ('462 patent) at 7:26-30. Moreover, similar to the prior art discussed above relying on animal models to study type 2 diabetes, the '462 patent relies on data obtained from animal models including minipigs, pigs, mice, and rats. *Id.* at 24:62-27:17.

103. As I stated in my First Declaration, in my opinion, a skilled artisan would have understood that prior to undergoing the semaglutide phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide to support safety, efficacy, and tolerability of semaglutide in humans. *See, e.g.*, EX1005 (First Decl.) ¶¶ 232, 260, 287; EX1047 (Tamimi) at 3; EX1066 (Knudsen 2010b) at 1.

2. Arrowsmith (EX2006)

104. Dr. Rosenstock relies on a review article titled “Phase II failures: 2008–2010” (“Arrowsmith”), which he states was published in May 2011. *See* EX2010

(Rosenstock Decl.) ¶ 119. Arrowsmith is a three paragraph, one page article. EX2006 (Arrowsmith) at 1.

105. Dr. Rosenstock relies on Arrowsmith to assert that skilled artisans would have been aware that phase II trials often fail. *See* EX2010 (Rosenstock Decl.) ¶¶ 119-122, 303-304, 323, 360, 392, 404, 415. I disagree with Dr. Rosenstock's opinions regarding the purported phase II failures disclosed in Arrowsmith for the reasons I set forth below. *See* ¶¶ 106-115, 274, 292, 323, 341, 350, 356 below.

106. Dr. Rosenstock relies on the disclosure in Arrowsmith that states: "Analysis by the Centre For Medicines Research (CMR) of projects from a group of 16 companies (representing approximately 60% of global R&D spending) in the CMR International Global R&D database reveals that the Phase II success rates for new development projects have fallen from 28% (2006-2007) to 18% (2008-2009), although these success rates do vary between therapeutic areas and between small molecules and biologics." EX2010 (Rosenstock Decl.) ¶ 121 (citing EX2006 (Arrowsmith) at 1).

107. Citing the Phase II failure rates in Arrowsmith, Dr. Rosenstock asserts that "POSITA would have been aware of these high failure rates as of the priority date of the '462 patent. POSITA would have understood, based on these failure rates, that the fact that a particular medication has been selected for testing in a Phase II trial, and that the basic information on the study design was reported in

ClinicalTrials.gov without yet results being available, does not mean POSITA would have found it reasonably likely on that basis that the trial would be successful in showing the tested medication is safe, efficacious, and tolerable.” EX2010 (Rosenstock Decl.) ¶ 122; *see also id* ¶¶ 303-304, 323, 360, 392, 404, 415.

108. I disagree with Dr. Rosenstock’s reliance on the purported low failure rates disclosed in Arrowsmith. In my opinion, a skilled artisan would not have been dissuaded from pursuing the once-weekly 1.0 mg semaglutide dose based on Arrowsmith because they would not have looked to Arrowsmith as a reliable source for understanding phase II clinical trial rate success for several reasons.

109. First, I note that the ’462 patent claims do not require any particular level of efficacy or tolerability. *See* Section IV (Claim Construction) above.

110. Second, Arrowsmith stated that the data relied upon by Dr. Rosenstock were generated by the Centre For Medicines Research (CMR) from the CMR International Global R&D database. EX2006 (Arrowsmith) at 1. But Arrowsmith does not indicate how and where CMR obtained its data, nor is there any indication of why or how the 16 companies were chosen for data analyses. Moreover, there is no indication in Arrowsmith how many trials were assessed from these 16 companies.

111. Third, there is no indication in Arrowsmith of how the stated “Phase II success rates for new development projects” of “28% (2006-2007) to 18% (2008-

2009)” correlate to the success rate of the total number of phase II trials for each given year. For example, as shown in Califf, the total number of phase 2 clinical trials registered between October 2007-September 2010 was 8484, which when divided by three to account for the three-year span, would have amounted to ~2800 phase II trials per year. EX1279 (Califf) at 6. Note that this number does not account for the phase 2 studies that were included in the total number of phase 1/2 trials (2105 trials) and total number of phase 2/3 trials (1055 trials) in Califf (*id.*); thus, the total number of phase 2 trials for each year would likely be even higher than ~2800. Regardless, skilled artisans would have been aware that Arrowsmith’s use of such a small sample size from only 16 companies compared to the total number of over ~2800 trials per year would likely lead to substantial bias in results. In my opinion, skilled artisans would not have relied on the results in Arrowsmith in regards to understanding purported phase II trial failures.

112. Fourth, there is no indication in Arrowsmith as to what criteria would have been considered for the reported “28% (2006-2007) to 18% (2008-2009)” phase II trials to be considered “successful” (EX2006 (Arrowsmith) at 1), such that the trials would move on to a phase III and not be considered a failure. For example, in another study disclosed in Arrowsmith analyzing 108 reported phase II failures from 2008 to 2010, the majority of the reasons for failure were due to “insufficient efficacy,” “strategic reasons,” or “not reported.” *Id.* For the failures that were

reported, only 20% were related to pharmacokinetics, bioavailability, or safety. Thus, skilled artisans would have understood that “failed” phase II clinical trials that did not move on to phase III reported in Arrowsmith could be due to reasons other than how well the drug is performing. For example, there could be strategic reasons that a drug does not move forward. Moreover, there is no discussion about what thresholds were used to determine what constitutes a failure due to efficacy, strategic, safety, and pharmacokinetics/bioavailability. In my opinion, skilled artisans would not have relied on the phase II success or failure rates disclosed in Arrowsmith when contemplating whether the semaglutide phase II trial “would be successful in showing the tested medication is safe, efficacious, and tolerable.” EX2010 (Rosenstock Decl.) ¶ 122. Indeed, Arrowsmith itself states that “it is difficult to draw conclusions from these data.” EX2006 (Arrowsmith) at 1.

113. Fifth, Arrowsmith does not identify any of the phase II trials it purports to analyze, much less that any of the phase II trials were related to diabetes. EX2006 (Arrowsmith) at 1. Similar to his reliance on animal models, Dr. Rosenstock looks to all phase II clinical trials generally without regard to what was known in the art about the success of phase II clinical trials for the treatment of diabetes. For example, skilled artisans would have been aware of the success of GLP-1 receptor agonist phase II trials for the treatment of type 2 diabetes, for example, those of liraglutide and exenatide. *See* EX1032 (Knudsen 2004) (discussing the completed phase 2 trials

of liraglutide); EX1012 (Lovshin) at 3 (disclosing that “the success of exenatide has accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration.”). Before the priority date, skilled artisans would have also been aware that Novo Nordisk reported that the NCT657 phase II study “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.” See EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12 (“Novo Nordisk very recently finalised a phase 2 study investigating safety and efficacy of five doses of semaglutide (NN9535), a once-weekly human GLP-1 analogue, versus placebo and open-label liraglutide add-on therapy in people with type 2 diabetes.... The 12-week multi-centre, multinational, double-blind, placebo-controlled, randomised dose-finding trial, which included a little more than 400 patients, demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.”).

114. Dr. Rosenstock further states that a skilled artisan would have been aware of numerous failed and withdrawn investigational once-weekly GLP-1 receptor agonists, such as taspoglutide, albiglutide, LY2428757, and CJC-1134-PC. See EX2010 (Rosenstock Decl.) ¶¶ 192-201. But as I discuss below, I disagree with Dr. Rosenstock’s characterization of at least two of these GLP-1 receptor agonists (taspoglutide and albiglutide) and skilled artisans would not have known about the

other GLP-1 receptor agonists purported failures because the documents cited by Dr. Rosenstock are post-priority date publications. *See* Section VII below.

115. As I stated in my First Declaration, in my opinion, the appreciation that several other agents were in development for once weekly dosing (e.g., EX1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. EX1005 (First Decl.) ¶¶ 68-73, 238, 266, 293. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would have been successful as a method for treating type 2 diabetes.

3. Novo Nordisk Annual Report 2010 (EX2065)

116. Dr. Rosenstock relies on the Novo Nordisk Annual Report 2010, which he states was published on February 1, 2011. *See* EX2010 (Rosenstock Decl.) ¶ 123.

117. Dr. Rosenstock relies on the Novo Nordisk Annual Report 2010 to assert that skilled artisans would have understood that the phase I and phase II semaglutide trials were “postponed” due to “unfavorable trial outcomes.” *See* EX2010 (Rosenstock Decl.) ¶ 127 (citing EX2065 (Novo Nordisk Annual Report 2010) at 26); *see also id.* ¶¶ 163-164, 336, 374, 377. For the reasons I discuss below, I disagree with Dr. Rosenstock's opinion about how skilled artisans would have

interpreted the Novo Nordisk Annual Report 2010 disclosures and the phase I and II semaglutide clinical trials. See ¶¶ 73, 118-128, 304, 330-331.

118. The Novo Nordisk Annual Report 2010 discloses that “Phase 3 initiation [of semaglutide] was postponed in June 2010 pending a long-acting portfolio development strategy decision.” EX2065 (Novo Nordisk Annual Report 2010) at 26. Dr. Rosenstock states that a “POSITA would have understood that this could have been due to unfavorable trial outcomes in the then-completed Phase I and Phase II trials of semaglutide and thus would not have expected that the (untested) 1.0 mg dose would have been successful as Dr. Bantle asserts.” EX2010 (Rosenstock Decl.) ¶ 127 (emphasis omitted). I disagree with Dr. Rosenstock’s assessment of the Novo Nordisk Annual Report 2010.

119. First, the statement that “Phase 3 initiation [of semaglutide] was postponed in June 2010” is in a table under the heading “Pipeline overview,” and a sentence stating “[t]his overview illustrates key development activities, including entries into the pipeline and progression of development compounds.” EX2065 (Novo Nordisk Annual Report 2010) at 26. In my opinion, this indicates that there were further expectations of developing the listed compounds in the table (i.e., Degludec, DegludecPlus, Semaglutide, NN9068, NN1218, NN1952, NN9924, Liraglutide), which is why the statement for semaglutide includes the phrase “. . . pending a long-acting portfolio development strategy decision.” *Id.* This indicates

that Phase 3 of semaglutide was not to be discontinued, but that Novo Nordisk was in an evaluation stage of its long-acting GLP-1 receptor agonist portfolio. If the semaglutide phase I and II trials had “unfavorable trial outcomes” as Dr. Rosenstock suggests, semaglutide would likely no longer be listed in the “Pipeline overview” section or Novo Nordisk could have listed it as “failed,” “discontinued,” or “closed” as it had done with other drugs. See EX1131 (Novo Nordisk SEC Filing (2011)) at 16 (“Oral GLP-1 project, NN9925, closed [a]fter review of phase 1 data” . . . “Obesity project, NN9161, closed [d]ue to an unfavourable benefit-risk profile observed during the phase 1 trial”).

120. That Novo Nordisk was continuing to actively investigate semaglutide was further confirmed by other available prior art. For example, skilled artisans would have been aware that the phase II NCT657 trial was successful based on Novo Nordisk’s public disclosure:

Novo Nordisk very recently finalised a phase 2 study investigating safety and efficacy of five doses of semaglutide (NN9535), a once-weekly human GLP-1 analogue, versus placebo and open-label liraglutide add-on therapy in people with type 2 diabetes. At study start, patients were treated with metformin or controlled with diet and exercise. *The 12-week multi-centre, multinational, double-blind, placebo-controlled, randomised dose-finding trial*, which included a little more than 400 patients, *demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide*. Semaglutide

was generally well tolerated and was not associated with an increase in injection site reactions, antibody formation or calcitonin levels. After more detailed analysis of the dose-response findings on efficacy and safety, Novo Nordisk will discuss the future plans for semaglutide development with regulatory authorities before initiation of phase 3 development.

EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12 (emphasis added).

121. Moreover, captures of the Novo Pipeline on August 19, 2010, November 25, 2010, and January 27, 2011 reported that “[s]emaglutide (NN9535) is a once weekly human GLP-1 analogue, which is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin, and additionally lowers body weight. The phase 2 programme including more than 400 people was completed in 2009. EX1283 (Novo Pipeline) at 1-3. And as of at least July 26, 2010, Novo Nordisk provided information about “[a] once weekly human GLP-1 analogue, semaglutide (NN9535, Novo Nordisk) (see Table 3), ... currently being developed for the treatment of [type 2 diabetes]. Semaglutide recently completed phase 2 clinical trials involving more than 400 people.” See EX1284 (Marre) at 5 (citing Novo Pipeline status as of July 26, 2010).

122. Another reference published in 2010, Bhansali, also reported that semaglutide was in active development by Novo Nordisk and that the phase 2 program was completed:

Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin and lowers body weight. The phase 2 programme with more than 400 people was completed in 2009.

EX1137 (Bhansali) at 4.

123. In my opinion, these references further confirm that skilled artisans would not have understood that there were “unfavorable outcomes” in the phase I and II semaglutide trials.

124. That the phase III semaglutide initiation was postponed due to Novo Nordisk evaluating the GLP-1 long-acting portfolio was further confirmed by a February 2, 2012 Novo Nordisk’s earnings call.⁴ EX1285 (Novo Nordisk Earnings Call (Feb. 2, 2012)) at 5. In particular, on the earnings call, Mads Krogsgaard

⁴ My opinion that the claims of the ’462 patent are anticipated and obvious does not require the disclosures of the Novo Nordisk February 2, 2012 Earnings Call Transcript (EX1285). Exhibit 1285 merely confirms the other prior art set forth in my First Declaration and this declaration.

Thomsen, Executive Vice President and Chief Science Officer of Novo Nordisk provided an update on Novo Nordisk's diabetes portfolio stating "Finally, once weekly Semaglutide is ready for the Phase III [indiscernable] decision once its profile could be compared up against the Liraglutide clinical data emerging later this half prior to the selection of which once-weekly GLP-1 compound to develop from Phase III." *Id.* at 4-5. This confirms that Novo Nordisk was evaluating the strategy moving forward with once-weekly GLP-1 receptor agonists.

125. Later in the earnings call, a representative of Carnegie Investment bank asked the following question to Mads Thomsen:

Just 2 questions here to start off with. One for, first one for Mads, on your long-acting Victoza or Semaglutide, and why you are now starting the Phase I trial with the LA [long-acting] Victoza. Does this mean that you are closer to making a decision about which one of these moleculars [sic] you'll work on going forward? And also in that relation, will you skip Phase II and go directly into Phase III, when you have complete Phase I trials?

Id. at 13.

126. Mads Thomsen responded:

Right. *As regards new molecule, namely Semaglutide, first of all we'll be announcing the long-awaited Phase II data at conferences this year.* That being said, of course, we've also kind of shaped up the molecule *in preparation of this decision as to whether this one goes into Phase*

III or the Liraglutide depot formulation receives further development. Semaglutide will be ready for entering Phase III with a highly competitive profile, whereas Liraglutide depot, we simply don't know yet. And that's the whole dilemma, that we're getting to new clinical data later in this first half of the year, and then they will enable management come summertime to make a decision of which one to enter into final development.

Id. at 13 (emphasis added).

127. Thus, it is clear that Novo Nordisk was evaluating whether to move forward with its long-acting semaglutide or a long-acting liraglutide formulation, which is in line with the Novo Nordisk Annual Report 2010 disclosing that “Phase 3 initiation [of semaglutide] was postponed in June 2010 pending a long-acting portfolio development strategy decision.” EX2065 (Novo Nordisk Annual Report 2010) at 26. Moreover, Mads Thomsen stated “[s]emaglutide will be ready for entering Phase III with a highly competitive profile” (EX1285 at 13), which would further confirm that a skilled artisan would not have thought that there were “unfavorable trial outcomes in the then-completed Phase I and Phase II trials of semaglutide” as Dr. Rosenstock suggests. EX2010 (Rosenstock Decl.) ¶ 127.

128. The Novo Nordisk Annual Report 2011⁵ further confirms that skilled artisans would have understood that there were no unfavorable outcomes from the phase II semaglutide trials. EX1130 (Novo Nordisk Annual Report 2011). For example, the Novo Nordisk Annual Report 2011 reported that “[o]ur late-stage GLP-1 pipeline includes two new treatments, a fixed combination of Victoza with Degludec, which may offer the benefits of both compounds in a convenient solution, and a novel once-weekly GLP-1 analogue, semaglutide.” *Id.* at 21. Later in the report under the heading “Pipeline overview” it is disclosed that the semaglutide once-weekly GLP-1 analogue phase 2 is “completed.” *Id.* at 28. Thus, skilled artisans would have understood that the phase II semaglutide study was completed and that Novo Nordisk’s pipeline included the once-weekly semaglutide treatment.

4. Report on the Deliberation Results (EX2067)

129. Dr. Rosenstock relies on an English-language version of a report titled “Report on the Deliberation Results” of the Japanese Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, related to the drug “Victoza

⁵ My opinion that the claims of the ’462 patent are anticipated and obvious does not require the disclosures of the Novo Nordisk Annual Report 2011 (EX1130). Exhibit 1130 merely confirms the other prior art set forth in my First Declaration and this declaration.

Subcutaneous Injection 18 mg” (“Report on the Deliberation Results”), which Dr. Rosenstock states was published on December 3, 2009. *See* EX2010 (Rosenstock Decl.) ¶¶ 128-130.

130. Dr. Rosenstock states that “even to the extent it is assumed POSITA would have relied on information about liraglutide to inform semaglutide dosing decisions (as Dr. Bantle and Dr. Jusko contend), POSITA would have seen that it is often the case that in certain populations, such as Japanese people, dosing of GLP-1 receptor agonists must be reduced to account for potential tolerability issues.” EX2010 (Rosenstock Decl.) ¶ 130.

131. As I discuss above with respect to Seino (EX1038), in my opinion, skilled artisans would have been aware of potential drug metabolism differences that may occur between different populations of patients and the need for potential dose adjustment but should have still been able to estimate the semaglutide doses in the general patient population. *See* Section VI.A.7 above.

132. Moreover, my reliance on liraglutide for semaglutide dosing is based on liraglutide’s classic, sigmoidal dose/response profile for lowering HbA1c shown in Seino. *See* EX1038 (Seino) at 4, Fig. 1. This would be relevant whether the patients were Japanese or Caucasian. As I discuss above and in my First Declaration, “because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect

a similar dose response relationship for lowering HbA1c.” EX1005 (First Decl.) ¶ 293; Section VI.A.7 above. Further, despite the structural differences between liraglutide and semaglutide, in my opinion, “the animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., EX1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA1c in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau.” *Id.* Thus, my opinion is not that liraglutide and semaglutide would have had the same dose response curves as Dr. Rosenstock states. In my opinion, semaglutide would exhibit a similar overall shaped dose response curve as liraglutide, i.e., a classic, sigmoidal dose/response profile for lowering HbA1c, and thus a skilled artisan would have reasonably expected to see increases in efficacy with increasing doses of semaglutide. *See, e.g.,* EX1005 (First Decl.) ¶¶ 70-73, 85-86, 238.

133. Further, the ’462 patent claims are not limited to any particular population, including race or nationality. In my opinion, it would have been reasonable for skilled artisans to have relied on information from a specific

population (e.g., Japanese patients) to pursue a once weekly 1.0 mg semaglutide dose for treating type 2 diabetes.

5. Kim (EX2066)

134. Dr. Rosenstock relies on a journal article titled “Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms” by Kiman Kim and coauthors (“Kim”), which Dr. Rosenstock states was published in October 2004. *See* EX2010 (Rosenstock Decl.) ¶¶ 131-135.

135. Dr. Rosenstock relies on statements in Kim regarding differences in metabolism between East Asians and Caucasians to support his argument that a POSA would have known that variability amongst ethnic groups “can cause unexpected outcomes such as therapeutic failure, adverse effects, and toxicity.” EX2010 (Rosenstock Decl.) ¶ 410; *see* EX2010 (Rosenstock Decl.) ¶¶ 133-135.

