IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH	)	
Plaintiffs,	)	
v.	)	C.A. No. 15-1102-GMS
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	

MEMORANDUM

I. INTRODUCTION

In this patent infringement action, Shire Orphan Therapies, LLC, and Sanofi-Aventis Deutschland GMBH, (collectively, "Plaintiffs") allege that Fresenius Kabi USA, LLC, ("Defendant") filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") to manufacture and sell a generic version of FIRAZYR® prior to the expiration of U.S. Patent No. 5,648,333 ("the '333 Patent"). The court held a four-day bench trial in this matter beginning on January 29, 2018. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patent-in-suit, specifically whether the asserted claims are invalid under the doctrine of obviousness-type double patenting ("OTDP") in light of the prior art and whether prosecution laches bars recovery. (D.I. 111); (D.I. 112 at 35.)

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that the asserted claims of the patents-in-suit

are not invalid due to obviousness-type double patenting and that the doctrine of prosecution laches does not bar recovery because there was no unreasonable or unexplained delay in prosecution. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Shire Orphan Therapies, LLC ("Shire") is a limited-liability company organized and existing under the laws of the State of Delaware, with its principal place of business located at 300 Shire Way, Lexington, Massachusetts 02421. Shire Orphan Therapies, LLC was formerly known as Shire Orphan Therapies, Inc.

2. Plaintiff Sanofi-Aventis Deutschland GmbH ("Sanofi") is a company organized and existing under the laws of Germany, with its principal place of business located at Brüningstrasse 50, D-65926, Frankfurt am Main, Germany.

3. Defendant Fresenius Kabi USA, LLC ("Fresenius") is a limited-liability company organized and existing under the laws of the State of Delaware, with its principal place of business located at Three Corporate Drive, Lake Zurich, Illinois 60047.

4. The court has subject matter jurisdiction and personal jurisdiction over all parties.

B. Background[2]

5. This is a civil action for patent infringement arising under the patent laws, 35 U.S.C. § 100 *et seq.*, and the Hatch-Waxman Act, codified as amended at 21 U.S.C. § 355(j) and 35 U.S.C. § 271(e). (D.I. 94 at 2.)

6. Shire is the holder of New Drug Application ("NDA") No. 022150, which provides for the use of FIRAZYR® (icatibant) Injection for the treatment of acute attacks of hereditary angioedema ("HAE") in adults 18 years of age and older. (D.I. 94 at 2.)

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 94, Ex. 2.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

[2] The background was taken from the parties' Proposed Joint Final Pretrial Order, introduction section. (D.I. 94 at 2-3.) This case does not involve any claim for damages, though, both parties reserve their rights to file for attorneys fees and costs. (D.I. 94 at 14.) Plaintiffs also reserve the right to file for damages and a jury trial if Defendant manufactures, uses, sells, offers to sell, or imports its ANDA product prior to the expiration of the '333 Patent.

7. FIRAZYR® (icatibant acetate) is supplied as a single-use, prefilled syringe for subcutaneous administration, each prefilled syringe delivering 3 mL of a solution equivalent to a 30 mg icatibant (free base) dose. (D.I. 94 at 2.)

8. The '333 Patent is listed in the FDA's publication "Approved Drug Products with Therapeutic Equvalence Evaluations" (commonly known as the "Orange Book") as covering FIRAZYR®. (D.I. 94 at 2.)

9. The '333 patent, entitled "Peptides Having Bradykinin Antagonist Action," was issued on July 15, 1997. Sanofi currently owns the '333 Patent, and Shire is the current exclusive licensee of the '333 patent.

10. By letter dated October 27, 2015, Fresenius provided notice to Plaintiffs that it had filed ANDA No. 208317 with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification") to obtain FDA approval to engage in the commercial manufacture, use, or sale of icatibant prior to the expiration of the '333 Patent.

11. On November 30, 2015, Plaintiffs filed suit against Fresenius, asserting infringement of the '333 patent by Fresenius's submission of ANDA No. 208317 and proposed commercial manufacture, use, sale, offer for sale, and/or importation of icatibant thereunder. (D.I. 1.)

12. Fresenius answered Plaintiffs' Complaint on January 13, 2016, asserting counterclaims for declaratory judgment of invalidity of the '333 Patent under 35 U.S.C. §§ 101, 102, 103, and/or 112 and non-infringement of the '333 Patent. (D.I. 11.) Plaintiffs answered Fresenius's counterclaims on February 8, 2016. (D.I. 14.)

13. On August 12, 2016, Fresenius filed an Amended Answer and Counterclaim, which added a counterclaim for declaratory judgment of unenforceability of the '333 Patent under the doctrine of prosecution laches. (D.I. 41.) Plaintiffs answered Fresenius's amended counterclaims on September 6, 2016. (D.I. 43.)

14. On December 15, 2017, Fresenius filed a Second Amended Answer and Counterclaim (D.I. 93), which amended its counterclaim for declaratory judgment of invalidity of the '333 Patent by adding an assertion of obviousness-type double patenting.

15. On January 22, 2018, the parties agreed to dismiss the 35 U.S.C. § 103 challenge to the '333 Patent. (D.I. 99.)

C. The Patents-in-Suit

16. The '333 Patent may be referred to as the "Patent-in-suit."

17. The '333 Patent entitled, "Peptides Having Bradykinin Antagonist Action," was issued on July 15, 1997 to inventors Stephan Henke, Hiristo Anagnostopulos, Gerhard Breipohl, Jochen Knolle, Jens Stechl, Bernward Schölkens, Hans-Wolfram Fehlhaber, Hermann Gerhards, and Franz Hock.

18. The application resulting in the '333 Patent, U.S. Application No. 08/487,442, filed June 7, 1995, is a continuation of U.S. Application No. 08/236,018, filed May 2, 1994, which is a continuation of U.S. Application No. 08/012,849, filed February 3, 1993, which is a continuation-in-part of U.S. Application No. 07/982,052, filed November 25, 1992, U.S. Application No. 07/837,090, filed February 18, 1992, and U.S. Application No. 07/969,523, filed Oct. 30, 1992, which is a continuation of U.S. Application No. 07/841,766, filed March 2, 1992, which is a continuation of U.S. Application No. 07/690,297, filed April 24, 1991, which is a continuation-in-part of U.S. Application No. 07/374,162, filed June 30, 1989 and U.S. Application No. 07/565,270, filed August 10, 1990, which is a continuation-in-part of U.S. Application No. 07/374,162, said U.S. Application No. 07/982,052, is a continuation of U.S. Application No. 07/746,149, filed August 14, 1991, which is a continuation-in-part of U.S. Application No. 07/374,162, said U.S. Application No. 07/837,090, is a continuation-in-part of U.S. Application No. 07/565,270, and U.S. Application No. 07/746,149.

19. The rights to the invention claimed in the '333 Patent were originally assigned from the inventors to Hoechst Aktiengesellschaft ("Hoechst"), then from Hoechst to Hoechst GmbH, and then from Hoechst GmbH to Sanofi. Sanofi is the current owner of the '333 Patent.

20. Including a five-year patent term extension, the '333 Patent will expire on July 15, 2019.

21. The '333 Patent is listed in the FDA publication entitled "*Approved Drug Products with Therapeutic Equivalence Evaluations*" (commonly known as the "Orange Book") as covering FIRAZYR®.

1. <u>The Asserted Claim</u>

22. Plaintiffs have asserted Claim 14 of the '333 Patent.

23. Claim 14 of the '333 Patent claims:

A peptide of the formula
H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH
or a physiologically tolerable salt of said peptide.

2. <u>The Accused Products</u>

i. Firazyr®

24. Shire is the holder of New Drug Application ("NDA") No. 022150.

25. NDA No. 022150 was approved by the United States Food and Drug Administration ("FDA") on August 25, 2011.

26. NDA No. 022150 provides for the use of FIRAZYR® (icatibant) Injection for the treatment of acute attacks of hereditary angioedema in adults 18 years of age and older.

27. FIRAZYR® was subject to five-year New Chemical Entity Exclusivity, which expired on August 25, 2016.

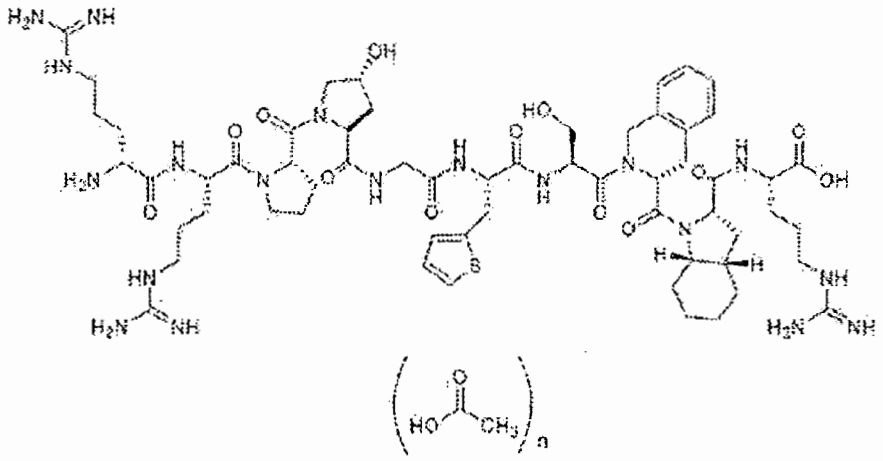
28. FIRAZYR® is supplied in a single-use, prefilled syringe for subcutaneous administration, each syringe delivering 3 mL of a sterile solution of icatibant 30 mg (as icatibant acetate).

