IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FERRING PHARMACEUTICALS INC., FERRING INTERNATIONAL CENTER, S.A., FERRING B.V., and POLYPEPTIDE LABORATORIES A/S,	)	
Plaintiffs,	)	
	)	C.A. No. 20-431 (MN)
v.	)	
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	

MEMORANDUM OPINION

Mary W. Bourke, Dana K. Severance, Daniel M. Attaway, John B. Bourke, WOMBLE BOND DICKINSON (US) LLP, Wilmington, DE; Joshua P. Davis, WOMBLE BOND DICKINSON (US) LLP, Houston, TX – Attorneys for Plaintiffs

Brian E. Farnan, Michael J. Farnan, FARNAN LLP, Wilmington, DE; Imron T. Aly, Joel M. Wallace, Thomas R. Rammer, SCHIFF HARDIN, LLP, Chicago, IL; John K. Hsu, SCHIFF HARDIN LLP, Washington, DC – Attorneys for Defendant

December 12, 2022
Wilmington, Delaware

NOREIKA, U.S. DISTRICT JUDGE:

Plaintiffs Ferring Pharmaceuticals Inc., Ferring International Center, S.A., Ferring B.V. and Polypeptide Laboratories A/S (collectively, "Plaintiffs" or "Ferring") brought this Hatch-Waxman action against Defendant Fresenius Kabi USA, LLC ("Defendant" or "Fresenius"). Fresenius filed Abbreviated New Drug Application No. 211999 ("Fresenius's ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market a generic version ("ANDA product") of Ferring's FIRMAGON® product before the expiration of United States Patent Nos. 9,579,359 ("the '359 patent"), 10,729,739 ("the '739 patent"), 10,973,870 ("the '870 patent"), 9,415,085 ("the '085 patent"), 10,695,398 ("the '398 patent"), 8,828,938 ("the '938 patent"), 8,841,081 ("the '081 patent") and 9,877,999 ("the '999 patent"). Plaintiffs allege that Fresenius infringes claim 10 of the '938 patent and that with its ANDA product, Fresenius will induce infringement of claims 3 and 13 of the '359 patent, claims 16 and 26 of the '739 patent, claims 3, 5, 8 and 14 of the '870 patent, claim 2 of the '085 patent and claim 2 of the '398 patent.[1] The parties stipulated to infringement of claim 10 of the '938 patent (D.I. 189), but Fresenius denies inducing infringement of the other asserted claims and asserts that all asserted claims are invalid.

The Court construed disputed claim terms on June 14, 2021. (D.I. 141). In January 2022, the Court conducted a four-day bench trial. (*See* D.I. 197-200 ("Tr.")). The parties completed post-trial briefing on March 11, 2022. (D.I. 202, 204, 208, 211, 215, 217). With their briefing, the parties submitted proposed findings of fact. (D.I. 203, 205, 209, 210). The Court heard additional argument on July 27, 2022. (D.I. 219).

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[1] The parties agreed to stipulate to the dismissal of U.S. Patent Nos. 8,841,081 and 9,877,999, but could not agree whether that dismissal should be with or without prejudice. (D.I. 180). The Court addresses that dispute *infra*.

After considering the entire record and the applicable law, the Court concludes that: (1) Ferring has proved that Fresenius will induce infringement of claims 3 and 13 of the '359 patent and claims 16 and 26 of the '739 patent and that Fresenius infringes claim 10 of the '938 patent;[2] (2) Ferring has not proved that Fresenius will induce infringement of any of claims 3, 5, 8 and 14 of the '870 patent, claim 2 of the '085 patent and claim 2 of the '398 patent; (3) Fresenius has proved that claims 3 and 13 of the '359 patent and claims 16 and 26 of the '739 patent are invalid for obviousness; (4) Fresenius has not proved that any of claims 3, 5, 8 and 14 of the '870 patent, claim 2 of the '085 patent, claim 2 of the '398 patent and claim 10 of the '938 patent is invalid. This opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a) of the Federal Rules of Civil Procedure.

I. FINDINGS OF FACT ("FF")

A. The Parties

1. Plaintiff Ferring Pharmaceuticals Inc. ("Ferring Pharma") is a Delaware corporation having an office in Parsippany, New Jersey. (D.I. 169-1 ¶ 1).

2. Plaintiff Ferring International Center S.A ("FICSA") is a Swiss private limited liability company having an office in Switzerland. (*Id.* ¶ 2).

3. Plaintiff Ferring B.V. is a Dutch private limited liability company having an office in the Netherlands. (*Id.* ¶ 3).

4. Plaintiff PolyPeptide Laboratories A/S ("PPL") is a company organized and existing under the laws of Denmark and having its registered offices in Denmark. (*Id.* ¶ 4).

[2] Defendant stipulated to infringement of claim 10 of the '938 patent. (D.I. 189).

5. Defendant Fresenius Kabi USA, LLC is a corporation organized and existing under the laws of Delaware and having its principal place of business at Three Corporate Drive, Lake Zurich, Illinois 60047. (*Id.* ¶ 5).

B. Prostate Cancer Treatment

6. Prostate cancer is hormone-sensitive and testosterone promotes growth of the cancer. (Tr. at 46:21-25).

7. Treating advanced prostate cancer may require medically castrating patients by lowering their testosterone level to below 0.5 nanograms per milliliter. (Tr. at 46:21-47:2).

8. One method of treating prostate cancer uses a Gonadotrophin-releasing hormone ("GnRH") agonist, which binds to receptors in the pituitary gland. This initially stimulates production of testosterone (a phenomenon known as a "testosterone flare" or "testosterone spike") and then by negative feedback, reduces testosterone to the medical castration level. (Tr. at 47:3-17; JTX-4 at 1:62-2:34).

9. Leuprolide (brand name Lupron®) is an example of a GnRH agonist. (Tr. at 75:7-8; PTX-356).

10. Another method of treating prostate cancer uses a GnRH antagonist, which blocks the production of pituitary hormones, resulting in the suppression of testosterone such that the medical castration level is achieved without causing a testosterone spike. (*Id.*).

11. Degarelix is a selective GnRH antagonist that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of gonadotrophins and consequently testosterone, without inducing a testosterone spike. (JTX-4 at 10:42-51).

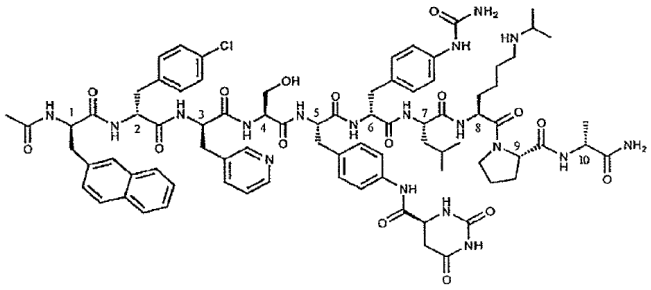
12. Degarelix was developed in the 1990s. (Tr. at 79:14-21). It was known to be a GnRH antagonist useful for "the long-term inhibition of testosterone and progesterone secretion

in GnRH-related conditions such as steroid-dependent tumors" prior to the priority date of any of the asserted patents. (*Id.*; DTX-040_5).

13. Ferring patented degarelix in the United States with U.S. Patent No. 5,925,730 (DTX-239), which is now expired. (*See* DTX-040_5).

14. Degarelix is a complex synthetic decapeptide with the structure shown:

FIGURE 1



(JTX-4, Figure 1).

15. Compared to treatment with a GnRH agonist, treatment with degarelix reduces the likelihood of certain side effects, including a testosterone spike, and administering degarelix naturally results in a decreased likelihood of certain side effects, including musculoskeletal and connective tissue disorders, urinary tract infections and cardiovascular events. (Tr. at 456:23-457:7 (Dr. Shore testifying that "[i]f a doctor gives degarelix to a patient with locally advanced prostate cancer, that patient will experience a reduced likelihood of experiencing arthralgia [or a musculoskeletal side effect] as compared to treatment with leuprolide"); Tr. at 284:16-285:6 (Dr. Yun testifying that "in dosing degarelix, you will necessarily naturally and inherently avoid any of the spiked side effects [and non-spiked side effects] because none of the patients who received degarelix will experience those side effects.")).

C. The Patents-in-Suit

1. The Side Effect Patents

16. The ’359 patent, the ’739 patent and the ’870 patent (collectively, the “side effect patents”) are titled “Method of Treating Prostate Cancer with GnRH Antagonist” and name Tine Kold Olesen, Bo-Eric Persson, Per Cantor, Egbert A. van der Meulen and Jens-Kristian Slott Jensen as inventors. (D.I. 169-1 ¶¶ 12, 14, 16). The ’359 patent issued on February 28, 2017; the ’739 patent issued on August 4, 2020; and the ’870 patent issued on April 13, 2021. (D.I. 169-1 ¶¶ 12, 14, 16). These patents share a common specification and claim priority to U.S. Provisional Application No. 61/027,741, which was filed on February 11, 2008.

17. Ferring B.V. is the owner by assignment of the side effect patents and Ferring Pharma is an exclusive licensee. (D.I. 169-1 ¶¶ 13, 15, 17).

18. The side effect patents are listed in the FDA’s APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (“the Orange Book”) as covering FIRMAGON. (D.I. 169-1 ¶ 28).

19. Plaintiffs assert claims 3 and 13 of the ’359 patent. Claims 3 and 13 are dependent on claim 1, which claims:

> A method of treating prostate cancer in a subject with a reduced likelihood of causing a testosterone spike or other gonadotrophin releasing hormone (GnRH) agonist side effect comprising:
>
> administering an initial dose of 160-320 mg of degarelix to the subject, wherein the initial dose is administered as two subcutaneous injections; and
>
> administering a maintenance dose of 60-160 mg of degarelix to the subject once every 20-36 days thereafter, wherein the maintenance dose results in a testosterone suppression below 0.5 ng/mL,

> thereby treating prostate cancer in the subject with a reduced likelihood of causing a testosterone spike or other GnRH agonist side effect.

(JTX-4 at cl. 1).

20. Claim 3 adds: "The method of claim 1, wherein the treated subject has a decreased likelihood of developing or experiencing an undesirable side effect during treatment compared to treatment with the gonadotrophin releasing hormone (GnRH) agonist leuprolide." (JTX-4 at cl. 3).

21. Asserted claim 13 is dependent on claim 12, which claims: "The method of claim 1, wherein the maintenance dose is administered at a concentration ranging from 5 mg/mL to 40 mg/mL of degarelix." (JTX-4 at cl. 12).

22. Claim 13 adds: "The method of claim 12, wherein the maintenance dose is administered at a concentration of 20 mg/mL of degarelix." (JTX-4 at cl. 13).

23. Plaintiffs also assert claims 16 and 26 of the '739 patent. Claims 16 and 26 are dependent on claim 14, which claims:

> A method of treating prostate cancer in a subject with a reduced likelihood of causing a testosterone spike or other gonadotrophin releasing hormone (GnRH) agonist side-effect comprising:
>
> administering an initial dose of 160-320 mg of degarelix to the subject, wherein the initial dose is administered subcutaneously; and
>
> administering a maintenance dose of 60-160 mg of degarelix to the subject once every 28 days thereafter for 364 days, wherein the maintenance dose results in a testosterone suppression below 0.5 ng / mL;
>
> wherein the testosterone suppression is less than or equal to 0.5 ng / mL from day 28 to day 364 of treatment, and wherein the initial dose is administered as two subcutaneous injections.

(JTX-7 at cl. 14).

24. Claim 16 adds: "The method of claim 14, wherein the subject has a decreased likelihood of developing or experiencing an undesirable side effect during treatment compared to treatment with gonadotrophin releasing hormone (GnRH) agonist leuprolide." (JTX-7 at cl. 16).

25. Claim 26 adds: "The method of claim 14, wherein the maintenance dose is administered at a concentration of 20 mg/mL." (JTX-7 at cl. 26).

26. Plaintiffs also assert claims 3, 5, 8 and 14 of the '870 patent. All asserted claims of the '870 patent are dependent on claim 1, which claims:

> A method of treating locally advanced prostate cancer in a subject, comprising:
>
> choosing a dosing regimen of degarelix over gonadotrophin releasing hormone (GnRH) agonist treatment to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment when treating prostate cancer in the subject; and
>
> administering the dosing regimen of degarelix of an initial dose of 160-320 mg of degarelix to the subject and a maintenance dose of 60-160 mg of degarelix to the subject, wherein following the initial dose, the maintenance dose is administered once every 20-36 days thereafter.

(JTX-8 at cl. 1).

27. Claim 3 adds: "The method of claim 1, wherein the treatment provides a decreased likelihood of developing or experiencing an increase in arthralgia compared to the treatment with the GnRH agonist." (JTX-8 at cl. 3).

28. Claim 5 claims: "The method of claim 1, wherein the initial dose is 240 mg of degarelix and the maintenance dose is about 80 mg of degarelix, wherein the maintenance dose is administered once every approximately 28 days of treatment." (JTX-8 at cl. 5).

29. Claim 8 adds: "The method of claim 1, wherein the GnRH agonist is leuprolide." (JTX-8 at cl. 8).

30. Claim 14 claims: "The method of claim 1, wherein the maintenance dose of degarelix is administered at a concentration of 20 mg/mL." (JTX-8 at cl. 14).

2. The CV Patents

31. The '085 patent and the '398 patent (collectively, the "CV patents") are titled "Method of Treating Prostate Cancer with GnRH Antagonist" and name Egbert A. van der Meulen and László Balázs Tankó as inventors. (D.I. 169-1 ¶¶ 18, 20). The '085 patent issued on August 16, 2016, and the '398 patent issued on June 30, 2020. (D.I. 169-1 ¶¶ 18, 20). The two patents claim priority to Application No. 13/458,330, filed on April 27, 2012.[3]

32. Ferring B.V. is the owner by assignment of the CV patents and Ferring Pharma is an exclusive licensee. (D.I. 169-1 ¶¶ 19, 21).

33. Like the side effect patents, the CV patents are listed in the Orange Book as covering FIRMAGON. (D.I. 169-1 ¶ 28).

34. Plaintiffs assert claim 2 from the '085 patent. Claim 2 is dependent on claim 1, which claims:

> A method of treating prostate cancer in a subject, comprising:
>
> selecting a subject with a history of at least one cardiovascular event and prostate cancer,
>
> administering degarelix to the subject, wherein administration of degarelix to the subject decreases the frequency of an additional cardiovascular event in the subject as compared to the frequency of an additional cardiovascular event upon treatment with a gonadotrophin releasing hormone (GnRH) agonist in a subject with a history of at least one cardiovascular event,

[3] There is apparently a dispute as to whether the '085 patent was entitled to an earlier priority date. (D.I. 203 ¶¶ 91-94). That dispute, however, is not relevant in this case as "Fresenius did not assert invalidity based on any intervening prior art between [the date Ferring asserted] and April 27, 2012." (D.I. 210 ¶ 206).

> wherein the at least one cardiovascular event is chosen from myocardial infarction, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and other arterial thrombotic/embolic events.

(JTX-3 at cl. 1).

35. Claim 2 adds: "The method of claim 1, wherein administering degarelix to the subject comprises administering an initial dose of about 240 mg of degarelix; and administering a maintenance does of about 80 mg degarelix, once every approximately 28 days thereafter." (JTX-3 at cl. 2).

36. Plaintiffs also assert claim 2 of the '398 patent. Claim 2 of the '398 patent is dependent on claim 1, which claims:

> A method for treating a subject that has prostate cancer with a gonadotrophin releasing hormone (GnRH) antagonist, the method comprising:
>
> selecting a subject that has a history of at least one cardiovascular event; and
>
> administering degarelix to the subject having a history of at least one cardiovascular event,
>
> wherein a risk of developing or experiencing an additional cardiovascular event upon treatment with degarelix is diminished compared to a risk of developing or experiencing an additional cardiovascular event upon treatment with a GnRH agonist, and
>
> wherein the at least one cardiovascular event is chosen from myocardial infarction, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and other arterial thrombotic/embolic events.

(JTX-6 at cl. 1)

37. Claim 2 adds: "The method of claim 1, wherein administering degarelix to the subject comprises administering an initial dose of about 240 mg of degarelix; and administering a maintenance dose of about 80 mg degarelix, once every approximately 28 days thereafter." (JTX-6 at cl. 2).

3. The ’938 Patent

38. The ’938 patent bears the title “Method for the Manufacture of Degarelix” and names Haixiang Zhang, Jens Fomsgaard and Gunnar Staerkaer as inventors. (D.I. 169-1 ¶ 26). The ’938 patent issued on September 9, 2014 from U.S. Patent Application No. 13/265,402. (JTX-1).

39. PPL is the owner by assignment of the ’938 patent, and FICSA and its affiliates are exclusive licensees of the ’938 patent and have the first right to bring an infringement action to enforce the ’938 patent. (D.I. 169-1 ¶ 27).

40. The ’938 patent claims priority to a PCT patent application, PCT/EP2010/002550, filed April 26, 2010, and ultimately, through the PCT application, to a Swedish patent application, 0900558, filed on April 24, 2009. (JTX-1).

41. Plaintiffs assert claim 10 of the ’938 patent. Claim 10 is dependent on claims 1 and 2. Claim 1 claims:

> A method of manufacture of degarelix, Ac-D-2Nal-D-Phe(4C1)-D-3Pal-Ser-4Aph(Hor)-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein Aph is 4-amino-phenylaniline, (Hor) is (L-hydroorotyl), and (Cbm) is (carbamoyl), contain ing 0.3% by weight or less of Ac-D-2Nal-D-Phe(4C1)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine, comprising step-wise providing a solution of an amino acid or peptide in which an α-amino group is protected by Fmoc; contacting a solid support having an amino group linked thereto with the solution in the presence of reagent which forms a peptide bond between a carboxyl group of the dissolved amino acid or peptide and the amino group linked to the support for a time sufficient to form said peptide bond; removing Fmoc by contacting the support with an organic base selected from the group consisting of piperidine and C-alkyl substituted piperidine, wherein the alkyl is branched or straight chained and has from 1 to 6 atoms, in an organic solvent.

(JTX-1 at cl. 1).

42. Claim 2 adds: "The method of claim 1, wherein the organic base is piperidine." (JTX-1 at cl. 2).

43. Claim 10 claims: "The method of claim 2, wherein the organic solvent is dimethyl formamide." (JTX-1 at cl. 10).

44. Defendant stipulated to infringement of claim 10 of the '938 patent. (D.I. 189).

D. Trial Witnesses

1. Fact Witnesses

45. Dr. Tine Olesen testified live. Dr. Olesen worked in Ferring's clinical group from 2001 to 2020 and was responsible for overseeing efforts to develop and bring degarelix to market. (Tr. at 45:17-46:4). He is a named inventor on the side effect patents.