136. But although Kim discusses differences between East Asians and Caucasians, it does not specifically disclose how ethnic factors may impact the effect of GLP-1 receptor agonists, such as semaglutide. *See* EX2066 (Kim). Moreover, as I discussed above with respect to Seino (EX1038) and Report on the Deliberation Results (EX2067), in my opinion, overall trends and results from studies in one particular population (e.g., Japanese or Caucasian) would have been instructive to skilled artisans when considering the general patient population. *See* Sections VI.A.7, VI.B.4 above. Further, the ’462 patent claims are not limited to any

particular population, including race or nationality. In my opinion, it would have been reasonable for skilled artisans to have relied on information from a specific population (e.g., Japanese patients) to pursue a once weekly 1.0 mg semaglutide dose for treating type 2 diabetes.

6. Rosenstock 2009 (EX2062)

137. Dr. Rosenstock relies on a journal article titled “Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes,” by Dr. Rosenstock and other co-authors (“Rosenstock 2009”), which Dr. Rosenstock states was published in October 2009. EX2010 (Rosenstock Decl.) ¶ 136.

138. Dr. Rosenstock relies on Rosenstock 2009 to assert that skilled artisans would have known about the tolerability issues with once-monthly dosing with albiglutide and would have been dissuaded from pursuing the once weekly semaglutide dose. See EX2010 (Rosenstock Decl.) ¶¶ 89, 136-141, 198, 353. I disagree with Dr. Rosenstock’s opinions regarding tolerability of albiglutide for the reasons I set forth below. See ¶¶ 75, 139-143, 172-173 below.

139. Rosenstock 2009 reported results from a randomized controlled trial of patients with type 2 diabetes who “received subcutaneous placebo or albiglutide (weekly [4, 15, or 30 mg], biweekly [15, 30, or 50 mg], or monthly [50 or 100 mg]) or exenatide twice daily ... over 16 weeks.” EX2062 (Rosenstock 2009) at 1. Rosenstock 2009 reported that “[t]he incidence of gastrointestinal adverse events in

subjects receiving albiglutide 30 mg weekly was less than that observed for the highest biweekly and monthly doses of albiglutide or exenatide.” *Id.* at 1. The highest biweekly and monthly doses of albiglutide were 50 mg and 100 mg, respectively. *Id.* at Table 1. Rosenstock 2009 stated:

In conclusion, albiglutide improved glucose control in a dose-dependent manner when given weekly and biweekly. Higher monthly doses of albiglutide were efficacious, but their use was constrained by the higher frequency of GI-related adverse events. *Weekly albiglutide significantly improved glycemic control with an acceptable safety and tolerability profile and modest weight loss without increasing the risk of hypoglycemia or immunological response in subjects with type 2 diabetes.* Future studies may elucidate whether titration dosing or biweekly scheduling could be options for patients who respond to and tolerate the initial weekly regimen.

Id. at 6 (emphasis added). Thus, as Rosenstock 2009 stated, once-weekly albiglutide demonstrated an acceptable safety and tolerability profile.

140. Dr. Rosenstock focuses on the statement that the higher biweekly and monthly doses of albiglutide were “constrained,” and states a “POSITA would have known about the tolerability issues with once-monthly albiglutide reported by Rosenstock 2009. POSITA would have also known this was the case despite albiglutide’s long half-life of about 5 days (reported by Rosenstock 2009), thus contradicting Dr. Bantle’s and Dr. Jusko’s broad generalizations that a GLP-1

analogue with a longer half-life will reduce nausea and vomiting.” EX2010 (Rosenstock Decl.) ¶ 141 (citing EX1003 (Bantle Decl.), ¶ 323; EX1005 (First Decl.), ¶ 81). I disagree.

141. In my opinion, Rosenstock 2009 supports that skilled artisans would have been motivated to pursue a once-weekly dose of semaglutide and that the benefit of the once-weekly dosing is that “[n]ausea may be best avoided by a long half-life” as I stated in my First Declaration. *See, e.g.*, EX1005 (First Decl.) ¶ 81. Although the monthly 100 mg and biweekly 50 mg doses of albiglutide were “constrained by the higher frequency of GI-related adverse events,” these doses were 70 and 20 mgs higher, respectively, than the 30 mg once-weekly doses of albiglutide. Thus, skilled artisans would have understood the tolerability issues seen with albiglutide were due to a much higher dose as stated in Rosenstock 2009 and would not have been concerned with tolerability of once-weekly GLP-1 receptor agonists generally. Indeed, Rosenstock 2009 taught that the once weekly albiglutide dose had an “acceptable safety and tolerability profile.” EX2062 (Rosenstock 2009) at 6.

142. Moreover, Rosenstock 2009 reported that “[a]n escalating-dose titration for the biweekly regimen might have resulted in a lower frequency of GI [gastrointestinal] events.” EX2062 (Rosenstock 2009) at 6. Rosenstock 2009 also stated that one of the weaknesses of the albiglutide trial was that “no escalating doses were tested for biweekly and monthly dosing, which may have attenuated GI adverse

events and FPG [fasting plasma glucose] fluctuations.” *Id.* Therefore, in my opinion skilled artisans would have understood that escalating doses, such as the titration scheme used in the phase I (NCT773) and phase II (NCT657) studies would help mitigate GI side effects. Thus, in contrast to Dr. Rosenstock’s opinion, skilled artisans would not be concerned by Rosenstock 2009’s disclosure that the higher doses of albiglutide were “constrained by the higher frequency of GI-related adverse events.”

143. Thus, skilled artisans would not have been concerned about potential tolerability issues with GLP-1 receptor agonists in view of Rosenstock 2009 but would have been further motivated with a reasonable expectation of success to pursue a once-weekly dose of semaglutide based on the positive once-weekly reports of albiglutide reported in Rosenstock 2009.

7. Madsbad 2004 (EX2075)

144. Dr. Rosenstock relies on a journal article titled “Improved Glycemic Control With No Weight Increase in Patients With Type 2 Diabetes After Once-Daily Treatment With the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)” coauthored by Madsbad and others, which Dr. Rosenstock states was published in June 2004. EX2010 (Rosenstock Decl.) ¶ 142.

145. Dr. Rosenstock relies on Madsbad 2004 to assert that skilled artisans would have known that liraglutide in the dose finding phase II study in Madsbad

2004 purportedly did not include the highest liraglutide dose for efficacy and weight loss. See EX2010 (Rosenstock Decl.) ¶¶ 143-148, 228, 322, 357, 361, 370. As I discuss below, I disagree with Dr. Rosenstock's opinions regarding how skilled artisans would have interpreted the results of the phase II liraglutide study in Madsbad. See ¶¶ 146-157, 291, 319, 329 below.

146. Madsbad 2004 was a 12-week, double-blind, randomized, controlled trial that assessed the efficacy and safety of liraglutide treatment in type 2 diabetic patients. EX2075 (Madsbad 2004) at 1. "Patients were randomly assigned to one of six fixed-dosage groups of liraglutide (0.045, 0.225, 0.45, 0.60, or 0.75 mg), placebo, or open-label sulfonylurea (glimepiride, 1-4 mg)." *Id.* "The primary end point was HbA_{1c} after 12 weeks; secondary end points were fasting serum glucose, fasting C-peptide, fasting glucagon, fasting insulin, β -cell function, body weight, adverse events, and hypoglycemic episodes." *Id.*

147. Madsbad 2004 reported that "HbA_{1c} decreased in all but the lowest liraglutide dosage group." *Id.* Madsbad reported that for the 0.45-mg liraglutide dosage group, "a statistically significant decrease, compared with placebo was observed" (*id.* at 4), but that "treatment with liraglutide caused no weight increase." *Id.* at 6. Madsbad 2004 stated "[t]he full dosage-response curve for liraglutide remains to be elucidated, and future trials will investigate higher dosages of drug, but the current trial confirmed the proposed once-daily dosing regimen for

liraglutide.” *Id.* at 6. Madsbad concluded “[t]his trial was the first to demonstrate a sustained improvement in glycemic control after long-term treatment with the GLP-1 analog liraglutide, administered once daily.” *Id.* at 5. “[T]he long-acting GLP-1 analog liraglutide shows considerable promise as a once-daily therapy in type 2 diabetes for lowering blood glucose without weight gain or substantial risk of hypoglycemia.” *Id.* at 6.

148. Dr. Rosenstock states that “contrary to Dr. Bantle and Dr. Jusko’s broad generalizations that any dose-ranging study would have been expected to test the *optimal* doses of a given candidate drug, Madsbad 2004 failed to do so with liraglutide as to both glycemic control and weight.” EX2010 (Rosenstock Decl.) ¶ 146 (emphasis in original). First, Dr. Rosenstock provides no citation so it is unknown what portion of my testimony he is referencing. In my First Declaration I explained that phase I and phase II dose ranging studies include selecting doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 255, 261, 282, 284, 287; EX1047 (Tamimi) at 3-4; EX1048 (FDA Exposure Response 2003) at 7; EX1049 (ICH 1994) at 1-2, 4, 6; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

149. In my opinion, the results reported in Madsbad 2004 are consistent with my opinion from my First Declaration about dose-ranging studies. In particular,

Madsbad 2004 reported that the dosages in the study “were chosen based on observations from previous trials.” EX2075 (Madsbad 2004) at 2. Madsbad 2004 explained that in one of those studies a single dose (corresponding to ~0.80 mg) “showed significant effects on glycemia, but 2 of 11 patients reported nausea.” *Id.* “Further, once daily dosing for 7 days showed a 40% increase in $C_{\max}$ in the steady state.” *Id.* Madsbad 2004 reported, “[t]herefore to avoid causing unacceptable side effects, the highest dosage included in this trial was 0.75 mg.” *Id.* “The lowest dosage of 0.045 mg was considered too low to have any significant effect on glycemic control.” *Id.*

150. Thus, as Madsbad 2004 explained, the range of doses tested (0.045, 0.225, 0.45, 0.60, or 0.75 mg liraglutide) in the study were based on knowledge from previous studies. The highest dose tested, 0.75 mg, was chosen because a prior study showed that a dose of ~0.80 mg resulted in “significant effects on glycemia” but patients reported side effects. EX2075 (Madsbad 2004) at 2.

151. Moreover, the primary end-point in the Madsbad 2004 study was HbA_{1c} after 12 weeks, “body weight” was only one of seven other listed secondary endpoints. EX2075 (Madsbad 2004) at 1. Madsbad 2004 reported that “ HbA_{1c} decreased in all but the lowest liraglutide dosage group” and “[t]reatment with the two highest dosages reduced HbA_{1c} significantly more than placebo.” EX2075 (Madsbad 2004) at 3.

152. Therefore, the Madsbad 2004 study included selecting doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects, which is consistent with my First Declaration. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 255, 261, 282, 284, 287.

153. Dr. Rosenstock states that liraglutide was later shown to cause weight loss at higher doses and greater glycemic control at those higher doses (EX2010 (Rosenstock Decl.) ¶ 146), but those higher doses of liraglutide were later used with a titration scheme to reduce the side effects caused by the dose. EX1039 (Victoza label) at 2 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose “to reduce gastrointestinal symptoms during initial titration”).

154. The doses in Madsbad did not include a titration scheme, therefore, the doses used in Madsbad were chosen because they included the most effective doses with the least side effects, consistent with my description of a dose-response study. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 255, 261, 282, 284, 287.

155. Dr. Rosenstock states that “that the study [Madsbad 2004] did not show weight loss would have been considered a failure.” EX2010 (Rosenstock Decl.) ¶ 146. I disagree. The primary end-point in the Madsbad 2004 study was HbA_{1c} after 12 weeks and “body weight” was only one of seven other listed secondary endpoints. EX2075 (Madsbad 2004) at 1. Madsbad 2004 reported that “HbA_{1c} decreased in all

but the lowest liraglutide dosage group” and “[t]reatment with the two highest dosages reduced HbA1c significantly more than placebo.” EX2075 (Madsbad 2004) at 3. In my opinion, skilled artisans would not have considered Madsbad 2004 to be a failure. Indeed, Dr. Rosenstock’s conclusion is inconsistent with that of the authors: “In conclusion, the long-acting GLP-1 analog liraglutide shows considerable promise as a once-daily therapy in type 2 diabetes for lowering blood glucose without weight gain or substantial risk of hypoglycemia.” *Id.* at 6.

156. As I discussed in my First Declaration, information about other GLP-1 receptor agonists, such as liraglutide, helped inform a skilled artisan about semaglutide. For example, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.*, EX1039 (Victoza label) at 2 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose “to reduce gastrointestinal symptoms during initial titration.”). Thus, a skilled artisan would have been motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the semaglutide clinical trials (NCT657 and NCT773), to provide effective treatment without unwanted side effects.

157. Dr. Rosenstock lists differences between liraglutide and semaglutide, of which skilled artisans would have been aware. EX2010 (Rosenstock Decl.) ¶ 148. Dr. Rosenstock states that I “admitted that liraglutide and semaglutide are different molecules with significant structural differences,” but this is an incorrect description

of my deposition testimony. *Id.* (citing EX2019⁶ (Jusko Tr.) at 54:22-55:5, 95:6-20); *see also id.* ¶ 364. It is Dr. Rosenstock who described the differences between liraglutide and semaglutide as being “significant,” not me. *Id.* ¶ 148 (stating “[l]iraglutide and semaglutide also had other significant differences.”); *see also id.* ¶¶ 147, 364. During my deposition I stated that liraglutide has “different pharmacokinetic properties” compared to semaglutide. EX2019 (Jusko Tr.) at 54:22-55:5. I also discussed the difference between liraglutide and semaglutide’s fatty acid side chains, but I did not describe this difference as being “significant.” *Id.* at 95:6-20.

158. In my First Declaration I opined that “a skilled artisan would have a strong scientific basis to expect a similar dose response relationship for lowering HbA1c” as liraglutide’s classic, sigmoidal dose/response profile for lowering HbA1c. *See, e.g.,* EX1005 (First Decl.) ¶¶ 238, 266, 293. Despite any structural differences between liraglutide and semaglutide, in my opinion, “the animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., EX1012 (Lovshin)

⁶ Dr. Rosenstock cites “EX2018 (Jusko Tr.)” but it is my understanding that the transcript from my January 5, 2024 deposition was submitted as EX2019.

at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA1c in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau.” EX1005 (First Decl.) ¶¶ 238, 266, 293.

8. Nordqvist (EX2061)

159. Dr. Rosenstock relies on a media report in Medical News Today titled “Experimental Diabetes Drug Taspoglutide Late-Stage Trials Suspended” written by Christian Nordqvist (“Nordqvist”), which Dr. Rosenstock states was published on September 13, 2010. EX2010 (Rosenstock Decl.) ¶ 149.

160. Dr. Rosenstock relies on Nordqvist to assert that skilled artisans would have known that taspoglutide was a purported failed GLP-1 receptor agonist. *See* EX2010 (Rosenstock Decl.) ¶¶ 87-88, 150-156, 195, 349-350, 360. As I discuss below, I disagree with Dr. Rosenstock’s opinions regarding how skilled artisans would have interpreted the disclosure of Nordqvist. *See* ¶¶ 161-171, 323 below.

161. Nordqvist stated that :

Experimental diabetes drug, taspoglutide, a joint development between Roche (Switzerland) and Ipsen (France), had its late-stage trials suspended because of side effects. Roche announced that it had stopped giving patients taspoglutide because of adverse gastrointestinal reactions. The drug already has some “*hypersensitivity problems.*”

The Swiss pharmaceutical company says it is not abandoning taspoglutide. In an announcement the company said it is considering a reformulation of the medication. However, any kind of reformulation will most likely result in a significant delay in the approval process and date.

* * *

These discontinuation rates compromise interpretation of the long-term safety data from the T-emerge studies, therefore continuing treatment with the current taspoglutide formulation is not considered to be in the best interest of patients.

EX2061 (Nordqvist) at 1, 3 (emphasis in original).

162. Based on Nordqvist, a skilled artisan would have understood that the taspoglutide trials were discontinued not because of the drug itself, but because of a concern with the formulation. In my opinion, a skilled artisan reading Nordqvist would not be concerned about tolerability issues with GLP-1 receptor agonists as Dr. Rosenstock asserts but would have understood that something other than taspoglutide in the formulation was resulting in tolerability issues. Indeed, Nordqvist stated “[t]he Swiss pharmaceutical company says it is not abandoning taspoglutide.” EX2061 (Nordqvist) at 1.

163. Dr. Rosenstock states that the results discussed in Nordqvist were reported in a later publication titled “The Fate of Taspoglutide, a Weekly GLP-1 Receptor Agonist, Versus Twice-Daily Exenatide for Type 2 Diabetes”

(“Rosenstock 2013,” EX2060), which Dr. Rosenstock states was published in March 2013. EX2010 (Rosenstock Decl.) ¶ 154. But Rosenstock 2013 was not published until 2013, which I understand means that Rosenstock 2013 is not prior art to the ’462 patent. Thus, a skilled artisan would not have had knowledge of Rosenstock 2013 at the priority date. Dr. Rosenstock does not assert that Rosenstock 2013 should be considered to be prior art to the ’462 patent.

164. Regardless, Rosenstock 2013 confirms that it was something in the “taspoglutide formulation” that lead to nausea and vomiting stating:

The greater proportion of taspoglutide-treated patients who experienced nausea and/or vomiting compared with exenatide may reflect pharmacokinetic differences between once-weekly and twice-daily formulations, as episodes tended to occur more frequently on the day of injection for taspoglutide, which is probably related to the initial higher maximum plasma concentration of taspoglutide, *an effect that may be related to the specific nature of the taspoglutide formulation tested* (data not shown).

EX2060 (Rosenstock 2013) at 5-6 (emphasis added).

165. This confirms that skilled artisans would have understood that the taspoglutide *formulation* resulted in the tolerability issues, not the drug itself, and would not have been dissuaded from pursuing the once-weekly 1.0 mg semaglutide dose for treating type 2 diabetes.

VII. PURPORTED FAILED AND WITHDRAWN GLP-1 RECEPTOR AGONISTS

166. Dr. Rosenstock states that I “provide an incomplete overview of the literature regarding GLP-1 RAs” by “omitting to address the numerous failed investigational once-weekly GLP-1 RAs” discussed in the references upon which we rely. EX2010 (Rosenstock Decl.) ¶ 192. I disagree. As I discuss below, skilled artisans would have understood that taspoglutide had a tolerability issue because of the formulation, not the drug; albiglutide was not a failed study; and skilled artisans would not have known about the other GLP-1 receptor agonist purported failures because the documents cited by Dr. Rosenstock are post-priority date publications. Moreover, skilled artisans would have been aware of the success of liraglutide, a once-weekly GLP-1 receptor agonist, in addition to the phase I and II semaglutide clinical trials being pursued by Novo Nordisk, and would not have been dissuaded by the other GLP-1 receptor agonists as Dr. Rosenstock suggests.

167. Dr. Rosenstock focuses on several of the GLP-1 receptor agonists that he states “were ‘being investigated’ for once-weekly administration but were either never approved or were withdrawn from the market after approval.” EX2010 (Rosenstock Decl.) ¶ 193 (citing EX1012 (Lovshin) at Table 1); *see also id.* Section VI.G.

168. Dr. Rosenstock first focuses on taspoglutide, citing Rosenstock 2013 and stating that “Phase III trials of taspoglutide were terminated and development was abandoned due to ‘unacceptable levels of nausea/vomiting, injection-site reactions, and systemic allergic reactions.’” EX2010 (Rosenstock Decl.) ¶ 194 (citing EX2060 (Rosenstock 2013) at 1). But as I discussed above in Section VI.B.6, Dr. Rosenstock states that Rosenstock 2013 was not published until March 2013, which I understand means that Rosenstock 2013 is not prior art to even the latest alleged priority date of the ’462 patent (July 1, 2012). Dr. Rosenstock states that he was “personally involved in this Phase III trial and observed the significant side effects that trial subjects experienced.” EX2010 (Rosenstock Decl.) ¶ 194. However, the skilled artisan would not have been aware of the Phase III trial results that Dr. Rosenstock personally observed or that were reported in Rosenstock 2013.