29. Icatibant acetate is the active pharmaceutical ingredient contained in FIRAZYR®.

30. The chemical name of icatibant is D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]-L-arginine.

31. A chemical abbreviation for icatibant is H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-DTic-Oic-Arg-OH.

32. A chemical structure of icatibant acetate is presented below:



ii. ANDA No. 208317

33. Fresenius prepared, submitted, and filed Abbreviated New Drug Application ("ANDA") No. 208317 under § 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (codified at 21 U.S.C. § 355(j)) for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, or sale of its Icatibant Injection, 30 mg/3 mL prefilled syringe (the "ANDA Product") before the expiration of the '333 Patent.

34. Included in ANDA No. 208317 is Fresenius's certification pursuant to § 505(j)(2)(A)(vii)(IV) of the FDCA and 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the '333 Patent is

either invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Fresenius' ANDA Product.

35. ANDA No. 208317 was submitted to the FDA on August 25, 2015.

36. By letter dated October 27, 2015 to Shire and Sanofi, Fresenius provided notice under § 505(j)(2)(B) of the FDCA and 21 U.S.C. § 355(j)(2)(B) that it had submitted ANDA No. 208317 with a Paragraph IV Certification to obtain approval to engage in the commercial manufacture, use, or sale of its ANDA Product before the expiration of the '333 Patent.

37. Included in ANDA No. 208317 is Fresenius's request under 21 C.F.R. § 320.22(a) for a waiver of *in vivo* bioavailability/bioequivalence requirements, based on 21 C.F.R. § 320.22(b), which states that for certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident.

38. The active pharmaceutical ingredient, route of administration, dosage form, and strength of the Fresenius ANDA Product are the same as that of FIRAZYR®, as required by law.

39. The Fresenius ANDA No. 208317 seeks FDA approval of its ANDA Product for the same indication as FIRAZYR®.

4. Obviousness-Type Double Patenting

40. U.S. Patent No. 5,597,803 ("the '7,803 Patent"), entitled "Bradykinin Peptides Having Modifications At the N-Terminus," issued on January 28, 1997 to inventors Gerhard Breipohl, Stephan Henke, Jochen Knolle, Bernward Schölkens, Hans-Georg Alpermann, Hermann Gerhards, Klaus Wirth.

41. Claim 1 of the '7,803 Patent claims:

"A peptide of the formula I
Z-P-A-B-C-E-F-K-(D)Q-G-M-F'-I
in which
Z is Fmoc, dibenzylacetyl, cyclohexylcarbonyl, N,N-dibenzyl-glycyl, 2-(4-isobutylphenyl)propionyl, (2-R-(tert butylsulfonylmethyl)-3-(1-naphthyl) propionyl, indole-3-yl-acetyl, 6-(4-benzoyl-benzoylamino)hexanoyl, 1,8-naphthalimidoacetyl, 7-theophyllineacetyl, or N-benzoyl;
P is a direct linkage, Aoc, e-aminohexanoyl, D-Aoc, Aeg(Fmoc), 4-aminocyclohexylcarbonyl or Oic;
A is (D)- or (L)-Arg, (D)- or (L)-Lys, or is a bond;
B is Arg;
C is Pro-Hyp-Gly;
E is Thia;
F is Ser;
K is a direct linkage;
Q is Tic;

M is a direct linkage;
G is cis-endo-, cis-exo-, trans-octahydroindole-2-carboxylic acid;
F' is Arg; and
I is OH."

5. Prosecution Laches

42. **GATT Legislation:**

43. On December 8, 1994, the Uruguay Round of the General Agreement on Tariffs and Trade, P.L. 103-465 ("GATT") was signed into law. The changes went into effect on June 8, 1995.

44. The GATT legislation changed the term of U.S. patents issued for an application filed on or after June 8, 1995, to 20 years from the filing date of the original application. Applications filed before June 8, 1995, continued to have a seventeen-year term from the date of issuance or 20 years from the filing date of the original application, whichever was longer.

45. Continuation applications and continuation-in-part ("CIP") applications are two types of continuing applications authorized by statute.

46. The '333 Patent issued from U.S. Patent Application 08/487,442 ("the '442 Application"), which was filed on June 7, 1995. The '442 Application claims priority to five German patent applications and ten U.S. patent applications.

47. German Patent Applications Include: (1) DE 38 39 581.9 was filed on November 24, 1988; (2) DE 39 16 291.5 was filed on May 19, 1989; (3) DE 39 18 225.8 was filed on June 3, 1989; (4) DE 39 26 822.5 was filed on August 14, 1989; and (5) DE 40 13 270.6 was filed on April 26, 1990.

48. **United States Patent Applications:**

i. The '162 Application

49. The '162 Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on June 30, 1989.

50. The '162 Application claimed priority to German patent applications DE 38 39 581.9, DE 39 16 291.5, and DE 39 18 225.8.

51. The '162 Application contained 6 claims, 164 examples, and *in vitro* IC_{50} data for 25 of those examples.

52. Example 59 is the peptide icatibant.

53. The '162 Application contained *in vitro* IC_{50} data for Example 59.

ii. The '149 CIP Application

54. The '149 CIP Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on August 14, 1991, as a CIP of the '162 Application.

iii. The '052 Application

55. The '052 Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on November 25, 1992, as a continuation of the '149 CIP Application.

iv. The '849 Application

56. The '849 CIP Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on February 3, 1993, as a CIP of the '052 Application, application 07/837,090, and application 07/969,523.

v. The '018 Application

57. The '018 Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on May 2, 1994, as a continuation of the '849 CIP Application.

vi. The '442 Application

58. The '442 Application, entitled "Peptides Having Bradykinin Antagonist Action," was filed on June 7, 1995, as a continuation of the '018 Application.

59. On December 24, 1996, the examiner issued a Notice of Allowability.

60. The applicants paid the issue fee within the statutory three-month period.

61. On July 15, 1997, the '442 Application issued as the '333 Patent.

62. Claim 48 was renumbered as Claim 14 when it issued.

vii. The '270 Application

63. The '270 Application was filed on August 10, 1990, as a CIP of the '162 Application.

viii. The '090 Application

64. The '090 Application was filed on February 18, 1992, as a CIP of the '270 Application and the'149 Application.

ix. The '297 Application

65. The '297 Application was filed on April 24, 1991, as a CIP of the '162 Application and the '270 Application.

x. The '766 Application

66. The '766 Application was filed on March 2, 1992, as a continuation of the '297 Application.

xi. The '523 Application

67. The '523 Application was filed on October 30, 1992, as a continuation of the '766 Application.

6. State of the Art

68. The amino acid sequence of the peptide B-3824 is D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Thi-Arg.

69. B-3824 is also known as NPC 349, among other things.

70. Below is a chart comparing the differences in the amino acid sequences between bradykinin, B-3824, and the peptide of Claim 14 of the '333 Patent (icatibant):

Peptide	0	1	2	3	4	5	6	7	8	9
Bradykinin		Arg	Pro	Pro	Gly	Phe	Ser	Pro	Phe	Arg
B-3824	D-Arg	Arg	Pro	Hyp	Gly	Thia	Ser	D-Phe	Thia	Arg
Icatibant	D-Arg	Arg	Pro	Hyp	Gly	Thia	Ser	D-Tic	Oic	Arg

71. "Oshima" refers to the article "*Cleavage of des-Arg9-bradykinin by angiotensin Iconverting enzyme from pig kidney cortex*" by G. Oshima *et al.*, 41 EXPERIENTIA 325 (1985).

72. "Kazmierski I" refers to the article "*A new approach to receptor ligand design: synthesis and conformation of a new class of potent and highly selective μ opioid antagonists utilizing tetrahydroisoquinoline carboxylic acid*" by W. Kazmierski and V. J. Hruby, 44 TETRAHEDRON 697 (1988).

73. "Kazmierski II" refers to the article "*Design and synthesis of somatostatin analogues with topographical properties that lead to highly potent and specific μ opioid receptor antagonists with greatly reduced binding at somatostatin receptors*" by W. Kazmierski *et al.*, 31 J. MED. CHEM. 2170 (1988).

74. "The '803 Patent" refers to U.S. Patent No. 4,515,803.

75. "Hruby" refers to the article "*Conformational restrictions of biologically active peptides via amino acid side chain groups*" by V. J. Hruby, 31 LIFE SCIENCES 189 (1982).

76. "Stewart II" refers to the article "*Development of competitive antagonists of bradykinin*" by J. Stewart *et al.*, in ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY 81 (1989).

77. "Stewart III" refers to the article "*Applications for bradykinin antagonists*" by J. Stewart *et al.*, in PEPTIDES 1988: PROCEEDINGS OF THE 20TH EUROPEAN PEPTIDE SYMPOSIUM 559 (1989).