46. Dr. Arunya Usayapant testified by deposition. Dr. Usayapant is the senior director of formulation development at Fresenius and testified as a Rule 30(b)(6) witness. (Tr. at 112:21-113:1).[4]

47. Dr. Arthur Harms testified by deposition. Dr. Harms is the senior technical manager at Fresenius and testified as a Rule 30(b)(6) witness. (Tr. at 113:3-8).

48. Brad Schmitt testified by deposition. Mr. Schmitt is a director of regulatory affairs at Fresenius and testified as a Rule 30(b)(6) witness. (Tr. at 114:20-23).

49. Dr. Corinna Sundermann testified by deposition. Dr. Sundermann is a Senior Vice-President of Intellectual Property at (non-party) Fresenius Kabi Deutschland and testified as a Rule 30(b)(6) witness. (Tr. at 116:195-117:3).

[4] Ferring did not offer testimony about the employer or position of many of the witnesses testifying by deposition. Instead, Ferring's counsel simply stated on the record who the person was and where he or she worked. Although such statements of counsel are not evidence, the positions and employers of these individuals are not disputed. Thus, the Court refers to the statements made by counsel.

50. Dr. László Tankó testified by deposition. Dr. Tankó is a named inventor of the CV patents and testified as a Rule 30(b)(6) witness. (Tr. at 388:22-25; JTX-3; JTX-6). He was the Global Director of Medical Science while employed by Ferring. (Tr. at 388:25-389:1).

51. Dr. Fabrizzio Badalassi testified by deposition. Dr. Badalassi is a former employee of Ferring. (Tr. at 612:20-23). He testified about the development of part of the process used to make degarelix. (Tr. at 613:4-616:18).

52. Jens Fomsgaard testified by deposition. Mr. Fomsgaard is a named inventor of the '938 patent as well as a peptide chemist employed as a manager at PPL. (Tr. at 584:15-20).

53. Gunnar Staerkaer testified by deposition. Mr. Staerkaer is a named inventor of the '938 patent and a peptide chemist and manager at PPL. (Tr. at 601:1-7).

2. <u>Plaintiffs' Expert Witnesses</u>

54. Dr. Neal Shore testified live. Dr. Shore is a full-time practicing, board-certified urologist. (Tr. at 122:7-10, 122:22-24; JTX-24_1). He is a senior partner with the Atlantic Urology Clinics, medical director of Carolina Urologic Research Center and chief medical officer and the head of global prostate cancer research for Genesis Care US. (Tr. at 122:11-21, 123:12-22; JTX-24_2). Dr. Shore has conducted more than 400 clinical trials focused on advanced cancers with the majority being advanced prostate cancer (Tr. at 123:12-22) and has had his research published in hundreds of publications (Tr. at 123:23-124:2). Dr. Shore consulted on the pivotal Phase III trial of degarelix referred to as CS21. (Tr. at 124:16-125:11). The Court recognized Dr. Shore as a clinical expert in the field of urology and, more particularly, in the field of advanced prostate cancer. (Tr. at 125:13-18).

55. Dr. Thomas Keane testified live. Dr. Keane is a practicing urologist at the Medical University of South Carolina where he has been the chairman of the Department of Urology for

19 years. (Tr. at 179:12-180:4; JTX-25_1). Dr. Keane has been the principal investigator for more than thirty studies and has more than 60 papers published on androgen deprivation therapy or prostate cancer. (Tr. at 180:24-181:6). The Court recognized Dr. Keane as an expert in urology specializing in the treatment of prostate cancer. (Tr. at 182:12-17).

56. Dr. Kaare Rasmussen testified live. Dr. Rasmussen received his M.Sc. in chemistry-biotechnology in 1995 and his Ph.D. in organic chemistry in 1997, both from the University of Aarhus. (Tr. at 619:10-15; JTX-19_2). He has worked in the industry, doing both process chemistry and scale-up for peptides and small molecules. (Tr. at 619:19-620:2). The Court recognized Dr. Rasmussen as an expert in peptide synthesis, including solid-phase synthesis and purification. (Tr. at 620:21-25).

57. Dr. Knud Jorgen Jensen testified live. Dr. Jensen received his M.A. in philosophy in 1987, his M.Sc.in organic chemistry in 1990 and his Ph.D. in bioorganic chemistry in 1992, all from the University of Copenhagen. (Tr. at 642:22-643:9; JTX-20_1). Dr. Jensen is a full professor at the University of Copenhagen. (*Id.*). His research is "active within chemical pathology and bioscience, specifically related to peptide synthesis" and he has developed new solid-phase peptide synthesis ("SPPS") methods and used Fmoc-SPPS over the course of his career. (Tr. at 643:10-21). Dr. Jensen has published articles and a well-recognized textbook on SPPS. (Tr. at 643:22-644:3). The Court recognized Dr. Jensen as an expert in peptide synthesis, specifically with respect to the application of new methodology and the solid-phase synthesis of unusual peptides. (Tr. at 645:6-13). The Court found Dr. Jensen to be a particularly credible witness.

3. Defendants' Expert Witnesses

58. Dr. Edward Yun is an assistant clinical professor in the Department of Urology at the University of California Irvine Medical School. (Tr. at 226:9-20). He is a board-certified urologist practicing at the Urology Center in Southern California. (Tr. at 223:1-18). Dr. Yun also serves as the Vice Chair of Urology at Riverside Community Hospital where he previously served as the Chair of Urology. (DTX-104, Tr. at 225:14-24). Dr. Yun serves as one of two urologist experts to the Medical Board of California. (Tr. at 225:25-226:8). The Court recognized Dr. Yun as an expert in urology and the treatment of advanced prostate cancer. (Tr. at 228:11-15).

59. Dr. James Bruce Robertson is a clinical professor for the University of Washington's WWAMI program and a clinical professor at the Idaho College of Osteopathic Medicine (Tr. at 410:25-411:13) as well as a board-certified urologist (Tr. at 411:25-412:3). He completed his undergraduate studies at the University of Houston and University of Texas at Arlington followed by medical school at the University of Texas Health Sciences Center at Dallas Southwestern Medical School. (JTX-18, Tr. at 410:11-15). The Court recognized Dr. Robertson as an expert in the field of urology, including prostate cancer treatment. (Tr. at 412:6-10).

60. Dr. Zhaohui "Sunny" Zhou is a faculty member at Northeastern University in chemistry and chemical biology. (Tr. at 496:14-19). He received a Ph.D. in bioorganic chemistry from Scripps Research Institute in 1997. Dr. Zhou's research is focused on protein modifications and analysis, as well as pharmaceutical applications of those technologies, including peptide synthesis. (Tr. at 496:20-497:2). He teaches courses on protein chemistry and has designed a course on chemistry and the design of protein pharmaceuticals. (Tr. at 497:3-8). Dr. Zhou has been published in peer-reviewed journals and serves as an editor on Monoclonal Antibodies,

Antibody Therapeutics and Molecules. (Tr. at 497:19-498:1). The Court recognized Dr. Zhou as an expert in the field of peptide chemistry, including peptide synthesis. (Tr. at 499:3-7).

E. Facts Related to Infringement

1. Fresenius's ANDA Product

61. Ferring Pharma is the holder of New Drug Application ("NDA") No. 022201 for FIRMAGON (degarelix acetate) for injection, 80 mg and 120 mg. (D.I. 169-1, ¶ 10)

62. FIRMAGON, which is indicated for treatment of patients with advanced prostate cancer (Tr. at 46:11-15), was approved on December 24, 2008 (Tr. at 68:23-25), and has been on the market since then (Tr. at 127:21-128:2).

63. Fresenius's ANDA seeks approval to market the ANDA product, a generic version of FIRMAGON, prior to the expiration of the Orange Book listed patents. (D.I. 169-1, ¶ 30).

64. By letter dated February 10, 2020, Defendant informed Plaintiffs of its certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the '359 and '085 patents are invalid, unenforceable and/or will not be infringed by the ANDA product.[5] (D.I. 91 ¶ 60).

65. Fresenius's ANDA product is "indicated for treatment of patients with advanced prostate cancer." (PTX-272_2).

66. Administration of the ANDA product consists of an initial dose of "240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL" followed by a "maintenance dosage" of "80 mg given as one subcutaneous injection at a concentration of 20 mg/mL" once "every 28 days." (PTX-272_2).

[5] It is unclear from the parties submissions whether Fresenius similarly provided notice of any other asserted patents.

67. Administration of the ANDA product pursuant to the dosing instructions in the package insert results in a reduced likelihood of a testosterone spike. (PTX-272_17 (Figure 2)).

68. Administration of the ANDA product pursuant to the dosing instructions in the package insert will result in testosterone suppression below 0.5 ng/ml from at least day 28 to day 364 of treatment. (PTX-272_15).

69. Administration of the ANDA product pursuant to the dosing instructions in the package insert will naturally result in the treating of prostate cancer with the reduced likelihood of causing a testosterone spike or other GnRH side effects. (Tr. at 106:1-9 (Dr. Olesen opining that the administration of degarelix as claimed "will naturally result in the treating of prostate cancer with the reduced likelihood of causing testosterone spike or other GnRH side effects"); *see also* Tr. at 456:23-457:7 (Dr. Shore explaining that if a doctor gives degarelix to a patient, the patient will experience a reduced likelihood of either developing arthralgia or experiencing another musculoskeletal side effect); Tr. at 284:14-285:5 (Dr. Yun opining that administering degarelix "necessarily[,] inherently and naturally" avoids the side effects associated with leuprolide)).

70. Section 6.1 of Fresenius's package insert titled "Adverse Reactions" contains a section on "Clinical Trials Experience" that explains that degarelix was "studied in a randomized, open-label trial in which patients with prostate cancer were randomized to receive [degarelix] or leuprolide (intramuscular) monthly for 12 months." (PTX-272_10).

71. Section 6.1 further states that "[a]dverse reactions reported in ≥5% of patients treated with [degarelix] 240 mg starting dose and then 80 mg maintenance dose once every 28 days or who were treated with 7.5 mg of leuprolide (intramuscular) every 28 days are shown in Table 2." (PTX-272_10).

72. Before presenting Table 2, the proposed package insert states that "[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice." (*Id.*).

73. Table 2 provides:

Table 2: Adverse Reactions Reported in ≥5% of Patients

	Degarelix for Injection 240/80 mg (subcutaneous) N = 207	Leuprolide 7.5 mg (intramuscular) N = 201
Any adverse reaction	79%	78%
Body as a whole		
Injection site reactions[a]	35%	<1%
Weight increase	9%	12%
Chills	5%	0%
Cardiovascular system		
Hot flash	26%	21%
Hypertension	6%	4%
Digestive system		
Increases in Transaminases and GGT	10%	5%
Constipation	5%	5%
Musculoskeletal system		
Back pain	6%	8%
Arthralgia	5%	9%
Urogenital system		
Urinary tract infection	5%	9%

[a] Includes pain, erythema, swelling, induration, or nodule.

(PTX-272_10). There is no indication that the data presented in Table 2 is statistically significant or that any differences between degarelix and leuprolide are statistically significant.

74. The data in Table 2 comes from the pivotal Phase III trial, known as CS21, that led to FDA approval of FIRMAGON. (Tr. at 62:4-11, 167:23-168:3). CS21 was a noninferiority study and was not designed to show superiority of degarelix over leuprolide as it relates to efficacy or side effects. (Tr. at 99:13-100:19).

2. The ’359 and ’739 Patents

75. Fresenius does not dispute that healthcare providers will directly infringe the asserted claims of the ’359 and ’739 patents when following the package insert for the ANDA product.[6] (D.I. 219 at 4).

76. Fresenius disputes that it induces infringement of the asserted claims of these patents.

77. Healthcare providers review and follow the package inserts for the drugs they use to treat their patents. (*See* Tr. at 130:1-13, 184:2-11, 349:22-23, 423:8-14). A healthcare provider administering Fresenius’s ANDA product will administer the drug in accordance with the label’s instructions. (Tr. at 142:11-143:6).

78. Fresenius had knowledge of the ’359 and ’739 patents prior to the submission of its ANDA as they are listed in the Orange Book as covering FIRMAGON. (D.I. 169-1 ¶ 28). Moreover, Fresenius monitored Ferring’s patents and pending patent applications on degarelix since at least February 2016. (Tr. at 113:3-114:11; PTX-295_1, 12).

79. At a Fresenius Management Board Meeting on June 17, 2015, the slideshow presented to Fresenius’s Management Board to obtain approval for pursuing the degarelix project contained information on the findings of clinical trials involving degarelix. (PTX-269; Tr. at 109:24-112:17).

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[6] Fresenius offered no expert testimony about direct infringement, but purported to hold Ferring to its burden of proof. (*See* D.I. 208 at 15 (Fresenius explaining that “Plaintiffs should be held to their burden on these patents[.]”); D.I. 219 at 2-3). Fresenius also believes that “a physician administering degarelix will inherently achieve side effect reduction, so the claims are directly infringed and invalid over the prior art for the same reason.” (D.I. 208 at 15).

80. One slide from the presentation stated that degarelix "offers several strengths over the agonists," one of which is that it "reduces testosterone levels . . . without the initial flare that occurs with [] agonists." (PTX-269_5).

81. Another slide addressing "Risks" and "Opportunities" stated that an opportunity arising from developing a generic version of degarelix was that "[b]etter clinical outcomes vs. alternatives may drive higher usage, faster adoption of the superior clinical profile vs. competitors, such as faster testosterone reductions without testosterone surges, improved disease control, fewer instances of urinary infections, and a lower risk of CV events." (PTX-269_11, Tr. at 153:11-154:2).

82. Thus, Fresenius knew that administering degarelix to a patient with advanced prostate cancer in the manner instructed by its package insert would decrease the likelihood that a patient experience certain side effects covered by the '359 and '739 patents.

3. '870 Patent

83. The '359 and '739 patents are substantially similar to the '870 patent, and therefore the above findings of fact, to the extent relevant, are incorporated in this section.

84. Unlike the '359 and '739 patents, the asserted claims of the '870 patent require "choosing a dosing regimen of degarelix over gonadotrophin releasing hormone ("GnRH") agonist treatment to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment when treating prostate cancer in the subject." (JTX-8 at cl. 1).

85. The "choosing . . . degarelix . . . to decrease the likelihood of developing a musculosekeletal disorder" limitation is the only limitation in dispute as to infringement of the four asserted claims of the '870 patent. (D.I. 219 at 4).

86. At least some healthcare providers will administer Fresenius's ANDA product to decrease the likelihood that a patient experiences a musculoskeletal or connective tissue disorder during treatment. (Tr. at 150:19-154-4 (Dr. Shore testifying that he has chosen to prescribe degarelix over a GnRH agonist for patients that already have arthralgia in order to reduce the risk of arthralgia); Tr. at 353:16-25 (Dr. Yun acknowledging that at least some physicians may choose an antagonist to decrease the likelihood of an increase in arthralgia)).

87. Fresenius had knowledge of the '870 patent as it is listed in the Orange Book as covering FIRMAGON. (D.I. 169-1 ¶ 28; Tr. at 113:3-114:11; PTX-295_1, 12; PTX-269).

88. There is no evidence that Fresenius knew that administration of degarelix would decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment. (*See* PTX-269_11 (referring only to "fewer instances of urinary infections, and a lower risk of CV events" as side effects)).

89. There is also no evidence that any action taken by Fresenius would induce healthcare providers to choose degarelix over a GnRH agonist to decrease the likelihood of developing a musculoskeletal disorder or connective tissue disorder.

90. "Fresenius's proposed product insert does not explicitly instruct to administer degarelix over an agonist to reduce the likelihood of developing an increase in arthralgia." (D.I. 204 at 13).

91. As noted above at paragraph 65, Fresenius's ANDA product is "indicated for treatment of patients with advanced prostate cancer." (PTX-272_2). This indication is not directed to the reduction of musculoskeletal side effects. (Tr. at 236:1-5).

92. Nothing in Fresenius's indication instructs, encourages, recommends or promotes a physician to choose to use degarelix over a GnRH agonist based on musculoskeletal side effects. (Tr. at 163:10-17, 236:1-9).

93. The sole mention of a musculoskeletal disorder[7] in Fresenius's package insert is in Section 6.1, "Clinical Trials Experience." (PTX-272_10). That section includes Table 2, which is reproduced in paragraph 73, *supra*.

94. Table 2 of Fresenius's package insert underlies all of Plaintiffs' arguments of inducement of infringement of the '870 patent.[8] (D.I. 204).

95. An entry in Table 2 reports 5% arthralgia incidence for degarelix versus 9% for leuprolide.

96. As noted in paragraph 72, the section containing Table 2 begins with the preface: "[b]ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice." (*Id.*).

97. There is nothing advising healthcare providers that the results presented in Table 2 are statistically significant or that the differences in any results are meaningful. (Tr. at 237:1-5).

98. The data in Table 2 is based on Ferring's Phase III study CS21, which was not designed to show superiority of degarelix over leuprolide as it relates to side effects. (Tr. at 99:13-100:12).

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[7] There is no mention of connective tissue disorders in Fresenius's package insert.

[8] Plaintiffs offered some conclusory testimony from Dr. Shore referring to Table 2 and Fresenisus's proposed package insert. The Court attempted (and failed) to ascertain from Dr. Shore a clear explanation of how Fresenius would instruct healthcare providers to choose degarelix over a GnRH agonist to decrease the likelihood of developing a musculosekeletal disorder. (Tr. at 154:18-156:15).

99. The data in Table 2 does not instruct, encourage, recommend or promote a physician to choose to use degarelix over a GnRH agonist based on musculoskeletal side effects.

4. The CV Patents

100. The asserted claims of the two CV patents are directed to a method of treating prostate cancer which involves "selecting a subject with a history of at least one cardiovascular event and prostate cancer,"[9] and administering degarelix to treat prostate cancer and decrease the frequency of an additional cardiovascular event as compared to treatment with a GnRH agonist. (*See* JTX-3 at cl. 2; JTX-6 at cl. 2).

101. The "selecting a subject with a history of at least one cardiovascular event and prostate cancer" limitation is the only one in dispute as to infringement of the CV patents. (D.I. 219 at 5).

102. Both Plaintiffs' and Defendant's experts agreed that the "selecting" limitations require the affirmative step of selecting an individual with at least one prior cardiovascular event. (Tr. at 242:23-243:7, 208:4-12).

103. At least some healthcare providers are aware that cardiovascular disease is a common and significant issue for patients with prostate cancer. (Tr. at 193:9-194:2, 194:11-22, 354:13-17).

104. At least some healthcare providers are aware of the cardiovascular advantages of administering degarelix, rather than a GnRH agonist, to advanced prostate cancer patients with a history of at least one cardiovascular event. (Tr. at 183:11-184:11, 354:2-7). Indeed, it is now generally known that there is an increased risk of cardiovascular events with GnRH agonist

[9] Claim 2 of the '398 patent requires "selection a subject that has a history of at least one cardiovascular event."

treatment compared to degarelix treatment. (Tr. at 354:2-7). Plaintiffs' expert, Dr. Keane, agreed, testifying that he prescribes an agonist over an antagonist because it is "better" – for example, it has "significant cardiovascular benefits." (Tr. at 183:11-18).