169. Relying on Nordqvist, Dr. Rosenstock states that “POSITA would have been well aware of this prior to the ’462 patent, as Roche (the sponsor of the study) had ‘announced that it had stopped giving patients taspoglutide because of adverse gastrointestinal reactions.’” EX2010 (Rosenstock Decl.) ¶ 195 (quoting EX2061 (Nordqvist) at 1). As I discussed above in Section VI.B.8, a skilled artisan reading Nordqvist would have understood that the taspoglutide trials were discontinued not because of the drug itself, but because of a concern with the formulation. In my opinion, a skilled artisan reading Nordqvist would not have been concerned about

tolerability issues with GLP-1 receptor agonists as Dr. Rosenstock asserts but would have understood that something other than taspoglutide in the formulation was resulting in tolerability issues. Indeed, Nordqvist stated “[t]he Swiss pharmaceutical company says it is not abandoning taspoglutide.” EX2061 (Nordqvist) at 1. And although it should not be considered prior art, as I stated above in Section VI.B.8, Rosenstock 2013 confirms that the taspoglutide formulation tolerability issues seen in the Phase III trial were due to “an effect that may be *related to the specific nature of the taspoglutide formulation* tested,” not taspoglutide itself. EX2060 (Rosenstock 2013) at 6 (emphasis added).

170. Without providing any citation, Dr. Rosenstock states that “[d]evelopment of taspoglutide was eventually abandoned.” EX2010 (Rosenstock Decl.) ¶ 195. That taspoglutide was eventually abandoned would not have been known to a skilled artisan as of any of the invention or priority dates asserted by Novo Nordisk, and Dr. Rosenstock provides no citation to any prior art (or any art) that supports this statement. As Nordqvist stated “[t]he Swiss pharmaceutical company says it is not abandoning taspoglutide.” EX2061 (Nordqvist) at 1.

171. Thus, Dr. Rosenstock’s statement that “[t]his information—which would have been known to a POSITA—is inconsistent with Dr. Bantle and Jusko’s opinions that semaglutide . . . would have been expected to be ‘be [sic] ‘safe and

efficacious,”” is incorrect. EX2010 (Rosenstock Decl.) ¶ 196 (citing EX1003 (Bantle Decl.), ¶ 326; EX1005 (First Decl.), ¶ 228).

172. Dr. Rosenstock next discusses albiglutide, another GLP-1 receptor agonist cited in Lovshin Table 1. EX2010 (Rosenstock Decl.) ¶ 197 (citing EX1012 (Lovshin) at Table 1). Dr. Rosenstock focuses on the tolerability issues seen with the higher doses for the monthly and biweekly doses of albiglutide disclosed in Rosenstock 2009 and states that these results “contradict . . . Dr. Bantle’s and Dr. Jusko’s broad generalizations that a GLP-1 analogue with a longer half-life will reduce nausea and vomiting.” EX2010 (Rosenstock Decl.) ¶ 198 (citing EX1003 (Bantle Decl.) ¶ 329 and EX1005 (First Decl.) ¶ 266). But as I discussed above, although the monthly 100 mg and biweekly 50 mg doses of albiglutide were “constrained by the higher frequency of GI-related adverse events,” these doses were 70 and 20 mgs higher, respectively, than the 30 mg once-weekly doses of albiglutide. See Section VI.B.6 above. Thus, skilled artisans would have understood the tolerability issues seen with albiglutide were due to a much higher dose and would not be concerned with GLP-1 receptor agonist tolerability generally. *Id.* Indeed, Rosenstock 2009 teaches that the once weekly albiglutide dose had an “acceptable safety and tolerability profile.” EX2062 (Rosenstock 2009) at 6.

173. Moreover, as I discussed above, Rosenstock 2009 reported that “[a]n escalating-dose titration for the biweekly regimen might have resulted in a lower

frequency of GI [gastrointestinal] events.” *Id.* Rosenstock 2009 also discussed that one of the weaknesses of the albiglutide trial was that “no escalating doses were tested for biweekly and monthly dosing, which may have attenuated GI adverse events and FPG [fasting plasma glucose] fluctuations.” *Id.* Therefore, in my opinion skilled artisans would understand that escalating doses, such as the titration scheme used in the phase I (NCT773) and phase II (NCT657) studies would help mitigate GI side effects. Thus, in contrast to Dr. Rosenstock’s opinion, skilled artisans would not have been discouraged by Rosenstock 2009’s disclosures from pursuing the 1.0 mg semaglutide weekly dose for treating type 2 diabetes.

174. Therefore, as I stated in my First Declaration, in my opinion, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., EX1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA1c in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. *See* EX1005 (First Decl.) ¶¶ 238, 266, 293. Rosenstock 2009’s teaching that “[w]eekly albiglutide significantly improved glycemic control with an acceptable safety and tolerability profile and modest weight loss without increasing the risk of hypoglycemia or immunological response in subjects with type 2 diabetes” provides even further

motivation and reasonable expectation of success for skilled artisans to pursue the 1.0 mg semaglutide weekly dose for treating type 2 diabetes.

175. Dr. Rosenstock references my opinion that skilled artisans would have appreciated from Lovshin Table 1 that other GLP-1 receptor agonists were in development for once-weekly administration and therefore a skilled artisan would have expected consistency in responses between liraglutide and semaglutide. EX2010 (Rosenstock Decl.) ¶ 198 (citing EX1005 (First Decl.) ¶ 266). Relying on “Tanzeum® (albiglutide) – Drug Discontinuation,” which Dr. Rosenstock notes was purportedly published in 2017 (EX2010 (Rosenstock Decl.) Appendix B), Dr. Rosenstock states that “[a]lbiglutide improved glucose control and had some weight loss but was considerably inferior to other GLP-1 RAs and eventually GSK decided to withdraw albiglutide from the market for commercial reasons.” EX2010 (Rosenstock Decl.) ¶ 198 (citing EX2063 (Tanzeum® (albiglutide) – Drug Discontinuation)). But my opinions in my First Declaration regarding anticipation and obviousness and in this declaration are based on what would have been known to a skilled artisan at the asserted priority dates. At that time, skilled artisans would not have known that albiglutide was withdrawn from the market. Moreover, Tanzeum® (albiglutide) – Drug Discontinuation discloses that “[t]he discontinuation of Tanzeum [albiglutide] is not due to any safety concerns,” but due to “limited prescribing of the medicine.” EX2063 (Tanzeum® (albiglutide) – Drug

Discontinuation). Nothing in Tanzeum® (albiglutide) – Drug Discontinuation suggests that albiglutide was withdrawn because of tolerability issues.

176. Two other once-weekly GLP-1 receptor agonists that were cited in Lovshin Table 1 as “being investigated” are LY2428757 and CJC-1134-PC. EX1012 (Lovshin) at Table 1. Similar to taspoglutide and albiglutide, Dr. Rosenstock relies on another reference that was published well after the asserted priority dates to discuss information that would not have been known to skilled artisans. EX2010 (Rosenstock Decl.) ¶ 199 (citing EX2064 (Pegylated GLP-1 Analogue (LY2428757))). Pegylated GLP-1 Analogue (LY2428757) is noted by Dr. Rosenstock as being “last updated December 27, 2023” (EX2010 (Rosenstock Decl.) Appendix B). Dr. Rosenstock states that “LY2428757, a pegylated GLP-1 analogue that was being studied by Eli Lilly for once-weekly administration was abandoned during development.” EX2010 (Rosenstock Decl.) ¶ 199 (citing EX2064 (Pegylated GLP-1 Analogue (LY2428757))). But as of the latest asserted priority date (July 1, 2012), skilled artisans would not have been aware of this information. Moreover, drug companies discontinue drugs for many different reasons that are unrelated to the drug’s efficacy or tolerability, such as commercial reasons.

177. Dr. Rosenstock also states that CJC-1134-PC has not been approved or marketed anywhere in the world. EX2010 (Rosenstock Decl.) ¶ 200. But as of the latest asserted priority date (July 1, 2012), skilled artisans would not have been aware

of this information and would have understood based on Table 1 of Lovshin that CJC-1134-PC was another once-weekly GLP-1 receptor agonist that was being investigated. EX1012 (Lovshin) at Table 1.

178. Dr. Rosenstock takes issue because he states that Dr. Bantle and I did not identify any semaglutide or dulaglutide data for any dosing frequency available before the '462 patent. EX2010 (Rosenstock Decl.) ¶ 201. But as I stated throughout my First Declaration, skilled artisans would have been aware of all of the prior art disclosures such as that Novo Nordisk was investigating a once weekly dose using specific dosages (0.1, 0.2, 0.4, 0.8, 1.2, and 1.6 mg) of semaglutide being tested in the phase I and phase II studies. *See, e.g.*, EX1005 (First Decl.) ¶ 227. The skilled artisan would have understood that the doses (or exposures) tested in phase I and II studies had already been tested in preclinical models and would have been safe for human administration. *See, e.g., id.* ¶ 228.

179. In sum, in my opinion, the disclosure in Lovshin Table 1 listing other GLP-1 receptor agonists that were in development and “being investigated” for once-weekly dosing further supported the skilled artisan’s reasonable expectation that a once weekly 1.0 mg semaglutide dose would have been successful for treating type 2 diabetes. Nothing cited or discussed by Dr. Rosenstock regarding the once-weekly GLP-1 receptor agonists listed in Lovshin Table 1 (e.g., taspoglutide, albiglutide, LY2428757, CJC-1134-PC) changes my opinion—Dr. Rosenstock’s

discussion about these GLP-1 receptor agonists instead further confirms my opinions in my First Declaration.

VIII. UNPATENTABILITY OF THE '462 PATENT

A. GROUND 1: WO421 ANTICIPATED CLAIMS 1-3 OF THE '462 PATENT

180. For the reasons stated in my First Declaration, I still conclude that claims 1-3 of the '462 patent are unpatentable as anticipated by WO421. *See, e.g.*, EX1005 (First Decl.) ¶¶ 178-201. Dr. Rosenstock opines that WO421 does not anticipate claims 1-3 of the '462 patent. *See* EX2010 (Rosenstock Decl.) ¶¶ 206-265. As I discuss in detail below, I disagree with Dr. Rosenstock's opinions.

1. WO421 anticipated claim 1

181. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” As I set forth in my First Declaration, in my opinion, WO421 taught each element of claim 1 of the '462 patent. EX1005 (First Decl.) ¶¶ 180-195.

182. As I discussed previously, the Board construed the preamble, “[a]method for treating type 2 diabetes,” as not requiring any particular level of efficacy. *See* Section IV (Claim Construction) above.

a. A skilled artisan would have understood that the 0.1 – 1.6 mg range in WO421 discloses the 1.0 mg dose and would have immediately envisaged the 1.0 mg dose

183. As I discussed in my First Declaration, WO '421 disclosed the element “once weekly in an amount of 1.0 mg.” EX1005 (First Decl.) ¶¶ 217-220. The specification of WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1 to 1.6 mg).” EX1011 (WO421) at 44:14.

184. As Dr. Rosenstock acknowledges, WO421 discloses that “[s]uitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art.” EX2010 (Rosenstock Decl.) ¶ 213 (quoting EX1011 (WO421) at 43:2-3). As I discuss in my First Declaration, in my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. See EX1039 (Victoza label) at 2. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk’s phase II clinical study (see EX1013 (NCT657) at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk’s phase I clinical study (see EX1014 (NCT773) at 7). Therefore, a skilled artisan would have pursued dosing

increments of no less than 0.1 mg/dose and would have immediately envisaged all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg).

185. And as I discussed above, the Board found that the claims do not require any particular level of efficacy. *See* Section IV (Claim Construction) above.

186. Dr. Rosenstock agrees with me that skilled artisans would have looked to Novo Nordisk's NCT657 study testing weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg. EX2010 (Rosenstock Decl.) ¶¶ 210-217; EX1013 (NCT657) at 15-16. I disagree with Dr. Rosenstock that a skilled artisan looking to Novo Nordisk's NCT657 study to understand WO421's 0.1-1.6 mg range would have understood WO421's range to include only the doses tested in NCT657 that increased by doubling in amount. EX2010 (Rosenstock Decl.) ¶ 210. Dr. Rosenstock asserts that "[u]pon looking at NCT657, POSITA would have seen that doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested but that a dose of 1.0 mg was not tested" and "would have understood WO421's 'range' to include only those five tested doses and not 1.0 mg." *Id.* ¶ 214.

187. As I stated above in my First Declaration, a skilled artisan looking to Novo Nordisk's NCT657 would have known that weekly semaglutide doses of 0.1

mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk's phase II clinical study (see EX1013 (NCT657) at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk's phase I clinical study (see EX1014 (NCT773) at 7). Skilled artisans would have understood that suboptimal to maximally effective doses are typically investigated in phase II studies to determine the optimal doses, which are doses with an acceptable balance of beneficial effects and undesirable effects. See EX1005 (First Decl.) ¶¶ 68-73. Moreover, skilled artisans would also have understood that effectiveness of a dose that was not tested in the phase II study, such as once-weekly 1.0 mg semaglutide, could be estimated based on extrapolation from the dose response curve. *Id.*; see also ¶¶ 63-64 above. The doses tested in the NCT657 and NCT773 studies were all in 0.1 mg increments, with 0.1 mg being the lowest dose, and therefore, a skilled artisan would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisaged all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses. See also EX1005 (First Decl.) ¶¶ 189-192.

188. Dr. Rosenstock states that a POSITA would not have at once envisaged the claimed 1.0 mg dose because "POSITA would have understood there to be at least 320 doses in WO421's 0.1-1.6 mg 'range.'" EX2010 (Rosenstock Decl.) ¶ 221; see also *id.* ¶¶ 222-233. Dr. Rosenstock opines that "POSITA reading WO421 would

have looked to the dosing increments of other GLP-1 receptor agonists for information about semaglutide.” *Id.* ¶ 222. I disagree that skilled artisans would have looked to dosing of all other GLP-1 receptor agonists for information about semaglutide dosing.

189. In particular, skilled artisans would have known that the larger group of GLP-1 receptor agonists includes the smaller subgroups of both GLP-1 analogues and exendin analogues. Skilled artisans would have understood that GLP-1 analogues are molecules based on the structure of native human GLP-1 and exendin analogues are molecules based on the naturally occurring protein, exendin-4. EX1035 (Lund) at 2, 8 (“Whether based on exendin-4 or a modified GLP-1 analogue, the GLP-1R agonists seem to utilize the beneficial pleiotropic effects of native GLP-1.”). As shown in Figure 1 of Lund below, the larger group of GLP-1 receptor agonists are separated into two subgroups, GLP-1-based (the GLP-1 analogues) and exendin-4-based (the exendin analogues):

GLP-1 receptor agonists for sc injection			
GLP-1-based		Exendin-4-based	
Daily	Weekly	Daily	Weekly
Liraglutide	Albiglutide	Exenatide	Exenatide-LAR
	Dulaglutide	Lixisenatide	CJC-1134-PC
	Semaglutide		

Id. at 3, Fig. 1.

190. The '462 patent confirms that skilled artisans distinguished GLP-1 receptor agonists that are GLP-1 peptides from exendin peptides. *See* '462 patent at 9:26-39; *see also id.* at 5:51-57 (disclosing “GLP-1 analogue” as being a “GLP-1 peptide” and an “exendin-4 analogue” as being an “exendin-4 peptide”).

191. In my opinion, because semaglutide is a GLP-1 based GLP-1 analogue, skilled artisans would not have looked to exenatide analogues in WO421 for information about semaglutide dosing.

192. WO421 disclosed dose ranges for subcutaneous injections of eight GLP-1 receptor agonists (i.e., exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide, and dulaglutide). *See* EX1011 (WO421) at 44:1-19. These GLP-1 receptor agonists can be separated into two subcategories (1) GLP-1 analogues (liraglutide, taspoglutide, semaglutide, albiglutide, and dulaglutide) and (2) exendin analogues (exenatide, exenatide LAR, lixisenatide).

193. As shown in WO421, each of the GLP-1 analogue doses was in an amount measured in milligrams. *Id.* at 44:9-19 (liraglutide, taspoglutide, semaglutide, albiglutide, dulaglutide). Moreover, among the doses disclosed for the GLP-analogues (i.e., 0.25 mg, 0.5 mg, 0.6 mg, 0.75 mg, 0.9 mg, 1 mg, 1.0 mg, 1.2 mg, 1.5 mg, 1.8 mg, 2.0 mg, 3.0 mg, 4 mg, 8 mg, 10 mg, 15 mg, 20 mg, 30 mg), only two of these doses were not expressed in even tenths of a milligram (i.e., dulaglutide doses of 0.25 mg and 0.75 mg). *Id.* at 44:9-19. In contrast only exendin analogues (exenatide and lixisenatide) list doses in an amount measured in micrograms. *Id.* at 44:4-8, 16-17.

194. Dr. Rosenstock states that a skilled artisan would have “seen that WO421 disclosed multiple GLP-1 analogues that are dosed at amounts other than exact, round tenths of a milligram,” such as those dosed in micrograms. EX2010 (Rosenstock Decl.) ¶ 224; *see also id.* ¶¶ 225-235.

195. First, I disagree that skilled artisans would have looked to other GLP-1 analogues that were dosed in increments other than 0.1 mg, given the knowledge of the semaglutide dosing used in Novo Nordisk’s phase I and phase II trials, and especially given that WO421 provides no dose increments for semaglutide itself, as acknowledged by Dr. Rosenstock. EX2010 (Rosenstock Decl.) ¶ 223 (citing EX1011 (WO421) at 43:1-19). For example, in my opinion, skilled artisans would not rely on dosing of dulaglutide, which WO421 states is “administered once weekly

by subcutaneous injection (0.25-3mg, specific dosage strengths are 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, or 3.0 mg),” when the doses of the Novo Nordisk phase I and phase II trials testing semaglutide were well known and did not include increments of 0.05 mg. EX2010 (Rosenstock Decl.) ¶ 224 (quoting EX1011 (WO421) at 43:18-19).

196. Second, as I discussed above, skilled artisans would have relied on dosing of GLP-1 based analogues, not exendin analogues, for information regarding semaglutide dosing. The doses of exenatide and lixisenatide are in substantially smaller increments of micrograms, unlike the semaglutide doses in the phase I and II trials, which were provided in increments of milligrams. There would have been no reason for a skilled artisan to want to test such small increments when the semaglutide doses tested in increments of 0.1 mg in clinical trials were already known.

197. Dr. Rosenstock opines that “dosing in amounts including five hundredths of a milligram (*i.e.*, 0.05 mg) was common in this field at the time and with GLP-1 analogues in particular” and therefore a “POSITA would have understood from these examples that WO421’s range included at least 32 possible doses (*e.g.*, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, etc.).” EX2010 (Rosenstock Decl.) ¶ 226. Dr. Rosenstock relies on a protocol for the Phase I first-in-human trial of semaglutide

to support his theory. *See id.* ¶ 227 (citing EX2070 (Dose Escalation Trial)). I disagree with Dr. Rosenstock.

198. First, as I discussed above, in my opinion, skilled artisans would have envisaged discrete 0.1 mg doses based on the Novo Nordisk phase I and phase II semaglutide trials investigating doses with 0.1 mg being the smallest increment.