78. "Spragg" refers to the article "*The inhibition of glandular kallikrein by peptide analog antagonists of bradykinin*" by J. Spragg *et al.*, 9 PEPTIDES 203 (1988).

79. "The '749 Patent" refers to U.S. Patent No. 4,818,749.

80. "The '202 Patent" refers to U.S. Patent No. 4,847,202.

81. "The '484 Patent" refers to U.S. Patent No. 4,720,484.

82. "The '850 Patent" refers to U.S. Patent No. 4,483,850.

83. "Blankley" refers to the article "*Synthesis and structure-activity relationships of potent new angiotensin converting enzyme inhibitors containing saturated bicyclic amino acids*" by C. J. Blankley *et al.*, 30 J. MED. CHEM. 992 (1987).

84. "The '963 Patent" refers to U.S. Patent No. 4,923,963.

85. "Kinin Antagonists" refers to the article "*Kinin Antagonists*" by J. Barabe *et al.*, 163 METHODS IN ENZYMOLOGY 282 (1988).

86. "The '204 Patent" refers to U.S. Patent No. 4,837,204.

87. "Bodanszky" refers to the textbook "PEPTIDE CHEMISTRY" by M. Bodanszky (1988).

88. "Benetos I" refers to the article "*Hypertensive Effect of a Bradykinin Antagonist in Normotensive Rats*" by Benetos, Gavras & Gavras, 8 HYPERTENSION 1089 (1986).

89. "Benetos II" refers to the article "*Vasodepressor Role of Endogenous Bradykinin Assess by a Bradykinin Antagonist*" by Benetos *et al.*, 8 HYPERTENSION 971 (1986).

90. "Barton" refers to the article "*The Effect of a Bradykinin Antagonist on Vasodilator Responses with Particular Reference to the Submandibular Gland of the Cat*" by Barton, Karpinski & Schachter, 44 EXPERIENTIA 897 (1988).

91. "Breipohl" refers to the article "*Synthesis of Atriopeptin III by Fragment Condensation and Solid Phase Synthesis*" by Breipohl, Knolle & Konig, 64 KLIN WOCHENSCHR 16 (Suppl. VI, 1986).

92. "Chang" refers to the article "*Solid-Phase Peptide Synthesis Using Mild Base Cleavage of Nα-Fluorenylmethyoxucarbonylamino Acids, Exemplified by a Synthesis of Dihydrosomatostatin*" by Chang *et al.*, 11 INT. J. PEPTIDE PROTEIN RES. 246 (1978).

93. "Greene" refers to the book "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS" by Greene (1981).

94. "Griesbacher I" refers to the article "*Effect of Bradykinin Antagonists on Bradykinin-induced Plasma Extravasation, Venoconstriction, Prostaglandin E2 release, Nociceptor Stimulation and Contraction of the Iris Sphincter Muscle in the Rabbit*" by Griesbacher & Lembeck, 92 BR. J. PHARMACOLOGY 333 (1987).

95. "Huffman" refers to the article "*Reverse Turn Mimics*" by Huffman *et al.*, PEPTIDES CHEMISTRY & BIOLOGY, PROCEEDINGS OF THE TENTH AMERICAN PEPTIDE SYMPOSIUM May 23-28, 1987, 105 (Garland R. Marshall ed., 1988).

96. "Regoli I" refers to the article "*Pharmacology of Bradykinin and Related Kinins*" by Regoli *et al.*, AM. SOCIETY FOR PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS EDS., Vol. 32 1980.

97. "Regoli II" refers to the article "*The Actions of Kinin Antagonists on B1 and B2 Receptor Systems*" by Regoli *et al.*, 123 EUROPEAN J. PHARMACOLOGY 61 (1986).

98. "Rifo" refers to the article "*Bradykinin Receptor Antagonists Used to Characterize the Heterogeneity of Bradykinin-Induced Responses in Rat Vas Deferens*" by Rifo *et al.*, 142 EUROPEAN J. PHARMACOLOGY 305 (1987).

99. "Schachter" refers to the article "*New Synthetic Antagonists of Bradykinin*" by Schachter *et al.*, 92 BR. J. PHARMACOLOGY 851 (1987).

100. "Steranka I" refers to the article "Bradykinin as a Pain Mediator: Receptors are Localized to Sensory Neurons, and Antagonists have Analgesic Actions" by Steranka *et al.*, 84 PROC. NAT'L. ACAD. SCI. 3245 (1988).

101. "Steranka II" refers to the article "*Multiple Bradykinin Receptors: Results of Studies using a Novel Class of Receptor Antagonists*" by Steranka *et al.*, NEURORECEPTORS & SIGNAL TRANSDUCTION 111 (1987).

102. "Stewart I" refers to the article "*Bradykinin Competitive Antagonists: Design and Activities*" by Stewart & Vavrek, 65 ADVANCES IN THE BIOSCIENCES 73 (1987).

103. "Stoineva" refers to the article "*Chemical-Enzymatic Incorporation of D-Amino Acids into Peptides: Synthesis of Diastereomeric (D-Ala2, D-Leu5) enkephalinamides*" by Stoineva & Petkov, 183 FEBS LETTERS 103 (1985).

104. "Tourwe" refers to the article "*Synthesis and Biological Activity of Bradykinin Analogues with Reduced and Ethylenic Isosteric Peptide Bond Replacements*" by Tourwe *et al.*, PEPTIDES 1988: PROCEEDINGS OF THE 20TH EUROPEAN PEPTIDE SYMPOSIUM, September 4-9, 1988 (Gunther Jung & Ernst Bayer eds., Walter de Gruyter 1989).

105. "Vavrek II" refers to the article "*Smooth Muscle Selectivity in Bradykinin Analogs with Multiple D-Amino Acid Substitutes*" by Vavrek & Stewart, PLENUM PRESS, 543-547 (L.M. Greenbaum *et al.* eds., Plenum Press NY 1986).

106. "Vavrek III" refers to the article "*Bradykinin Antagonists Containing Hydroxyproline*" by Vavrek & Stewart, Proceedings of the 19th European Peptide Symposium, (D. Thedoropoulus ed., 1986).

107. "Whalley" refers to the article "*The Effect of Kinin Agonists and Antagonists on the Pain Response of the Human Blister Base*" by Whalley *et al.*, 336 ARCH. PHARMACOL. 652 (1987).

108. "Dorer" refers to the article "Hydrolysis of Bradykinin by Angiotensin-Converting Enzyme" by Dorer *et al.*, 34 CIRCULATION RES. J. AM. HEART ASS'N 824 (1974).

109. "Matsas" refers to the article "*The Metabolism of Neuropeptides, The Hydrolysis of Peptides, Including Enkephalins, Tachykinins and Their Analogues, by Endopeptidase-24.11*" by Matsas *et al.*, 223 BIOCHEM. J. 433 (1984).

110. "Wirth" refers to the article "*Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vivo Studies*" by Wirth *et al.*, 102 BR. J. PHARMACOL. 774 (1991).

111. "The '100 Patent" refers to U.S. Patent No. 4,791,100.

112. "The '613 Patent" refers to U.S. Patent No. 4,801,613.

113. "The '755 Patent" refers to U.S. Patent No. 4,861,755.

114. "The '993 Patent" refers to U.S. Patent No. 4,693,993.

D. Procedural History

115. Within 45 days of receiving Fresenius's Notice Letter, Plaintiffs brought this action, asserting infringement of the '333 Patent based on Fresenius's submission of ANDA No. 208317 and proposed manufacture, use, or sale of its ANDA Product before the expiration of the '333 Patent.

116. Plaintiffs' filing of a complaint under the Hatch-Waxman Act within 45 days of receipt of Fresenius's Notice Letter, which was during the one-year period beginning forty-eight months after FIRAZYR®'s date of approval, triggered a stay of FDA approval of Fresenius's ANDA,

which does not expire until seven-and-one-half years from FIRAZYR®'s date of approval (February 25, 2019), or until ordered by the court.

117. Plaintiffs' Complaint asserted infringement of the '333 Patent.

118. Fresenius answered Plaintiffs' Complaint on January 13, 2016, pleading affirmative defenses of non-infringement, invalidity, and failure to state a claim, and asserting declaratory judgment counterclaims of invalidity and non-infringement. Plaintiffs answered those counterclaims on February 8, 2016.

119. Fresenius filed an amended answer on August 12, 2016, pleading affirmative defenses of non-infringement, invalidity, failure to state a claim, and unenforceability, and asserting declaratory judgment counterclaims of invalidity, non-infringement, and unenforceability. Plaintiffs answered those counterclaims on September 6, 2016.

120. On July 5, 2017, the court entered a Stipulation of Asserted Claims and Order under which the Parties assert their respective claims, counterclaims, and defenses regarding only Claim 14 of the '333 Patent.

III. DISCUSSION AND CONCLUSIONS OF LAW

These consolidated cases arise under the patent laws of the United States. The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a). Venue is proper in this court under 28 U.S.C. §§ 1391, and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that the Defendant has failed to establish by clear and convincing evidence that the asserted claim of the '333 Patent would be invalid due to obviousness-type double patenting and that there was an unreasonable or unexplained delay in prosecution. The court's reasoning follows.