105. Healthcare providers review and follow the package inserts for the drugs they use to treat their patents. (*See* Tr. at 130:1-13, 184:2-11, 349:22-23, 423:8-14). A healthcare provider administering Fresenius's ANDA product will administer the drug in accordance with the label's instructions. (Tr. at 142:11-143:6).

106. Administration of the ANDA product pursuant to the dosing instructions in the package insert will result in a reduced risk of an additional cardiovascular event. (Tr. at 201:14-203:4, 354:18-24).

107. Given that at least some healthcare providers currently know about the relative cardiovascular profiles of GnRH agonists and antagonists, at least some healthcare providers will select a patient with a history of at least one cardiovascular event and prostate cancer and administer Fresenius's ANDA product in accordance with the dosing instructions on the label to reduce the likelihood of a future cardiovascular event.

108. The FDA requires that all GnRH agonists contain a cardiovascular safety warning in their package insert. (*See* Tr. at 194:24-195:24; PTX 356_8 at § 5.3).

109. A cardiovascular safety warning is not required for GnRH antagonists. (Tr. at 187:12-22, 196:12-17).

110. The package inserts for products containing degarelix, a GnRH antagonist, do not include a cardiovascular warning. (PTX-272_1; PTX-266_1).

111. Ferring requested a label change for FIRMAGON to state that treatment with degarelix was associated with "a significantly lower risk of CV morbidity versus leuprolide." (PTX-573_23; Tr. at 216:9-217:3). The FDA has not approved that request. (Tr. at 217:4-11).

112. As described above (¶ 81), Fresenius was aware of cardiovascular benefits of treating prostate cancer with degarelix relative to GnRH agonists. (PTX-269_11).

113. Fresenius was aware of the '085 and '398 patents, which are listed in the Orange Book as covering FIRMAGON. (D.I. 169 ¶ 28).

114. Fresenius's package insert does not instruct, encourage, recommend or promote healthcare providers to select a patient with a prior history of at least one cardiovascular event in order to diminish the risk or reduce the frequency of a subsequent cardiovascular event. (PTX-272; Tr. at 208:16-24, 212:1-7 (Dr. Keane acknowledging that he "didn't see any instruction telling a physician to select a patient for administration of degarelix based on any history of a cardiovascular event.")).

115. The clinical trials section of Fresenius's package insert does not discuss or disclose any of the cardiovascular events specified in the claims (*i.e.*, myocardial infarction, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and other arterial thrombotic/embolic events). (Tr. at 212:8-13; *see* PTX-272_10).

116. The fact that Fresenius's ANDA product does not have a black box warning regarding cardiovascular health is not a result of any action by Fresenius, but a reflection of the fact that degarelix does not require such a warning. (Tr. at 209:13-25).[10] Accordingly, the lack of

[10] Dr. Olesen testified that, at the time the FDA implemented the agonist warning, there was not enough data on degarelix available to draw any conclusions because degarelix had just been approved. (Tr. at 70:17-71:3).

a black box warning on Fresenius's ANDA does not evidence Fresenius's intent to induce infringement of the asserted claims of the '085 and '398 patents.

5. The '938 Patent

117. Defendant stipulated to infringement of claim 10 of the '938 patent. (D.I. 189).

F. Facts Related to Validity

1. Person of Ordinary Skill in the Art

a. The Side Effect and CV Patents

118. There is no dispute that a person of ordinary skill in the art ("POSA") with respect to the side effect and CV patents is a person with a medical degree and at least two to three years of experience treating prostate cancer patients.

119. Dr. Yun, Defendant's expert, testified that for the asserted claims of the side effect patents and the CV patents a POSA is a person with a medical degree and at least two years of experience treating advanced prostate cancer patients. (Tr. at 248:9-16, 308:11-19). Defendant's expert, Dr Robertson similarly testified that a POSA is a "person with a medical degree and at least two to three years of experience treating cancer patients, including patients with prostate cancer." (Tr. at 412:19-24).[11]

120. Each of the experts who testified as to the side effect or CV patents (Dr. Shore, Dr. Keane, Dr. Yun and Dr. Robertson) meets the definition of a POSA. (*See supra* ¶¶ 54 (Shore), 55 (Keane), 58 (Yun), 59 (Robertson)).

[11] Plaintiffs' experts, Dr. Shore and Dr. Keane, never opined on the qualifications of a POSA or stated what definition they were using for their opinions. In its post-trial submissions, Plaintiffs cite to Dr. Robertson's definition when referencing Dr. Shore's opinions.

b. The '938 Patent

121. A POSA for the '938 patent would have a Ph.D. in chemistry, biochemistry or a related field with two to three years of experience in peptide chemistry. Alternatively, a POSA would have a Master's degree in chemistry or biochemistry with additional years of experience in peptide chemistry. (Tr. at 499:14-20, 622:1-12, 648:15-21).[12]

122. Dr. Rasmussen, Dr. Jensen and Dr. Zhou meet the definitions of a POSA offered by both sides. (*See* supra ¶¶ 56 (Rasmussen), 57 (Jensen), 60 (Zhou)).

2. The Prior Art

a. The Side Effect Patents

123. Fresenius asserts that claims 3, 5 and 8 of the '870 patent are anticipated by Christian Doehn, *et al.*, Drug evaluation: Degarelix – a potential new therapy for prostate cancer, 9(8) iDrugs 565-572 (2006) ("Doehn") and that all asserted claims of the three side effect patents are obvious over Doehn alone or Doehn in combination with International Patent Application WO 03/006049 ("WO '049").

124. There is no dispute that Doehn and WO '049 are prior art to the side effect patents. (D.I. 211 at 11 (Ferring referring to Doehn and WO '049 as prior art)).

i. Doehn

125. Doehn was published in 2006. It describes the pre-clinical and clinical development of degarelix, a GnRH antagonist, and suggests its use as a potential prostate cancer therapy in place of GnRH agonists. (DTX-040).

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[12] Plaintiffs' proposed definition requires an extra year of experience. The Court can discern no meaningful difference between the definitions with respect to the issues in this case, and neither party suggests that the difference impacts opinions presented. (*See* D.I. 84 at 84).

126. Doehn teaches that GnRH antagonists had been known and developed for more than 30 years and have an advantage over agonists by avoiding side effects and the initial testosterone flare. (DTX-040_001, _006; Tr. at 254:10-25).

127. Doehn discloses that degarelix successfully suppresses testosterone and prostate specific antigens (PSA), as is required to treat prostate cancer. (DTX-040_001, 004).

128. Doehn discloses that "treatment with degarelix over the course of 364 days, or a year, resulted in a rapid and sustained suppression of testosterone defined as less than 0.5 nanograms per milliliter and a fast, profound, and sustained decrease in PSA." (DTX-040_004; Tr. at 262:3-24).

129. Doehn discloses results of three Phase II trials. (DTX-040_004; Tr. at 260:23-263:10).

130. In the first Phase II trial, at the highest dose of degarelix (80/80/40 mg), 97.5% of patients experienced a reduction in testosterone to <0.5 ng/ml within 3 days of treatment and 100% reached target suppression levels within 28 days. (DTX-040_004).[13] Dr. Yun testified that 80/80/40 indicates that the initial dose of 160 mg was split between two injections of 80 mg each and the maintenance dose was 40 mg. (DTX-040_004; Tr. at 259:4-13, 305:6-11).

131. Splitting the initiation dose into two subcutaneous injections is consistent with Doehn's disclosure that "[s]mall injection volumes increased the subcutaneous release of degarelix compared with large injection volumes[,]" and "dose concentration was negatively correlated to bioavailability." (DTX-040_004, Tr. at 257:2-258:2).

[13] Dr. Yun later testified that Doehn does not "expressly disclose two administrations for the subcutaneous injection for the initial dose of degarelix." (Tr. at 273:23-274:4).

132. In the second Phase II trial, 96% of the patients receiving an initial dose of 240 mg (40 mg/mL), which amounts to a 6 mL dose, achieved castration levels. (DTX-040_004).

133. In the third Phase II trial reported, an initial dose of 200 or 240 mg was followed by maintenance doses of 80 mg, 120 mg or 160 mg of degarelix every 28 days for up to 364 days. (DTX-040_004). In patients treated with a 240 mg initial dose of degarelix, 92% and 95% had testosterone levels ≤0.5 ng/ml at days 3 and 28, respectively. (*Id.*). Those receiving 160 mg maintenance doses had testosterone levels ≤0.5 ng/ml from day 28 to day 364. (*Id.*). The authors of the study concluded that treatment of degarelix for a year resulted in rapid and sustained suppression of testosterone and a fast, profound and sustained decrease of PSA. (*Id.*).

134. Thus, in describing the three Phase II trials, Doehn teaches an initiation dose of degarelix of 160-240 mg as well as splitting the initiation dose into two subcutaneous injections. (DTX-040_004 (first Phase II trial and explaining that "[s]mall injection volumes increased the subcutaneous release of degarelix compared with large injection volumes")). Doehn also teaches that maintenance doses of 160 mg of degarelix administered subcutaneously every 28 days for up to 364 days resulted in testosterone levels of below 0.5 ng/ml for all patients receiving that dosage. (*Id.* (third Phase II trial)).

135. Doehn teaches that treatment with a GnRH agonist causes a testosterone flare and that the testosterone flare produces symptoms such as bone pain. (DTX-040_001). Doehn also teaches that treatment with a GnRH antagonist avoids the initial testosterone flare. (*Id.*). Accordingly, Doehn teaches that treatment with a GnRH antagonist avoids symptoms caused by a testosterone flare, such as bone pain.

136. Bone pain is different than arthralgia. There is an "unequivocal difference" between the two. (Tr. at 174:15-19). Bone pain occurs in metastatic deposits as a result of the

testosterone flare. (Tr. at 174:15-175:3). In contrast, arthralgia occurs both in patients who receive a GnRH antagonist (and therefore do not experience a testosterone flare) and who receive a GnRH agonist (and therefore do experience a testosterone flare). (Tr. at 175:8-23).

137. In the same paragraph that Doehn discloses the clinical flare effect, Doehn cites a paper entitled *Is the Flare Phenomenon Clinically Significant?* by Glenn J. Bubley, which was published in UROLOGY. (DTX_040_001). Bubley discloses that patients at risk from clinical flare are overwhelmingly those with metastatic prostate cancer, especially those patients with widespread metastasis. (PTX-079_002; see Tr. at 359:9-361:1). Bubley further explains that clinical flare responses are rare for those who do not have metastatic disease. (PTX-079_002; Tr. at 359:9-361:10).

138. Dr. Yun acknowledged that bone pain is associated with metastatic disease and that metastatic prostate cancer spreads to other parts of the body, which may include a patient's bones. (Tr. at 358:23-359:7). He agreed that Bubley concluded that clinical flare responses are very rare in those who do not have metastatic cancer. (Tr. at 361:2-7). Thus, bone pain is generally not a concern to those treating the locally advanced prostate cancer that is subject of the claims of the '870 patent. (Tr. at 438:9-439:4).[14]

139. Doehn also disclosed that in January 2006 Ferring and Astellas Pharma Inc. entered into a licensing agreement granting Astellas the exclusive right to develop and market degarelix for treatment of prostate cancer in Japan. (DTX-040_006).

[14] There appears to be no dispute that the "locally advanced cancer" claimed is different from "metastatic cancer."

ii. WO ’049

140. WO ’049 was published on January 23, 2003. (DTX-242_002). The applicant for WO ’049 is Ferring BV. (*Id.*)

141. WO ’049 “relates to a pharmaceutical composition for the administration of a GnRH antagonist peptide useful in the treatment of sex hormone-dependent diseases” and conditions “such as prostate cancer . . . .” (DTX-242_003).

142. WO ’049 also states that “the present invention comprises a method of treating [prostate cancer] by the administration to an individual in need of such treatment of a therapeutically effective amount of [the compositions described.]” (DTX-242_007).

143. WO ’049 refers to the disclosure in the ’730 patent of GnRH antagonist peptides according to general formula 1. Degarelix is one of the GnRH antagonist peptides according to general formula 1. (Tr. at 502:16-503:6).

144. Doehn describes WO ’049 as “relating to injectable formulations of GnRH antagonist peptides, specifically degarelix.” (DTX-040_005).

145. WO ’049 describes administering peptides in such a way that they turn into a gel after subcutaneous injection, and the gel acts as a depot from which the peptide is released over a period of weeks or months. (DTX-242_004).

146. WO ’049 describes the problem facing one seeking to have a peptide be released over a period of weeks or even months. “If the solution is too dilute then no depot is formed and the long duration of action is lost [but] [i]f the solution is too concentrated then gel formation will occur before the drug can be administered.” (DTX-242_004; Tr. at 50:1-24).

147. WO ’049 teaches that “[a]dministration will be by subcutaneous or intramuscular injection, preferably by subcutaneous injection, at a single site or divided between two or more sites.” (DTX-242_008).

148. WO ’049 discloses that “administration will be repeated at appropriate intervals of two weeks to three months for the duration of treatment.” (DTX-242_0008). This timeframe coincides with Doehn’s teaching that maintenance doses should be administered once every 28 days. (DTX-040_004). This timeframe also ensures that patients will have degarelix in their systems until their check-up visit, permitting their urologist to check their PSA. (Tr. at 61:16-62:1, 269:16-23, 306:10-23).

149. WO ’049 teaches that the concentration of the composition must be at least 0.3 mg/mL and no more than 120 mg/mL. (DTX-242_007). WO ’049 disclosed preferred embodiments of the concentration of the peptides, stating that the preferred concentration is not more than 80 mg/mL, a more preferred embodiment is not more than 40 mg/mL and not less than 1 mg/mL. WO ’049 discloses a still further preferred embodiment in which the concentration of the peptide is between 5mg/m1 and 80mg/ml and states that “[p]eptide at concentrations within this range (for example 20mg/ml, or 25mg/m1) may be used to form a gel after administration which releases the peptide over a period of at least two weeks, preferably for a period of three months.” (*Id.*). As Dr. Yun explained, this time interval is ideal for the follow-up treatment of prostate cancer patients. (Tr. at 269:9-23).

150. WO ’049 teaches that degarelix in the disclosed concentrations is effective for the suppression of sex steroid hormones and thus useful in the treatment of prostate cancer. (DTX-242_007).

iii. Secondary Considerations[15]

151. Ferring asserts that (1) there was a long-felt but unmet medical need for the claimed inventions of the side effect patents and (2) the reduced likelihood of developing an undesirable side effect by administering degarelix was unexpected. (D.I. 211 at 23, 25).

152. As to long felt need, Ferring argues that "[a]s of 2008, there was a long felt but unmet medical need for an improved androgen deprivation therapy that would avoid the counterintuitive mechanism of action of GnRH agonist therapy and had an improved safety profile. … Plaintiffs have demonstrated that ***Degarelix met that need***." (D.I. 211 at 23 (emphasis added)).

153. Plaintiffs tie the asserted benefits to administering degarelix, a compound already known for the treatment of prostate cancer. Plaintiffs, however, have not shown that any long felt but unmet need has been met by the claimed inventions, which include more than administration of degarelix with a lower incidence of side effects.

154. The closest that Plaintiffs come to addressing any other aspects of the claims is the single conclusory sentence:

> Degarelix was developed to have a slow release from its subcutaneous depot resulting in the desired long duration of action. This was not just a result of the uniqueness of the molecule itself, but also due to the unique dosing regimen; dosing, volume, and concentration all play a role.[16]

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[15] The Court refers to these considerations as "secondary" not to minimize their role in the obviousness analysis, but simply in keeping with the nomenclature adopted by the Supreme Court. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966) (referring to "secondary considerations" such as commercial success, long felt but unsolved needs, failure of others).

[16] In support of this statement, Ferring cites to its proposed Finding of Fact No. 188. That proposed finding, however, is simply the same conclusory recitation included in its brief. (*See* D.I. 210 at 29 (citing to Doehn, which Plaintiffs assert does not disclose multiple elements of the claimed invention and excerpts of Dr. Oleson's testimony which do not address the claimed dosing regimen; dosing, volume and concentration)).

(D.I. 211 at 24).

155. As to unexpected results, Ferring similarly argues that it was unknown that there were "claimed undesirable side effects" unrelated to the testosterone spike "that resulted in a greater likelihood of incidence with GnRH agonist treatment ***compared to treatment with degarelix***" and that the "reasons for this ***improved safety profile for degarelix*** relative to the agonist" remains unclear. (D.I. 211 at 25 (emphasis added)). Again Ferring does not tie these arguments to the claimed inventions, but to degarelix itself.[17]

156. The secondary considerations Ferring asserts relate to inherent properties of degarelix when used to treat prostate cancer and not the claimed inventions. Thus, Plaintiffs have failed to establish a nexus between the asserted secondary considerations and the claimed inventions.

b. <u>The CV Patents</u>

157. Fresenius argues that claim 2 of the '085 patent is anticipated by Smith *et al.*, Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group Phase III trial in patients with prostate cancer, J. UROL. 184(6):2313-2319 (2010) ("Smith 2010") and that both asserted claims of the CV patents are obvious in light of Smith 2010

[17] Ferring distinguishes between the testosterone effects and "claimed undesirable side effects." (D.I. 211 at 25). Two of the claims (claim 16 of the '359 patent and claim 26 of the '739 patent), however, are not limited to the "claimed undesirable side effects." Those claims depend from claim 14, which includes both "a reduced likelihood of causing a testosterone spike" as well as the "claimed undesirable side effects." Thus, Ferring's argument distinguishing testosterone effects from other undesirable effects does not appear relevant to these claims.

combined with (1) Van Poppel 2008[18] and Levine 2010[19] or (2) van Poppel 2008, Tanriverdi 2004[20] and Gotsman 2008.[21] (D.I. 202 at 28).

158. None of the asserted prior art teaches "selecting a subject with a history of at least one cardiovascular event and prostate cancer" (as required by claim 2 of the '085 patent) or "selecting a subject that has history of at least one cardiovascular event" (as required by claim 2 of the '398 patent).

i. Smith 2010

159. Smith 2010 describes itself as the "first report . . . on cardiovascular safety data from a completed 1-year randomized controlled trial of leuprolide acetate vs degarelix." (DTX-233_0002).

160. In Smith 2010, the authors assessed the cardiovascular ("CV") safety of degarelix by analyzing CV events and QT/QTc prolongation from Ferring's CS21 study – "a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer." (DTX-233_2).

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18 van Poppel H and Nilsson S, *Testosterone surge: rationale for gonadotrophin-releasing hormone blockers*? UROL. 71:1001-1006 (2008).

19 Levine GN et al., *Androgen-deprivation therapy in prostate cancer and cardiovascular risk*, CIRCULATION 121:833-840 (2010).