199. Second, it is my understanding that the Phase I clinical trial cited by Dr. Rosenstock is not prior art. Although the study completion date is “2007-10-08” (EX2070 (Dose Escalation Trial) at 2), there is nothing that indicates that the disclosure of EX2070 was publicly available before any of the asserted priority dates. Moreover, Dr. Rosenstock’s citation to the clinical trial does not provide a date, but just states “last visited December 28, 2023.” EX2010 (Rosenstock Decl.) at Appendix B (providing that the “Ex2070” website was “last visited December 28, 2023.”). Thus, a skilled artisan as of any of the asserted priority dates would not have had knowledge of the disclosure of the Phase I study including the dosing scheme, and therefore, Dr. Rosenstock’s on the Dose Escalation Trial reliance is improper.

200. Further, I disagree with Dr. Rosenstock that skilled artisans would have dosed in amounts of “five hundredths of a milligram (*i.e.*, 0.05 mg)” because it “was common in this field at the time and with GLP-1 analogues in particular.” EX2010 (Rosenstock Decl.) ¶ 226. As I discussed above, out of ~20 doses disclosed in WO421 for GLP-1 based analogues, only two of these doses were expressed in

hundredths of a milligram. EX1011 (WO421) at 44:4-8, 16-17. In my opinion, skilled artisans would not have looked to dosing in five hundredths of a milligram for semaglutide dosing, especially in view of the known semaglutide 0.1 mg increment doses disclosed in the NCT657 and NCT773 clinical trials.

201. Although it is my opinion that skilled artisans would have envisaged discrete 0.1 mg doses based on the Novo Nordisk phase I and phase II semaglutide trials investigating doses with 0.1 mg, even if it is assumed that the range in WO421 discloses a range of at least 32 possible doses (*e.g.*, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, etc.) as Dr. Rosenstock suggests (EX2010 (Rosenstock Decl.) ¶ 226), in my opinion, 32 doses would still be considered to be a limited number of doses from which to choose such that a skilled artisan would have immediately envisaged the 1.0 mg dose.

202. Dr. Rosenstock continues even further, stating that skilled artisans reading WO421 would look to increments of five thousandths of a milligram (0.5 µg or 0.005 mg) and even five ten-thousandths of a milligram, which demonstrates the nonsensical nature of the argument. EX2010 (Rosenstock Decl.) ¶¶ 231, 233.

203. Dr. Rosenstock relies on the Victoza labels disclosure of a “single dose of 7.5 mcg/kg ... (~0.7 mg)” to support that liraglutide was “also not exact tenths of a milligram (as shown by ‘~’).” EX2010 (Rosenstock Decl.) ¶ 231 (citing EX2068 (Victoza® Prescribing Information (January 2010))). In my opinion, this disclosure

further confirms my opinion that skilled artisans would round up doses to 0.1 mg increments as shown by the use of “~”. In my opinion, Dr. Rosenstock’s opinion that skilled artisans would dose in five ten-thousandths of a milligram is unreasonable.

204. I disagree with Dr. Rosenstock that “POSITA would have recognized that WO421 disclosed ‘range’ encompasses at least 320 possible doses.” EX2010 (Rosenstock Decl.) ¶ 233. Nevertheless, although it is my opinion that skilled artisans would have envisaged discrete 0.1 mg doses based on the Novo Nordisk phase I and phase II semaglutide trials investigating doses with 0.1 mg, even if it is assumed that the range in WO421 discloses a range of at least 320 possible doses, in my opinion, 320 doses would still be considered to be a limited number of doses from which to choose such that a skilled artisan would have immediately envisaged the 1.0 mg dose.

205. Dr. Rosenstock asserts that skilled artisans would look to 320 possible doses given WO421’s disclosure of “dozens of embodiments relating to fifty-nine diseases and conditions . . . and combination therapy with a DPP-4 inhibitor.” EX2010 (Rosenstock Decl.) ¶ 234. In my opinion, skilled artisans would have looked to NCT657, as Dr. Rosenstock acknowledges, and would have understood the disclosed once-weekly semaglutide 0.1-1.6 mg dosing range was the range of doses used in NCT657 for treating type 2 diabetes. Thus, skilled artisans would not have looked to other diseases and conditions as Dr. Rosenstock suggests.

206. In my opinion, skilled artisans would not have ignored the disclosures of dose doubling in the NCT657 (EX2010 (Rosenstock Decl.) ¶ 235) but would have understood the doubling to be the known dose adjustments used in phase II dose ranging studies to define the minimally and maximally effective doses. *See* EX1005 (First Decl.) ¶¶ 65-74. Thus, the disclosure of doses would not be limited to only those doses tested in the phase II study, but would include doses ranging across the dose-response curve in 0.1 mg increments because that was the smallest dose tested in the semaglutide phase I and phase II studies that were available as prior art.

207. Dr. Rosenstock relies on semaglutide's FDA approved label for his opinions related to determining the dosing intervals. EX2010 (Rosenstock Decl.) ¶¶ 237-239. But as Dr. Rosenstock admits, the FDA-approved label for Ozempic® is not prior art as Ozempic® was approved in 2017, well after the latest asserted priority date (June 1, 2012), and the Ozempic® Prescribing Label relied upon by Dr. Rosenstock is the 9/2023 revision. EX2069 (Ozempic® Prescribing Label) at 1. Thus, skilled artisans would not have been aware of the approved titration scheme for Ozempic® at any of the asserted priority dates.

208. But even considering the Ozempic® FDA-approved label, if doses of 0.05 mg increments in the titration scheme for Ozempic® were considered, the number of doses included in the 0.1-1.6 mg range would be 32 doses, which is still

a limited number of doses in the range such that a skilled artisan would have immediately envisaged the 1.0 mg dose.

209. For at least my opinions in this declaration and my First Declaration, WO421 disclosed the claimed 1.0 mg once-weekly semaglutide dose.

b. The 1.0 mg dose is not critical

210. Dr. Rosenstock asserts that “the claimed 1.0 mg once-weekly semaglutide dose for treating type 2 diabetes was critical, because the claimed 1.0 mg once-weekly dose operates differently as to both efficacy and tolerability than other doses within WO421’s ‘range.’” EX2010 (Rosenstock Decl.) ¶ 241; *see also id.* ¶ 243. As I discuss in detail below, I disagree that with Dr. Rosenstock’s opinions that the claimed 1.0 mg dose was “critical.”

211. As I discussed above, it is my understanding for a claimed feature to be considered “critical,” such that it is not anticipated by a prior art disclosure, the question is whether that difference is “critical to the operability of the claimed invention.” I understand that the criticality question is not just whether the claimed feature creates any difference relative to a broader prior art disclosure. *See* Section II above.

212. In my opinion, Dr. Rosenstock’s assertions that the 1.0 mg dose is critical based on purported differences in its level of efficacy and tolerability as compared to adjacent doses are not relevant because the ’462 patent claims do not

require any particular level of efficacy at all. *See* Section IV (Claim Construction) above. The '462 patent claims also do not require a particular level of tolerability.

213. Dr. Rosenstock relies on a sentence in the '462 patent stating that “[i]n one embodiment the methods of the present invention provide[] *surprisingly... improved* reduction of HbA1c.” EX2010 (Rosenstock Decl.) ¶ 242 (quoting EX1001 ('462 patent), 2:56-58). First, it is my understanding that the claims do not require any particular level of efficacy, including an “improved reduction of HbA1c.” *See* Section IV (Claim Construction). Second, the statement that Dr. Rosenstock quotes from the '462 patent does not mention the 1.0 mg dose, or any particular dose for that matter.

214. Dr. Rosenstock also opines that the '462 patent “states that only certain doses showed statistically significant improvement over placebo, and repeatedly discloses that only once-weekly doses of *0.8 mg or greater* showed improvements over once daily liraglutide.” EX2010 (Rosenstock Decl.) ¶ 242. As I discussed above, it is my understanding that the claims do not require any particular level of efficacy, including any type of comparison to the efficacy of a particular daily dose of liraglutide. Additionally, the data that Dr. Rosenstock cites from the '462 patent does not mention the 1.0 mg dose. Indeed, as Dr. Rosenstock points out, the '462 patent focuses on “once-weekly doses of *0.8 mg or greater*,” EX2010 (Rosenstock

Decl.) ¶ 242. Dr. Rosenstock does not show that there is anything critical about the 1.0 mg dose compared with other doses based on the data in the '462 patent.

215. I also disagree with Dr. Rosenstock's statement that "the claimed once-weekly 1.0 mg dose is critical with respect to both efficacy and tolerability" "as was not known in the prior art." EX2010 (Rosenstock Decl.) ¶ 242 (citing EX1001 ('462 patent) at 22:1-5)). First, the claims do not require particular levels of efficacy or tolerability. Second, nothing cited by Dr. Rosenstock discusses anything about tolerability. Third, the '462 patent does not highlight the 1.0 mg dose over other doses and the 1.0 mg dose was not even tested in the patent. Fourth, as I discussed in my First Declaration, skilled artisans would have reasonably expected doses to be more efficacious and less tolerable with an increase in dose. EX1005 (First Decl.) ¶¶ 68-73 (citing EX1045 (Shargel) at 81-82, Figs. 19-1, 19-2).

216. Moreover, all of the doses within the 0.1-1.6 mg range disclosed in WO421 would be operable within the claims as methods for treating type 2 diabetes, especially given that the claims do not require any particular level of efficacy, tolerability, or weight loss.

(i) The claims do not require any particular level of efficacy

217. Dr. Rosenstock spends numerous paragraphs discussing the different levels of efficacy seen within the disclosed once-weekly semaglutide 0.1-1.6 mg

range in WO421 based on the data in the '462 patent. EX2010 (Rosenstock Decl.) ¶¶ 244-253. As I discussed above, it is my understanding that the claims do not require any particular level of efficacy. *See* Section IV (Claim Construction) above.

218. For example, Dr. Rosenstock discusses that all of the doses with the 0.1-1.6 mg range showed different levels of reduction of HbA1c from baseline as compared to placebo, and that only doses of 0.8 mg and above brought subject's HbA1c to levels that were "clinically meaningful" and "statistically significant." EX2010 (Rosenstock Decl.) ¶¶ 244-246. But it is my understanding that the claims do not require any particular level of efficacy, much less any of the levels of efficacy discussed by Dr. Rosenstock such as being "clinically meaningful" and "statistically significant." Moreover, there is nothing to distinguish that the 1.0 mg dose was more critical than some of the other doses, e.g., 0.8 mg or greater doses of semaglutide. Additionally, I note that the '462 patent specification reports that "semaglutide (≥ 0.2 mg) dose-dependently reduced HbA1c from baseline (FIG. 1), and increased the likelihood of achieving HbA1c $<7\%$ ($p<0.05$ vs. placebo for doses ≥ 0.2 mg)." EX1001 ('462 patent) at 22:1-5. Because the claims require no particular level of efficacy, in my opinion this shows there is nothing critical about the 1.0 mg dose.

219. Dr. Rosenstock again focuses on the generic excerpt in the '462 patent that states: "In one embodiment the methods of the present invention provides surprisingly showed improved reduction of HbA1c and reduction of body weight."

EX2010 (Rosenstock Decl.) ¶ 247 (citing EX1001 ('462 patent), 2:56-58)). But nothing in this sentence points to any particular dose that provides such a result, much less the 1.0 mg dose.

220. Dr. Rosenstock agrees that skilled artisans would have understood that doses within the 0.1-1.6 mg range would have different levels of efficacy and tolerability depending on where they are in the dose-response curve (EX2010 (Rosenstock Decl.) ¶ 247), which the phase I and phase II trials indicate based on the dosing regimen.

221. Dr. Rosenstock also relies on data in the '462 patent reporting the comparison between the semaglutide doses over once-daily liraglutide, stating that doses 0.8 mg or greater “offered significant improvement over once-daily liraglutide.” EX2010 (Rosenstock Decl.) ¶ 248 (discussing EX1001 ('462 patent) at 22:21-25, Fig.3A, 3B); *see also* EX2010 (Rosenstock Decl.) ¶ 249. But it is my understanding that the claims do not require any particular level of efficacy, much less that the claimed dose “offer[] significant improvement over once-daily liraglutide.” Moreover, there is nothing to distinguish that the 1.0 mg dose was more critical than some of the other doses, e.g., 0.8 mg or greater doses.

222. Dr. Rosenstock’s focus on weight loss with the 0.8 mg or greater doses compared to liraglutide (EX2010 (Rosenstock Decl.) ¶ 250) is also not relevant as the claims do not require that the 1.0 mg dose result in weight loss, much less

compared to liraglutide. Moreover, there is nothing to suggest that the 1.0 mg dose is critical as opposed to other doses greater than 0.8 mg semaglutide.

223. I disagree with Dr. Rosenstock's statements that the '462 patent data "underscore the differences between how semaglutide doses in different parts of WO421's disclosed range operate as to HbA1c reduction, weight loss, or both, and this would not have been predictable prior to '462 [sic]." EX2010 (Rosenstock Decl.) ¶ 253.

224. In my opinion, even though the doses within the disclosed WO421 range of 0.1-1.6 mg semaglutide may produce different levels of efficacy or tolerability, it is my understanding that the claims do not require any particular level of efficacy or tolerability. In my opinion, all of the semaglutide doses recited within the WO421 disclosed range of 0.1-1.6 mg could be considered doses that could be operable, i.e., used in the claimed method for treating type 2 diabetes because doses in the range (0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg) were used in the NCT657 phase II study to treat type 2 diabetes patients. Thus, in my opinion, even though the doses may have different levels of efficacy and tolerability depending on where they fall within the 0.1-1.6 mg range, this would be well-known to a skilled artisan. Moreover, none of the doses within the 0.1-1.6 mg range would be considered inoperable such that they would not be considered doses that could be used in the

claimed method for treating type 2 diabetes, in particular, because the Board did not require any particular level of efficacy for the claims.

225. Further, similar to the liraglutide phase II study about which Seino reported that “[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy” (EX1038 (Seino) at 6), skilled artisans would similarly expect that all of the once weekly doses of semaglutide tested in NCT00696657 and NCT00851773 would exhibit some degree of efficacy.

226. Moreover, there is nothing critical about the 1.0 mg dose as compared to certain other doses in the range, for example, doses greater than 0.7 mg semaglutide.

(ii) The claims do not require any particular level of tolerability

227. Similar to his arguments related to efficacy and weight loss, Dr. Rosenstock argues that “there are differences in tolerability across WO421’s disclosed ‘range’ that further show that the claimed 1.0 mg dose was critical.” EX2010 (Rosenstock Decl.) ¶ 254.

228. For at least all of the same reasons I stated with respect to efficacy and weight loss, I disagree that Dr. Rosenstock’s arguments related to tolerability are relevant to criticality of the 1.0 mg once-weekly dose.

229. First, the claims of the '462 patent do not require that the 1.0 mg once-weekly semaglutide dose have any particular level of tolerability.

230. Second, Dr. Rosenstock does not show that the 1.0 mg dose was more tolerable compared to other doses in the 0.1-1.6 mg range. Indeed, the 0.8 mg and 1.6 mg doses of semaglutide were titrated doses in the phase II studies.

231. Third, that doses are less tolerable with increasing doses of semaglutide would have been expected as I stated in my First Declaration. EX1005 (First Decl.) ¶¶ 68-73 (citing EX1045 (Shargel) at 81-82, Figs. 19-1, 19-2). Dr. Rosenstock also agrees with Dr. Bantle that it “would have been expected” that higher doses of semaglutide would result in “greater nausea” and “greater instances of vomiting.” EX2010 (Rosenstock Decl.) ¶ 255 (quoting EX2018 (Bantle Tr.) 45:5-16, 88:8-89:11); *see also* EX2010 (Rosenstock Decl.) ¶ 257 (citing EX1005 (First Decl.) ¶ 234).

232. Dr. Rosenstock asserts that tolerability could be “ameliorated by titration,” but that the titration schedule or whether it was effective was not known in the art. EX2010 (Rosenstock Decl.) ¶ 256. First, the claims do not require a particular titration schedule. Second, skilled artisans would have been aware that the 0.8 and 1.6 mg doses in the semaglutide phase I and phase II trials were titrated doses. EX1013 (NCT657) at 16 (disclosing titration of 0.8 mg and 1.6 mg doses); EX1014 (NCT773) at 11 (disclosing titration of 0.8 mg and 1.6 mg doses). Skilled

artisans would have also been aware that a common titration scheme used doubling of doses, such as the titration scheme used in NCT773. EX1014 (NCT773) at 11 (disclosing 0.4 mg once weekly for 1 week and then 0.8 mg once weekly for 7 weeks, 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, and then 1.6 mg once weekly for 6 weeks). Further, skilled artisans would have been aware that skilled artisans commonly used titration schedules with GLP-1 receptor agonists to mitigate adverse effects. *See* EX1039 (Victoza label) at 2 (disclosing titration of liraglutide via doubling of doses); EX1022 (Drab) at 10 (as with exenatide, nausea with liraglutide can be limited by gradual dosage titration).

233. I disagree with Dr. Rosenstock's statement that "the claimed 1.0 mg once-weekly semaglutide dose for treating type two diabetes was critical for the additional reason that doses within WO421's disclosed 'range' endpoints operate differently with respect to tolerability at various points within the range as compared to the claimed 1.0 mg dose, and POSITA could not have predicted it based on the prior art and knowing only the basic design of the NCT657 dose-range study." EX2010 (Rosenstock Decl.) ¶ 258. This contradicts Dr. Rosenstock's previous reliance on Dr. Bantle stating: "Dr. Bantle confirmed that 'at higher doses [of semaglutide], some patients experience greater nausea' and greater instances of vomiting, and this would have been expected." EX2010 (Rosenstock Decl.) ¶ 255.

234. In my opinion, WO421 anticipated claim 1 of the '462 patent.

2. WO421 anticipated claims 2 and 3

235. As I set forth in my First Declaration, in my opinion, WO421 anticipated claims 2 and 3 of the '462 patent. EX1005 (First Decl.) ¶¶ 196-201.

236. Claim 2 recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 2 therefore limits the subject matter of claim 1 to “parenteral” administration. Claim 3 recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.” Claim 3 therefore limits that parenteral administration to a subcutaneous solution injection.

237. In my opinion, WO421 taught the subject matter of claims 2 and 3. WO421 expressly disclosed injectable formulations as “injectable solutions.” EX1011 (WO421) at 40:23-26. WO421 expressly stated that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” EX1011 (WO421) at 44:13.

238. Claim 3 recites that administration is “by subcutaneous injection” and the term “the solution” is used when referring to claim 2, from which it depends. However, claim 1 and claim 2 do not recite a solution. EX1001 ('462 patent) at 35:42-48. In my opinion, the claimed subcutaneous injection is necessarily understood to be a solution.

239. In my opinion, that the claimed subcutaneous injection is necessarily a solution is consistent with the '462 patent, which refers to “an injection solution,” (*id.* at 15:61-62), and a “dissolved” injected compound, (*id.* at 9:5-7).

240. Relying on Miller, Dr. Rosenstock asserts that “[f]ormulations administered by subcutaneous injection also include ‘suspensions.’” EX2010 (Rosenstock Decl.) ¶ 263 (emphasis omitted) (citing EX2004 (Miller) at 2); *see also* EX2077 (Mueller) at 1, 3. In my opinion, Miller is supportive of my opinion that skilled artisans would have understood the subcutaneous injections in WO421’s disclosure to be solutions. In particular, Miller taught that there were “relatively few examples” of suspensions reported for medicinal purposes, and provided examples that were in bovine with “a large 14- to 16- gauge needle for injection, whereas the preferred needle size for human is ~25-27 gauge.” EX2004 (Miller) at 2. Miller discussed that “injection of ... suspensions with a larger 21-gauge needle causes significant pain leading to noncompliance,” which skilled artisans would know would be problematic for patients with type 2 diabetes. *Id.* at 2. Moreover, Miller further discussed another option of suspensions using a crystallization method that “can be very difficult.” *Id.*

241. In my opinion, Miller confirms that skilled artisans would have understood the injected subcutaneous doses taught by WO421 to be solutions.