A. Obviousness-Type Double Patenting

1. The Legal Standard

The judicially created doctrine of obviousness-type double patenting prevents a patentee from extending the term of exclusivity for a single invention by obtaining additional patents with only slight variations from the original, earlier-expiring, invention. *Abbvie Inc. v. Mathilda &*

Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1366 (Fed. Cir. 2014); *Takeda Pharm. Co., Ltd. v. Doll*, 561 F.3d 1372, 1375 (Fed. Cir. 2009); *Bayer Pharma AG v. Watson Labs., Inc.*, 212 F. Supp. 3d 489, 513 (D. Del. 2016), *appeal dismissed*, No. 17-1538, 2017 WL 3222934 (Fed. Cir. July 5, 2017) (citing *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1379 (Fed. Cir. 2012)(emphasis in original)); *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010) (internal quotations omitted). "The obviousness-type double patenting analysis entails two steps: (1) construction of the claims in the earlier patent and the claim in the later patent to identify any differences[;] and (2) [making a] determination of whether the differences in subject matter between the claims render the claims patentably distinct." *Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009). The second step of the analysis is analogous to an obviousness analysis under 35 U.S.C. § 103 in that the court must determine whether a person of ordinary skill in the art would consider the later invention an obvious variation of the prior invention. *Id.* at 1361-62.[3] At step two, to be "patentably distinct" and valid a claim must not be obvious over or anticipated by an earlier claim by the same inventor. *Abbvie*, 764 F.3d at 1374. The Court of Appeals for the Federal Circuit has explained that

> In general, the obviousness analysis applies to double patenting, except for three distinctions. First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. [*Geneva Pharm. Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373,] 1377 n.1 [(Fed. Cir. 2003)]. Second, double patenting does not require inquiry into a motivation to modify the prior art. *Id.* Finally, double patenting does not *require* inquiry into objective criteria suggesting non-obviousness. *Id.*

[3] The court takes notice of the fact that obviousness-type double patenting and statutory obviousness under 35 U.S.C. § 103 are different. Obviousness under § 103 requires comparing the patent to the prior art, while obviousness-type double patenting only requires comparing the claims in the earlier patent to those in the later patent. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 536 F. Supp. 2d 476, 495 (D. Del. 2008) (Farnan, J.), *aff'd sub nom.*, 566 F.3d 989 (Fed. Cir. 2009); *Geneva Pharm.*, 349 F.3d at 1377; *Kraft Foods Grp. Brands LLC v. TC Heartland, LLC*, No. CV 14-28-LPS, 2017 WL 123457, at *2 (D. Del. Jan. 12, 2017).

Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 999 (Fed. Cir. 2009).

In the context of claimed chemical compounds, an analysis of OTDP—like "an analysis under § 103—entails determining, among other things, whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success. There is no other way to consider the obviousness of compound B over compound A without considering whether one of ordinary skill would have had reason to modify A to make B." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc*, 678 F.3d 1280, 1298 (Fed. Cir. 2012). While the compounds being compared "may have . . . the same general function, changes in the structure of the compounds can have significant effects on their function within the body," rendering the modification nonobvious for OTDP purposes. *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 803 F. Supp. 2d 409, 450–51 (E.D. Va. 2011).

2. <u>The Level of Ordinary Skill in the Art</u>

A person having ordinary skill in the art ("POSA") with respect to the patent-in-suit would have a Ph.D in organic chemistry, medicinal chemistry, pharmacology, or a related field, and have a working knowledge of the chemistry and biochemistry of bradykinin or peptide chemistry for the purposes of drug development. Tr. 55:14-56:4, 494:1-10.[4]

a. *The Scope and Content of the Prior Art*

As of November 24, 1988, the priority date of the '333 Patent, the main treatment for attacks of the rare genetic disease hereditary angioedema ("HAE") treatments included Berinert, a drug administered by an IV, and Kalbitor, a drug with a "black box" warning that it cannot be self-

[4] The parties' definition of a POSA is nearly identical. The court's definition is drawn from the testimony of Plaintiffs' expert Dr. Loren Walensky (Tr. 493:20-496:5.) Defendant's identification of a POSA is derived from Dr. William Bachovchin. Tr. 55:14-56:4; (D.I. 112 at 27); (D.I. 111 at 3 n.2.)

administered. Tr. 32:15-33:5.[5] Both Berinert and Kalbitor were approved in 2009 by the FDA. Tr. 34:18-20. FIRAZYR®, an icatibant self-injection, was approved by the FDA in August of 2011 as the first self-administered HAE treatment. Tr. 32:15-23. No other self-administered HAE treatment was available at the time and no other self-administered treatment has since been approved. Tr. 32:21-25.

In 1985, J. Barabé and D. Regoli published the "Kinin Antagonists" reference, entitled "Kinin Antagonists." JTX-39. This study demonstrated that some B2 receptor antagonists are very active histamine releasers, which means a histamine release results from treatment. JTX-39 at 11; Tr. 524:18-23. The study also showed that the histamine release is reduced or eliminated by acetylation of the N-terminal amide. The study showed that having such antagonist activity is reduced by the addition of a D-Arg at the N-terminal and by the replacement of Pro by hydroxyproline. Thus, an unwanted side effect of a histamine release is eliminated by adding an acetyl group at the N-terminus. Examples 4 and 5 of Table 5 highlight that adding one acetyl group maintains the activity of the peptide and eliminates a side effect while maintaining biological activity.

The '204 Patent, filed on May 9, 1988 and issued on June 6, 1989, is entitled "Functionalized Peptidyl Aminodiols and Triols." JTX-40; Tr. 526:25-527:7. The '204 Patent teaches N-terminal modifications to, among other things, "protect the N-terminus against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the final compounds. . . . " Tr. 526:25-528:1; JTX-40 at 3:1-6. The '204 Patent identifies tert-butyloxycarbonyl ("Boc") and carbobenzyloxycarbonyl groups, both routinely used as N-terminal

[5] A drug with a "black box" warning means that the pharmaceutical has serious safety problems. Tr. 33:2-3. The black box warning is the most serious type of warning mandated by the FDA to warn prescribers about serious adverse reactions. Kalbitor's black box warning means that the drug must be administered under the supervision of a health care professional. Tr. 413:21-21, 622:11-14.

protecting groups during peptide synthesis like Fluorenylmethyloxycarbonyl ("Fmoc"), as options for N-terminal modifications in a final product to protect against enzymatic degradation. Tr. 164:16-165:8; JTX-40 at 3:1-10.

The reference entitled "PEPTIDE CHEMISTRY: A PRACTICAL TEXTBOOK" written by Miklos Bodanszky was published in 1988. JTX-15; Tr. 529. The book explains that several simple amine protecting groups derived from carboxylic acids and commonly used in organic synthesis are not suitable in peptide synthesis. JTX-15 at 31. Bodanszky states that it is obvious that certain groups are not suitable; for example "acetylation or benzoylation of amino groups is impractical, because the vigorous hydrolysis needed for deacylation cleaves peptide bonds as well." JTX-15.31.

The Stewart, *et al.*'613 Patent entitled "Bradykinin Antagonist Peptides," was filed on June 17, 1987 and issued on January 31, 1989. JTX-30. This reference explains that the substitution of the L-Pro at the 7-position of the peptide hormone bradykinin or other substituted analogs of bradykinin with an aromatic amino acid of the D-configuration converts bradykinin antagonists into a bradykinin antagonist.

The '963 Patent, Patent No. 4,923,963, entitled "Bradykinin Antagonist Peptides," was invented by John M. Stewart and Raymond J. Vavrek and issued on May 8, 1990. JTX-38 at Tables I, II. This patent recommends "N-terminal enzyme protecting group[s] selected from the group comprising acyl-type protecting groups [and] aromatic urethane-type protecting groups" on bradykinin antagonists to confer enzymatic resistance. JTX-38 at Tables I, II; Tr. 520:15-521:11. This patent also includes examples of peptides with an acetyl group at the N-terminus and shows that biological data demonstrates that bradykinin analogs with an acetyl group could convert a weak bradykinin agonist into an antagonist. Tr. 522:5-524:1; JTX-38 at Tables I, II, V.

Patent No. 4,693,993 ("the '993 Patent") entitled "Bradykinin Antagonist Peptides," was also invented by John M. Stewart and issued on September 15, 1987. JTX-28. Dr. Stewart's data explains both substitutions in bradykinin antagonists and characteristics of bradykinin antagonists. JTX-28 at 3. By correlating the activity of their bradykinin analogue peptides in *in vitro* and *in vivo* testing, Dr. Stewart's group developed "structure activity relationship" ("SAR") data. Tr. 85:9–86:12. This SAR data highlights the effects of making changes at various positions within the peptide. Tr. 86:9-14.

b. Amino Acid Nomenclature

Before considering the obviousness-type double patenting analysis, the court finds it beneficial to provide a brief explanation of peptides for purposes of its analysis.[6] A peptide is a polymer of amino acids bound together covalently by "peptide bonds." Tr. 99:6-9, 60:13-22, 47:25-48:1. The proteins attached to each other by peptide bonds are "like beads mixed linked on a string." Tr. 47:25-48:1. Each amino acid (an organic compound) has an amino group, a carboxylic acid group, and an "R group," which differs between amino acids and gives each amino acid its distinct chemical properties. Tr. 56:19-57:17, 57:14-17. A peptide is defined by the sequence of amino acids, starting with the amino group of the first amino acid on the left at the amino-terminus or "N-terminus" and proceeding along the chain of amino acids to the last amino acid on the right at the carboxy-terminus known as the "C-terminus." Tr. 61:21-63:13; (D.I. 111 at vi-vii.) In writing peptide formulas, the atoms of a peptide are numbered to indicate a substitution of a peptide or to simply number the atoms within a residue. An amino acid at the N-terminus would be numbered one and an amino acid at the C-terminus would be numbered nine.