20 Tanriverdi F et al., *Expression of gonadotropinreleasing hormone type-I (GnRH-I) and type-II (GnRH-II) in human peripheral blood mononuclear cells (PBMCs) and regulation of B-Lymphoblastoid cell proliferation by GnRH-I and GnRH-II*, EXP. CLIN. ENDRICO. DIABETES 112:587-594 (2004).

21 Gotsman I et al., *T-Cell costimulation and coinhibition in atherosclerosis*, CIRCULATION RES 103:1220-1231 (2008).

161. The patients in CS21 were randomized to receive either leuprolide or degarelix regardless of their CV history and there were no exclusion criteria for those that did not have a prior CV event. (DTX-233_3; DTX-233_10 (Table 1); Tr. at 377:7-15).

162. Under "Materials and Methods," Smith 2010 explains that the "[t]he trial design and subject population have been described for the original study [CS21] that evaluated the efficacy and safety of degarelix 240/80 mg, degarelix 240/160 mg and leuprolide 7.5 mg." (DTX-233_3 (citing to Klotz 2008, PTX-309)). In Klotz 2008, the authors explain that patients were randomized to one of three treatment arms:

> In all, 610 patients were randomized and received either a degarelix s.c. starting dose of 240 mg (given as two x 3 mL injections) and thereafter 12 monthly (every 28 days) maintenance doses of 80 mg (one 4 mL injection of 20 mg/mL; 207 men) or 160 mg (40 mg/mL; 202 men), or 12-monthly (every 28 days) i.m. injections of leuprolide 7.5 mg (given as one injection of ≈1 mL; TAP Pharmaceuticals; 201 men) (Fig. 1).

(PTX-309_2). Neither Smith 2010 nor Klotz 2008 discloses that subjects were affirmatively selected for treatment on the basis of their cardiovascular history. (Tr. at 335:6-13).

163. Smith 2010 explains that baseline demographics and clinical characteristics were similar between the three treatment groups. (DTX-233_4). Table 1 reflects that about 30% of the patients in each treatment group had baseline ischemic heart disease, while 70% did not. (DTX-233_10).

164. Table 6, which reports the "[i]ncidence of other [CV] related treatment emergent AEs", reflects that some patients in the degarelix and leuprolide groups experienced ischemic heart disease during the study. (DTX-233_15). Table 6 does not, however, indicate if any of those patients had a prior history of a CV event. (Tr. at 377:16-21).

165. Smith 2010 summarizes the results of the study, stating: "In summary, these analyses indicate that degarelix has an overall CV safety profile similar to that of leuprolide." (DTX-233_7; *see also* DTX-233_6 ("Although the incidence of events was relatively low, the numerical data suggest a comparable safety profile for the 2 drugs.")). Thus, Smith 2010 does not teach that either leuprolide or degarelix is superior from a cardiovascular safety perspective.

166. Smith 2010 concludes:

> In men with prostate cancer degarelix and leuprolide have similar CV safety profiles. Marked prolongation of the QTc interval was uncommon (1% or less) with either agent. The incidence of arrhythmias during a 1-year period was similar for subjects treated with degarelix and leuprolide. These observations suggest that the CV effects of both agents result from hypogonadism[22] rather than a direct drug effect.

(DTX-233_7; *see also* DTX-233_2 ("In men with prostate cancer degarelix and leuprolide have similar [CV] safety profiles. These observations suggest that the [CV] events associated with both agents result from hypogonadism rather than a direct drug effect.")).

167. Because Smith 2010 posits that degarelix and leuprolide have comparable drug profiles, and that the CV events that result from their use are caused by hypogonadism rather than direct drug effects, a POSA would not conclude, based on Smith, that treating prostate cancer with a GnRH agonist carries heightened cardiovascular risk over treating with a GnRH antagonist.

168. During the prosecution of the application that resulted in the '085 patent, the Patent Examiner considered and rejected the argument that Smith 2010 discloses the "selecting step" of the CV patents. Before the pending claims recited the selecting step, the Examiner rejected the claims as being anticipated by Smith 2010. (PTX-381_6; Tr. at 463:15-464:16). In response, the

[22] Hypogonadism refers to testosterone suppression. (Tr. at 379:13-17, 467:23-468:14). Thus, hypogonadism is the result of treatment with both degarelix and leuprolide.

patentee amended the pending claims to recite the selecting step and argued that Smith 2010 does not disclose the selecting step. (PTX-5_2; Tr. at 464:17-465:13). The claims were subsequently allowed with no further anticipation rejection. (PTX-377_1; Tr. at 465:14-15, 466:5-11).

ii. Levine 2010

169. In Levine 2010, the American Heart Association, American Cancer Society and American Urological Association published warnings that there may be a relationship between androgen deprivation therapy ("ADT") with GnRH agonists and increased risk of CV disease. (DTX-101_8). Levine 2010 states that "[t]he writing group emphasizes that the purpose of this advisory is strictly informative." (DTX-101_3).

170. Levine 2010 states that "[s]everal recently published reports have suggested that there may be an association between ADT with GnRH therapy (with or without an antiandrogen) or bilateral orchiectomy and incident cardiovascular disease and cardiovascular mortality." (DTX-101_4). Levine 2010 further states, "Although the above-discussed studies have detected a relationship between ADT and [CV] risk, not all published studies have reported such a relationship." (DTX-101_5).

171. Levine 2010 postulates several explanations for the varying observations regarding the association between ADT and CV mortality:

> Several potential explanations for the discordant observations regarding the association between ADT and [CV] mortality may include factors such as differences in patient populations studied, study design, selection bias in men offered ADT, and the limited number of [CV] events in some studies. A competing risks issue has also been suggested to explain the findings in the studies that have not detected a relationship between ADT and [CV] events, which emphasizes that the ability to measure an increase in the risk of [CV] mortality decreases as the risk of prostate cancer-specific mortality increases. It may also be that any increased risk occurs primarily in those with existing, overt coronary artery disease. Finally, another important potential explanation for the discordant

> findings is that there is no actual causal relationship between ADT and [CV] mortality and that positive studies are the result of uncontrollable confounding factors or the result of post hoc analyses.

(DTX-101_5).

172. Ultimately, Levine 2010 considered it "plausible that ADT could increase cardiovascular risk on the basis of its adverse impact on risk factors for cardiovascular disease." (DTX-101_8). Levine 2010 specified, however, that "[n]ot surprisingly, given all of these considerations, whether an association (or an actual cause-and-effect relationship) between ADT use and [CV] events and mortality exists remains controversial and continues to be studied. The writing group believes that at this point, it is reasonable, on the basis of the above data, to state that there may be a relationship between ADT and [CV] events and death." (DTX-101_5). As Dr. Keane testified, this conclusion is the simple observation that more work was needed to understand the relationship, if any, between androgen-deprivation therapy and cardiovascular health. (Tr. at 470:15-471:3).

173. Thus, a POSA would not understand that GnRH agonists lead to heightened cardiovascular risk based on Levine 2010.

iii. van Poppel 2008

174. van Poppel 2008 suggests that the cause of the increased [CV] risk was due to the testosterone surge resulting from administration of a GnRH agonist. (DTX-75).

175. van Poppel 2008 is a review article "discuss[ing] the available evidence to suggest that the testosterone surge associated with GnRH agonists might adversely affect the outcome of treatment with GnRH agonists and the promising data for GnRH antagonists, a new class of drug that is showing promise in the management of advanced prostate cancer." (DTX-75_2).

176. Under "Characteristics of Testosterone Surge and Clinical Flare," van Poppel 2008 states that "[t]he main symptoms associated with a clinical flare include bone pain, bladder outlet obstruction, ureteral obstruction, spinal cord compression, and cardiovascular effects." (DTX-75_2). van Poppel 2008 then further states:

> Various studies have reported the incidence of cardiovascular events shortly after initiation of GnRH agonist therapy. For example, Peeling reported cardiovascular events in 6 (5%) of 124 patients. These events might have been related to the high testosterone levels, ***although cardiovascular events are also quite common in elderly men; therefore, the events recorded in the study by Peeling might not necessarily have been related to GnRH agonist treatment***.

(DTX-75_2 (emphasis added)).

177. Under "Clinical Effect of Testosterone Surge," van Poppel 2008 discusses whether "GnRH agonists might be inferior to orchiectomy for improving survival in patients with advanced prostate cancer." (DTX-75_3). van Poppel summarizes the results of studies comparing agonists of orchiectomy stating:

> Seidenfeld et al. identified five large randomized studies that compared GnRH agonists with orchiectomy. Although none of the five studies showed a statistically significant difference in overall survival between the two treatments, three of them reported superior survival for orchiectomy and a fourth reported identical survival for both treatment groups. These investigators also performed a meta-analysis of data from 12 studies (involving 1539 patients) comparing GnRH agonists and orchiectomy. The hazard ratio for GnRH agonists relative to orchiectomy was 1.262 (95% confidence interval 0.915 to 1.386), with no clear survival advantage for any procedure, although numerically orchiectomy had some advantage.

(DTX-75_3 (footnotes omitted)). van Poppel 2008 then states, "Somewhat inferior efficacy for GnRH agonists compared with orchiectomy could reflect the effect of the testosterone surge or other factors such as the level of testosterone suppression achieved and also how effectively the testosterone suppression is maintained." (DTX-75_3 to DTX-75_4).

iv. Tanriverdi 2004

178. Fresenius contends that Tanriverdi 2004 (DTX-172) teaches "that the increased [CV] risk is due to activation of GnRH receptors in Tcells by the agonist, leading to an immune response," (D.I. 203 ¶ 129). Tanriverdi 2004, however, mentions nothing about cardiovascular risk, or prostate cancer. (DTX-172).

179. Tanriverdi 2004 focused on the expression of different isoforms of GnRH receptors, specifically GnRH I and GnRH II, in different lymphocytes. (DTX-172_1).

180. Neither Dr. Keane nor Dr. Yun had read Tanriverdi prior to this litigation. (Tr. at 473:10-14, 383:24-384:4).

v. Gotsman 2008

181. Fresenius relies on Gotsman 2008 as prior art as teaching "the relationship between T-cell stimulation and cardiovascular events as possibly caused by inflammation in plaque, which leads to atherosclerotic plaque." (D.I. 203, ¶ 143).

182. Gotsman 2008 is a "basic science," preclinical research paper that does not mention prostate cancer. (Tr. at 474:12-475:3; DTX-168).

183. Gotsman 2008 "provide[s] a background on the role of T lymphocyte in atherosclerosis, and the regulation of T cell responses by costimulatory and coinhibitory molecules" and "then review[s] the evidence that T cell costimulators and coinhibitors influence atherosclerotic disease." (DTX-168_3).

184. Neither Dr. Keane nor Dr. Yun had read Gotsman prior to this litigation. (Tr. at 473:10-14, 383:24-384:4).

vi. Unexpected Results

185. Ferring argues that it has "demonstrated that the unexpected reduction in risk of developing or experiencing an additional CV event by administering degarelix over a GnRH agonist to a patient with a history of a prior CV event supports a finding of nonobviousness." (D.I. 211 at 37).

186. As discussed in connection with the side effect patents, Plaintiffs' asserted unexpected result ties the result to administering degarelix, a compound already known for the treatment of prostate cancer rather than to the inventions claimed (which involve more than administering degarelix instead of a GnRH agonist to a patient with a history of a prior CV event). Thus, Plaintiffs have failed to establish a nexus between the asserted unexpected results and the claimed inventions.

c. The '938 Patent

187. Fresenius argues that claim 10 of the '938 patent is anticipated by the '730 patent and rendered obvious by the combination of the '730 patent with M. Amblard et al., "Method and Protocol of Modern Solid Phase Peptide Synthesis." ("Amblard").

188. There is no dispute that the '730 patent and Amblard are prior art to the '938 patent.

189. The '730 patent was before the Patent Examiner and extensively discussed during prosecution. It was referred to as "Semple."

190. Claim 10 claims a method of manufacturing degarelix using Fmoc α-amino protecting groups during solid phase peptide synthesis ("Fmoc-SPPS") where the resulting degarelix product contains 0.3% by weight or less of a specific impurity, known as the hydantoin impurity. (JTX-1 cl. 1, 2, 10).

191. Degarelix is a complex synthetic decapeptide. (JTX-1 at 1:6-8; *see also* Tr. at 50:1-9, 622:20-24).

192. Degarelix has "a highly unusual structure" because "most of the amino acids are modified, and it has the very unusual [hydroorotyl] moiety." (Tr. at 647:4-12). The structure is so unusual that Dr. Jensen "ha[s] been using it in [his] peptide chemistry class to show how complex a structure of a peptide can be and how far this can be from a standard peptide." (Tr. at 647:4-12).

193. When scientists work with nonnatural, nonstandard amino acids, such as degarelix it is "a totally different game when you have to start the planning of . . . synthesis from the start and you cannot assume that it will just work." (Tr. at 648:9-14).

i. The '938 Patent and Its Prosecution

194. At the time of the invention of the '938 patent, the only known use for degarelix was in pharmaceutical products for which pharmaceutical grade degarelix is needed. (Tr. at 696:12-19; *see also* JTX-1 at 2:65-3:1 ("Degarelix is the active ingredient of a drug for administration to humans. Therefore it must not be contaminated by any impurity exceeding 0.3% by weight of the product.")).

195. In the Summary of the Invention, the '938 patent explains, "[t]he inventors have surprisingly found that pharmaceutically pure degarelix can be manufactured by solid phase synthesis using Fmoc as α-amino protecting group. 'Pharmaceutically pure' indicates the product does not contain more than 0.3% by weight of any single impurity." (JTX-1 at 3:46-50; *see also* Tr. at 695:24-696:11).

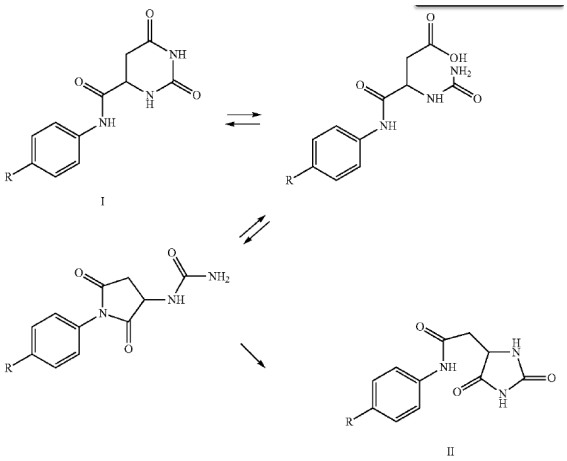
196. The "classical" approach for peptide synthesis was a liquid phase synthesis process ("LPPS"), but by the time of the invention, "[a]nother current and commonly used approach for peptide synthesis [was SPPS]." (JTX-1 at 1:13-47).

197. In SPPS, the first amino acid is covalently attached to a solid support resin and then the additional amino acids are added in a step-wise fashion until "the desired length and sequence is achieved." (JTX-1 at 1:47-50).

198. Dr. Jensen explained that, when discussing and naming a peptide, the N-terminal (*i.e.*, the amino terminal) "is placed to the left-hand side and the carboxy terminal is placed to the right-hand side." (Tr. at 649:20-650:3). Dr. Jensen also explained that the amino acid that is attached to the solid support is attached at the carboxy terminal (which should be on the right hand side) . (Tr. at 650:10-19). In other words, during synthesis, the amino acids are coupled from the carboxy terminal side, such that the first amino acid to be used is the last in the peptide sequence. (Tr. at 650:10-651:9; *see also* PTX-133_3-5 (showing a graphical depiction of JYMed's synthetic route, which starts with amino acid sequence 10 and ends with amino acid sequence 1)).

199. The '938 patent further explains that "[t]he fifth amino acid moiety from the amino terminal of degarelix corresponds to the non-natural amino acid Aph(L-hor)." (JTX- 1 at 1:66-2:1; *see also* Tr. at 623:2-7). This refers to the hydroorotyl group included in the side chain of the amino acid, which can also by referred to as the hydroorotic moiety, the "Hor" moiety or group, or as the "dihydrouracil moiety." (Tr. at 510:6-8, 623:2-7, 665:8-18).

200. It is undisputed that, under basic conditions, the hydroorotyl group can convert into a hydantoin group, which means that the six-membered hydroorotyl ring converts into a five-membered hydantoin ring. (Tr. at 623:2-7, 524:16-25; JTX-1 at 2:2-49). The '938 patent graphically depicts the rearrangement:



201. The Hor moiety is shown in the upper left hand corner as "I". (Tr. at 510:19-23; *see also* Tr. at 622:25-623:16, 664:20- 665:18). The hydantoin moiety is shown in the lower right hand corner as "II". (Tr. at 510:24-511:2; *see also* Tr. at 622:25-623:16, 664:20-665:18; JTX-1 at 2:2-49).

202. The '938 patent indicates that the hydantoin impurity "is structurally very similar to degarelix" such that "their separation is difficult." (JTX-1 at 3:4-5). This observation is supported by Dr. Rasmussen, who testified that the change from a six-membered ring to a five-membered ring "is the only difference between the two molecules . . . and that makes the molecules very similar, and as far as I know, no one has been able to separate these on a preparative scale." (Tr. at 623:8-16).[23]

203. The '938 patent also notes that "[t]he synthesis of degarelix is disclosed in U.S. Pat. No. 5,925,730A" and that the preferred α-amino protecting group disclosed in that synthesis "and which has been used in all Examples is the tert-butyloxy-carbonyl group (Boc)." (JTX-1 at 3:10-13). The Boc group is removed under acidic conditions. (JTX-1 at 3:16-18; *see also* Tr. at 583:15-584:5). In contrast to Boc-SPPS, Fmoc-SPPS uses basic conditions. (JTX-1 at 3:7-9, 3:50-54).

[23] A "preparative scale" is a purification process. (Tr. at 623:17-22).

204. Because Fmoc-SPPS uses basic conditions, a POSA would be concerned that making degarelix using Fmoc-SPPS would result in formations of the hydantoin moiety.

205. Examples 3 and 4 of the ’938 patent are embodiments of the claimed synthesis method and indicate that the hydantoin impurity “could not be detected in the product.” (JTX-1 at 18:65-20:25).

206. As noted above at paragraphs 38 and 40, the ’938 patent issued on September 9, 2014 and claims priority to a PCT patent application, PCT/EP2010/002550, filed April 26, 2010. (JTX-1).

207. The International Search Report for the PCT application that ultimately became the ’938 patent lists the ’730 patent as a “document[] considered to be relevant.” (JTX-9_3).

208. After the PCT application was nationalized in the United States, in the first substantive office action, the Examiner rejected the pending claims as obvious over the ’730 patent in view of four other references. (JTX-9_242). The Examiner stated that “Semple [the ’730 patent] does not teach a method of making degarelix using the Fmoc strategy of solid phase peptide synthesis.” (JTX-9_242). The Examiner, however, combined the method of making degarelix taught the ’730 patent with the “Fmoc strategy taught by the prior art in general and especially in [the secondary references].” (JTX-9_245).