Moreover, WO421 expressly discloses “injectable solutions.” EX1011 (WO421) at 40:23-26.

242. In my opinion, WO421 anticipated claims 2 and 3 of the ’462 patent.

B. GROUND 2: LOVSHIN ANTICIPATED CLAIMS 1-3 OF THE ’462 PATENT

243. For the reasons stated in my First Declaration, I still conclude that claims 1-3 of the ’462 patent are unpatentable as anticipated by Lovshin. *See, e.g.*, EX1005 (First Decl.) ¶¶ 202-218.

1. Lovshin anticipated claim 1

244. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, Lovshin taught each element of claim 1 of the ’462 patent. Lovshin disclosed the preamble of claim 1 of the ’462 patent. As I discussed previously, the Board construed the preamble, “[a]method for treating type 2 diabetes,” as not requiring any particular level of efficacy. *See* Section IV (Claim Construction) above.

a. A skilled artisan would have understood that the 0.1 – 1.6 mg range in Lovshin discloses the 1.0 mg dose and would have immediately envisaged the 1.0 mg dose

245. Dr. Rosenstock sets forth many of the same arguments as he did with respect to his WO421 analysis (EX2010 (Rosenstock Decl.) ¶ 267), which I address above in Section VIII.A.

246. I disagree with Dr. Rosenstock that “Lovshin fails to disclose administration of semaglutide to ‘a subject in need thereof.’” EX2010 (Rosenstock Decl.) ¶ 267; *see also id.* ¶¶ 286-289. First, the preamble of claim 1 recites “[a] method for treating type 2 diabetes,” therefore, a skilled artisan would understand that “a subject in need thereof” would be a subject with type 2 diabetes. Second, the title of Lovshin is “Incretin-based therapies for type 2 diabetes mellitus,” and thus skilled artisans would have understood Lovshin to disclose therapies for treating subjects with type 2 diabetes. EX1012 (Lovshin) at 1. Third, as I discussed in my First Declaration regarding Lovshin’s disclosures with respect to the preamble “[a]method for treating diabetes,” Lovshin disclosed “[i]ncretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus.” EX1005 (First Decl.) ¶ 206 (citing EX1012 (Lovshin) at 12). I also stated that “Lovshin also disclosed, ‘multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1).’” EX1005 (First Decl.) ¶ 206 (citing EX1012 (Lovshin) at 5).

247. Fourth, as I discussed in my First Declaration and as Dr. Rosenstock agrees, a skilled artisan would have understood from Lovshin that “NN9535” is “being investigated” in phase I-II studies. The skilled artisan would have known from at least the NCT657 study that semaglutide was administered to patients with

type 2 diabetes. EX2010 (Rosenstock Decl.) ¶ 268 (citing EX1005 (First Decl.) ¶ 95); EX1013 (NCT657) at 19 (stating “Official Title: A Dose Finding Trial Establishing Efficacy and Safety of NN9535 in Comparison With Placebo and Liraglutide in Type 2 Diabetes.”).

248. Similar to his analysis for WO421, Dr. Rosenstock agrees with me that skilled artisans would have looked to the once-weekly doses tested in Novo Nordisk’s phase I and II clinical studies to understand the dose range of 0.1-1.6 mg in Lovshin. EX2010 (Rosenstock Decl.) ¶ 269.

249. I disagree with Dr. Rosenstock that a skilled artisan would have understood the 0.1-1.6 mg range disclosed in Lovshin to only include the specific doses being tested in the NCT657 trial. EX2010 (Rosenstock Decl.) ¶ 271. As I discuss in my First Declaration, in my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. EX1005 (First Decl.) ¶¶ 209-210. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. *See* EX1039 (Victoza label) at 2. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk’s phase II clinical study (*see* EX1013 (NCT657) at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4

mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk's phase I clinical study (see EX1014 (NCT773) at 7). Therefore, a skilled artisan would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisaged all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg). EX1005 (First Decl.) ¶ 209.

250. I disagree with Dr. Rosenstock's opinion that "POSITA reviewing Lovshin's list of other GLP-1 analogues would have seen they are not all dosed in round tenths of a milligram." EX2010 (Rosenstock Decl.) ¶ 274. As I discussed above in Section VIII.A.1.a with respect to WO421 anticipation, skilled artisans would have looked to the doses set forth in the protocols of the known phase I and phase II clinical trials of semaglutide for information regarding semaglutide dosing. Further, in my opinion, skilled artisans would not rely on dosing of GLP-1 receptor agonists that suggest much smaller increments of dosing in micrograms, given that semaglutide is dosed in milligrams in the phase I and II trials. See Section VIII.A.1.a. Notably, two of the three GLP-1 receptor agonists that Dr. Rosenstock pointed to in Table 1 of Lovshin are exendin analogues dosed in micrograms (i.e., exenatide (5-10 µg) and AVA0010 (5-30 µg)). EX2010 (Rosenstock Decl.) ¶¶ 274, 278

(discussing EX1012 (Lovshin) at Table 1 and focusing on the doses for dulaglutide, exenatide, and AA0010).

251. Dr. Rosenstock asserts the same arguments with respect to dosing in smaller increments as he did with WO421 anticipation (EX2010 (Rosenstock Decl.) ¶¶ 275-279, but I disagree with his analysis as I discuss above. See Section VIII.A.1.a. above. In my opinion, skilled artisans would have envisaged a group of 16 discrete 0.1 mg semaglutide doses, including 1.0 mg, based on the Novo Nordisk phase I and phase II semaglutide trials investigating doses with 0.1 mg being the smallest increment. EX1005 (First Decl.) ¶ 209.

252. And even if it is assumed that the range in Lovshin discloses a range of at least 32 possible doses or 320 possible doses as Dr. Rosenstock suggests (EX2010 (Rosenstock Decl.) ¶¶ 275-277), in my opinion, both 32 doses and 320 doses would still have been considered to be a limited number of doses from which to choose such that a skilled artisan would have immediately envisaged the 1.0 mg dose, as I discussed above.

253. Dr. Rosenstock states that I do not point to a prior art study in which 1.0 mg semaglutide was dosed (EX2010 (Rosenstock Decl.) ¶¶ 280, 286-287), but as I discussed in my First Declaration and in this declaration, in my opinion, a skilled artisan would have immediately envisaged the 1.0 mg semaglutide dose based on the disclosure of the 0.1-1.6 mg range in Lovshin. EX1005 (First Decl.) ¶¶ 209-211.

b. The 1 mg dose is not critical

254. Similar to his opinions with respect to the WO421 and anticipation, Dr. Rosenstock asserts that the 1.0 mg dose is critical because the '462 patent shows that “the claimed once-weekly 1.0 mg dose operates differently than at other doses within the 0.1-1.6 mg ‘range’ endpoints as to both efficacy (as to HbA1c reduction and weight loss) and tolerability.” EX2010 (Rosenstock Decl.) ¶ 281 (citing *id.* ¶¶ 240-259); *see also id.* ¶¶ 282-285. As I discussed above with respect to the WO421 and anticipation, in my opinion, Dr. Rosenstock has not shown that the 1.0 mg dose is critical. *See* Section VIII.A.1.b. above.

2. Lovshin anticipated claims 2 and 3

255. As I set forth in my First Declaration, in my opinion, Lovshin anticipated claims 2 and 3 of the '462 patent. EX1005 (First Decl.) ¶¶ 214-219.

256. Claim 2 recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.” Claim 2 therefore limits the subject matter of claim 1 to “parenteral” administration. Claim 3 recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.” Claim 3 therefore limits that parenteral administration to a subcutaneous solution injection.

257. In my opinion, Lovshin taught the subject matter of claims 2 and 3. Lovshin disclosed that the dose of NN9535 (semaglutide) to be administered to a

patient is “0.1–1.6 mg once weekly,” given by “subcutaneous injection” to treat type 2 diabetes. EX1012 (Lovshin) at 2. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

258. Claim 3 recites that administration is “by subcutaneous injection” and the term “the solution” is used when referring to claim 2, from which it depends. However, claim 1 and claim 2 do not recite a solution. EX1001 (’462 patent) at 35:42-48. In my opinion, the claimed subcutaneous injection is necessarily understood to be a solution.

259. In my opinion, that the claimed subcutaneous injection is necessarily a solution is consistent with the ’462 patent, which refers to “an injection solution,” (*id.* at 15:61-62), and a “dissolved” injected compound, (*id.* at 9:5-7).

260. Relying on Miller, Dr. Rosenstock asserts that “[f]ormulations administered by subcutaneous injection also include ‘suspensions.’” EX2010 (Rosenstock Decl.) ¶ 293 (emphasis omitted) (citing EX2004 (Miller) at 2); *see also* EX2077 (Mueller) at 1, 3. In my opinion, Miller is supportive of my opinion that skilled artisans would have understood that semaglutide subcutaneous injections would be solutions. In particular, Miller taught that there were “relatively few examples” of suspensions reported for medicinal purposes, and provided examples that were in bovine with “a large 14- to 16- gauge needle for injection, whereas the preferred needle size for human is ~25-27 gauge.” EX2004 (Miller) at 2. Miller

discussed that “injection of ... suspensions with a larger 21-gauge needle causes significant pain leading to noncompliance,” which skilled artisans would know would be problematic for patients with type 2 diabetes. *Id.* at 2. Moreover, Miller further discussed another option of suspensions using a crystallization method that “can be very difficult.” *Id.*

261. In my opinion, Miller confirms that skilled artisans would understand the injected doses taught by Lovshin to be solutions.

262. In my opinion, Lovshin anticipated claims 2 and 3 of the '462 patent.

C. GROUND 3-5: CLAIMS 1-10 OF THE '462 Patent WOULD HAVE BEEN OBVIOUS

263. For the reasons stated in my First Declaration and in this declaration, I still conclude that claims 1-10 of the '462 patent would have been obvious over WO421 (Ground 3), WO537 considering Lovshin (Ground 4), and NCT657 and NCT773 (Ground 5). *See, e.g.*, EX1005 (First Decl.) ¶¶ 220-301.

1. A skilled artisan would have been motivated to pursue a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

264. As I discussed in my First Declaration, in my opinion “skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance.” EX1005 (First Decl.) ¶ 224. Although Dr. Rosenstock states he disagrees with my opinion (EX2010 (Rosenstock Decl.) ¶ 297 (quoting EX1005

(First Decl.) ¶ 224)), it appears that he agrees with me. In particular, when discussing the frequent administration of Victoza® (once daily) and Byetta® (twice daily) he stated: “This frequent administration leads to reduced patient adherence, particularly because many patients prefer less frequent injections, it is easier for patients to remember to take once-weekly injections as compared to once-daily injections, and less frequent injections reduce the risk of injection site reactions.” EX2010 (Rosenstock Decl.) ¶ 190.

265. I disagree with Dr. Rosenstock’s opinion that “even if it were assumed that POSITA were motivated to pursue any dose based on the mere fact of a planned Phase II study and a planned Phase I study on specific doses, in my opinion POSITA would have been motivated to pursue one of the specified doses that was actually going to be tested in those studies (which did not include 1.0 mg).” EX2010 (Rosenstock Decl.) ¶ 300.

266. As I discussed in my First Declaration, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would have been understood that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* EX1047

(Tamimi) at 3-4; EX1048 (FDA Exposure Response 2003) at 7; EX1049 (ICH 1994) at 1-2, 4, 6; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

267. Further, skilled artisans would also have been aware that in the NCT657 study the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. *See* EX1013 (NCT657) at 15-16. That the 0.8 mg dose was tested in NCT657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Moreover, the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg, because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects.

268. Similarly, skilled artisans would also have been aware that Novo Nordisk was originally investigating a dose range of 0.1-1.6 mg semaglutide once weekly in the phase I NCT773 study, similar to NCT657. *See* NCT773 at 11-12. Also disclosed in the NCT773 protocol was that the 0.8 mg dose was tested with and without titration, whereas the 1.6 dose was tested only with titration. *Id.* at 11. There

was also an optional dose to be “determined based on safety and tolerability of previous dose steps” that will “only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” *Id.* Similar to NCT657, that the 0.8 mg dose was tested in NCT773 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Thus, this further confirms the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects.

269. Moreover, skilled artisans would have understood that only a select number of doses would have been chosen for phase I and phase II studies. For example, Tamimi discusses that in Phase IIb dose ranging studies such as the NCT657 study, “several dose levels are tested in the target population (dose-ranging studies) to define the minimally effective or non-effective dose and to decide the optimal dose, based on clinical efficacy and safety, to take to the next stage.” EX1047 (Tamimi) at 4. Thus, skilled artisans would have known that not every dose

that could be considered effective and safe would have been tested in the phase I and phase II studies, but that the doses selected to be tested would provide a range of doses that could be considered effective and safe.

270. Further, just because other doses would have been considered efficacious (EX2010 (Rosenstock Decl.) ¶ 300), does not mean that a skilled artisan would not continue optimizing the dose. Skilled artisans are continuously looking to optimize doses to find the most safe, effective, and tolerable doses.

271. Dr. Rosenstock states that “the mere existence of both ongoing Phase I trials (in healthy volunteers) and ongoing Phase II trials (with efficacy still under investigation) does not show the claimed once-weekly 1.0 mg semaglutide dose for treating type 2 diabetes was safe, effective, and tolerable.” EX2010 (Rosenstock Decl.) ¶ 302. First, it is my understanding that the claims require no particular tolerability level, and the Board construed the preamble as having no particular level of efficacy. *See* Section IV (Claim Construction) above.

272. Second, in my opinion, a skilled artisan would have had a reasonable expectation of success of practicing the claimed “method for treating type 2 diabetes” with a 1.0 mg dose because the skilled artisan would have expected the 1.0 mg to have some efficacy. As I noted above, I understand that the Board construed the preamble so that it does not require any particular degree or minimum threshold of efficacy. *See* Section VI (Claim Construction) above. My conclusion from the

prior art therefore applies to the method for treating type 2 diabetes as the Board has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Board's interpretation requires in terms of efficacy. That is, in my opinion, the prior art would have motivated skilled artisans to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide more than a minimal level of efficacy in treating type 2 diabetes.

273. As I discussed in my First Declaration, a skilled artisan would have also understood that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., in vitro and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See* EX1047 (Tamimi) at 3; EX1066 (Knudsen 2010b) at 1. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were supported by a wealth of internal preclinical studies and knowledge about semaglutide to support the phase I and II study doses being both safe and efficacious in human patients. EX1005 (First Decl.) ¶¶ 228, 232, 256, 260, 283, 287. Dr. Rosenstock agrees that skilled artisans "would already have assumed safety and efficacy of other doses of semaglutide from the fact of the ongoing trials." EX2010 (Rosenstock Decl.) ¶ 301.

274. Citing Arrowsmith (EX2006), Dr. Rosenstock states that "it is often the case that Phase II clinical trials fail, even where the drug being tested has gone

through preclinical testing.” EX2010 (Rosenstock Decl.) ¶ 303; *see also id.* ¶ 304. But as I discussed above, Arrowsmith has significant flaws and discusses phase II studies generally, but skilled artisans would have had knowledge of the success of other GLP-1 receptor analogues and the wealth of knowledge of other GLP-1 receptor agonists. *See* Section VI.B.2 above. Additionally, before the priority date, skilled artisans would have been aware that Novo Nordisk reported that the NCT657 phase II study “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.” *See* EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12.

275. Dr. Rosenstock states that “it still would have been unknown to POSITA whether any of the doses being tested (which did not even include 1.0mg) would have tolerability, safety, or efficacy issues that would have made them unsuitable for use in treating type 2 diabetes as required by the claims of the ’462 patent.” EX2010 (Rosenstock Decl.) ¶ 305. I disagree with Dr. Rosenstock that the claims require any particular level of tolerability or efficacy. Indeed, it is my understanding that the Board held that the claims do not require any particular level of efficacy.

276. I also disagree with Dr. Rosenstock’s opinion regarding the purported “prior art of failed GLP-1 RAs, including taspoglutide and albiglutide.” EX2010 (Rosenstock Decl.) ¶ 305 (emphasis omitted). As I discuss above, taspoglutide had

a tolerability issue because of the formulation, not the drug; albiglutide was not a failed GLP-1 receptor agonist, and skilled artisans would not have known about the other GLP-1 receptor agonist purported failures because the documents cited by Dr. Rosenstock are post-priority date publications. See ¶¶ Section VII above. In my opinion, skilled artisans would have been further motivated to pursue a once weekly semaglutide dose based on the other GLP-1 receptor agonists that were, for example, cited in Table 1 of Lovshin as being in development and “being investigated” for once-weekly dosing. That these once-weekly GLP-1 receptor agonists were also “being investigated” further supported the skilled artisan’s reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

277. In my opinion, contrary to Dr. Rosenstock’s opinion, a skilled artisan would not have needed to see data for semaglutide doses to be motivated to pursue a once-weekly 1.0 mg semaglutide dose. EX2010 (Rosenstock Decl.) ¶¶ 306, 308, 310, 311, 334, 355 (relying on (EX1052 (Madsbad) at 2). Even though there were no data, skilled artisans would have been motivated to pursue the 1.0 mg semaglutide dose. As I discussed above and in my First Declaration, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would have been understood that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses

to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* EX1005 (First Decl.) ¶¶ 68-73, 231-237, 255, 261, 282, 284, 287; EX1047 (Tamimi) at 3-4; EX1048 (FDA Exposure Response 2003) at 7; EX1049 (ICH 1994) at 1-2, 4, 6; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

278. Further, skilled artisans would also have been aware that in the NCT657 and NCT773 study the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. *See* EX1013 (NCT657) at 15-16; *See* EX1014 (NCT773) at 11. That the 0.8 mg dose was tested in NCT657 and NCT773 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Moreover, the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg, because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects. A skilled artisan would have been motivated to

try a 1.0 mg dose because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

279. Likewise, the later NCT773 protocol showing that the 1.6 mg dose was reduced to a 1.2 mg dose also indicates that Novo Nordisk may be apprehensive of the highest 1.6 mg dose, suggesting that doses closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further motivation to try the once weekly 1.0 mg semaglutide dose for treating type 2 diabetes.

280. I also disagree with Dr. Rosenstock's opinion that the 0.1-1.6 mg range in WO421 and Lovshin would have disclosed "at least 320 doses." EX2010 (Rosenstock Decl.) ¶ 307. As I discussed above, in my opinion, the 0.1-1.6 mg range would have disclosed dosing increments of no less than 0.1 mg/dose at the smallest reasonable step size, which would have included at most a group of just 16 doses. See Section VIII.A.1.a, VIII.B.1.a. Moreover, skilled artisans would have been aware that in the NCT657 and NCT773 study the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. See EX1013 (NCT657) at 15-16; See EX1014 (NCT773) at 11. Therefore, the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg

dose was being tested with and without titration, which suggests that the 0.8 mg dose could be tolerated without titration, and therefore doses lower than 1.6 mg and closer to the 0.8 mg dose would have a better balance between efficacy and side effects. This would narrow the scope of potential doses to consider even further.

2. A skilled artisan would have had a reasonable expectation of success pursuing a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

281. As I stated in my First Declaration, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies and the skilled artisan would have been motivated with a reasonable expectation of success to optimize the weekly dose to 1.0 mg for treating type 2 diabetes. In my opinion, a skilled artisan would have reasonably expected that the doses on the lower end of the range (e.g., ~0.1 mg doses) would have some efficacy but would be suboptimal doses (*see* EX1038 (Seino) at 6 (“[a]ll doses of liraglutide tested showed a degree of efficacy”)), in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See* EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

282. As I noted above, I understand that the Board construed the preamble so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2

diabetes as the Board has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Board's interpretation requires in terms of efficacy. That is, in my opinion the prior art would motivate skilled artisans to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide more than a minimal level of efficacy in treating type 2 diabetes.