[6] This explanation is drawn from trial testimony, the parties' joint exhibits, and proposed findings of fact and conclusions of law. Paragraph 70 of the "Findings of Fact" Section, *supra*, is an example of writing peptide formulas.

Tr. 63:8-13. A parenthesis around a number indicates a modification in the starting molecule. Tr. 64:1-11.

Unlike chemical modification of residues, which often is reversible, processing, or removal of peptide segments, of some proteins cause irreversible changes that alter their activity. In the most common form of processing, residues are removed from the C or N-terminus of a polypeptide by cleavage of the peptide bond in a reaction catalyzed by proteases. In 1989 the most common method for synthesizing a peptide was a method referred to as "solid phase peptide synthesis." Tr. 67:5-7. During this process, resin beads are added to a solution containing a protected amino acid and are then "cleaved" or added and removed in the solution. After cleaving the sequence, the remaining step is to collect the desired amino acid peptide. Tr. 74:5-9. In the context of peptide synthesis, Fmoc is a protecting group that shields the amino group of each amino acid as it is added to the growing peptide chain. Tr. 512:22-514:9, 515:12-516:12; DTX-59. After an N-protected amino acid is added, Fmoc is removed. *Id.* This process repeats until the last amino acid is added to the peptide. *Id.*

Bradykinin, at issue in this case, is a naturally occurring peptide in the human body and has nine amino acids. Tr. 61:21-63:13, 400:15-17. Bradykinin is involved in several biological effects, including pain, inflammation, and contraction of smooth muscle, and it elicits those effects by binding to the bradykinin receptor. Tr. 79:23-80:10, 401:2-9. Bradykinin's effects, however, can become problematic when present in excessive quantities. Tr. 82:5-83:4; JTX-28.2 at 1:1-8. A peptide having "bradykinin antagonist action" prevents the natural peptide from binding to its receptor by disrupting the natural interaction between the hormone and receptor. Tr. 498:7-10. Similarly, a bradykinin *analog* is a peptide based on the structure of bradykinin where changes make it slightly different from bradykinin. Tr. 63:14-22.

3. Obviousness-Type Double Patenting[7]

The court will consider whether Defendant has established a *prima facie* case of obviousness-type double patenting in light of the evidence adduced at trial. Specifically, Defendant asserts Claim 14 of the '333 Patent is invalid for obviousness-type double patenting in light of Claim 1 of the '7,803 Patent. The obviousness-type double patenting analysis hinges on whether (1) the removal of the N-terminal modification Fmoc from the peptides of Claim 1 of the '7,803 Patent results in Claim 14 of the '333 Patent; and (2) whether the N-terminal modifications in the '7,803 Patent are intended to be permanent and integral components of the final peptide. (D.I. 112 at 1.)

a. Differences Between Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent

The first step of the obviousness-type double patenting analysis requires the court to consider the differences between Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent. (D.I. 111 at 12); (DTX-59); (JTX-1.) In assessing those differences, the court will look to the patents and the claim language itself.[8]

[7] The '7,803 Patent was not mentioned during prosecution of the '333 Patent because the '333 Patent was filed about 4-years prior to the '7,803 Patent. Thus, the '7,803 Patent is not prior art to the '333 Patent. Tr. 785:3-16. *Eli Lilly & Co. v. Barr Labs. Inc.*, 251 F.3d 955, 973 (Fed. Cir. 2001).

[8] The court would normally start with the claim construction order issued after a *Markman* Hearing. On September 2, 2016, however, the *Markman* Hearing was terminated as a result of the agreement by the parties that there are no disputed terms to be construed. (D.I. 42.) Because there was no *Markman* Hearing, the court takes the time to explain the differences between the claims at issue at step one of the obviousness-type double patenting analysis and then proceeds to step two to explain the differences in the subject matter in more detail. At step two the court recognizes that it and the parties are not conflating the requirements of OTDP. The court first goes through the differences between the subject matter of the claims and then uses the prior art as evidence to support its analysis.

Table 1: The Claims at Issue

Claim 14, '333 Patent	Claim 1, '7,803 Patent
14. A peptide of the formula H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH or a physiologically tolerable salt of said peptide.	1. A peptide of the formula I Z-P-A-B-C-E-F-K-(D)Q-G-M-F-I in which Z is Fmoc, dibenzylacetyl, cyclohexylcarbonyl, N,Ndibenzyl-glycyl, 2-(4-isobutylphenyl)propionyl, (2-R-(tert butylsulfonylmethyl)-3-(1-naphthyl)propionyl, indole-3-yl-acetyl, 6-(4-benzoyl-benzoylamino)hex anoyl, 1,8-naphthalimidoacetyl, 7-theophyllineacetyl or N-benzoyl; P is a direct linkage, Aoc, e-aminohexanoyl, D-Aoc, Aeg(Fmoc), 4-aminocyclohexylcarbonyl or Oic; A is (D)- or (L)-Arg, (D)- or (L)-Lys, or is a bond; B is Arg; C is Pro-Hyp-Gly; E is Thia; F is Ser; K is a direct linkage; Q is Tic; M is a direct linkage; G is cis-endo-, cis-exo-, trans-octahydroindole-2-carboxylic acid; F" is Arg; and I is OH.

At the outset, while there was no *Markman* Hearing in this case, the parties have identified claim construction disputes with respect to Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent. (D.I. 42.)[9] The court, therefore, turns to the specification to shed light on the utility of the claims. *Abvvie*, 764 F.3d at 1380-81 ("[i]n considering the question [of obviousness-type double patenting], the patent disclosure may not be used as prior art. *This does not mean that the disclosure may not be used at all.*"). The court would be raising form over substance not to engage the use of the specification merely because parties previously indicated there was no claim construction dispute. (D.I. 42.) Plaintiffs assert that Claim 14 of the '333 Patent should be construed in light of

[9] The parties' dispute centers over whether a POSA would interpret the Z component of Claim 1 of the '7,803 Patent to be permanent and integral to the final patent. The meaning of Z, which can be the chemical moiety Fmoc, is disputed. Tr. 502:20-503:3. Dr. Bachovchin believes that a POSA looking at Claim 1 of the '7,803 Patent would understand the purpose of the Z group could be multiple, including that the Z group could "be left over from synthesis and would therefore think that it should be removed." Tr. 143:17-24, 146:15-147:15. The specification of the '7,803 Patent is consistent with the language of Claim 1 that the peptides of formula 1 have a Z group that is not to be removed and a P group with one of seven choices. *Sun Pharm. Indus.*, 611 F.3d at 1387. There were no motions in limine, but regardless, a *Markman* dispute still exists. The court acknowledges that the law is unsettled with respect to the role of the specification, as opposed to the claims, in the OTDP analysis. *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 625 F.3d 719, 721 (Fed. Cir. 2010) (Newman, J., dissenting); *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 2011 WL 3236037, at *2 (D. Del. July 28, 2011) (Sleet, J.), *aff'd*, 689 F.3d 1368 (Fed. Cir. 2012).

the patent's specification, which shows bradykinin antagonism, while Defendant argues Claim 14 itself and the specification require no activity for the claimed peptide. (D.I. 111 at 24.) Similarly, Plaintiffs argue Claim 1 of the '7,803 Patent requires the Z group to be permanent, while Defendant asserts that interpretation improperly reads limitations into the claim. (D.I. 111 at 24.) Plainly, much is the same between the Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent. Both patents claim a peptide sequence, they share five inventors, and are both assigned to Hoechst AG. Tr. 98:9-21. Claim 14 of the '333 Patent claims a single ten-amino acid peptide known as icatibant and relates to "Peptides Having Bradykinin Antagonist Action." JTX-1; Tr. 553:7-10.[10] In contrast, the '7,803 Patent relates to "Bradykinin Peptides with Modifications at the N-Terminus" and covers Fmoc-icatibant. DTX-59; Tr.107:6-23, 559:8-25; (D.I. 111 at 25.)