209. In response (JTX-9_255-58), the applicants for the ’938 patent argued that “[b]ased on the prior art, production of pharmaceutical grade degarelix with less than 0.3% contaminant is surprising, unexpected, and unpredictable.” (JTX-9_257). Applicants also disputed the Examiner’s characterization of the Kaneti reference (DTX-333), arguing that it teaches that “the rate of reaction may be dependent on the alkalinity of the reaction mixture in some cases, but that is not the same thing as saying the rearrangement does not occur.” (JTX-9_257-58).

210. The Examiner rejected those arguments and made the rejection final on February 4, 2014. (JTX-9_262-72). In doing so, the Examiner repeated her earlier findings that it would have been obvious to a POSA to use the Fmoc strategy taught by the prior art in general to make degarelix, a POSA would have been capable of applying the method to the synthesis of degarelix and the results would have been predictable. (JTX-9_245; JTX-9_266-67).

211. Applicants responded that "[w]hat may or may not have been obvious to the applicant after completing the invention is not a proper basis for rejection." (JTX-9_276). The applicants also again explained the relevance of Kaneti:

> Kaneti discloses that the rearrangement of dihydororotic [sic] acids to hydantoninacetic acids in aqueous media is base catalyzed. It states that the rate of formation of 3 shows a first order dependence on base concentration and an intramolecular reaction of 1d would be independent of hydroxide concentration (page 1100, first paragraph). Being "independent of hydroxide concentration" is the same as saying the degree of basicity is not relevant. Figure 1 shows that the reaction rate of rearrangement is linear down to a KOH concentration of 0, and there is even measurable rearrangement at pH 7. Thus, what is being said and shown is that even if the rate of reaction may be dependent on the alkalinity of the reaction mixture in some cases, rearrangement occurs. **The skilled person would therefore expect the arrangement to occur under all alkaline conditions.** This is not merely an argument of counsel. It is a report of what Kaneti says and illustrates. The attempt to avoid this teaching by saying Kaneti "does not specifically mention piperidine" (Final Rejection page 9, penultimate sentence) is once again an improper attempt to rely on silence.

(JTX-9_279) (emphasis added).

212. Following this response and a subsequent teleconference on June 12, 2014, the Examiner allowed the claims. (JTX-9_286-92). In the Notice of Allowance, the Examiner stated that "the results presented in Example 3 of the original specification wherein degarelix is synthesized using the Fmoc strategy without the generation of the hydantoin contaminant is unexpected in view of Koedijkov and Kaneti and Examples 1 and 2 of the specification." (JTX-

9_291; *see also* Tr. at 669:24-671:11 (Dr. Jensen discussing the Examiner's reasoning for allowability and noting that they are consistent with his opinions)).

213. "[W]ithout generation of the hydantoin contaminant" is understood to mean the claimed requirement that there be 0.3% by weight or less of the hydantoin. (*See* JTX-1 at 3:46-50; *see also* Tr. at 695:24-696:11).

ii. The European Opposition

214. At trial, both parties discussed the opposition to the European counterpart to the '938 patent, European Patent No. 2 421 887 ("EP 887"). (*See, e.g.*, Tr. at 513:13-514:12, 547:13-549:1, 553:23-555:17, 657:18-660:21).

215. Initially, the opposition to EP 887 was rejected; *i.e.,* the validity of EP 887 was upheld. (Tr. at 658:23-659:10; *see also* DTX-243B_540 ("The opposition is rejected, because none of the grounds of opposition raised by the opponent prejudice the maintenance of the European patent (Art. 101(2) EPC).")). The decision was appealed. (Tr. at 659:11-14).

216. On appeal, the Board of Appeal revoked EP 887 based on a combination of the European counterpart to the '730 patent (D1) and other references. (DTX-440_26, _32; Tr. at 548:11-15). The Board of Appeal stated that an approach that "replace[s] all the Boc protecting groups on the incoming amino acids [with] Fmoc groups and vice versa . . . would have made use only of protecting groups and reaction conditions which are already disclosed in [the '730 patent]." (DTX-440_22). The Board of Appeal then stated that "[i]t cannot therefore be seen why such an approach should have led to side reactions." (DTX-440_22). To that end, the Board of Appeal found:

> It goes without saying that, apart from the exchange of protecting groups as described above, further adjustments to the first synthesis strategy of D1 would not have been necessary, because all three side chain protecting groups (Bzl, t-Bu and Z) are only removed at the

> very end of the synthesis, when degarelix is cleaved from the resin with HF.

(DTX-440_20).

217. Dr. Jensen disagreed with the Board of Appeal's decision because it "totally ignores the complexity of peptide synthesis" by failing to account for all of the various factors that must be considered during synthesis of a complex peptide and further, because the theoretical method that the Board of Appeal relied on to invalidate EP 887 would not have been considered by a POSA. (Tr. at 660:6-21).

218. According to Dr. Jensen, the theoretical method devised by the Board of Appeal would "combine the disadvantages of Fmoc-SPPS with the disadvantages of Boc-SPPS. It's just terrible." (Tr. at 660:6-21).

iii. The '730 Patent

219. The '730 patent issued on July 20, 1999 and disclosed GnRH antagonist peptides including degarelix as well as methods for synthesis of those peptides. (DTX-239).

220. The '730 patent discloses numerous decapeptides, the number of which Dr. Jensen characterized as being in the "thousands." (Tr. at 654:23-25).

221. The '730 patent discloses the use of Boc-SPPS for the synthesis of degarelix. (Tr. at 507:5-8, 653:2-19; DTX-239 at 11:38-13:63 (Example 1)).

222. As the Patent Examiner found during prosecution, the '730 patent does not disclose synthesizing degarelix using Fmoc-SPPS. (JTX-9_242).

223. A POSA would not modify a Boc-SPPS process for degarelix to an Fmoc-SPPS process because Boc-SPPS and Fmoc-SPPS "are very different processes." (Tr. at 661:4-10).

224. As the '938 patent specification indicates, "the '730 patent discloses . . . a wide range of other well-known protecting groups, including the Fmoc group." (Tr. at 559:21-25; JTX-

1 at 3:13-16). The '730 patent indicates that these protecting groups are "α-amino protecting group[s] of the type known to be useful in the art in the stepwise synthesis of polypeptides." (DTX-239 at 8:65-66).

225. The '730 patent included "any protecting group one could consider at that time [i.e., April 2009]," (Tr. at 653:20-654:4; DTX-239 at 8:65-9:23), and "[p]robably most of these alpha amino protecting [groups] would not give a peptide" (Tr. at 654:8-17). Notably the '730 patent included the dithiasuccinoyl moiety, or Dts, which Dr. Jensen referred to as "the best protecting group that never worked." (Tr. at 654:8-17).

226. The only protecting group identified in the '730 patent as a "preferred" α-amino protecting group is Boc. (Tr. at 563:1-5, 652:20-654:7; DTX-239 at 9:23).

227. The '730 patent does not disclose any use of Fmoc as an α-amino protecting group, but instead uses Fmoc as a side chain protecting group. (Tr. at 508:16-509:10, 655:10-14; DTX-239 at 11:39-14:18 (Example 1)). There is, however, "a big difference between a side chain protecting group and an alpha protecting group" (Tr. at 652:11-21):

> A side chain protecting group is normally very different from an alpha amino protecting group. It has to fulfill different criteria. It's being removed, basically, only once during the synthesis, whereas an alpha amino protecting group has to be removed repeatedly. You have to look at the conditions for removal of the side chain protecting groups only apply once[.] [F]or an alpha protecting group[, i]t's repeated treatments with these conditions, so there is an accumulated exposure time to the conditions needed for removal of [an] alpha amino group.

(Tr. at 655:15-656:3; *see also* Tr. at 563:22-25). Dr. Jensen further explained that, when talking about stability of a peptide, it is accumulated or cumulative exposure time that matters. (Tr. at 656:4-11). The accumulated exposure time explains the applicability of Example 2 because "to remove an Fmoc group, you have two base treatments, so you have to combine those times and

then you have to multiply this number with a number of amino acid[s] that are sent subsequently culled and deprotected, so this goes into the hours." (Tr. at 656:12-22).

228. The '730 patent does not disclose or discuss the hydantoin. (Tr. at 652:19-20).

iv. Amblard

229. Amblard was published in 2006 and taught strategic considerations and practical procedures for solid state peptide synthesis. (DTX-207).

230. Amblard disclosed that Boc and Fmoc were the two commonly used protecting groups for SPPS. (DTX-207_003; Tr. at 517:4-7, 687:18-20 ("Fmoc and Boc were the two major forms of SPPS.")).

231. Amblard is "a user's manual guide for non-expert" regarding the synthesis of certain peptides using standard amino acids. (Tr. at 516:21-517:1; *see also* Tr. at 663:15-21 (noting that degarelix is a "highly unusual peptide" "whereas Amblard is [a] general text aimed at the nonexpert in the field solely with the standard common amino acids")).

232. Amblard addresses synthesis using the amino acids described in Table 1, which are referred to as "Proteinogenic Amino Acids." (DTX-207_4; Tr. at 663:22-664:13).[24] Proteinogenic amino acids are common amino acids – those that are naturally occurring. (Tr. at 664:8-13; *see also* DTX-207_4 (noting that "[a]ll the 20 DNA-encoded or proteinogenic α-amino acids are of L stereochemistry")). Thus, "it's clear that [] Amblard deals solely with common peptide[s] made of general amino acids." (Tr. at 663:22-664:7).

[24] The "Materials" section in Amblard notes that the materials include "Fmoc-amino-acids with protected side-chains (Table 1)." (DTX-207_3; Tr. at 663:22-664:7).

233. Because Amblard deals solely with common amino acids and its purpose is to allow a nonexpert to synthesize peptides, a POSA would not reference Amblard because "a nonexpert would have no business trying to synthesize degarelix from this." (Tr. at 664:14-19).

234. Degarelix is not a common amino acid and it is not easy to synthesize. (Tr. at 647:13-648:3). Dr. Jensen explained that:

> One has to differentiate between a synthesis of standard – peptides containing standard amino acid[s] and Fmoc-protected amino acid[s]. It was common amino acids and that synthesis [i.e., Fmoc-SPPS] was developed for that. When you work with nonnatural, nonstandard amino acids, you're in a different viewpoint with suppression. It's a totally different game when you have to start the planning of this synthesis from the start and you cannot assume that it will just work.

(Tr. at 648:5-14).

235. Amblard does not disclose or discuss the hydantoin limitation.

v. The Hydantoin Limitation

236. As noted, neither the '730 patent nor Amblard disclose or discuss the hydantoin limitation. Instead, Fresenius asserts that this limitation is inherent in the prior art.

237. Dr. Zhou opined that any "standard" Fmoc-SPPS method for the manufacture of degarelix would inherently result in degarelix having 0.3% or less of the hydantoin impurity. (*See*, *e.g.*, Tr. at 575:4-7, 519:11-15). He acknowledged, however, that his definition of "standard Fmoc-SPPS conditions" is not a set definition (Tr. at 569:22-570:25) and has evolved over time (Tr. at 571:1-4). By April of 2009, Dr. Zhou's definition would encompass "numerous organic bases" and "a number of different organic solvents." (Tr. at 661:11-662:2). Dr. Zhou, however,

offered no credible basis for the Court to find that all such combinations or organic bases and organic solvents would invariably lead to less than 0.3% hydantoin.[25]

238. Additionally, there are no "standard" or "common" Fmoc-SPPS conditions for non-standard amino acids like degarelix. (Tr. at 679:15-680:2). A POSA would understand that peptides incorporating unusual or highly modified amino acids, require individualized attention. (*Id.*).

239. A patent application filed by a subsidiary of Fresenius in 2010 concurs. (PTX-474). The Fresenius application states that "[t]he synthesis of peptides carrying at least one p-amino-phenylalanine (Aph) derivative, such as for example Aph(Hor), Aph(Cbm), or Aph(Atz) in their amino acid sequence is challenging. The synthesis often results in a product with a high amount of impurities . . . ." (PTX-474_2). According to the application"[t]he most prominent example of such a peptide is degarelix." (*Id.*).

240. The Fresenius application further states that, "[t]he presence of unnatural amino acids, which are susceptible for rearrangements and side reactions, in the structure of degarelix complicates its chemical synthesis using the conventional methods of peptide chemistry." (PTX-474_2-3). It goes on to recognize that "[o]ne of the main problems in the preparation of degarelix is the high sensitivity of the (L)dihydroorotic acid (indicated as Hor) moiety of the Aph(Hor) residue in position 5 of the sequence in the presence of an aqueous basic solution" and that "the possibility of dihydroorotic moiety rearrangement during peptide synthesis in the presence of bases

[25] The evidence of record suggests that not all of standard Fmoc conditions lead to less than 0.3% hydantoin. For example, Example 2 of the '938 patent states that 2% DBU in DMF (a standard Fmoc-SPPS condition) "resulted in the formation of 1.8% hydantoin" and that if 5% water were present in the mixture (simulating wet DMF), "the amount was increased to 7%." (JTX-1 at 18:14-44 (Example 2)).

significantly limits the choice of deprotection mixtures and, therefore, the applicability of Fmoc-based protection in the preparation of degarelix remains a challenge." (PTX-474_3-4).

241. Fresenius has not proven that the claim limitation less than 0.3% hydantoin was inherent in the prior art.

vi. Secondary Considerations

242. Ferring asserts that a number of secondary considerations support non-obviousness of the '938 patent: (1) unexpected results, (2) skepticism, (3) long-felt but unmet medical need and (4) copying. (D.I. 211 at 59-63).

a. Blocking patent

243. Fresenius argues that the '730 patent is a blocking patent. (D.I. 203 at 80; D.I. 204 at 49). The basis for Fresenius's argument, however, is unclear as it does not appear to relate to the '938 patent. The only proposed finding of fact relating Fresenius's blocking patent argument states:

> The argument for unexpected results is blunted by Ferring's 730 blocking patent. The 730 patent claimed degarelix "for the long-term inhibition of testosterone and progesterone secretion in GnRH-related conditions such as steroid-dependent tumors." DTX 40_005. Ferring's patent barred others from confirming using degarelix and confirming its side effect profile at the time of the CV patents.

(D.I. 203 at 80 (¶ 453); *see also* D.I. 203 at 48 (¶ 248), 50 (¶ 255 referring back to ¶ 453)).

244. The proposed findings, which appear in the section addressing the side effect and CV patents, do not address what the claims of the '730 actually cover.

245. Moreover, as Dr. Jensen explained, "Ferring [had rights to] the '730 patent, but they rely on contract[] [manufacturers] for synthesis of their peptide drugs. [And] a contract manufacturer would be encouraged [not blocked] to try to develop a better synthesis of degarelix and then offer that to the patent owner, Ferring." (Tr. at 681:24-682:7).

246. That testimony is further supported by Dr. Badalassi, who was employed at Ferring at the time. According to Dr. Badalassi, "during the period 2009, up to 2015, we [Ferring] didn't have laboratories for process development. So, there was no, what we call 'wet chemistry' ongoing in our labs." (Tr. at 613:4-13). The "wet chemistry" was done "at PPL, but not exclusively at PPL and, at the time of the invention, Ferring was working with at least Dr. Reddy's Laboratories and Lonza in Switzerland "around the process chemistry for degarelix." (Tr. at 613:14-614:4).

247. Accordingly, the '730 patent is not a blocking patent as to claim 10 of the '938 patent.

b. Unexpected results

248. Ferring argues that it was unexpected that the method of claim 10 suppressed the rearrangement of the Hor moiety into hydantoin.

249. Neither of the parties' experts explained their opinions as to unexpected results with clarity.

250. The Examiner, however, allowed the claim after finding that "the results presented in Example 3 of the original specification wherein degarelix is synthesized using the Fmoc strategy without the generation of the hydantoin contaminant is unexpected in view of Koedijkov and Kaneti and Examples 1 and 2 of the specification." (JTX-9_291; *see also* Tr. at 669:24-671:11).

251. The Examiner's cited evidence suggest that it was unexpected that Fmoc-SPPS would work because the hydantoin moiety would have been expected to form in basic conditions.

252. Thus, there is some evidence of unexpected results.

c. Skepticism

253. Similarly, there is some evidence of skepticism in the record. Dr. Badalassi, explained that he didn't think Fmoc process was a viable way to make degarelix," testifying:

> I think the – how the Fmoc process proceeded is by the [de]block[ing] Fmoc using bases. And it was known that degarelix had some side chain sensitive to basic condition. So if you have some side chain that are sensitive to basic condition, you don't want to go to a process where you expose each and every time you do a coupling to basic condition; right? So that was basically the rationale, at that moment. The knowledge at the moment we had, to think that Fmoc would have not been working for degarelix.

(Tr. at 614:5-17).[26]

d. Long felt but unmet need

254. The '938 patent explains that one of the disadvantages of Boc-SPPS is that it uses trifluoroacetic acid ("TFA") to deblock the α-amino groups. (JTX-1 at 3:16-23). The '938 patent explains that TFA is highly toxic to humans and the environment (JTX-1 at 3:16- 23), and further notes that one of the objects of the invention was to provide a degarelix synthesis method that does not put human health or the environment at risk because it is less toxic. (JTX-1 at 3:27-35). It is undisputed that TFA is a "risky chemical to work with." (Tr. at 693:22-694:2, 517:8-518:5).

255. This is consistent with statements in the 2020 Fresenius patent application that, even ten years after the invention of the '938 patent, "there remains a need to develop an efficient, simple and industrially viable synthetic process for the preparation of degarelix" (PTX-474_4), and particularly a method that "results in an even lower formation of the hydantoin impurity than when piperidine is used." (PTX-474_6).

e. Copying

256. Ferring relies on the testimony of Dr. Rasmussen to supports its assertions of copying.

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[26] Similarly, Mr. Staerkaer, a named inventor on the '938 patent, testified that he did not think Fmoc-SPPS would be a good way to make degarelix based on several concerns about the compound's reactivities. (Tr. at 603:24-604:23).

257. Dr. Rasmussen, however, provided a "high level of analysis" that did not specify details like times or temperatures or conditions. (Tr. at 634:15-23).

258. The only item that Dr. Rasmussen clearly asserted was copied was a chemical drawing showing how the hydantoin impurity can be formed – a possibility known to a POSA from the prior art. (*See* Tr. at 666:20-667:14).

259. There is no evidence of copying substantial enough to evidence nonobviousness.

3. Enablement

a. The Side Effect Patents

260. Fresenius alleges that all of the asserted claims of the '359 and '739 patents, and claims 3, 8 and 14 of the '870 Patent are invalid as not enabled because they claim ranges of initiation doses, maintenance doses and dose timing.