283. Dr. Rosenstock repeatedly asserts that the prior art did not disclose 1.0 mg once-weekly dosing and that Dr. Bantle and I failed to show that skilled artisans would have optimized with a dosing range of 0.1-1.2 mg. *See, e.g.*, EX2010 (Rosenstock Decl.) ¶ 313. I disagree. As I discussed in my First Declaration and this declaration, skilled artisans would have been motivated to pursue once-weekly 1.0 mg dosing with a reasonable expectation of success based on, among other things, the knowledge of the dosing schemes of the phase I (0.1-1.2 mg) and phase II (0.1-1.6 mg) semaglutide studies. *See, e.g.*, EX1005 (First Decl.) ¶¶ 281-293; *see also* ¶¶ 266-270 above.

284. Dr. Rosenstock states that my assertion that the entire dose range “would have been expected to work” is inconsistent with my opinion about that “Phase II studies define the minimally effective or non-effective dose . . .” EX2010 (Rosenstock Decl.) ¶ 314 (citing EX1005 (First Decl.) ¶ 164) (emphasis omitted). But the quotation that Dr. Rosenstock relies upon is a quote from Tamimi. EX1005

(First Decl.) ¶ 164 (quoting EX1047 (Tamimi) at 3. Indeed, Seino reported that in the liraglutide phase II study doses of even 0.1 mg/day “showed a degree of efficacy.” EX1038 (Seino) at 6. Regardless, the ’462 patent claims do not require any particular level of efficacy. *See* Section IV (Claim Construction).

a. A skilled artisan would have had a reasonable expectation of success in optimizing to reach a method for treating type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

285. Dr. Rosenstock again repeatedly focuses on the absence of prior-art data showing that semaglutide at any range was effective (EX2010 (Rosenstock Decl.) ¶ 318, 323), but as I discussed above (and below), a skilled artisan would not have needed prior-art data for any dose, including the 1.0 mg once-weekly semaglutide dose, to understand that optimizing the dose between at least the 0.8 mg and 1.6 mg or 0.8 mg and 1.2 mg doses would result in a dose with a better balance between efficacy and side effects. *See* ¶¶ 277-279, 297-298, 308, 313; *see also e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 231-237.

286. In particular, skilled artisans would have been aware that in the NCT657 and NCT773 study the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. *See* EX1013 (NCT657) at 15-16; *See* EX1014 (NCT773) at 11. That the 0.8 mg dose was tested in NCT657 and NCT773 with and without titration and the 1.6 mg dose was tested only with titration

would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Moreover, the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg, because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects. Skilled artisans would have had a reasonable expectation that the 1.0 mg dose would have been successful as “[a] method for treating type 2 diabetes” within the meaning of the claims. *See, e.g.*, EX1005 (First Decl.) ¶¶ 231-237.

287. Likewise, the later NCT773 protocol showing that the 1.6 mg dose was reduced to a 1.2 mg dose also indicates that Novo Nordisk may be apprehensive of the highest 1.6 mg dose, suggesting that doses closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further reasonable expectation that the once weekly 1.0 mg semaglutide dose would have been successful as “[a] method for treating type 2

diabetes” within the meaning of the claims. *See e.g.*, EX1005 (First Decl) ¶¶ 234-237.

288. Dr. Rosenstock states that Dr. Bantle and I “do not show that the 1.0 mg dose is an optimum that would be reached by some process they describe.” EX2010 (Rosenstock Decl.) ¶ 319. However, it is my understanding that skilled artisans do not need to be motivated to optimize just one particular dose. As I discussed in my First Declaration, skilled artisans would have been motivated to optimize the weekly dose to one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg. *See* EX1005 (First. Decl.) at Sections IX.C, IX.D, IX.E. And given the disclosure of the reduction of dose from 1.6 mg to 1.2 mg in the NCT773 study (EX1014 (NCT773) at 7), skilled artisans would have been further motivated to optimize between the even more narrow range of 0.8 mg to 1.2 mg semaglutide and would have arrived at the 1.0 mg weekly dose. *Id.*

289. Dr. Rosenstock states that Dr. Bantle and I “do not show that experimentation to optimize for semaglutide was known” (EX2010 (Rosenstock Decl.) ¶ 320) and focuses on the amount of experimentation necessary to show “whether a drug might be safe, effective, and tolerable at any dose (let alone at the specific claimed dose and once-weekly dosing regimen).” EX2010 (Rosenstock Decl.) ¶ 321. I disagree with Dr. Rosenstock. The skilled artisan would have been aware of the known phase I and II study protocols for determining safety,

tolerability, and/or efficacy of semaglutide. EX1013 (NCT657) and EX1014 (NCT773). These studies would have provided the protocol for a skilled artisan to follow to optimize the once-weekly dose of semaglutide.

290. Dr. Rosenstock relies on Blüher to assert that “‘general principles of dose selection’ do not supply a one-size-fits-all solution to drug development” and that “[t]his complex study design [in Blüher] in which both different dose amounts and dose frequencies were tested shows how dose selection experimentation varies even among GLP-1 receptor agonists.” EX2010 (Rosenstock Decl.) ¶ 321 (citing EX2078 (Blüher). First, Blüher was published in 2023 (EX2078 (Blüher) at 1), well after the asserted priority dates, and thus Blüher is not prior art to the ’462 patent. Second, skilled artisans would have been aware of the prior art phase I and II study protocols for determining safety, tolerability, and/or efficacy of semaglutide, which Novo Nordisk would have designed based on internal preclinical studies and knowledge about semaglutide. EX1013 (NCT657); EX1014 (NCT773); *see* EX1005 (First Decl.) ¶¶ 232, 260, 287.

291. Dr. Rosenstock relies on the phase II study in Madsbad 2004 testing liraglutide and asserts that the disclosures in Madsbad contradict my opinion regarding what skilled artisans would have expected from a range of doses tested in a dose-finding study. EX2010 (Rosenstock Decl.) ¶ 322 (discussing EX2075 (Madsbad 2004). But as I discuss above in Section VI.B.7, Madsbad 2004 included

a selection of liraglutide doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects, which is consistent with my opinions regarding dose finding studies in my First Declaration. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 255, 261, 282, 284, 287.

292. Dr. Rosenstock again relies on the Arrowsmith reference stating that “the vast majority of all Phase II clinical trials fail.” EX2010 (Rosenstock Decl.) ¶ 323. But as I discussed above, I disagree with Dr. Rosenstock’s assessment of Arrowsmith and phase II trials. *See* Section VI.B.2. Additionally, before the priority date, skilled artisans would have been aware that Novo Nordisk reported that the NCT657 phase II study “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.” *See* EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12.

293. Dr. Rosenstock states that Dr. Bantle and I ignore that WO421 contemplates co-administration of a DPP-4 inhibitor and semaglutide. EX2010 (Rosenstock Decl.) ¶¶ 325-26. I disagree. As I discuss in my First Declaration, skilled artisans would have understood that WO421’s disclosures to include simultaneous, separate or sequential administration of a GLP-1 receptor agonist (e.g., semaglutide) and a DPP-4 inhibitor. EX1005 (First Decl.) ¶¶ 184-187 (EX1011 (WO421) at 11:14-20, 37:2-24, 65:26-31 (claim 17)). I also stated that

claim 1 of the '462 patent uses the term “comprising,” meaning that additional limitations may also be present in an embodiment of the claims, which would allow for coadministration even if that were described and contemplated by WO421. *See* EX1005 (First Decl.) ¶¶ 184-188. In my opinion, WO421 also disclosed semaglutide and liraglutide monotherapy and skilled artisans would have pursued optimization of the once weekly semaglutide dose for treating type 2 diabetes with semaglutide once weekly, yielding the 1.0 mg once daily dose.

294. Dr. Rosenstock states that Dr. Bantle and I “have also not shown that any experimentation . . . would be nothing more than routine.” EX2010 (Rosenstock Decl.) ¶¶ 327-329. Dr. Rosenstock states that testing every possible dose in the 0.1-1.6 mg or 0.1-1.2 mg dose range would be time consuming and expensive. *Id.* ¶ 327. But I did not suggest testing every possible dose in the 0.1-1.6 mg or 0.1-1.2 mg dose ranges. As I discussed in my First Declaration, skilled artisans would have looked to the narrow range of possible doses to optimize between 0.8 to 1.6 or 0.8 to 1.2 mg. *See, e.g.,* EX1005 (First Decl.) ¶¶ 233-237. Skilled artisans would also have understood that not every possible dose within a range in a dose finding study would need to be tested to determine the effectiveness of a dose because that information could be estimated based on extrapolation from the resulting dose response curve. *See id.* ¶¶ 68-73.

295. I also disagree with Dr. Rosenstock that phase II trials such as NCT657 are “anything but ‘routine’” and would be a “massive undertaking requiring significant funding and planning, subject enrollment and screening, randomization, blinding, medical, safety and ethical monitoring, and reporting.” EX2010 (Rosenstock Decl.) ¶ 328; *see id.* ¶ 329 (relying on the phase II clinical trial results disclosed in the ’462 patent). Although I agree that clinical trials are often time consuming and expensive, the steps that Dr. Rosenstock lists are routinely performed by skilled artisans for thousands of trials each year. *See, e.g.*, EX1279 (Califf) at 4 (listing > 40,000 clinical trials from October 2007-September 2010). Moreover, at the asserted priority dates of the ’462 patent, skilled artisans would have been aware of successful clinical trials of GLP-1 receptor agonists. *See* EX1032 (Knudsen 2004) (discussing the completed phase 2 trials of liraglutide); EX1012 (Lovshin) at 3 (disclosing that “the success of exenatide has accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration.”). And skilled artisans would have been aware that Novo Nordisk reported that the NCT657 clinical trial “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.” EX1282 (Novo Nordisk Form 6-K (May 1, 2009)) at 12.

296. I also disagree with Dr. Rosenstock’s opinion that the 0.1-1.6 mg range in the prior art would have disclosed “at least 320” doses. EX2010 (Rosenstock

Decl.) ¶ 330. As I discussed above and in my First Declaration, in my opinion, the 0.1-1.6 mg range would have disclosed dosing increments of no less than 0.1 mg/dose at the smallest reasonable step size, which would have included at most a group of just 16 doses. *See* Section VIII.A.b., VIII.B.1.a.

297. Moreover, a skilled artisan would have been further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. *See, e.g.*, EX1005 (First Decl.) ¶¶ 231-233; *see also* ¶ 277-279, 308, 313. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg. *Id.*

298. Moreover, skilled artisans would have been aware that in the NCT657 and NCT773 study the 0.8 mg dose was tested with and without titration and the 1.6 mg dose was tested only with titration. *See* EX1013 (NCT657) at 15-16; *See* EX1014 (NCT773) at 11. Therefore, the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that the 0.8 mg dose could be tolerated without titration, and therefore doses lower than 1.6 mg and closer to the 0.8 mg dose would have a better balance between efficacy and side effects. Moreover, the knowledge

of the dose reduction from 1.6 mg to 1.2 mg in the NCT773 trial would narrow the scope of potential doses to consider even further. *See, e.g.*, EX1005 (First Decl.) ¶¶ 234-237.

299. And even considering 320 doses (or 32 doses) as Dr. Rosenstock suggests (EX2010 (Rosenstock Decl.) ¶ 330), skilled artisans would have been motivated to optimize within a narrow range of doses of between 0.8 to 1.6 mg or 0.8 to 1.2 mg semaglutide. *See, e.g.*, EX1005 (First Decl.) ¶¶ 231-237.

300. Dr. Rosenstock mischaracterizes my testimony regarding paragraphs 189-192 in my First Declaration. Dr. Rosenstock states that my “sweeping statement that GLP-1 receptor agonists have efficacy ‘across [a] range’ of doses . . . EX1005 (First Decl.), ¶¶ 189-192),” ignores the differences across the broad compound class. EX2010 (Rosenstock Decl.) ¶ 331. I disagree. In the cited paragraphs, I discussed the liraglutide trial in Seino, which reported that “[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy.” EX1005 (First Decl.) ¶¶ 189-192 (citing (EX1038 (Seino) at 6)). As I discussed in my First Declaration, Seino showed that higher doses of liraglutide resulted in stronger effects (efficacy) than lower doses indicating a clear dose response relationship for HbA_{1c} and a classic sigmoidal dose response curve. EX1005 (First Decl.) ¶¶ 85-86. In my opinion, because of the similarities in structure and mechanism of action between liraglutide and semaglutide, skilled artisans would

have reasonably expected consistency in responses between liraglutide and semaglutide, including that similar to liraglutide, higher doses of semaglutide would produce increased efficacy compared with lower doses. Thus, skilled artisans would have reasonably expected that the once weekly doses of semaglutide tested in NCT657 and NCT773 would exhibit some degree of efficacy as the dose increases. Regardless, the claims do not require any particular level of efficacy.

b. The claims do not require that the once-weekly 1.0 mg dose of semaglutide have a particular level of efficacy or tolerability

301. Dr. Rosenstock repeatedly argues that I have “failed to show POSITA would have had a reasonable expectation of success that a 1.0 mg once-weekly dose of semaglutide would have been safe, effective, and tolerable.” As discussed above, the Board found in its Institution Decision, the preamble, “[a] method for treating type 2 diabetes,” did not require any particular degree or minimum threshold of efficacy. *See* Section IV (Claim Construction) above. Moreover, the claims do not require that the once-weekly 1.0 mg semaglutide dose have a particular level of tolerability. Regardless, as I discussed in my First Declaration, skilled artisans would have understood that for the semaglutide phase I and phase II studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See, e.g.*, EX1005 (First Decl.) ¶¶ 228, 256, 283.

302. I disagree with Dr. Rosenstock that I opined that “liraglutide and semaglutide had the same dose response curves.” EX2010 (Rosenstock Decl.) ¶ 335; *see also id.* ¶ 358. Dr. Rosenstock provides no citation to my testimony. In my First Declaration I stated “because liraglutide was shown to exhibit the classic, sigmoidal dose/response profile for lowering HbA1c, (*see* EX1038 (Seino) at 4, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship for lowering HbA1c.” EX1005 (First Decl.) ¶ 68-73, 293. Further, despite the structural differences between liraglutide and semaglutide, in my opinion, “[t]he animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., EX1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA1c in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau.” *Id.*

303. Thus, my opinion is not that liraglutide and semaglutide “had the same dose response curves” as Dr. Rosenstock states. In my opinion, semaglutide would exhibit a similar overall shaped dose response curve as liraglutide, i.e., a classic, sigmoidal dose/response profile for lowering HbA1c, and thus a skilled artisan

would be able to reasonably expect to see increases in efficacy with increasing doses of semaglutide. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 85-86, 238.

304. For at least the same reasons as discussed above, skilled artisans would not have been concerned that the Phase 3 semaglutide trial was “on hold” as Dr. Rosenstock suggests. EX2010 (Rosenstock Decl.) ¶ 336 (citing EX1035 (Lovshin) Table 1), EX2065 (Novo Nordisk Annual Report 2010)); *see* Section VI.B.3 above.

305. And as I discussed above, my opinions cited by Dr. Rosenstock in paragraphs 189-192 of my First Declaration, discuss liraglutide, not all GLP-1 analogues. EX2010 (Rosenstock Decl.) ¶ 337 (citing EX1005 (First Decl.) ¶¶ 189-192). In my opinion, similar to liraglutide in the Seino trial, skilled artisans would have had a reasonable expectation that the once weekly doses of semaglutide tested in NCT657 and NCT773 would exhibit some degree of efficacy, and increased efficacy as semaglutide doses increase. *See* ¶¶ 300, 302-303 above. Regardless, the claims do not require any particular level of efficacy.

306. In my opinion, given the substantial amount of knowledge available in the prior art about GLP-1 receptor agonists including liraglutide (*see* ¶¶ 300, 302-303 above) and the knowledge of the doses being tested in the phase I (NCT773) and phase II (NCT657) clinical studies, in my opinion, despite the lack of available data from the semaglutide phase I and phase II clinical studies, skilled artisans would

have a reasonable expectation of success in pursuing a 1.0 mg semaglutide dose as “[a] methods for treating type 2 diabetes.”

(i) A skilled artisan would not have needed to have reported results from a semaglutide clinical trial to have had a reasonable expectation of success

307. Dr. Rosenstock opines that Dr. Bantle and I fail to establish a reasonable expectation of success because “their opinions rest on the incorrect premise that, simply because testing had begun in a Phase I (healthy volunteers) trial and a Phase II trial on semaglutide doses other than 1.0 mg, POSITA would somehow have had a reasonable expectation that the claimed 1.0 mg dose would be safe, effective, and tolerable even in the absence of any data.” EX2010 (Rosenstock Decl.) ¶ 340. I disagree.

308. As I stated repeatedly in my First Declaration and in this declaration, my opinion is not only based on the fact that semaglutide was being tested in phase I and phase II trials. My opinion is also based on the wealth of knowledge available about GLP-1 receptor agonists, including liraglutide (*see* ¶¶ 300, 302-303 above), and the knowledge of dose-response curves generally. *See, e.g.*, EX1005 (First Decl.) ¶¶ 70-73, 85-86, 238. In my opinion, skilled artisan would reasonably expect to see increases in efficacy with increasing doses of semaglutide. Moreover, a skilled artisan would have been motivated to optimize to a 1.0 mg dose within the 0.8 mg

to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. *See, e.g.*, EX1005 (First Decl.) ¶¶ 231-234. A skilled artisan would also have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that the 0.8 mg dose could be tolerated without titration, and therefore doses lower than 1.6 mg and closer to the 0.8 mg dose would have a better balance between efficacy and side effects. This would narrow the scope of potential doses to consider even further. Thus, the skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg. *Id.* ¶ 234; *see* ¶¶ 297-298 above. Moreover, the knowledge of the dose reduction from 1.6 mg to 1.2 mg in the NCT773 trial would narrow the scope of potential doses to consider even further. *See, e.g.*, EX1005 (First Decl.) ¶¶ 233-237.

309. Dr. Rosenstock asserts that skilled artisans would have needed to test dosages outside of the doses that were being tested in the NCT657 and NCT773 trials or even abandon semaglutide altogether. EX2010 (Rosenstock Decl.) ¶ 341. For all of the reasons I set forth above, I disagree. *See, e.g.*, ¶ 308.

310. In my First Declaration I stated that “a skilled artisan would have understood that the doses selected in Novo Nordisk’s dose-ranging study were supported by a wealth of internal preclinical studies and knowledge about semaglutide” (EX1005 (First Decl.) ¶ 232), but Dr. Rosenstock states that I “do not even attempt to assert that any of these data (whatever they may have been) were known to POSITA.” EX2010 (Rosenstock Decl.) ¶ 342 (citing EX1005 (First Decl.) ¶ 232)). In my opinion, skilled artisans would not have needed to have had knowledge of the actual preclinical data. That phase I and phase II studies need to be supported by pre-clinical data, in addition to all of the reasons I stated with respect to GLP-1 receptor agonists (including liraglutide) and dose-ranging studies generally, provide a reasonable expectation of success with the once-weekly semaglutide dose for “[a] method for treating type 2 diabetes.” *See, e.g.*, ¶ 308 above.

311. Dr. Rosenstock again references his opinions regarding purported failed clinical trials (EX2010 (Rosenstock Decl.) ¶ 344 (citing Section IX.A)), of which I disagree as set forth above. *See* Section VIII.C.1. Dr. Rosenstock states I ignore the statement in Tamimi stating “[e]xperience tells us that approximately only 1 in 10 drugs that start the clinical phase will make it to the market.” EX2010 (Rosenstock Decl.) ¶ 344 (citing EX1047 (Tamimi) at 1). In my opinion, the referenced statement from Tamimi would not dissuade a skilled artisan from pursuing the 1.0 mg dose for all of the reasons I explain above. *See, e.g.*, ¶ 308 above.