Notwithstanding the similarities, obviousness-type double patenting requires the court to focus on the differences. While Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent both disclose icatibant compounds, the claims differ substantially in their scope. Whereas Claim 14 of the '333 Patent claims the single compound icatibant, the '7,803 Patent is directed towards a genus of bradykinin analog peptides that have various modifications at the N-terminus. Tr. 101:4-17, 4:8-10, 5:11-12, 11:22-25; (D.I. 111 at 3.) The '7,803 Patent discloses bradykinin antagonists with lipophilic N-terminal modifications, or "sticky compounds," such as Fmoc. Tr. 467:7-13; DTX-59 at 18:43-45. By contrast, the peptide icatibant disclosed in the '333 Patent is not a sticky compound and is not N-terminally modified. Tr. 466:3-7, 468:20-21. The '7,803 Patent N-terminus modifications are at the Z and P positions of the peptide. Tr. 54:19-23; DTX-59. For example, Claim 1 of the '7,803 Patent requires the Z component to be one of eleven chemical moieties, including Fmoc, indicating a permanent N-terminal modification. Tr. 502:16-503:13;

[10] Icatibant was synthesized on January 11, 1989, and was determined to be a bradykinin antagonist on January 19, 1989. JTX-1; Tr. 450:3-451:11. The '333 Patent issued on July 15, 1997 and expires on July 15, 2019. JTX-1.

DTX-59 at 20:28-33; (D.I. 112 at 4.)[11] Similarly, Claim 1 of the '7,803 Patent permits component P to be one of six chemical moieties or a "direct linkage"—meaning a chemical bond, chemical moiety, or no P group at all—with no option prioritized over another. Tr. 205:22-206:3, 505:1-12; DTX-59 at 20:34-35. This interpretation is consistent with the examples and biological data in the '7,803 patent. Tr. 505:25-508:25; DTX-59 at Tables I, II. Turning to the specification, every peptide listed in Table I of the '7,803 Patent has a permanent Z group and some have a permanent P group. Tr. 507:1-10. Importantly, the most potent peptide in Table I is Example 5, which has a permanent Z and P group. Tr. 507: 16-19. Because potency of the peptide is known to enhance efficacy, the court finds that the POSA would believe that Example 5 indicates permanency of the Z and P groups. Tr. 84:7-9. Having no chemical moiety—*e.g.*, a direct linkage—is an option for P and not an option for Z, which demonstrates that Z is a permanent part of the '7,803 peptide and differs from Claim 14 of the '333 Patent. Tr. 206:1-6, 503:7-505:8-16, 548:17-21; DTX-59 at 20:28-33; (D.I. 112 at 4.) The specification of the '7,803 Patent provides an additional twenty-six examples in columns 18 through 20 that show a permanent Z group. Tr. 506. Adding further support, all eleven moieties for Z share an acyl group, which indicates the permanence of the Z group because the acyl group is a feature that indicates entry into the Z group. Tr. 502:12-15, 503:20-504:21. Because Claim 1 of the '7,803 Patent allows for modifications in the peptide sequence at two positions, the court finds that the claims themselves are different under step one of the analysis even though they share some inventors and are assigned to the same company.

[11] In organic chemistry, a moiety is a part of a molecule. A "functional group" is a moiety that participates in similar chemical reactions in most molecules that contain it. In turn, the parts of the group are termed moieties. No chemical moiety would mean that the letter positioned in the formula would not need to be in the sequence. Tr. 205:19-206:6.

b. Differences in the Subject Matter Render Claims Patentably Distinct.[12]

Obviousness-type double patenting "prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *Eli Lilly & Co. v. Barr Labs. Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001). Thus, the second step of the obviousness-type double patenting analysis requires the court to consider whether the differences in subject matter of the two patents render the claims patentably distinct—*i.e.*, the later claim is not obvious over or anticipated by an earlier claim. The court recognizes that this step of the analysis is analogous to the statutory § 103 analysis. As such, the court finds that the differences between Claim 14 of the '333 Patent and Claim 1 of the '7,803 Patent render the respective claims patentably distinct for the reasons that follow.

In arguing that the claims are not patentably distinct, Defendant makes three primary arguments. First, Defendant argues that the only difference between Claim 1 of the '7,803 Patent and Claim 14 of the '333 Patent is the presence or absence of the extra N-protecting groups—the Z and P groups. (D.I. 111 at 26.) Second, Defendant argues that the only difference between Fmoc-icatibant and icatibant is the presence of Fmoc. *Id.* Third, Defendant argues it presented clear and convincing evidence demonstrating that a POSA would have been motivated to remove the Fmoc and that they would have had a reasonable expectation that the resulting peptide would be a bradykinin antagonist. *Id.* The court will address each of Defendant's arguments in turn.

[12] It is settled law that a claim to a genus of chemical compounds does not necessarily render a patent to a species within that genus obvious or anticipated. *Abbvie*, 764 F.3d at 1379; *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003); *see Brigham & Women's Hosp. Inc. v. Teva Pharm. USA. Inc.*, 761 F. Supp. 2d 210, 224 (D. Del. 2011) ("[A]n earlier patent claiming a large genus of pharmaceutical compounds does not preclude a later patent claiming a species within that genus, so long as the species is novel, useful, and nonobvious.").

i. A POSA Would Have Believed That the N-Terminal Modifications in Claim 1 of the '7,803 Patent are Permanent

Defendant argues that a POSA starting with Fmoc-icatibant would have been motivated to make icatibant without Fmoc, *i.e.*, without the Z or P groups. (D.I. 111 at 12.) First, Defendant asserts that the peptides of the '7,803 patent with Fmoc at the N-terminus resemble "intermediates" made during peptide synthesis, suggesting that a POSA would have been motivated to remove the Fmoc. Tr. 17:2-4. Second, Defendant asserts that the language requiring the Z and P groups is only found in Claims 2 and 3 and its absence in Claim 1 demonstrates the Z and P groups are not permanent. Third, Defendant asserts that based on the bradykinin antagonist prior art, a POSA would have recognized that positions A through I of Claim 1 constituted a bradykinin antagonist peptide, and that positions Z and P were N-terminal modifications of that peptide. (D.I. 111 at 9); Tr. 101:12-17; 104:1-6. The court disagrees.

The court finds that persons having ordinary skill in the art would not have removed Fmoc based on the patent itself and the prior art. As of 1989, it was known that the addition of N-terminal modifications could confer significant benefits to the resulting peptide, including reduction of side effects and resistance to enzymatic degradation. Tr. 519:9-520:3, 548:9-549:4. For example, the Kinin Antagonists Article demonstrates how acetylation at the N-terminus of bradykinin antagonists could reduce or eliminate the side effect of histamine release, while additional modifications could reduce undesired agonist activity. Tr. 524:18-526:24; JTX-39.11, Table V. Similarly, the specification of the '7,803 patent contemplates two different functional roles for Fmoc: (1) a protecting group used during synthesis that is removed from a peptide under construction, meaning while that peptide is attached to the resin or still has side chain protective groups, or both; or (2) an integral component of the final peptide product. Tr. 512:12-519:5. Consistent with this teaching in the '7,803 patent, removal of Fmoc from a peptide in the prior art

only occurs when the peptide is under construction. Tr. 151:20-162:4; JTX-16.2-3; DTX-15 at 23:5-24:19; DTX-60.1-4. Contrary to Defendant's assertion, the peptides in the '7,803 Patent are not under construction and are, therefore, not intermediates. Tr. 141:14-143:16, 607:22-609:16. During prosecution of the '7,803 patent, the applicants distinguished peptide intermediates under construction having Fmoc and side chain protective groups from the peptides of the final claims. DTX-55.218, 238; (D.I. 112 at 7.) That distinction would have instructed the POSA that the modification was permanent, and would not have motivated the POSA to remove Fmoc.

Next, Defendant argues that because Claims 2 and 3 of the '7,803 Patent say the Z groups are "integral and permanent" and Claim 1 does not, a POSA would know the modifications are not permanent in Claim 1. (D.I. 111 at 14.) The court cannot agree. Claims 2 and 3 of the '7,803 Patent aid the court in understanding the utility of Claim 1. *Abbvie*, 764 F.3d at 1380. "Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment. . . [b]ecause claim terms are normally used consistently throughout the patent . . . ." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005). Claim 2 concerns the administration of an "effective amount of peptide of the formula I as claimed in [C]laim 1" and Claim 3 is directed to a "pharmaceutical composition containing a peptide of the formula I as claimed in [C]laim 1." DTX-59 at 20:50-57; (D.I. 112 at 5.) Both Claims 2 and 3 require the complete formula I from Claim 1, which indicates the inclusion and permanence of the Z group in Claim 1. Tr. 509:24-510:21; DTX-59 at 20:50-57.