261. Defendant's expert Dr. Yun mentioned undue experimentation during his testimony (Tr. at 302:25-303:4), but never addressed the quantity of experimentation necessary, the disclosures in the prior art involving doses within the ranges or the predictability or unpredictability of finding doses that work.

262. There is no evidence that the efficacy of degarelix is unpredictable within he claimed ranges.

263. Nor is there evidence that the efficacy of treatment with degarelix depends on the interaction between the initiation dose and maintenance dose. If a particular initiation dose is proven to be effective, and a particular maintenance dose is proven to be effective, then it appears that a POSA would not doubt that a dosing regimen using that initiation and maintenance dose would also be effective.

264. The prior art disclosed effective initiation doses, maintenance doses and dose timing. For example, Doehn discloses the "Tammela 2005"[27] trial where individuals received initiation doses ranging from 120 mg to 320 mg in concentrations ranging from 20 to 60 mg/mL. (DTX-040_004). The majority of individuals receiving a 120 mg initiation dose at 20 mg/mL and 40 mg/mL were medically castrated at days 3 and 28. (DTX-236_2). The vast majority individuals receiving a 320 mg dose at a 60 mg/mL concentration were medically castrated after 3 and 28 days. (*Id.*)

265. Doehn further discloses a trial where individuals received maintenance doses of 80, 120 or 160 mg every 28 days. The results, published in Van Poppel 2006, were that more than 90% of those receiving maintenance dose injections of 80, 120 mg and 160 mg, maintained castrate-levels at all monthly measurements. (DTX-040_2).

266. Doehn also summarized another trial, known as "Vienna Highlights" (Tr. at 258:20-25), presented in 2004 in Vienna at Highlights from the 29th European Society for Medical Oncology Congress, Clin. Prostate Cancer, 3(3): 136-140, at 137 (Dec. 2004) (DTX-298_3). This trial disclosed that 40 mg maintenance doses were effective in medically castrating more than three-quarters of participants. (DTX-298_3).

267. WO '049 states that the effective concentration range for a solution that is stable prior to administration, but turns to a gel immediately after administration, is "directly and positively verifiable by the simplest tests and observations requiring minimal experimentation." (DTX-242_007). It also teaches that the concentration of the composition must be at least 0.3 mg/mL and no more than 120 mg/mL. (DTX-242_007).

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[27] Tammela et al., Degarelix - a phase II multicentre, randomized dose-escalating study testing a novel GnRH receptor blocker in prostate cancer patients, Eur. Urol. Supl. 4(3):228 (2005)

268. Accordingly, the prior art discloses that the claimed range of the initiation and maintenance doses were effective in treating prostate cancer.

b. The '938 Patent

269. In its post-trial papers, Fresenius argues, without evidentiary support, that claim 10 of the '938 patent is invalid for lack of enablement because "Claim 10 requires nothing other than SPPS-Fmoc with piperidine and DMF, to achieve the claimed invention" so "[e]ither the 0.3% or less limitation is an inherent property, or else the claims should have been narrower in scope to cover what was allegedly discovered . . . ." These arguments were not included in the pretrial order (*compare* D.I. 172, ¶¶ 579-83 *with* D.I. 203, ¶¶ 563-64). And Dr. Zhou did not opine that claim 10 was invalid for lack of enablement. (Tr. at 556:21-25).

270. Fresenius has waived its asserted nonenablement defense for claim 10 of the '938 patent by failing to raise it in the pretrial proceedings or at trial.

II. LEGAL STANDARDS

A. Claim Construction

"[T]he ultimate question of the proper construction of the patent [is] a question of law," although subsidiary fact-finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015). "[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*) (cleaned up). Although "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Id.* at

1314. "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted).

The patent specification "is always highly relevant to the claim construction analysis . . . [as] it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). In addition to the specification, a court "should also consider the patent's prosecution history, if it is in evidence." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996).

In some cases, courts "will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva*, 135 S. Ct. at 841. Overall, however, although extrinsic evidence "may be useful to the court," it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

B. Infringement

1. Direct Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See Markman*, 52 F.3d at 976. First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.*

Literal infringement occurs where "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). In the context of an infringement action under 35 U.S.C. § 271(e)(2)(A), the inquiry is "whether, if a particular drug were put on the market, it would infringe the relevant patent." *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.*, 817 F.3d 755, 760 (Fed. Cir. 2016).

2. Induced Infringement

Liability for inducing infringement may arise "if, but only if, [there is] . . . direct infringement." *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961) (emphasis deleted); *see also Linear Tech. Corp. v. Impala Linear Corp.*, 379 F.3d 1311, 1326 (Fed. Cir. 2004) ("There can be no inducement or contributory infringement without an underlying act of direct infringement."). Induced infringement requires that "the alleged inducer knew of the patent, knowingly induced the infringing acts, and possessed a specific intent to encourage another's infringement of the patent." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009). Establishing the necessary specific intent "requires a plaintiff to show that the alleged infringer's actions induced infringing acts and that he knew or should have known his actions would induce actual infringements. While proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice. When a plaintiff relies on a drug's label accompanying the marketing of a drug to prove intent, the label must encourage, recommend, or promote infringement." *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1327 (Fed. Cir. 2021) (cleaned up). "[I]t is well-established that 'mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (citations omitted).

C. Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. To invalidate a patent, the party seeking invalidation must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original).

1. Anticipation

A patent claim is anticipated if each and every limitation is found, either expressly or inherently, in a single prior art reference. *See In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). Anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation. *U.S. Water Servs., Inc. v. Novozymes A/S*, 767 F. App'x 950, 954 (Fed. Cir. 2019) (citation omitted). Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013) (cleaned up).

2. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) secondary

considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). Although an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon ex post reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider secondary considerations or objective indicia of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). It is well-established, however, that in order to accord substantial weight to secondary considerations, "the evidence of secondary considerations must have a nexus to the claims, *i.e.*, there must be a legally and factually sufficient connection between the evidence and the patented invention. The patentee bears the burden of showing that a nexus exists. To determine whether the patentee has met that burden, [courts]

consider the correspondence between the objective evidence and the claim scope." *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360 (Fed. Cir. 2021) (cleaned up).

3. Enablement

"The enablement requirement asks whether the specification teaches those in the art to make and use the invention without undue experimentation." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1345 (Fed. Cir. 2019) (internal quotations omitted). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors may include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). A patent "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

III. CLAIM CONSTRUCTION

During the claim construction proceedings in this case, the parties agreed to the following constructions for the currently asserted patents:

> 1. "prostate cancer" means "any cancer of the prostate gland in which cells of the prostate mutate and begin to multiply out of control" ('359 patent cl. 1; '739 patent cl. 1, 14, 27; '085 patent cl. 1; '398 patent cl. 1, 8);
>
> 2. "monthly" means "about once every 28 days" ('359 patent cl. 2; '739 patent cl. 2, 15, 28; '085 patent cl. 3, 5, 9; '398 patent cl. 3, 5);

In addition, the Court construed seven disputed terms in the asserted patents as follows:

> 1. "in a subject with a reduced likelihood of causing a testosterone spike or other gonadotrophin releasing hormone (GnRH) agonist side-effect" shall have its plain and ordinary meaning ('359 patent cl. 1; '739 patent cl. 1, 14, 27);
>
> 2. "the [treated] subject has a decreased likelihood of developing or experiencing an undesirable side effect during treatment compared to treatment with [the] gonadotrophin releasing hormone (GnRH) agonist leuprolide" shall have its plain and ordinary meaning ('359 patent cl. 3; '739 patent cl. 3, 16);
>
> 3. "wherein administration of degarelix to the subject decreases the frequency of an additional cardiovascular event in the subject as compared to the frequency of an additional cardiovascular event upon treatment with a gonadotrophin releasing hormone (GnRH) agonist in a subject with a history of at least one cardiovascular event" shall have its plain and ordinary meaning ('085 patent cl. 1);
>
> 4. "wherein a risk of developing or experiencing an additional cardiovascular event upon treatment with degarelix is diminished compared to a risk of developing or experiencing an additional cardiovascular event upon treatment with a GnRH agonist" shall have its plain and ordinary meaning ('398 patent cl. 1);
>
> 5. "[a] method of manufacture of degarelix . . . containing 0.3% by weight or less of Ac-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine" means "[a] method of manufacture of degarelix . . . containing 0.3% by weight or less of

> [-D-2Nal-D-Phe(4Cl)-D-3Pal-Ser-X-D-4Aph(Cbm)-Leu-ILys-Pro-D-Ala-NH2, wherein X is 4-([2-(5-hydantoyl)]acetylamino)-phenylalanine using the claimed method and prior to purification steps directed at removing other impurities" ('938 patent cl. 1);[28]
>
> 6. "[a] method of manufacture of degarelix . . . comprising step-wise providing a solution of an amino acid or peptide in which an α-amino group is protected by Fmoc" shall have its plain and ordinary meaning, with the caveat that the ordinary meaning does not exclude further modifications[29] ('938 patent cl. 1); and
>
> 7. "to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment when treating prostate cancer in the subject" and "to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to leuprolide treatment when treating prostate cancer in the subject" shall have their plain and ordinary meaning ('870 patent cl. 1, 15).

It became apparent before trial that the Court's constructions did not resolve one dispute: the meaning of "undesirable side effects" in claim 3 of the '359 patent and claim 16 of the '739 patent. This term was initially construed to have its plain and ordinary meaning. (*See* D.I. 141 at 2). As the case progressed, however, the parties determined that they did not agree on what that plain and ordinary meaning is. The Court permitted the parties to submit evidence (and argument) relevant to construction of this term during trial.

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[28] In response to a request from the parties (D.I. 134), the Court clarified that "the requisite purity level – 0.3% by weight or less of the hydantoin moiety – must be obtained before any purification steps, regardless of whether those additional purification steps are directed to removing hydantoin or a different impurity." (D.I. 141 at 12). The Court further explained that "the parties need not show that the level of hydantoin was measured before purification" and that, in fact, it was "irrelevant when the level of hydantoin was actually ***measured***" as long as there is a way to show that the hydantoin limitation was met before purification. (D.I. 141 at 12 (emphasis in original)).

[29] At the hearing, the parties agreed upon the construction of this term. (*See* D.I. 127 at 7:8-21). The Court adopted this agreed-upon construction.

Plaintiffs propose that "undesirable side effect" means "musculoskeletal and connective tissue disorders such as arthralgia, renal and urinary disorders such as urinary tract infections, reproductive system and breast disorders, and cardiac disorders." (D.I. 204 at 5-6). Defendant claims that "undesirable side effects" means "an adverse event," or else is indefinite. (D.I. 202 at 15, 17-18). The Court agrees with Plaintiffs and construes "undesirable side effect" to mean "musculoskeletal and connective tissue disorders such as arthralgia, renal and urinary disorders such as urinary tract infections, reproductive system and breast disorders and cardiac disorders."

This construction is supported by the specification, which describes "cardiovascular disorders, [] arthralgia, [and] urinary tract [disorders]." (*See* JTX-4 at 27:1-38, 27:63-28:49; 29:8-45; 29:66-30:46; Tr. at 62:25-66:9, 135:6-25, 136:9-138:12). Defendant's assertion that "undesirable side effects" means the "opposite of desirable," on the other hand (*e.g.,* Tr. at 414:11-415:16), is not supported by the specification or the claim language. Defendant's proposed construction would encompass the testosterone spike as such a side effect because "the side effects associated with the testosterone spike are absolutely undesirable." (Tr. at 282:12-20). The patents, however, distinguish side effects experienced as a result of a testosterone flare with the other side effects disclosed, referred to as "undesirable side effects." (JTX-4 at 3:41-45; 3:49-56).

IV. INFRINGEMENT

A. The '359 and '739 Patents

1. Direct Infringement

Healthcare providers following the label for the ANDA product for patients with advanced prostate cancer will directly infringe the asserted claims of the '359 and '739 patents. Indeed, Defendant does not dispute direct infringement of the asserted claims of the '359 and '739 patents by healthcare providers following the label for the ANDA product. (*See* D.I. 219 at 4 (Defendant's

counsel stating: "No, we do not dispute direct infringement" of the asserted claims of the '359 and '739 patents based on the understanding that the lack of testosterone spike and fewer side effects are inherent in carrying out the claimed methods.)).

2. Induced Infringement

Fresenius does not contest that it had knowledge of the '359 and '739 patents. The patents are listed in the Orange Book for FIRMAGON, and Fresenius referenced the '359 patent in its Paragraph IV certification. (FF ¶ 78). In addition, Plaintiffs have shown that Fresenius's proposed label will induce infringing acts and that Fresenius knew that its actions would induce actual infringement of the '359 and '739 patents. (FF ¶¶ 79-82).

There are two active steps in the claims of the '359 and '739 patents: first, administering an initial dose of 160-320 mg of degarelix in two subcutaneous injections and, second, administering a maintenance dose of 60-160 mg of degarelix once every 20-36 days thereafter (claim 16 of the '359 patent and claim 26 of the '739 patent are more specifically directed to the concentration of the maintenance dose of degarelix). Fresenius's proposed label instructs healthcare providers to practice these steps to treat advanced prostate cancer. And, as described above (FF ¶ 69), administering the steps in the manner called for by the proposed label will result in the reduced likelihood of the side effects claimed by these patents.

Moreover, Plaintiffs have shown that Defendant knew that performing the steps in the manner directed by its proposed label would cause the claimed reduction in side effects. (FF ¶¶ 79-82) For example, in a 2015 Fresenius Management Board Meeting presentation, degarelix was proposed as a business opportunity in part because it featured "better clinical outcomes vs. alternatives . . . faster testosterone reductions without testosterone surges . . . [and] fewer instances of urinary infections." (FF ¶ 81). Plaintiffs have shown that Defendant specifically intends for

healthcare providers to administer the ANDA product in an infringing manner, and Defendant knows such administration will result in a reduced likelihood of certain events. Thus, Plaintiffs have shown that Defendant have the requisite specific intent to induce infringement of the asserted claims of the '359 and '739 patents.

To the extent that Defendant argues that it does not "instruct or encourage side effect reduction as a reason to administer degarelix" (D.I. 208 at 16), that is not persuasive. The asserted claims of the '359 and '739 patents do not require administering degarelix for any purpose other than for treating prostate cancer. Rather, the limitations of all asserted claims of the '359 and '739 patents jointly require "administering" degarelix in a specified manner, "thereby treating prostate cancer in a subject with a reduced likelihood of causing a testosterone spike or other GnRH agonist side effect," "wherein the subject has a decreased likelihood of developing or experiencing an undesirable side effect during treatment compared to treatment with gonadotrophin releasing hormone (GnRH) agonist leuprolide." These claims require that the side effect reductions occur, not that the healthcare provider intends for them to occur. As explained, Fresenius intends for these side effects to occur because its proposed label calls for administering degarelix in a manner that it knows will cause this side effect reduction. This is sufficient to prove inducement. *See Takeda*, 785 F.3d at 631 ("The label must encourage, recommend, or promote infringement"); *Vanda Pharms. Inc. v. West-Ward Pharms Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018) ("The contents of the label itself may permit the inference of specific intent to encourage, recommend, or promote infringement").

B. <u>The '870 Patent</u>

The only dispute about either direct or induced infringement of the asserted claims of the '870 patent is the presence of the claim element "choosing a dosing regimen of degarelix over

gonadotrophin releasing hormone (GnRH) agonist treatment to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment when treating prostate cancer in the subject." Therefore, the Court does not specifically address the other elements of the claims.[30]

1. Direct Infringement

At least some healthcare providers will use the ANDA product in a manner that directly infringes the asserted claims of the '870 patent. (FF ¶ 86). Healthcare providers generally seek to prescribe a course of treatment that is effective and that has minimal risk. Plaintiffs' expert, Dr. Shore, testified that, when deciding which medication to prescribe, he takes into account the drug's risk-profile and its effect on a patient's quality of life. He further testified that he personally has chosen to prescribe degarelix over a GnRH agonist for patients that already have arthralgia in order to reduce the risk of arthralgia. (*Id.*). Accordingly, healthcare providers believing that treating advanced prostate cancer with degarelix leads to a decreased risk of arthralgia may choose to treat their patient with degarelix for that reason. Therefore, at least some healthcare providers will directly infringe the claims of the '870 patent through use of the ANDA product.

2. Induced Infringement

The question of induced infringement of the claims of the '870 patent turns on whether Fresenius has the specific intent to induce healthcare providers to choose degarelix over a GnRH agonist to decrease the likelihood that a patient develop a musculoskeletal disorder (or specifically arthralgia in claim 3). The parties agree that "choosing" is not an inherent property, but rather an active step that must be performed. (D.I. 211 at 22 ("Plaintiffs agree that the choosing step requires

[30] To be clear, there is no dispute that Plaintiffs have proved that the other claim elements are met by the ANDA product. (*See* D.I. 208 at 9-11; D.I. 204 at 9-14). The Court thus treats these elements as being met for purposes of infringement.

an affirmative action"); D.I. 209 ¶¶ 65-69 (citing testimony of experts)). There is, however, no evidence that any action by Fresenius will induce infringing acts. In particular, there is no evidence that Fresenius's proposed label instructs, teaches or otherwise encourages users to perform the patented method by choosing to administer degarelix to decrease the likelihood of the claimed side effect. *AstraZeneca LP. v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of Apotex's affirmative intent to induce infringement."); *see also Vita–Mix Corp.*, 581 F.3d at 1329 n.2 ("The question is not . . . whether a user following the instructions may end up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent."); *see also GlaxoSmithKline*, 7 F.4th at 1327 ("When a plaintiff relies on a drug's label accompanying the marketing of a drug to prove intent, the label must encourage, recommend, or promote infringement.").

Here, Fresenius knew of the '870 patent and believed degarelix offered "better clinical outcomes" than alternatives. (FF 81, 87). But there is no evidence that Fresenius knew that administration of degarelix would decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment. (FF 88). Moreover, even if Fresenius had known, mere knowledge of potential infringing uses is insufficient to prove inducement. *Takeda*, 785 F.3d at 632. That is particularly true, where (as here), Plaintiffs have not claimed that degarelix is chosen primarily for avoiding musculoskeletal side effects (rather than for its indicated use of treating prostate cancer). Indeed, "where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has

actual knowledge that some users of its product may be infringing the patent." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).[31]

There is one indication on the proposed label: "treatment of patients with advanced prostate cancer." (FF 65). This indication is not directed to the reduction of musculoskeletal side effects. Indeed, Plaintiffs acknowledge that "Fresenius's proposed product insert does not explicitly instruct to administer degarelix over an agonist to reduce the likelihood of developing an increase in arthralgia." (D.I. 204 at 13). Instead, Plaintiffs point to an entry in Table 2 of the proposed label, which reports 5% arthralgia incidence for degarelix versus 9% for leuprolide. (D.I. 204 at 10-11). A bare reference in a general table about various side effects, however, "does not mean that the FDA has approved the use of the drug to produce those effects; it only ensures that physicians are aware of the full range of the drug's pharmacological effects." *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1323 (Fed. Cir. 2012). Moreover, Table 2 itself contains no information regarding statistical or clinical significance of the side effects listed. (FF 96-98). Plaintiffs' offered evidence is even less convincing than that deemed insufficient in *HZNP*, where the label "describ[ed] the infringing use" as an option, but still did "not encourage infringement, particularly where the label does not require" the claimed step. *HZNP Medicines LLC v. Actavis Labs UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019); *see also Grunenthal GmbH v. Alkem Labs Ltd.*, 919 F.3d 1333, 1339-40 (Fed. Cir. 2019) (affirming no inducement where label terminology included but did "not specifically encourage" infringing application).