Moreover, the '462 patent claims do not require an FDA approved drug that “make[s] it to the market” as referenced in Tamimi.

312. I disagree with Dr. Rosenstock that skilled artisans would have selected one of the doses that was actually tested in the NCT657 or NCT773 trials (i.e., 0.1, 0.2, 0.4, 0.8, or 1.6 mg). EX2010 (Rosenstock Decl.) ¶ 345. As I discuss above, a skilled artisan would have been motivated to pursue a dose within the range of 0.8 to 1.6 mg (or 0.8 to 1.2 mg), in particular, a dose closer to the 0.8 mg dose, such as 1.0 mg, which would have a better balance between efficacy and side effects. *See, e.g.*, ¶ 308 above.

313. In my opinion, Novo Nordisk selected the doses in the NCT657 study because it was a dose-ranging study to gain information about the dose response curve of a once-weekly 1.0 mg dose of semaglutide. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 255, 261, 282, 284, 287. A skilled artisan would have understood that only a limited number of doses are selected for the dose ranging study, thus, not every possible dose that may be safe, tolerable, and effective would have been tested in the dose ranging study. *See* EX1047 (Tamimi) at 4 (“Phase IIb follows on from the proof of concept in which several dose levels are tested in the target population (dose-ranging studies) to define the minimally effective or non-effective dose and to decide the optimal dose, based on clinical efficacy and safety, to take to the next stage.”). Skilled artisans would have understood that information regarding efficacy and

tolerability of the non-tested doses could be estimated based on extrapolation from the resulting dose response curve. As I discuss above, a skilled artisan would have been motivated to pursue a dose within the range of 0.8 to 1.6 mg (or a dose within the range of 0.8 to 1.2 mg based on the NCT773 study), in particular, a dose closer to the 0.8 mg dose, such as 1.0 mg, which would have a better balance between efficacy and side effects. *See, e.g.*, ¶ 308 above. In my opinion, a skilled artisan could have pursued any of the doses within this range with a reasonable expectation of success for “[a] method for treating type 2 diabetes” within the meaning of the claims. Moreover, the claims do not require any particular level of efficacy. *See* Section IV (Claim Construction).

314. Dr. Rosenstock discusses his experience with clinical trials generally (EX2010 (Rosenstock Decl.) ¶ 347 (citing VI.E.4)), but my opinions are focused on semaglutide and the NCT657 and NCT773 trials, not all other drugs. As I stated in my First Declaration, in my opinion, a skilled artisan would also have understood that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See* EX1047 (Tamimi) at 3; EX1066 (Knudsen 2010b) at 1. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk’s

dose-ranging study were supported by a wealth of internal preclinical studies and knowledge about semaglutide. *See, e.g.*, EX1005 (First Decl.) ¶¶ 260, 287.

315. Dr. Rosenstock states that I failed to address the numerous failures of GLP-1 receptor agonists. EX2010 (Rosenstock Decl.) ¶ 348 (citing Section VI.G)); *see also id.* ¶¶ 349-353 (discussing taspoglutide and albiglutide). But as I discuss above, I disagree with Dr. Rosenstock’s assessment of the purported failures of GLP-1 receptor agonists. *See* Sections VI.B.6, VI.B.8, VII above. In my opinion, skilled artisans would not have been dissuaded from pursuing the once weekly 1.0 mg semaglutide dose as Dr. Rosenstock suggests.

316. Dr. Rosenstock states that I “do not show that there were any data suggesting that semaglutide at any dose (let alone 1.0 mg) would be more effective or more tolerable than other GLP-1 analogues.” EX2010 (Rosenstock Decl.) ¶ 354. In my opinion, that semaglutide would be more tolerable than other GLP-1 analogues is not a requirement of the claims.

317. Dr. Rosenstock also states that skilled artisans would have known that “the ability of [animal] data to predict human clinical outcomes is materially uncertain, and the mere fact that such data had been collected and a drug proceeding to further testing (based in part on animal data) did not provide POSITA with a reasonable expectation of success.” EX2010 (Rosenstock Decl.) ¶ 356 (citing *id.* at Section VI.D.1 and EX2005 (Knight)). As I discuss above, I disagree with Dr.

Rosenstock's assertions regarding animal studies generally and his reliance on Knight (EX2005). See Section VI.B.1 above. In my opinion, skilled artisans would have known that while Knight addresses some disadvantages of translation of animal model data to humans generally, in the case of type 2 diabetes, type 2 diabetic animal models were regularly employed for studying the effects of type 2 diabetes drugs in GLP-1 receptor agonist molecules. *Id.* Indeed, Dr. Rosenstock often relied on animal models of diabetic disease and their predictive information when translated to human disease in his own publications. *Id.*

(ii) A skilled artisan would not have needed to know the specific shape of the semaglutide dose response curve to have had a reasonable expectation of success

318. As I discuss in my First Declaration, a skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. See EX1047 (Tamimi) at 3-4; EX1048 (FDA Exposure Response 2003) at 7; EX1049 (ICH 1994) at 1-2, 4, 6; EX1045 (Shargel) at 81-82, Figs. 19-1 and 19-2; EX1005 (First Decl.) ¶¶ 68-73.

319. Relying on Madsbad 2004, Dr. Rosenstock states that “many drugs, including those used to treat type 2 diabetes, do not adhere to this generic dose

curve.” EX2010 (Rosenstock Decl.) ¶ 357. As I discuss above (see Section VI.B.7), I disagree with Dr. Rosenstock’s opinions regarding how skilled artisans would have interpreted the results of Madsbad 2004 liraglutide clinical study. EX2010 (Rosenstock Decl.) ¶ 322 (discussing EX2075 (Madsbad 2004)).

320. Dr. Rosenstock states that I “conceded that POSITA would not have expected that the dose curve for semaglutide would necessarily be the same as liraglutide’s.” EX2010 (Rosenstock Decl.) ¶ 358 (citing EX2019 (Jusko Tr.) at 96:9-97:3. But I never opined that the dose response curves of liraglutide and semaglutide would be the same. As I discussed above, in my opinion, semaglutide would exhibit a similar overall shaped dose response curve as liraglutide, i.e., a classic, sigmoidal dose/response profile for lowering HbA1c, and thus a skilled artisan would reasonably expect to see increases in efficacy with increasing doses of semaglutide. *See, e.g.*, ¶¶ 302-303 above; *see also* EX1005 (First Decl.) ¶¶ 68-73, 293.

321. Dr. Rosenstock repeats many of the same opinions he stated previously about there being no data or no known dose response curve for semaglutide. EX2010 (Rosenstock Decl.) ¶ 359. But as I have discussed throughout my First Declaration and in this declaration, a skilled artisan would not have needed to have data or a dose response curve for semaglutide to have a reasonable expectation of success. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 233-237, 255, 261, 282, 284, 287.

322. Dr. Rosenstock focuses on the statement from my First Declaration that “Phase II studies define the minimally effective or non-effective dose . . .” EX2010 (Rosenstock Decl.) ¶ 360 (citing EX1005 (First Decl.) ¶¶ 164, 68)). But as I discussed previously, the quotation that Dr. Rosenstock relies upon is a quote from Tamimi. EX1005 (First Decl.) ¶ 164 (quoting EX1047 (Tamimi) at 3). Indeed, Seino reported that in the liraglutide phase II study all doses “showed a degree of efficacy.” EX1038 (Seino) at 6. Regardless, the ’462 patent claims do not require any particular level of efficacy. *See* Section IV (Claim Construction).

323. Dr. Rosenstock states that “it is common that not all doses (or even any doses) tested in a Phase II trial will turn out to be efficacious, safe, and tolerable.” EX2010 (Rosenstock Decl.) 360 (citing Sections VI.D.2 (discussing Phase II failures: 2008-2010 (EX2006)) and VI.G. (discussing “Failed and Withdrawn GLP-1 Receptor Agonists)). As I discussed above, I disagree with Dr. Rosenstock’s opinions relying on Arrowsmith, Rosenstock 2013, and Nordqvist. EX2010 (Rosenstock Decl.) ¶ 360 (citing VI.D.2; VI.G; EX2006 (Arrowsmith); EX2060 (Rosenstock 2013); EX2061 (Nordqvist)); *see* Sections VI.B.2; VI.B.8; VII above. Moreover, Dr. Rosenstock agrees that skilled artisans “would already have assumed safety and efficacy of other doses of semaglutide from the fact of the ongoing trials.” EX2010 (Rosenstock Decl.) ¶ 301.

324. Dr. Rosenstock relies on Madsbad 2004 to assert that the results in Madsbad 2004 with liraglutide contradict my opinion about the skilled artisans understanding that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. EX2010 (Rosenstock Decl.) ¶ 361 (citing EX1005 (First Decl) ¶¶ 68-69, 71-72, 260). But as I discuss above, I disagree with Dr. Rosenstock's opinions regarding Madsbad 2004. *See* Section VI.B.7 above. In my opinion, the highest dose tested in Madsbad 2004 included doses at the top of liraglutide's dose response curve for doses that were not titrated. As discussed above, the highest dose in Madsbad 2004 was selected because previous studies had shown side effects at a higher dose. *Id.* Dr. Rosenstock cites the FDA approved doses of 1.2 and 1.8 mg liraglutide for Victoza (EX2010 (Rosenstock Decl.) ¶ 361) but a skilled artisan would have known that these doses are doses that were titrated to reduce the side effects seen with liraglutide and discussed in Madsbad 2004.

325. Dr. Rosenstock refers to the approved doses from Ozempic® stating that Dr. Bantle and I were “wrong about where doses fell on semaglutide's dose curve,” apparently because Ozempic® includes once-weekly 0.5 mg and 2.0 mg approved doses, the latter of which he says is “well above 1.6 mg value at the top of the ‘range’ in WO421 and Lovshin.” EX2010 (Rosenstock Decl.) ¶ 362 (citing EX2008 (Ozempic Prescribing Information) at 2). But the approved dosing of

Ozempic® does not bear on the skilled artisan's knowledge at the asserted priority dates. As I discussed above, the FDA-approved label for Ozempic® is not prior art as Ozempic® was approved in 2017, well after the latest asserted priority date (June 1, 2012), and the Ozempic® Prescribing Label relied upon by Dr. Rosenstock is the 9/2023 revision. EX2069 (Ozempic® Prescribing Label) at 1. Thus, skilled artisans would not have been aware of the approved dosing for Ozempic® at any of the asserted priority dates.

326. Dr. Rosenstock again questions my reliance on liraglutide (EX2010 (Rosenstock Decl.) ¶¶ 363-370), but as I discussed in my First Declaration and above, I disagree with Dr. Rosenstock's assertions with respect to liraglutide. Regardless of the differences between liraglutide and semaglutide of which skilled artisans would have been aware, in my opinion, semaglutide would exhibit a similar overall shaped dose response curve as liraglutide, i.e., a classic, sigmoidal dose/response profile for lowering HbA1c, and thus a skilled artisan would be able to reasonably expect to see increases in efficacy with increasing doses of semaglutide. See (EX1005 (First Decl.) ¶¶ 68-73, 85-86, 238; *see also* ¶¶ 302-303 above.

327. Dr. Rosenstock suggests that "in the absence of any half-life or potency information," a POSA would have expected that "the weekly dose of semaglutide to have been the approved daily dose of liraglutide (1.2 mg or 1.8 mg) times seven to

maintain the same total weekly dose – not 1.0 mg once-weekly.” EX2010 (Rosenstock Decl.) ¶ 368 (emphasis omitted). I disagree. As I discussed above, my reliance on liraglutide is based on the overall shape of its dose response curve being a classic sigmoidal shape. *See* ¶¶ 302-303 above.

328. In my opinion, a skilled artisan would not be limited to only selecting the once-weekly 1.0 mg semaglutide dose. EX2010 (Rosenstock Decl.) ¶ 369. It is my understanding that for the once-weekly 1.0 mg dose to be obvious, this does not mean that it must be the only dose that a skilled artisan would have selected to pursue. Indeed, as I discussed previously, a skilled artisan would be motivated to select a dose within the range between 0.8 mg to 1.6 mg or 0.8 mg or 1.2 mg. *See, e.g.*, EX1005 (First Decl.) ¶¶ 68-73, 233-237, 255, 261, 282, 284, 287.

329. Relying on Madsbad 2004, Dr. Rosenstock states that “POSITA would have understood . . . that it was possible that even the highest 1.6 mg dose of semaglutide would not have been optimal or even effective --- such that higher doses would have been needed.” EX2010 (Rosenstock Decl.) ¶ 370 (citing EX2075 (Madsbad) and Section VI.D.7). As I discuss above, I disagree with Dr. Rosenstock’s opinions regarding Madsbad 2004 because the Madsbad 2004 study selected doses to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects, which is consistent with my First Declaration. *See* Section VI.B.7 above.

(iii) That the semaglutide phase III trial was “on hold” would not have dissuaded a skilled artisan from pursuing the claimed method

330. Dr. Rosenstock relies on Lund’s disclosure that the semaglutide Phase II trial was “[o]n hold” (EX1035 (Lund) at Table 1) and the Novo Nordisk Annual Report 2010 disclosure that semaglutide’s “Phase 3 initiation was postponed in June 2010” (EX2065 (Novo Nordisk Annual Report 2010) at 26). According to Dr. Rosenstock, this “would have caused POSITA to question the development status of semaglutide in the 2010-2011 timeframe” and conclude that the “Phase III trial was on hold and perhaps something unexpected was found with semaglutide that could have called into question its further development.” Dr. Rosenstock says this would “dissuade[] POSITA from pursuing the claimed invention until more information was known.” EX2010 (Rosenstock Decl.) ¶¶ 372-380.

331. As I discuss above, the Lund and the Novo Nordisk Annual Report 2010’s disclosures would not have caused a skilled artisan to conclude that the semaglutide trials were “[o]n hold” “due to unfavorable outcomes of those trials.” See Section VI.B.3. (Novo Nordisk Annual Report EX2065) above. For example, the Novo Nordisk Annual Report 2010 upon which Dr. Rosenstock replies, discloses that “Phase 3 initiation [of semaglutide] was postponed in June 2010 *pending a long-acting portfolio development strategy decision.*” EX2065 (Novo Nordisk Annual Report 2010) at 26 (emphasis added). This indicates that Phase 3 of semaglutide was

not to be discontinued, but that Novo Nordisk was in an evaluation stage of its long-acting GLP-1 receptor agonist portfolio. If the semaglutide phase I and II trials had “unfavorable trial outcomes” as Dr. Rosenstock suggests, semaglutide would likely no longer be listed in the “Pipeline overview” section of the Novo Nordisk Annual Report 2010. *Id.* And for the reasons I describe above, there were many reasons for POSAs to conclude that Novo Nordisk viewed semaglutide as a promising treatment for type 2 diabetes. *See* Sections VI.A.6, VI.B.3 above.

3. Ground 3: Claims 1-10 of the '462 Patent Would Have Been Obvious Over WO421

332. For the reasons stated in my First Declaration, I still conclude that claims 1-10 of the '462 patent would have been obvious over WO421. *See, e.g.,* EX1005 (First Decl.) ¶¶ 220-246.

a. Claim 1 would have been obvious over WO '421 considering the '424 publication

333. Dr. Rosenstock states that he disagrees with my opinions regarding motivation and reasonable expectation of success. EX2010 (Rosenstock Decl.) ¶ 381 (citing Sections IX.A, IX.B). For at least the reasons I set forth above, in my opinion, a skilled artisan would have been motivated with a reasonable expectation of success. *See* Sections VIII.C.1, VIII.C.2.

b. Claims 2-3 would have been obvious over WO '421 considering the '424 publication

334. In my opinion, claims 2-3 of the '462 patent would have been obvious over WO421. Dr. Rosenstock states that he disagrees with my opinions. EX2010 (Rosenstock Decl.) ¶ 384 (citing Sections IX.A, IX.B, VIII.A). For at least the reasons I set forth above, I disagree with Dr. Rosenstock. *See* Sections VIII.C.1, VIII.C.2, VIII.A, respectively.

c. Claims 4-10 would have been obvious over WO '421 considering the '424 publication

335. It is my understanding that Mylan's formulation expert, Dr. Dalby, submitted an expert declaration and provided an opinion that claims 4-10 of the '462 patent would have been obvious over WO421 considering the '424 publication. It is therefore my opinion that claims 4-10 of the '462 patent would have been obvious over WO421 considering the '424 publication for the reasons discussed above and for the reasons discussed by Dr. Dalby.

4. Ground 4: Claims 1-10 of the '462 Patent Would Have Been Obvious Over WO537 Considering Lovshin

336. For the reasons stated in my First Declaration, I still conclude that claims 1-10 of the '462 patent would have been obvious over WO537 considering Lovshin. *See, e.g.*, EX1005 (First Decl.) ¶¶ 247-274.

337. Dr. Rosenstock states that he disagrees with my opinions regarding motivation and reasonable expectation of success. EX2010 (Rosenstock Decl.) ¶ 386

(citing Sections IX.A, IX.B). For at least the reasons I set forth above, I disagree with Dr. Rosenstock. See Sections VIII.C.1, VIII.C.2.

a. Claim 1 would have been obvious over WO537 considering Lovshin

338. Independent claim 1 recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” In my opinion, claim 1 of the ’462 patent would have been obvious over WO537 considering Lovshin.

339. Dr. Rosenstock disagrees with my opinion that the 0.1-1.6 mg range in Lovshin discloses the once-weekly 1.0 mg semaglutide dose. EX2010 (Rosenstock Decl.) ¶ 390 (citing Section VIII.B). As I discuss above, I disagree with Dr. Rosenstock’s opinions. See Section VIII.B above.

340. Dr. Rosenstock states that he disagrees with my opinions regarding motivation and reasonable expectation of success. EX2010 (Rosenstock Decl.) ¶ 386 (citing Sections IX.A, IX.B). For at least the reasons I set forth above, I disagree with Dr. Rosenstock. See Sections VIII.C.1, VIII.C.2.

341. I disagree with Dr. Rosenstock’s opinions regarding the purported failure rates of clinical trials in Arrowsmith as discussed above. EX2010 (Rosenstock Decl.) ¶ 392; see Section VI.B.2. above.

342. Dr. Rosenstock states that skilled artisans would not have known what the magnitude of the maximal treatment effect would have been because there was no publicly available known semaglutide data at any dose in any animal or humans regarding side effects. EX2010 (Rosenstock Decl.) ¶ 393. But as I discussed above, a skilled artisan would not have needed prior-art data for any dose, including the 1.0 mg once-weekly semaglutide dose, to understand that optimizing the dose between at least the 0.8 mg and 1.6 mg or 0.8 mg and 1.2 mg doses would result in a dose with a better balance between efficacy and side effects. See ¶¶ 285-287 above.

343. Dr. Rosenstock also asserts that the 1.0 mg dose would not have been “obvious to try,” including because “there were not a finite number of identified predictable solutions.” EX2010 (Rosenstock Decl.) ¶ 394 (citing VIII.A.2; Section IX.A-IX.B)). For at least the reasons I discuss above, in my opinion, there were a finite number of identified predictable solutions and a once-weekly 1.0 mg semaglutide dose would be obvious to try. See Sections VIII.A.B, VIII.C.1, VIII.C.2 above.

b. Claims 2 and 3 would have been obvious over WO537 considering Lovshin

344. In my opinion, claims 2 and 3 of the '462 patent would have been obvious over WO537 considering Lovshin. Dr. Rosenstock states that he disagrees with my opinions. EX2010 (Rosenstock Decl.) ¶ 395 (citing *id.* ¶ 263). For at least

the reasons I set forth in my First Declaration and above, I disagree with Dr. Rosenstock. See EX1005 (First Decl.) ¶¶ 268-273; Sections VIII.A.2., VIII.B.2 above.

c. Claims 4-10 would have been obvious over WO537 considering Lovshin

345. It is my understanding that Mylan's formulation expert, Dr. Dalby submitted an expert declaration and provided an opinion that claims 4-10 of the '462 patent would have been obvious over WO537 considering Lovshin. It is therefore my opinion that claims 4-10 of the '462 patent would have been obvious over WO537 considering Lovshin for the reasons discussed above and for the reasons discussed by Dr. Dalby.