Finally, the court finds that, contrary to Defendant's assertion, every example of a peptide of formula I contains Z and every peptide evaluated for biological activity has a Z group. Tr. 511:2-512:1; DTX-59 at 14:28-15:26, 18:32-20:20. Additionally, the prior art taught the use and biological benefits of permanent N-terminal modifications on peptides, including on bradykinin

antagonists. (D.I. 112 at 1, 7.) For example, the biological data found in the '963 Patent demonstrates that bradykinin analogs with an acetyl group could convert a weak bradykinin agonist into an antagonist. Tr. 521:20-524:1; JTX-38 at 5:1-57, Tables I, II, V. Similarly, the '204 patent teaches N-terminal modifications to "protect the N-terminus against undesirable reactions during synthetic procedures *or* to prevent the attack of exopeptidases on the final compounds[.]" Tr. at 526:25-528:1; JTX-40 at 3:1-6. In the former case, the N-terminal group is removed so that it is not part of the final product, whereas in the latter case it is not removed and would remain part of the final compound. Tr. 162:5-164:1.[13] The '204 patent identifies Boc and carbobenzyloxycarbonyl groups, both routinely used as N-terminal protecting groups during peptide synthesis like Fmoc, as options for N-terminal modifications in a final product to protect against enzymatic degradation. Tr. 164:16-165:8; JTX-40 at 3:1-10. Defendant's expert, Dr. Bachovchin, even used Boc at the N-terminus of final peptidic molecules in the 1980's. Tr. 167:18-171:3. Like the peptidic compounds of the '204 patent, the peptides of formula I of the '7,803 patent have permanent N-terminal modifications Z that are acyl, acetyl, benzoyl, and other moieties routinely used in peptide synthesis. *Id.* at 150:12-151:1; Tr. 528:6-9; (D.I. 112 at 9.)[14]

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[13] A non-exhaustive list of the same chemical moieties suggested for use at the N-terminus for either of these objectives "includes but is not limited to acyl, acetyl, . . .tbutyloxycarbonyl ("Boc"), carbobenzyloxycarbonyl or benzoyl groups or an L or D- aminoacyl residue, which may itself be N-protected." Tr. 528:1-11; 165:9-14; JTX-40 at 3:6-10. The phrase "which may itself be N-protected" indicates that a D-amino acid added to the N-terminus may be further modified with an acetyl or acyl group. Tr. 528:7-18, 610:4-15.

[14] In considering amine-protecting groups in peptide synthesis, Bodanszky states that it is obvious that certain groups are not suitable; for example "acetylation or benzoylation of amino groups is impractical, because the vigorous hydrolysis needed for deacylation cleaves peptide bonds as well." *Id.* at 528:19-529:6; JTX-15.31. This speaks to the permanence of the Z groups of the peptides of formula I of the '7,803 patent, which include acetyl and benzoyl groups. Tr. 529:7-24; Tr. 150:12-151:1. (D.I. 112 at 9.)

In 1989, Nova Pharmaceutical Corporation ("Nova") discovered and gave high priority to researching compounds used to treat inflammatory diseases called leumedins, a series of amino acids containing Fmoc in the ultimate active ingredient—the same Fmoc moiety used in peptide synthesis and as an N-terminal Z group of the peptides of formula I of the '7,803 patent. Tr. 171:8-173:11; PTX-353.3, 11. Nova investigated NPC 15199, which was Fmoc attached to the standard amino acid leucine, and advanced it into clinical trials in April 1990. Tr. 173:12-174:21; 172:12-25; 256:22-257:14; PTX-353.3, 11. It was recommended that Nova's bradykinin antagonist program be stopped in favor of the leumedins. *Id.* at 255:1-18. The leumedins displayed a broad range of anti-inflammatory effects without the side effects associated with then-current therapeutic products, demonstrating the biological benefits of Fmoc in a final drug molecule. PTX-353.11; (D.I. 112 at 9-10.)

The court, therefore, finds that a POSA in 1989 using Claim 1 of the '7,803 Patent as her starting point, would not have been motivated to remove the N-terminal modifications from the peptides of Claim 1 of the '7,803 patent to result in Claim 14 of the '333 Patent.[15] Tr. 500:18-501:1, 548:17-21.

ii. A POSA Would Have Been Motivated to Modify Positions 7 and 8 in Accordance With Relevant Literature

By the 1989 priority date, persons having ordinary skill in the art knew little about the bradykinin receptor and its interaction with peptides. Tr. 495:14-17, 625:15-628:17; PTX-355.3; (D.I. 112 at 11.) It was also unknown how peptide modifications made to enhance potency would impact metabolic stability. Tr. 549:9-550:1; PTX-250.20. The prior art references as of the priority date did not teach or suggest: (1) the unnatural, conformationally constrained amino acids Tic or Oic in any position of a bradykinin antagonist; (2) conformationally constrained bicyclic amino acids like Tic or Oic in any position of a bradykinin antagonist; or (3) Tic or Oic to address the metabolic instability of a bradykinin antagonist. Tr. 529:25-530:22, 538:5-543:1, 184:24-185:23, 190:17-196:4; DTX-114.5, 7; (D.I. 112 at 10.) A POSA would have understood that different hormones are individualistic—each receptor having different specificity requirements. Tr. 550:2-551:24; PTX-250.13, 15, 22. Dr. Walensky explained, design principles in one biochemical system in which Tic or Oic were tested would generally be inapplicable to an unrelated receptor. Tr. 539:21-540:18, 543:2-20, 550:2-551:24; PTX-250.13, 15; (D.I. 112 at 11.)

Defendant asserts that a POSA would have been motivated to modify positions 7 and 8 based on the Stewart Structural Activity Relationship ("SAR") Data in the '993 Patent. (D.I. 111 at 11-12); JTX-28 at 3, Tables I, II. Defendant argues that D-Tic at position 7 of Fmoc-icatibant was

[15] The court recognizes that the amino acid sequence of a protein dictates its folding into a specific three-dimensional conformation, the native state. Thus, an addition or removal of part of an amino acid sequence can impact the actual conformation of the protein.

consistent with the prior art because Dr. Stewart's SAR data taught that the critical substitution to generate bradykinin antagonism was the inclusion of a D-aromatic amino acid position 7. (D.I. 111 at 11-12); Tr. 87:20-88:10; JTX-28.3 at Tables I, II. D-Tic is a D-aromatic amino acid and was a constrained analog of D-phenylalanine ("D-Phe"), a well-known position 7 substitution described in the Stewart SAR data and found in prior art antagonists such as B-3824. (D.I. 111 at 12); Tr. 111:1-8, 119:1-17. However, Dr. Walenskky testified that based on the Stewart SAR data, it was unknown how peptide modifications made to enhance potency would impact metabolic stability. Tr. 549:9-550:1; PTX-250 at 20. The court finds that a POSA would have had no reasonable expectation that D-Tic at Position 7 would confer bradykinin antagonism. (D.I. 112 at 11.) As of 1989, it was known that D-Phe15 at position 7 of a bradykinin analog conferred bradykinin antagonism, as well as only certain small D-aromatic amino acids. Tr. 535:2-536:5; 176:14-178:4; JTX-25.1-2, Table 1; (JTX-34.9). Dr. Bachovchin explained, the sensitivity of antagonist activity to simple structural changes at position 7 was evidenced by abolishment of such activity when replacing D-Phe with Dh-Phe16—merely adding a single methylene group. Tr. 183:3-13, 179:25-183:13; JTX-34.5-7. Dr. Bachovchin further explained that the SAR data in the '993 Patent emphasized that "the critical change for antagonist activity is in position 7." Tr. 87:11-12. Although D-Tic and D-Phe share some structural similarity—differing by one methylene group at the atomic level—they differ on both the two and three-dimensional scale. Tr. 531:19-534:19, 541:2-543:1. Dr. Walensky explained, "chemistry is a three-dimensional art[]" even though we "talk about everything on a two-dimensional plane. . . and to add the other level of complexity, it's a three-dimensional moving science." Tr. 531: 9-14. Bradykinin researchers recognized that although chemical structures may superficially appear similar, it is necessary to go to the atomic level to appreciate relevant differences. Tr. 644:13-648:2. A POSA would not have

been motivated to keep D-Tic at position 7 of the peptides of formula I, but rather would have used the amino acids taught in the prior art at position 7. Tr. 530:25-531:5, 536:6-538:3; JTX-28 at Table I; JTX-30 at 3:45-51, 20:13-32; JTX-38, Table I; (D.I. 112 at 12.)

Defendant also asserts that substitution of Oic at the G position, which corresponds to position 8 is consistent with prior art bradykinin antagonist literature because Oic was known in the prior art as a bulky, bicyclic amino acid analog of proline. (D.I. 111 at 11); (D.I. 112 at 11); Tr. 120:15-22, 126:11-25; DTX-58.1. Defendant argues that bulky, bicyclic, and constrained substitutions at position 8 maintained bradykinin antagonist activity in the relevant prior art and that Dr. Stewart taught the use of proline in Position 8. JTX-38.3; (D.I. 111 at 12); Tr. 125:8-17, 126:14-25. Oic has a five-membered ring that connects back to the peptide backbone, *i.e.*, it is conformationally constrained in the same sense that it cannot rotate freely around the peptide backbone. DTX-58.1. Although there was no information regarding the effect of Oic in a bradykinin antagonist, there was information as to the impact of Oic when substituted for proline in other biological systems. Tr. 543:2-20. The substitution of Oic for proline in angiotensin converting enzyme inhibitors lead to mixed results that would not have motivated a POSA to substitute Oic for proline with a reasonable expectation of success of making a potent or metabolically stable bradykinin antagonist. *Id.* at 538:22-24, 543:2-547:4; DTX-58.1, 3, 4. As such, a POSA would not have left Oic at position 8 of a peptide of the formula I, but instead would have inserted the amino acids taught in the prior art at position 8. Tr. 547:5-548:8; JTX-28 at 3:28-34, Table I; JTX-38 at 3:61-67, 4:45-48; (D.I. 112 at 12.)