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[31] The Court understands that labels need not "limit a drug only to a specific use in order to induce infringement," but they must instruct the infringing use, and "encourage some physicians to prescribe dronedarone to patients with risk factors." *Sanofi v. Glenmark Pharms. Inc., USA*, 204 F. Supp. 3d 665, 679-680 (D. Del. 2016). Here, there is no label instruction that degarelix works better (much less only) in patients with arthralgia, and still nothing in the label directing physicians to "choose" degarelix for that purpose.

Plaintiffs have failed to prove that Fresenius specifically intends to induce healthcare providers to administer degarelix to patients to reduce the likelihood that the patient suffers from a musculoskeletal or connective tissue disorder. Plaintiffs have thus failed to prove the Fresenius will induce infringement of the asserted claims of the '870 patent.

C. The CV Patents

1. Direct Infringement

Plaintiffs assert (and Fresenius does not dispute) that at least some healthcare providers will use the ANDA product in a manner that directly infringes the asserted claims of the CV patents. (*See* D.I. 204 at 14-15; D.I. 205 at 4-6). The Court agrees. Fresenius's expert, Dr. Yun, acknowledged that it is generally known that there is an increased risk of cardiovascular events with GnRH agonist treatment compared to degarelix and likely that at least some physicians who are aware of that increased risk would be motivated to choose an antagonist to treat certain patients. (FF 104). And Plaintiffs' expert, Dr. Keane, agreed, testifying that he prescribes an agonist over an antagonist because it is "better" – for example, it has "significant cardiovascular benefits." (*Id.*). Therefore, at least some healthcare providers will directly infringe the claims of the CV patents by administering the ANDA product.

2. Induced Infringement

The dispute as to inducing infringement of the CV patents centers on the claim language "selecting a subject with a history of at least one cardiovascular event and prostate cancer" in claim 2 of the '085 patent and "selecting a subject that has a history of at least one cardiovascular event" in claim 2 of the '398 patent.[32] The parties agree that selecting is an active step. (FF 102).

[32] As with the '870 patent, given the limited dispute, the Court does not specifically address the other elements of the claims.

Plaintiffs argue that Fresenius will induce infringement of these claims because Fresenius's proposed label does not contain a warning about cardiovascular risk whereas GnRH agonists do contain such a warning. Combining this with healthcare providers' knowledge about the cardiovascular risk attendant to treating prostate cancer with GnRH agonists and antagonists, Plaintiffs assert that the absence of a warning will encourage healthcare providers to use the ANDA product to infringe the asserted claims of the CV patents. Defendant counters that no action of Fresenius instructs a healthcare provider to "select" a patient based on their CV history or to reduce CV events. The Court agrees with Defendant.

There is simply no evidence that Defendant has the specific intent to induce infringement of the claims of the CV patents. The clinical trials section of Fresenius's package insert does not discuss or disclose any of the cardiovascular events specified in the claims (i.e., myocardial infarction, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and other arterial thrombotic/embolic events). (FF 115). The only evidence arguably tied to Defendant is that the proposed label contains no warning about cardiovascular risk. Plaintiffs do not assert that the package insert should contain such a warning, nor could they. The reason that Fresenius's package insert does not present a cardiovascular health warning is because the drug does not require such a warning. That healthcare providers might perceive the absence of a warning as an indication of its relatively safe cardiovascular risk profile is of little consequence, as "it is well-established that 'mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven.'" *Takeda*, 785 F.3d at 631 (quoting *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003)). Although it may be that Defendant and some healthcare providers know about diminished cardiovascular risks of

treatment with degarelix as compared to a GnRH agonist, Plaintiffs have not shown that Defendant did anything beyond leaving a warning that was not required off of its product.

Plaintiffs' citations to *Cephalon, Inc. v. Slayback Pharma LLC.* 456 F. Supp. 3d 594 (D. Del. 2020) and *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc*. 282 F. Supp. 3d 793 (D. Del. 2017) do not change the result. Neither case addresses anything akin to the "selecting" step at issue here. In *Cephalon*, inducement was found because Defendant knew its product met all the claim limitations and encouraged administration of the product in a manner that infringed the claimed method. *Cephalon*, 456. F. Supp. 3d at 626. And in *Orexigen*, Defendant's label instructed administering a product that met all of the limitations in the claim. 282 F. Supp. 3d at 816. Nothing in these cases lends support to the notion that the absence of a warning induces infringement of an affirmative "selecting" step.[33]

Ultimately, based on the evidence presented, the Court cannot infer specific intent to induce infringement of the claims of the CV patents. Plaintiffs have not met their burden of proving that Fresenius will induce infringement of the asserted claims of the CV patents.

V. VALIDITY

Defendant contends that all of the asserted claims are invalid as anticipated or obvious in light of the prior art or not enabled. The Court addresses the arguments below.

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[33] Plaintiffs arguably come closer to finding support in *Amarin Pharma, Inc. v. Hikma Pharms. USA Inc.*, 449. F Supp. 3d 967 (D. Nev. 2020). At issue in *Amarin* was whether the ANDA product's label suggested to doctors that the ANDA product will decrease triglyceride levels without raising low-density lipoprotein cholesterol levels. The District of Nevada (in a footnote) noted the lack of a warning about cholesterol increases in Defendants' labeling, and calling it a "further suggestion to doctors that Defendants' ANDA Products will decrease [triglyceride] levels without increasing [cholesterol] levels." *Id.* at 1002 n.19. That "lack of warning," however, was not the only (or the primary) basis for finding inducement. Indeed, the proposed package insert included a clinical studies section that demonstrated that patients experienced a reduction in triglyceride levels without an increase in low-density lipoprotein cholesterol levels. *Id.* at 1002.

A. The'359 and '739 Patents

1. Obviousness

Defendant argues that the asserted claims of the '359 and '739 patents are obvious in light of Doehn and WO '049. As described above, Doehn explains the methodology and results of several clinical trials in which degarelix was administered in varying dosages and frequencies to prostate cancer patients and WO '049 describes formulations for long-term administration of GnRH antagonist peptides, including degarelix. (FF 125-150).

There are seven limitations, including the preamble, across the asserted claims of the '359 and '739 patents. Plaintiffs do not contest that the majority of these limitations were known in the prior art. Instead, Plaintiffs argue that it would not be obvious to a POSA to employ three limitations in a method of treating prostate cancer with degarelix: (1) administering an initiation dose in two subcutaneous injections (all asserted claims), (2) treatment resulting in a "decreased likelihood of developing or experiencing an undesirable side effect compared to treatment with the gonadotrophin releasing hormone (GnRH) agonist leuprolide" (claim 3 of the '359 patent and claim 16 of the '739 patent) and (3) using a 20 mg/mL maintenance dose (claim 13 of the '359 patent and claim 26 of the '739 patent).

a. Claim 3 of the '359 Patent and Claim 16 of the '739 Patent

There is no question that Doehn disclosed treating prostate cancer by administering an initial dose in the range of 160-320 mg of degarelix subcutaneously followed by maintenance doses in the range of 60-160 mg of degarelix subcutaneously every 20-36 days to obtain testosterone suppression below 0.5 ng/mL. (FF 130-134). The dispute is whether the method including administering the initial dose into two subcutaneous injections and resulting in the

treated subject having a decreased likelihood of developing or experiencing an undesirable side effect compared to leuprolide was obvious.

With respect to two subcutaneous injections, Plaintiffs argue that it would not have been obvious to administer the initiation dose of degarelix in two subcutaneous injections because "[i]njections are not comfortable, so [clinicians] always like to have one injection versus more than one." (D.I. 211 at 17). The prior art, however, teaches the contrary. In the first phase II trial described in Doehn, the initiation dose was split into two subcutaneous injections. (FF 130). Doehn also explains that small injection volumes have benefits over larger volumes. (FF 131, 134). Additionally, WO '049 teaches that "[a]dministration will be by subcutaneous or intramuscular injection, preferably by subcutaneous injection, at a single site or divided between two or more sites." (FF 147). Although this statement is not specific to degarelix, Doehn makes clear that WO '049 is particularly focused on injectable formulations of degarelix. (FF 143). Thus, the prior art teaches splitting the initiation dose and the evidence demonstrates that a POSA would have ample motivation to do so with the expectation that it would work.

The second disputed limitation – whether the treated subject has a decreased likelihood of developing or experiencing an undesirable side effect compared to leuprolide – raises different issues. The Court has construed "undesirable side effects" to mean "musculoskeletal and connective tissue disorders such as arthralgia, renal and urinary disorders such as urinary tract infections, reproductive system and breast disorders, and cardiac disorders." Defendant first[34] contends that Doehn discloses this limitation because it describes how treating prostate cancer with GnRH antagonists avoids the flare reaction, and the bone pain caused thereby, which results from

[34] Defendant actually first contends that under its proposed construction, the claims cover spike issues and Doehn discloses those. (D.I. 202 at 14-15). Although that may be true, the Court has not adopted Defendant's proposed construction.

treating prostate cancer with GnRH agonists like leuprolide. (D.I. 202 at 15-16). Bone pain, however, is not within the Court's construction, because as explained above, the specification distinguishes "undesirable side effects" from those caused by a testosterone flare and the evidence indicates that "bone pain" is caused by the testosterone flare reaction and is distinct from arthralgia. (FF 135-137). Therefore, Doehn does not disclose that treatment with a GnRH antagonist decreases the likelihood of experiencing or developing an "undesirable side effect" associated with treatment with a GnRH agonist like leuprolide.

Defendant next argues that the claimed method is obvious because this disputed element is inherent. For inherency to "establish the existence of a claim limitation in the prior art . . . the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharma., Inc. v. TWI Pharmas., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Here, the experts for both sides agreed that the natural result of administering degarelix to a patient with prostate cancer is a reduced likelihood of experiencing the claimed side effects as compared to leuprolide. *See Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 606 (D. Del. 2018) (explaining that "[a]s *Par Pharmaceutical* makes clear, a property such as a food effect or a pharmacokinetic parameter, when claimed as a limitation, is inherent if it is necessarily present in the prior art combination."), *aff'd sub nom*., *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019). For example, Plaintiffs' expert, Dr. Shore, confirmed that "[i]f a doctor gives degarelix to a patient with locally advanced prostate cancer, that patient will experience a reduced likelihood of experiencing arthralgia [or a musculoskeletal side effect] as compared to treatment with leuprolide." (FF 69). And Dr. Yun, Defendant's expert concurred, testifying that "in dosing degarelix, you will necessarily naturally and inherently avoid any of the spiked side effects [and

non-spiked side effects] because none of the patients who received degarelix will experience those side effects." (*Id.*). Stated differently, the testimony makes clear that the reduced likelihood of the claimed side effects is an inherent property of degarelix itself.

Plaintiffs contend that even if the Court were to find this limitation to be inherent, "the asserted claims are not obvious because 'reducing the likelihood' is an unexpected result" and Defendant must show a reasonable likelihood of success. (D.I. 211 at 15-17). Plaintiffs assert that "[w]hat is important regarding properties that may be inherent, but unknown, is whether they are unexpected. All properties of a composition are inherent in that composition, but unexpected properties may cause what may appear to be obvious composition to be nonobvious." *Honeywell Intern. Inc v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017). Plaintiffs reliance on *Honeywell* is misplaced, however, because, as Judge Bryson explained in a similar context, "that case involved using an unknown but inherent property as a teaching in an obviousness analysis; it did not involve a limitation that recites an inherent property." *Pernix*, 323 F. Supp. 3d at 606-07. Unlike *Honeywell*, here the "undesirable side effects" limitation is both claimed and necessarily present in the prior art. Thus, this case is like *Pernix* in that the testimony of both sides' experts established that administering degarelix for the treatment of prostate cancer invariably leads the patient to experience a reduced likelihood of experiencing the claimed side effects. And there is no evidence that the decrease in undesirable side effects in the asserted claims is either absent from or only sometimes present in the prior art disclosing degarelix in the treatment of prostate cancer. Accordingly, under the governing precedents, the decrease in undesirable side effects is inherent. *See Pernix*, 323 F. Supp. 3d at 607.

As to Plaintiffs' argument as to expectation of success, "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving [the

property]." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). "To hold otherwise would allow any formulation – no matter how obvious – to become patentable merely by testing and claiming an inherent property." *Santarus, Inc. v. Par Pharm. Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). The Court can discern no reason why this does not hold when, as here, there is a method of treatment using a composition having the inherent property.

Finally, the Court must consider secondary considerations of nonobviousness. *Graham*, 383 U.S. at 17-18. Here, Defendant has established a *prima facie* case of obviousness, and Plaintiffs bear the burden of coming forward with evidence of nonobviousness to overcome the *prima facie* case. *See In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). Part of that burden requires Plaintiffs to show that a nexus exists between the asserted secondary considerations and the claim scope. *See Teva Pharms.,* 8 F.4th at 1360. Plaintiffs have failed to do so. As discussed above, the secondary considerations Plaintiffs assert relate to inherent properties of degarelix when used to treat prostate cancer (which was known) and not to the claimed inventions. (FF 151-156). Thus, Plaintiffs have failed to establish a nexus between the asserted secondary considerations and the claimed inventions.

For the foregoing reasons, the evidence as a whole establishes, clearly and convincingly and objectively, that asserted claim 3 of the '359 patent and claim 16 of the '739 patent would have been obvious to a POSA based on the teaching of Doehn and WO '049 (both of which disclose degarelix for the treatment of prostate cancer). It was obvious to split the initiation dose into two injections and the claimed reduction in likelihood of side effects is the natural result of administering degarelix.

b. Claim 13 of the '359 Patent and Claim 26 of the '739 Patent

The obviousness analysis of claim 13 of the '359 patent and claim 26 of the '739 patent includes the same dispute about administering the initial dose in two subcutaneous injections that has already been addressed. The remaining question of obviousness of these claims turns on the claim language "the maintenance dose is administered at a concentration of 20 mg/mL." Defendant asserts that this limitation is taught by Doehn and WO '049, which collectively disclose using a 20 mg/mL initiation dose and suggest using a maintenance dose in a range including 20 mg/mL. (D.I. 202 at 13-14).[35] Plaintiffs argue that the maintenance dose was not taught in the prior art and that a POSA would not think to use the 20 mg/mL concentration called for by the claims. (D.I. 211. at 18-20).

Here, the parties' witnesses agreed that an important goal of the maintenance dose is to ensure that degarelix is in the body at the time of a patient's follow-up appointment. (FF 148). WO '049 describes the problem facing one seeking to have a peptide be released over a period of weeks or even months. "If the solution is too dilute then no depot is formed and the long duration of action is lost [but] [i]f the solution is too concentrated then gel formation will occur before the drug can be administered." (FF 146). Although Plaintiffs argue that "WO '049 is not specific to degarelix" (D.I. 211 at 19), as Doehn made clear, WO '049 "relat[es] to GnRH antagonist peptides, specifically degarelix." (FF 144). WO '049 describes preferred concentrations to achieve a slow-release, submitting that "[i]n a still further preferred embodiment the concentration of the peptide is between 5 mg/ml and 80 mg/ml[,]" and goes on to cite 20 mg/mL (or 25 mg/mL) as an example

[35] There is no issue with respect to undesirable side effects as these claims, which depend on claim 1 and 14, include having a "reduced likelihood of causing a testosterone spike . . . side effect." Doehn discloses the treatment with a GnRH antagonist (such as degarelix) reduces the likelihood of bone pain, which is a side effect associated with a testosterone spike. (FF 135).

of a concentration that "may be used to form a gel after administration which releases the peptide over a period of at least two weeks, preferably for a period of three months." (FF 149). This timeframe corresponds to when clinicians wish to see their patients for check-ins, at which time doctors desire degarelix to still be in the patient's body. (*Id.*). This timeframe also coincides with the 28-day maintenance schedule reported in Doehn. (FF 148). Given WO '049's teaching of the problem faced and concentrations to be employed, a POSA would be motivated to use 20 mg/mL and would have a reasonable expectation of success.

Finally, as to secondary considerations of nonobviousness, Plaintiffs have failed to establish a nexus between the asserted secondary considerations and the claimed inventions. Indeed, for claim 13 of the '359 patent and claim 26 of the '739 patent the failure is starker given that these claims are not limited to the "undesirable side effects" that are the focus of Plaintiffs' alleged secondary considerations. They also include side effects caused by the testosterone spike. Moreover, Plaintiffs make no effort to tie the asserted secondary considerations to the claimed maintenance dose or spitting of the initiation dose.

For the foregoing reasons, the evidence as a whole establishes, clearly and convincingly, that the asserted claim 13 of the '359 patent and claim 26 of the '739 patent would have been obvious to a POSA based on the teachings of Doehn and WO '049.

B. Obviousness and Anticipation of the '870 Patent

Defendant contends that all asserted claims of the '870 patent (claims 3, 5, 8 and 14) are obvious in view of Doehn and WO '049. Defendant further asserts that claims 3, 5 and 8 are anticipated by Doehn. The Court addresses each argument in turn.

1. Obviousness of The Asserted Claims of the '870 Patent

Unasserted claim 1 of the '870 patent, from which all asserted claims depend, claims "[a] method of treating locally advanced prostate cancer in a subject," in which the first step is "choosing a dosing regimen of degarelix over gonadotrophin releasing hormone (GnRH) agonist treatment to decrease the likelihood of developing a musculoskeletal disorder or a connective tissue disorder compared to GnRH agonist treatment when treating prostate cancer in the subject." (FF 26-30). Defendant asserts that the prior art discloses the "choosing" limitation because Doehn teaches that treating prostate cancer with degarelix avoids testosterone flare, bone pain is caused by testosterone flare, bone pain is a musculoskeletal or connective tissue disorder and therefore Doehn teaches that treating prostate cancer with degarelix will lead to a decreased likelihood of developing a musculoskeletal or connective tissue disorder. The evidence, however, does not support Defendant's argument.