5. Ground 5: Claims 1-10 of the '462 Patent Would Have Been Obvious Over NCT657 and NCT773

346. For the reasons stated in my First Declaration, I still conclude that claims 1-10 of the '462 patent would have been obvious over NCT657 and NCT773. See, e.g., EX1005 (First Decl.) ¶¶ 275-301. As I discussed above, I disagree with Dr. Rosenstock's opinions regarding obviousness over NCT657 and NCT773. EX2010 (Rosenstock Decl.) ¶ 398 (citing Section IX.A, X.B); see Sections VIII.C.1, VIII.C.2 above.

347. Dr. Rosenstock states that the portions of NCT773 that disclose the 1.2 mg dose are not prior art. EX2010 (Rosenstock Decl.) ¶ 399. I understand that

whether the disclosures regarding NCT773 are prior art is a legal issue. In my opinion, the disclosure of NCT773 of the 1.2 mg dose is not required for my opinions regarding anticipation or obviousness. My opinions regarding the 1.2 mg dose in NCT773 merely confirms my opinion regarding the prior art, including the disclosure in the NCT657 study. As I discussed above, a skilled artisan would have understood that optimizing the dose between at least the 0.8 mg and 1.6 mg or 0.8 mg and 1.2 mg doses would result in a dose with a better balance between efficacy and side effects. See ¶¶ 285-287 above.

a. Claim 1 would have been obvious over NCT657 and NCT773

348. Dr. Rosenstock again asserts that he disagrees with my opinions regarding obviousness over NCT657 and NCT773. EX2010 (Rosenstock Decl.) ¶ 401 (citing Section IX.A, X.B). As I discuss above, in my opinion, a skilled artisan would have been motivated with a reasonable expectation of success in pursuing the once-weekly 1.0 mg semaglutide dose as a method for treating type 2 diabetes. See Sections VIII.C.1, VIII.C.2 above.

349. I disagree with Dr. Rosenstock's assertion that "POSITA would not have expected, from the mere fact that a Phase II study and a Phase I study existed, that any particular dose (let alone a dose that was not even tested) would be safe,

efficacious, and tolerable.” EX2010 (Rosenstock Decl.) ¶ 403 (citing *id.* ¶¶ 300-303); see ¶¶ 265-274 above.

350. Dr. Rosenstock again repeats his assertion that the results of the phase I and phase II semaglutide studies were not available and skilled artisans would have been aware that clinical studies often fail. EX2010 (Rosenstock Decl.) ¶ 404 (citing EX2006 (Arrowsmith); EX2010 (Rosenstock Decl.) ¶¶ 194-196, 303-304. As I discuss above, skilled artisans would not have needed to see the results of the phase I and phase II to have been motivated with a reasonable expectation of success. Moreover, the skilled artisans would not have been dissuaded from the 1.0 mg semaglutide dose based on the purported clinical trials that Dr. Rosenstock discusses. See Section VI.B.2 above.

351. As I discussed above, I disagree with Dr. Rosenstock regarding the fact that the 1.0 mg semaglutide dose was not tested in any of the prior art of which I rely upon. EX2010 (Rosenstock Decl.) ¶ 405 (citing Sections IX.A., IX.B). See Sections VIII.C.1, VIII.C.2 above.

352. I also disagree with Dr. Rosenstock’s reliance on Knight (EX2005) and his opinion that animal models are “insufficiently predictive of human outcomes.” EX2010 (Rosenstock Decl.) ¶ 405 (citing Sections VI.D.1 and EX2005 (Knight) at 6); see also EX2010 (Rosenstock Decl.) ¶ 389. As I discussed above, in my opinion, skilled artisans would have known that while Knight addresses some disadvantages

of translation of animal model data to humans generally, in the case of type 2 diabetes, type 2 diabetic animal models were regularly employed for studying the effects of type 2 diabetes drugs in GLP-1 receptor agonist molecules. *See* Section VI.B.1 above. Indeed, Dr. Rosenstock also relied on animal models of diabetic disease and their predictive information about human disease in his own publications. *Id.*

353. Dr. Rosenstock again asserts that “[i]n the absence of any data, POSITA would not have assumed that semaglutide’s dose response curve mimicked that of liraglutide, and in any event would not have known the doses at which any plateau would have occurred.” EX2010 (Rosenstock Decl.) ¶ 407 (citing ¶ 359). I disagree. As I discussed above in ¶ 302, in my opinion, semaglutide would exhibit a similar overall shaped dose response curve as liraglutide, i.e., a classic, sigmoidal dose/response profile for lowering HbA1c, and thus a skilled artisan would be able to reasonably expect to see increases in efficacy with increasing doses of semaglutide. *See* EX1005 (First Decl.) ¶¶ 70-73, 85-86, 238, 293.

354. Dr. Rosenstock states that “POSITA would have understood the removal of the 1.6 mg maximum dose would very likely have been to test a lower dose in a particular patient population that might have been expected to have adverse reactions to the 1.6 mg dose or to react differently to semaglutide due to differences in the pathophysiology of their type 2 diabetes.” EX2010 (Rosenstock Decl.) ¶ 412;

see also id. ¶¶ 409-411; Section VI.E.2 (EX1038 (Seino)); Section VI.D.4 (EX2067 (Report on the Deliberation Results)); Section VI.D.5 (EX2066 (Kim)). In my opinion, skilled artisans would not have dismissed the teachings of NCT773 because some of the subjects were Japanese but would have considered the reduction from 1.6 mg to 1.2 mg semaglutide when optimizing the once weekly 1.0 mg dose. Indeed, NCT773 stated that it was a trial “conducted in Europe” “to assess and compare the safety and tolerability” of weekly subcutaneous injections of semaglutide in “Japanese and Caucasian subjects.” EX1014 (NCT773) at 7; *id.* at 11. Thus, the subjects who were administered semaglutide in the NCT773 trial were Japanese and Caucasian. Moreover, the claims of the ’462 patent are not limited to any particular population, such as race or nationality. Thus, a POSA would have known that the method of claim 1 of the ’462 patent would be optimized to a dose that could be applied to broad patient population and would have considered the data for all available populations. *See also* Section VI.A.7; Section VI.B.4; Section VI.B.5 above.

355. Further, an earlier version of the NCT773 protocol stated “[d]ose to be determined based on safety and tolerability of previous dose steps. This dose is optional and will be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” EX1014 (NCT773) at 11. The “[d]ose to be determined” ultimately became the 1.2 mg dose. *Id.* at 7 (disclosing maximal dose of 1.2 mg once weekly for 6 weeks).

Thus, skilled artisans would have considered the reduction in maximal dose from 1.6 mg to 1.2 mg was likely to mitigate tolerability issues with the higher dose. *Id.* at 11.

356. Dr. Rosenstock again repeats his assertion regarding the purported “very high failure rate of clinical trials.” EX2010 (Rosenstock Decl.) ¶ 415 (citing *id.* ¶¶ 303-304; EX2006 (Arrowsmith)). As I discuss above, skilled artisans would not have been dissuaded from the 1.0 mg semaglutide dose based on the purported failed clinical trials that Dr. Rosenstock discusses. *See* Section VI.B.2, ¶¶ 168-171, 274. And contrary to Dr. Rosenstock’s assertion that I failed to explain why a skilled artisan would have selected the 1.0 mg dose as opposed to one of the other tested doses at the lower or higher end of the trial ranges (EX2010 (Rosenstock Decl.) ¶ 416), I provided a detailed analysis in my First Declaration of why skilled artisans would have been motivated to pursue the weekly 1.0 mg semaglutide dose for treating type 2 diabetes with a reasonable expectation of success. *See* EX1005 (First Decl.) at Section IX.E.1.b.

357. Dr. Rosenstock also asserts that the 1.0 mg dose would not have been “obvious to try” (EX2010 (Rosenstock Decl.) ¶ 417), including because “there were not a finite number of identified predictable solutions.” *Id.* ¶ 394 (citing Sections IX.A-IX.B)). For at least the reasons I discuss above, in my opinion, there were a finite number of identified predictable solutions and a once-weekly 1.0 mg

semaglutide dose would have been obvious to try. See Sections VIII.C.1, VIII.C.2 above.

b. Claim 2 and 3 would have been obvious over NCT657 and NCT773

358. In my opinion, claims 2 and 3 of the '462 patent would have been obvious over NCT657 and NCT773. Dr. Rosenstock states that he disagrees with my opinions. EX2010 (Rosenstock Decl.) ¶ 418 (citing *id.* ¶ 263). For at least the reasons I set forth in my First Declaration and above, I disagree with Dr. Rosenstock. See EX1005 (First Decl.) ¶¶ 295-300; Sections VIII.A.2, VIII.B.2 above.

c. Claims 4-10 would have been obvious over NCT657, NCT773, and the '424 publication

359. As I discussed above, it is my opinion that claims 1-3 of the '462 patent would have been obvious over NCT657 and NCT773. It is my understanding that Mylan's formulation expert, Dr. Dalby, submitted an expert declaration and provided an opinion that claims 4-10 of the '462 patent would have been obvious over NCT657, NCT773, and the '424 publication. It is therefore my opinion that claims 4-10 of the '462 patent would have been obvious over NCT657, NCT773, and the '424 publication for the reasons discussed above and for the reasons discussed by Dr. Dalby.

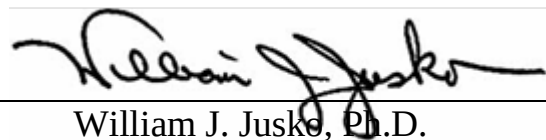
IX. CONCLUSION

360. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

361. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and 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.

Dated: 5/22/2024

By:



William J. Jusko, Ph.D.

EXHIBIT A

EXHIBIT A

Exhibit No.	Description
1001	U.S. Patent No. 10,335,462
1002	U.S. Patent No. 10,335,462 file history excerpts
1011	International Patent App. Pub. No. WO 2011/138421
1012	Lovshin, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus</i> , 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)
1013	Clinical Trial No. NCT00696657
1014	Clinical Trial No. NCT00851773
1015	International Patent App. Pub. No. WO 2006/097537
1016	U.S. Patent App. Pub. No. US2007/0010424
1017	U.S. Patent No. 5,512,549
1019	Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)
1022	Drab, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects</i> , 30 PHARMACOTHERAPY 609 (2010)
1027	Holst, <i>Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut</i> , 211 (2) FEBS LETTERS 169 (1987)
1031	Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26 DRUGS OF THE FUTURE 677 (2001)
1032	Knudsen, <i>Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47 J. MED. CHEMISTRY 4128 (2004)
1035	Lund, <i>Emerging GLP-1 Receptor Agonists</i> , 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)

Exhibit No.	Description
1036	Mojsov, <i>Insulinotropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas</i> , 79 J. CLIN. INVEST. 616 (1987)
1038	Seino, <i>Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes</i> , 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)
1039	Victoza, PHYSICIANS' DESK REFERENCE (65th ed. 2010)
1042	International Patent App. Pub. No. WO 91/11457
1043	U.S. Patent App. Pub. No. 2004/0102486
1044	Rohatagi, <i>Model-Based Development of a PPARγ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs</i> , 48 J. CLIN. PHARM. 1420 (2008)
1045	Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)
1046	Yun, <i>Pharmacokinetic and Pharmacodynamic Modelling of the Effects of Glimepiride on Insulin Secretion and Glucose Lowering in Healthy Humans</i> , 31 J. CLIN. PHARM. & THER. 469 (2006)
1047	Tamimi, <i>Drug Development: From Concept to Marketing!</i> , 113 NEPHRON CLIN PRACT C125 (2009)
1048	FDA Guidance for Industry, <i>Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications</i> (Apr. 2003)
1049	International Conference on Harmonisation; <i>Dose-Response Information to Support Drug Registration; Guideline; Availability</i> , 59 Fed. Reg. 55972 (Nov. 9, 1994) ("ICH 1994")
1050	Garber, <i>Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial</i> , 102 AM. J. MED. 491 (1997)

Exhibit No.	Description
1051	Landersdorfer, <i>Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus</i> , 47(7) CLIN PHARMACOKINET 417 (2008)
1052	Madsbad, <i>An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists - Available Efficacy and Safety Data and Perspectives for the Future</i> , 13 DIABETES, OBESITY & METABOLISM 394 (2011)
1053	Møller, <i>Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test</i> , 38 J. PHARMACOKINET PHARMACODYN 713 (2011)
1054	Landersdorfer, <i>Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV</i> , 73 Br J Clin Pharmacol 391 (2011) (“Landersdorfer 2011”)
1055	Landersdorfer, <i>Mechanism-Based Population Modelling of the Effects of Vildagliptin on GLP-1, Glucose and Insulin in Patients with Type 2 Diabetes</i> , 73 BR J CLIN PHARMACOL 373 (2011) (“Landersdorfer 2011b”)
1057	International Patent App. Pub. No. WO 2011/073328
1058	Blonde, <i>Comparison of Liraglutide Versus Other Incretin-Related Anti-Hyperglycaemic Agents</i> , 14 (suppl. 2) DIABETES, OBESITY & METABOLISM 20 (2012)
1059	Murphy, <i>Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus</i> , 46 ANN PHARMACOTHER 812 (2012)
1060	International Patent App. Pub. No. WO 2011/058193
1061	U.S. Patent App. Pub. No. 2011/0166321
1062	Zarin, <i>The ClinicalTrials.gov Results Database—Update and Key Issues</i> , 364 NEW ENGL. J. MED. 852 (2011)

Exhibit No.	Description
1063	Kirillova, <i>Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?</i> , 7(6) PLoS ONE 1 (2012)
1064	Monami, <i>Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis</i> , 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)
1065	Tasneem, <i>The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty</i> , 7(3) PLoS ONE 1(2012)
1066	Knudsen, <i>Liraglutide: The Therapeutic Promise from Animal Models</i> , 64(suppl 167) INT J CLIN PRACT 4 (2010) (“Knudsen 2010b”)
1078	U.S. Patent App. Pub. No. 2004/0102486
1084	EMA, <i>ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals</i> (June 2001)
1130	Novo Nordisk Annual Report 2011
1131	Novo Nordisk Form 6-K (Feb. 2, 2011)
1137	Bhansali et al., <i>Historical Overview of Incretin Based Therapies</i> , 58 SUPPL. TO JAPI 10 (2010)
1279	Califf, <i>Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010</i> , 307 J. Am. Med. Ass’n 1838 (2012)
1280	Knight, <i>The Beginning of the End for Chimpanzee Experiments?</i> , 3 PHILOSOPHY, ETHICS, & HUMANITIES IN MED. 1 (2008)
1282	Novo Nordisk Form 6-K (May 1, 2009))
1283	Novo Nordisk 2010-2011 Pipeline
1284	Marre, <i>GLP-1 Receptor Agonists Today</i> , 93 DIABETES RSCH & CLIN. PRACTICE 317 (2011)
1285	Novo Nordisk Earnings Call (Feb. 2, 2012)

Exhibit No.	Description
1287	Kendall, <i>Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients with Type 2 Diabetes Treated with Metformin and a Sulfonylurea</i> , 28 DIABETES CARE 1083 (2005)
1289	Rees, <i>Animal Models of Diabetes Mellitus</i> , 22 DIABET. MED. 359 (2005)
1290	Chatzigeorgiou et al., <i>The Use of Animal Models in the Study of Diabetes Mellitus</i> , 23 IN VIVO 245 (2009)
1291	Rosenstock, <i>Early Diabetic Nephropathy: Assessment and Potential Therapeutic Interventions</i> , 9 DIABETES CARE 529 (1986)
1302	Reply Declaration of Allen Spiegel, M.D.
1304	Reply Declaration of Arthur Z. Schwartzbard, M.D.
1306	Reply Declaration of Steven Coca, D.O., M.S.
1308	Reply Declaration of Deforest McDuff, Ph.D.
2004	Miller, M., et al., <i>Low Viscosity Highly Concentrated Injectable Nonaqueous Suspensions of Lysozyme Microparticles</i> , Langmuir, Author Manuscript (2011), PMC 2011 (Feb 17)
2005	Knight, A., <i>Systematic Reviews of Animal Experiments Demonstrate Poor Contributions Toward Human Healthcare</i> , Reviews on Recent Clinical Trials, Vol.3, Issue 2, 89-96 (2008)
2006	Arrowsmith, J., <i>Phase II failures: 2008–2010</i> , Nature Reviews, Drug Discovery, Vol. 10 (May 2011)
2010	Declaration of Julio Rosenstock, M.D.
2019	Transcript of January 5, 2024 Deposition of William J. Jusko, Ph.D.
2060	Rosenstock, J., et al., <i>The Fate of Taspoglutide, a Weekly GLP-1 Receptor Agonist, Versus Twice-Daily Exenatide for Type 2 Diabetes</i> , Diabetes Care, Vol.36, 498-504 (March 2013)

Exhibit No.	Description
2061	Nordqvist, C., <i>Experimental Diabetes Drug Taspoglutide Late-Stage Trials Suspended</i> , available at https://www.medicalnewstoday.com/articles/200893#1 (September 13, 2010)
2062	Rosenstock, J., et al., <i>Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes</i> , <i>Diabetes Care</i> , Vol.32, Issue 10, 1880-1886 (October 2009)
2063	OPTUMRx, <i>Tanzeum® (albiglutide) – Drug Discontinuation</i> , available at https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_tanzeum_2017-0801.pdf (2017)
2064	Synapse, <i>Pegylated GLP-1 analogue (LY2428757) – (Eli Lilly & Co.)</i> , available at https://synapse.patsnap.com/drug/482a547adeba4170ab23efa225fb966d (last updated December 27, 2023)
2065	Novo Nordisk Annual Report 2010 (February 1, 2011)
2066	Kim, K., et al., <i>Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms</i> , <i>J Clin Pharmacol</i> , Vol.44, 1083-1105 (2004)
2067	Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, <i>Report on the Deliberation Results</i> , available at https://www.pmda.go.jp/files/000153180.pdf (December 3, 2009)
2068	Victoza® Prescribing Information (January 2010)
2069	Ozempic® Prescribing Information (September 2023)
2070	NCT03144271, <i>Dose Escalation of Single Subcutaneous Doses of NNC 0113-0217 to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics in Healthy Male Subjects</i> , available at https://clinicaltrials.gov/study/NCT03144271 (last visited December 28, 2023)

Exhibit No.	Description
2075	Madsbad, S. et al., <i>Improved Glycemic Control With No Weight Increase in Patients With Type 2 Diabetes After Once-Daily Treatment With the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)</i> , Diabetes Care, Vol.27, Issue 6, 1335-1342 (June 2004)
2077	Mueller, C., <i>University of South Carolina Upstate, CHEM U109 Chemistry of Living Things, 9.1:Solutions</i> , available at https://chem.libretexts.org/Courses/University_of_South_Carolina_Upstate/USC_Upstate%3A_CHEM_U109__Chemistry_of_Living_Things_(Mueller)/09%3A_Solutions/9.1%3A_Solutions (last visited January 16, 2024)
2078	Blüher, M. et al., <i>Dose-response effects on HbA1c and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomized clinical trial</i> , Diabetologia (2023), available at https://link.springer.com/content/pdf/10.1007/s00125-023-06053-9.pdf
Paper No. 10	Decision Granting Institution of <i>Inter Partes</i> Review 35 U.S.C. § 314