Doehn discloses bone pain resulting from a testosterone flare, which occurs in patients who have metastatic disease, not locally advanced prostate cancer. (FF 135). Bone pain is different than arthralgia. (FF 136). Bone pain occurs in metastatic deposits as a result of the testosterone flare and arthralgia occurs both in patients who receive a GnRH antagonist (and therefore do not experience a testosterone flare) and who receive a GnRH agonist (and therefore do experience a testosterone flare). (*Id.*). Although Dr. Yun opined that bone pain can be associated with locally advanced prostate cancer, he acknowledged that bone pain is typically associated with metastatic disease. (FF 137). Indeed, in the same paragraph that Doehn discloses the clinical flare, Doehn cites a paper that states "[p]atients at risk for clinical flare are overwhelmingly those with stage D2 disease [metastatic cancer], especially those with widespread metastasis" and notes that clinical flare responses are very rare in those who do not have metastatic cancer. (*Id.*). Thus, the prior art

indicates that bone pain may occur as a result of the testosterone flare in patients who have metastatic cancer, rather than the locally advanced cancer claimed.

Defendant's assertion that Doehn's disclosure still pertains to those with locally advanced prostate cancer because some patients with locally advanced prostate cancer may have undetected metastatic deposits is unpersuasive. This contention supposes that some of those with locally advanced prostate cancer actually have undetected metastatic cancer, and so doctors who treat locally advanced prostate cancer may also be concerned with their patients avoiding symptoms of metastatic cancer. This, however, is too speculative and requires too many inferences to be "clear and convincing" evidence.

Thus, Doehn would not have provided one of skill in the art with motivation to choose degarelix over a GnRH agonist to avoid musculoskeletal or connective tissue disorders when treating locally advanced prostate cancer. Accordingly, a POSA would not be taught the "choosing" limitation. As all of the asserted claims of the '870 patent include this limitation, Fresenius has failed to prove that any asserted claim of the '870 patent is obvious.

Plaintiffs have asserted that long-felt but unmet need and unexpected results further support that the asserted claims of the '870 patent are not obvious. As discussed above (FF 151-156), Plaintiffs have not established a nexus between the asserted secondary considerations and the claimed inventions. Having found that Defendant failed to establish a *prima facie* case of obviousness for the asserted claims, however, the Court does not address the secondary considerations further here.

2. Anticipation of Claims 3, 5 and 8 of the '870 by Doehn

Defendant asserts that claims 3, 5 and 8 of the '870 patent are anticipated by Doehn. These claims all depend from claim 1, which includes the "choosing" limitation discussed above. "A

reference is anticipatory under § 102(b) when it satisfies particular requirements," among them "disclos[ing] each and every element of the claimed invention." *In re Gleave*, 560 F.3d at 1334. The Court has already found that Doehn does not teach or disclose the "choosing" limitation. Accordingly, the Court finds that Doehn does not anticipate claims 3, 5 and 8 of the '870 patent.

C. Enablement of the Side Effect Patents

The asserted claims of the '359 and '739 patents and claims 3, 8 and 14 of the '870 patent require an initiation dose between 160 mg and 320 mg and a maintenance dose of between 60 mg and 160 mg administered at specified intervals (every 20-36 days in the '359 and '870 patents and every 28 days in the '739 patent). Defendant argues that because the specification includes only two examples of degarelix trials: (1) an initiation dose of 240 mg and a maintenance dose of 80 mg administered every 28 days, and (2) an initiation dose of 240 mg and maintenance dose of 160 mg administered every 28 days, the claims are not enabled across the range of the initiation and maintenance dose limitations.[36] The Court disagrees.

Fresenius has failed to prove that a POSA would have to engage in undue experimentation to determine whether the full range of initiation doses and of maintenance doses work because the prior art discloses that they did. (FF 260-2668). Defendant's expert never addressed the quantity of experimentation necessary, the disclosures in the prior art involving doses within the ranges or the predictability or unpredictability of finding doses that work. (FF 261).

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[36] In its briefs, Defendant also asserts that limitations concerning concentration and volume are not enabled. (D.I. 202 at 26). Defendant, however, waived these arguments by not raising them in expert reports, in the pre-trial order or at trial. Although Defendant argues that it has not waived these arguments because "dose, concentration, and number of injections are all mathematically related" (D.I. 217 at 14), permitting Defendant to submit post-trial arguments that were not squarely presented at trial, let alone in pre-trial materials, would be prejudicial.

With respect to the prior art, Doehn discloses successful trials where individuals received initiation doses ranging from 120 mg to 320 mg at concentrations ranging from 20 to 60 mg/mL. (FF 264). The referenced study reports that all dose and concentration combinations were effective to provide testosterone suppression in a majority of patients. (*Id.*). As for the maintenance dose, Doehn discloses a trial where degarelix was initially administered subcutaneously at 200 or 240 mg, followed by maintenance doses of either 80, 120 or 160 mg every 28 days. (FF 265). This trial was reported to result in medically castrating participants successfully across all treatment groups. (*Id.*). Although this trial did not include the lower boundary of the claimed maintenance dose range, 60 mg, a separate study found that 40 mg maintenance doses were effective in medically castrating more than three-quarters of participants. (FF 266). Defendant has not submitted evidence suggesting that the efficacy of degarelix is unpredictable, and so the Court finds that the prior art disclosing a 40 and 80 mg dose is sufficient evidence to support the 60 mg maintenance dose, the lower end of the claimed range, as being enabled.

Thus, because the prior art demonstrated that the claimed ranges of the initiation and maintenance doses were effective in medically castrating those suffering from prostate cancer and because there is no evidence that the efficacy of treatment with degarelix depends on the interaction between a particular initiation dose and a particular maintenance dose, a POSA would not have to engage in undue experimentation to determine if the claims worked across their full ranges. Accordingly, the Court finds that Defendant has failed to meet its burden of proving that the claims are not enabled.

D. Obviousness of the CV Patents[37]

Defendant argues that the two asserted claims of the CV patents are obvious in view of Smith 2010 combined with (1) van Poppel 2008 and Levine 2010 or (2) van Poppel 2008, Tanriverdi 2004 and Gotsman 2008. (D.I. 202 at 28). Both claims require selecting a subject with prostate cancer and a history of at least one cardiovascular event, administering degarelix in specified dosages and frequencies to the subject, wherein administration of degarelix to the subject decreases the frequency of an additional cardiovascular event in the subject as compared to the frequency of an additional cardiovascular event upon treatment with a GnRH agonist. The claims limit "cardiovascular event" to myocardial infarction, ischemic heart disease, ischemic stroke, hemorrhagic stroke, and other arterial thrombotic/embolic events.

Defendant asserts that the "selecting" step was obvious in view of the prior art's disclosure that GnRH agonists pose increased cardiovascular risks. The Court disagrees. Neither combination relied on by Defendant discloses the "selecting" step. Both combinations rely on Smith 2010, which concludes that degarelix and leuprolide have comparable cardiovascular safety profiles. (FF 1645-1667). To the extent the cardiovascular events differed between the two drugs, Smith concludes that "the cardiovascular events associated with both agents result from hypogonadism rather than a direct drug effect." (FF 1656).

Similarly, Levine 2010 focuses on the cardiac effects of androgen deprivation therapy (which includes both leuprolide and degarelix) rather than a comparison of degarelix and another drug. Levine 2010 teaches that "[a] history of myocardial infarction >6 months before study randomization was the most common factor that contributed to the designation of moderate or

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[37] Defendant argues that if the "selecting" step in the claims "can somehow be met passively . . . then Smith 2010 would anticipate." (D.I. 202 at 32). Both parties agree, however, that the "selecting" step requires an affirmative step. (D.I. 202 at 28; D.I. 211 at 31).

severe comorbidities," but Levine 2010's tone elsewhere in the paper is more equivocal, stating that "whether an association (or an actual cause-and-effect relationship) between ADT use and cardiovascular events and mortality exists remains controversial and continues to be studied." (FF 172). Levine 2010 notes that an "important potential explanation for the discordant findings is that there is no actual causal relationship between ADT and [CV] mortality and that positive studies are the result of uncontrollable confounding factors or the result of *post hoc* analyses." (FF 171). In the conclusion of Levine 2010, the authors stated only that "there may be a relationship between ADT and cardiovascular risk." (FF 169-172).

So too, van Poppel 2008 which discussed evidence suggesting that the testosterone surge was associated with adverse effects, was at best equivocal as to whether the testosterone surge associated with GnRH agonists causes CV events, noting that the events "might have been related to the high testosterone levels, although cardiovascular events are also quite common in elderly men; therefore, the events recorded in the study by Peeling might not necessarily have been related to GnRH agonist treatment." (FF 174-177). Indeed, even two years after van Poppel 2008, Smith 2010 and Levine 2010 indicated that the cause of CV effects during treatment was unclear. [38]

In light of the actual teachings of the prior art, it is apparent that Defendant's obviousness argument is based on improper hindsight. Indeed, absent hindsight, Smith 2010 and Levine 2010 and van Poppel 2008 would not have left one of skill in the art with the impression that prostate cancer patients with at least one prior cardiovascular event should avoid a GnRH agonist in order to reduce the likelihood of a future event. At the relevant time, a POSA having read each paper

[38] This is true of Defendant's remaining references, Gotsman 2008 and Tanriverdi 2004, as well. Moreover, those are "basic science" preclinical research papers that do not address prostate cancer. Defendant has not shown that a POSA would have found them to be relevant and, indeed, neither Dr. Keane nor Dr. Yun had read Gotsman or Tanriverdi prior to this litigation.

would not have been taught that a relationship between GnRH agonist treatment and cardiovascular health exists. Instead, a POSA would have believed that such a relationship might or might not exist and more work had to be done. A glimmer of an idea is not a teaching and more is required for obviousness.[39] Thus, Defendant has failed to show by clear and convincing evidence that the asserted claims of the CV patents are obvious.

E. Validity of the'938 Patent

Defendant argues that claim 10 of the '938 patent is anticipated by the '730 patent and is obvious in light of the '730 patent combined with Amblard. It also argues that the claim is not enabled. The Court addresses the arguments below.

1. Anticipation

For the '730 patent to anticipate claim 10, it must disclose all elements as combined and arranged in the claim. *See SynQor*, 709 F.3d at 1375. It does not. The '730 patent does not teach Fmoc-SPPS of degarelix or disclose any specific conditions that would be suitable for Fmoc-SPPS. (FF 208, 221-222). The '730 patent discloses a single method of synthesizing degarelix and that method uses Boc-SPPS. (FF 221). Although the '730 patent refers to Fmoc as a potential α-amino protecting group in a list of dozens of other "α-amino protecting group[s] of the type known to be useful in the art in the stepwise synthesis of polypeptides," Boc – not Fmoc – is identified as being preferred. (FF 224-226). And there is no disclosure in the '730 patent that any of the other protecting groups, including Fmoc, work in the synthesis of the many disclosed peptides. In fact, Dr. Jensen's unrebutted testimony was that a POSA would recognize that most of the α-amino

[39] As discussed above (FF 185-186), Plaintiffs have not established a nexus between the asserted unexpected success and the claimed inventions. Having found that Defendant failed to establish a *prima facie* case of obviousness for the asserted claims, however, the Court does not address the secondary considerations further.

protecting groups listed in the ’730 patent would not work for the synthesis of the disclosed peptides. (FF 225).

2. Obviousness

Fresenius’s obviousness argument is that the disclosures of the ’730 patent regarding making degarelix with Boc-SPPS combined with a general Fmoc-SPPS reference, Amblard, teach the claimed invention. (D.I 202 at 43). The Patent Examiner, however, considered combinations of the ’730 patent with what the Examiner characterized as general prior art references disclosing Fmoc-SPPS and allowed the patent to issue. Thus, Fresenius faces a particularly heavy burden to show invalidity of the issued claim. *Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004).

There is no dispute that degarelix is a synthetic peptide with a highly unusual structure. As Dr. Jensen explained this means that its synthesis is not standard. (FF 192-193, 234, 238). Fresenius’s own patent application concurs. (FF 239-240). That application makes clear that the synthesis of peptides carrying at least one p-amino-phenylalanine (Aph) derivative – the most prominent example of which is degarelix – remained “challenging” in 2010 (*i.e.*, almost a decade after the ’938 patent). (FF 239). It is “[t]he presence of unnatural amino acids, which are susceptible for rearrangements and side reactions, in the structure of degarelix complicates its chemical synthesis using the conventional methods of peptide chemistry.” (FF 240). Thus, a POSA would not have been motivated to combine the ’730 patent with the general teachings of Fmoc in Amblard, which is directed to “non-experts” seeking to synthesize peptides using the 20 natural amino acids to make degarelix.

Further, a POSA would not have had a reasonable expectation of success in using Fmoc-SPPS for the manufacture of degarelix with 0.3% or less of the hydantoin impurity. Fmoc-SPPS

occurs in basic conditions (unlike Boc-SPPS, which occurs in acidic conditions). (FF 203). A POSA would recognize from references, including Kaneti, that the Hor moiety is sensitive to basic conditions and that the rearrangement of the moiety – to the hydantoin – is catalyzed by basic conditions. (FF 211-212). Therefore, a POSA would be concerned that Fmoc-SPPS would result in formation of hydantoin impurity. Again the Fresenius application concurs, stating "[o]ne of the main problems in the preparation of degarelix is the high sensitivity of the (L)dihydroorotic acid (indicated as Hor) moiety of the Aph(Hor) residue in position 5 of the sequence in the presence of an aqueous basic solution." Indeed, this "possibility of dihydroorotic moiety rearrangement during peptide synthesis in the presence of bases significantly limits the choice of deprotection mixtures and, therefore, the applicability of Fmoc-based protection in the preparation of degarelix remains a challenge." (FF 239-240).

In the end, although Defendant's argument that claim 10 of the '938 patent is obvious has superficial appeal, as is often the case, this obviousness issue comes down to weighing competing facts and expert testimony regarding what a POSA would have found obvious at the time of the invention. Here, in considering and weighing the evidence presented at trial, the Court found Plaintiffs' expert Dr. Jensen to be substantially more credible. Indeed, Defendant's expert's testimony relied on taking broad teachings from the '730 patent and Amblard and then extrapolating onto them (in largely conclusory fashion) the missing claim limitations based on what a POSA allegedly would have known or done. As such, Defendant's arguments suffer from significant and improper hindsight bias. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("Mylan's expert, . . . simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious. Of course, this reasoning is always inappropriate for an

obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it 'would have been obvious at the time the invention was made.'" (citation omitted)). Thus, the Court finds that Defendant has not shown by clear and convincing evidence that the claimed method of manufacture is obvious.

As discussed above (FF ¶¶ 248-259), the Court has found that at least some of the secondary considerations asserted by Plaintiffs further support the finding of non-obviousness. Having found that Defendant failed to establish a *prima facie* case of obviousness for claim 10, however, there is no need to further address that evidence.

3. Enablement

As noted above at paragraphs 269-270, Fresenius did not raise its current enablement argument in the pretrial order or put on evidence of it at trial. Thus, Fresenius has waived this defense. Even if that were not the case, however, Fresenius's attorney argument does not rise to the level of clear and convincing evidence.

VI. DISMISSAL OF THE S-ALP PATENTS

Prior to trial, the parties agreed to dismiss the '081 patent and '999 patent (collectively, the "S-ALP patents"). This decision was made in response to the Court's request that the parties focus and narrow the issues for trial. (D.I. 180). As explained in the parties' joint submission, dismissal of the S-ALP patents was the most efficient way to streamline the issues for trial in a substantive way:

> Eliminating the S-ALP patents remove[d] an entire patent family from the litigation, narrowing the issues for trial and eliminating one of Plaintiffs' expert witnesses (Dr. Celestia Higano). The parties' stipulation as to the S-ALP patents also rendered moot Plaintiffs' Motion in Limine #1. (*Id*. at 2).

Defendant argues that dismissal of these claims should be with prejudice. (*See* D.I. 202 at 53-54). Plaintiffs disagree, arguing that the dismissal is without prejudice. (*See* D.I. 211 at 64).

In the Court's view, Plaintiffs' dismissal of these claims is essentially a voluntary dismissal under Rule 41(a)(2) of the Federal Rules of Civil Procedure. *See* FED. R. CIV. P. 41(a)(2) ("[A]n action may be dismissed at the plaintiff's request only by court order, on terms that the court considers proper."). Dismissals under Rule 41(a)(2) are without prejudice unless the Court finds otherwise. Indeed, the Third Circuit has set a liberal policy in favor of voluntary dismissals. *See In re Paoli R.R. Yard PCB Litigation*, 916 F.3d 829, 863 (3d Cir. 1990) ("Rule 41 motions 'should be allowed unless defendant will suffer some prejudice other than the mere prospect of a second lawsuit.'" (quoting 5 J. MOORE, MOORE'S FEDERAL PRACTICE ¶ 41.05[1] at 41-62 (1988))).

Under the circumstances here, the Court will not dismiss the claims with prejudice. Plaintiffs were making good-faith, reasonable efforts to comply with the Court's directive to streamline issues for trial while also negotiating (in Plaintiffs' opinion unsuccessfully) with Defendant to reduce the asserted validity defenses. (D.I. 204 at 21). Moreover, the simple fact is that courts need to be able to control their dockets and conduct trial proceedings in a manageable and efficient way. This is especially true in Hatch-Waxman cases where a 30-month stay operates to press courts to conduct a bench trial and issue a detailed post-trial opinion on complex technology as quickly as possible. The most effective way to ensure a faster resolution of these cases is to reduce the number of asserted claims and defenses that are tried. In this case, the number of claims that were still asserted just prior to trial presented an unmanageable number for the Court to be able address in an expedient manner given the Court's busy docket. Here, Plaintiffs were dropping claims at the Court's request and apparently being stymied in their discussion with

Defendant to reduce defenses. It seems unfair to now tell Plaintiffs that that dismissal was with prejudice. Therefore, dismissal of the '081 and '999 patents is without prejudice.

That being said, the Court understands Defendant's concerns about potential prejudice and the Court has no interest in litigating complex Hatch-Waxman cases more than once. The Court, however, is skeptical that allowing the dismissal without prejudice with the facts of this case would result in such inefficiencies. Indeed, in reducing the number of claims for trial, the most reasonable choice for any plaintiff is to put forth their strongest asserted claims. It would be the rare case indeed where a plaintiff would fail to prevail on their strongest claims and expect victory on those previously deemed disposable.

VII. CONCLUSION

As discussed herein, after considering the entire record and the applicable law, the Court concludes that (1) Ferring has proved that Fresenius will induce infringement of claims 3 and 13 of the '359 patent and claims 16 and 26 of the '739 patent and that Fresenius infringes claim 10 of the '938 patent; (2) Ferring has not proved that Fresenius will induce infringement of any of claims 3, 5, 8 and 14 of the '870 patent, claim 2 of the '085 patent and claim 2 of the '398 patent; (3) Fresenius has proved that claims 3 and 13 of the '359 patent and claims 16 and 26 of the '739 patent are invalid for obviousness; (4) Fresenius has not proved that any of claims 3, 5, 8 and 14 of the '870 patent, claim 2 of the '085 patent, claim 2 of the '398 patent and claim 10 of the '938 patent are invalid. An appropriate order will be entered.