Because a POSA would not have known whether a peptide appearing to be a bradykinin analog with D-tic at position 7 and Oic at position 8 would be a bradykinin antagonist, a POSA would

have modified positions 7 and 8 in accordance with the teachings of the relevant literature. (D.I. 112 at 2, 10); Tr. 501:16-21.

iii. A POSA Would Have Believed that Claim 14 Has Bradykinin Antagonist Activity While Claim 1 of the '7,803 Patent Does Not When Removing Fmoc

Defendant next argues that a POSA would understand that Claim 14 of the '333 Patent does not recite any biological activity and that and Claim 1 of the '7,803 Patent recites biological activity but does not require it. (D.I. 111 at 3); Tr. 100:22-102:2, 554:16-18, 556:24-557:23. Specifically, Defendant asserts that the POSA would have reasonably expected the icatibant peptide remaining after Fmoc removal would be a bradykinin antagonist based on its structure and the icatibant peptide would be consistent with the prior art Stewart SAR Data. (D.I. 111 at 17.)

In contrast, Plaintiffs assert that Claim 14 of the '333 Patent concerns bradykinin antagonist activity because, among other reasons, every example in the '333 Patent is a bradykinin antagonist. (D.I. 112 at 28); JTX-1 at 44:44-46; Tr. 496:15-24. The scope of the claims cannot be broader than the disclosed invention. Thus, in light of the specification, which is limited to bradykinin antagonists, a POSA would have understood that Claim 14 requires bradykinin antagonist activity based on the biological data and the IC_{50} values, which have the ability to block bradykinin activity. Tr. 496:15-497:5, 507:11-15; (D.I. 112 at 3.)[16] The inhibitor concentration of the peptides that is required to block bradykinin activity ability to bind to its receptor by fifty percent all have bradykinin antagonist action. Tr. 499:9-14; JTX-1, Table 1. The Court of Appeals for the Federal Circuit has emphasized that 'predictability is a vital consideration in the obviousness analysis[,]' including obviousness-type double patenting." *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp.

[16] Dr. Walensky explained that Claim 14 itself informed his opinion. The specification explains that the invention relates to novel peptides having bradykinin antagonist action and to a process for their preparation. Tr. 498:15-18; '333 Patent at 1:44. Dr. Walensky testified that a POSA would have interpreted Claim 1 of the '7,803 Patent as D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH or a physiologically tolerable salt peptide of said peptide with bradykinin antagonist activity. Tr. 496:20-24.

3d 491, 531 (D. Del. 2016) (citing *Otsuka*, 678 F.3d at 1298) (citation omitted). Though the court previously found that Fmoc is a permanent and integral component to the final peptide, trial testimony confirmed that Fmoc on icatibant has known advantages over icatibant without the Fmoc protecting group. Thus, a POSA would not have had a reason to remove the Fmoc from icatibant to result in an unprotected peptide.

The court finds that Defendant has not proven by clear and convincing evidence that Claim 14 of the '333 Patent is an obvious variant of Claim 1 of the '7,803 Patent and, therefore, finds the claims patentably distinct.

4. Secondary Considerations[17]

"[I]n determining what would have been obvious to one of ordinary skill in the art at the time of invention, the use of hindsight is not permitted." *In re Alfuzosin Hydrochloride Patent Litig.*, No. 08-1941-GMS, 2010 WL 1956287, at *3 (D. Del. May 14, 2010). "The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Objective indicia serve no less an important role here, where obviousness-type double patenting relies on what would have been "obvious" to a POSA at the time of icatibant's invention. *UCB, Inc.*, 201 F. Supp. 3d at 536–40. Objective indicia are considered in rebuttal to OTDP, whether or not the reference patent was publicly available at the time of invention. *Eli Lilly*, 689 F.3d at 1373–74, 1381. The Federal Circuit has held that "the structure of a claimed compound and its properties" are "inseparable" considerations in the obviousness analysis. *Genetics Inst.,*

[17] When offered, secondary considerations should be considered; a fact-finder "must withhold judgment on an obviousness challenge until it has considered all relevant evidence, including that relating to the objective considerations." *Eli Lilly*, 689 F.3d at 1381 (quoting *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012)); *see Geneva Pharms.*, 349 F.3d at 1378 n.1 (inquiry into secondary considerations is not required in *every* obviousness-type double patenting analysis, but it is still relevant when offered).

LLC v. Novartis Vaccines and Diagnostics, Inc., 655 F.3d 1291, 1307 (Fed. Cir. 2011); *see In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). "[E]very property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness." *Genetics Inst., LLC*, 655 F.3d at 1307.

While Defendant has not made a *prima facie* case for obviousness-type double patenting, the court will still consider the secondary considerations discussed by the parties.

a. Long-Felt Need

Evidence of a long felt but unmet need may support a finding of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Long-felt need is assessed at the time of invention and has been found met where a patented compound treats a condition that was "recognized as a serious disease," for which "existing treatments were inadequate." *Procter & Gamble Co.*, 566 F.3d at 998. In 1989, HAE was a known, potentially life threatening condition, and fast and safe treatment options for an acute attack were not available.[18]

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[18] Hereditary Angioedema ("HAE"), which was first identified in 1888, is a genetic disorder characterized by attacks of localized edema (swelling) in various parts of the body. Tr. 394:18-395:7, 399:10-400:8; PTX-180.1. HAE is caused by a mutation in the gene that produces C1 Inhibitor ("C1 INH"), a blood protein that normally functions to regulate the production of bradykinin. Tr. 394:18-395:7. In patients with HAE, deficient or dysfunctional C1 INH levels can lead to the overproduction of bradykinin causing the swelling seen in an acute attack. *Id.* In 1983, Plaintiffs' expert Dr. Kaplan was among the first to identify bradykinin as the molecule directly responsible for the symptoms of an acute HAE attack. *Id.* at 391:13- 392:1; PTX-191.1. By 1987, HAE was among the pathological conditions that the bradykinin antagonist literature associated with overproduction of bradykinin. JTX-28.1, JTX-28 at 1:23-36. By 1989, it was known that HAE is a bradykinin-mediated disorder. An acute attack may occur without any apparent triggering event, and its symptoms may progress rapidly to a medical emergency. Tr. 392:2-10, 402:4-20; PTX-179.2. An acute attack falls into one of three general types: (1) peripheral; (2) visceral; and (3) laryngeal. Tr. 394:21-24. A peripheral attack involves the disfiguring and potentially disabling swelling of the hands, feet, face, or genitalia. *Id.* at 395:25-396:1, 396:25-397:24. A visceral attack involves swelling of the abdominal lining, accompanied by severe abdominal pain. *Id.* at 396:2-6. The most serious type is a laryngeal attack, in which swelling of the larynx may obstruct the airway and cause a patient to asphyxiate. *Id.* at 396:14-18, 397:25-398:21; (D.I. 112 at 13.)

According to Plaintiffs, after leaving Hoechst in 1998, Dr. Knolle, co-inventor of the '333 patent and former director of Hoechst's bradykinin antagonist project, approached Hoechst's successor company (Sanofi-Aventis) for a license to explore therapeutic applications of icatibant. Knolle Tr. 267:16-270:14, 302:17-304:20. At the time, Dr. Knolle was Chief Scientific Officer of Jerini AG ("Jerini"), a drug discovery and development company with around fifteen employees. *Id.* at 302:17-303:13. Based on his work at Hoechst, Dr. Knolle "knew and saw that [icatibant] had at least good safety and still had to find its place in the therapeutic field." *Id.* at 303:17- 304:3. Sanofi granted Jerini a license, which included—for free—6.2 kg of left-over product. *Id.* at 304:21-305:1. Dr. Knolle was "very happy with the deal," particularly because the 6.2 kg of icatibant that Jerini inherited "was still stable after sitting many years there in the dark." *Id.* at 304:11-305:1. After filing for and obtaining marketing authorization in the EU

At the time, there was no safe, effective, and convenient treatment for an acute attack of HAE. Tr. 392:2-18, 401:10-402:3. Treatment consisted of medical observation for worsening of symptoms while making the patient as comfortable as possible. *Id.* This may have entailed administration of intravenous fluids, pain medication, and—in case of a laryngeal attack—set-up for potential intubation or a tracheostomy. *Id.* Infusion of fresh frozen plasma derived from human donors was a treatment that was sometimes effective, although its use was controversial and not recommended to treat laryngeal attacks because it could exacerbate the symptoms of an attack. *Id.* at 402:21-404:4; PTX-179.3. In the case of visceral attacks, many patients became addicted to the pain medication prescribed for the acute pain attendant to such attacks or were subjected to unnecessary surgery. *Id.* at 396:2-13; (D.I. 112 at 14, 34.)

In 2009, Berinert and Kalbitor were both approved in the United States before FIRAZYR®'s 2011 approval. JTX-21; JTX-45; JTX-47; Tr. 404:5-17, 406:15-20, 408:15-18. Defendant argues there was no long-felt but unmet need fulfilled by the claimed icatibant peptide because Berinert and Kalbitor were safe, effective, and easily administered treatments were available in the US prior to FIRAZYR®'s approval. (D.I. 111 at 21.) Specifically, Defendant asserts that Dr. Kaplan's publication comparing acute HAE attack treatments rated Berinert and Kalbitor equal to FIRAZYR® in safety and efficacy, and Plaintiffs' 30(b)(6) witness testified that FIRAZYR® had not been shown to be superior to other acute HAE attack treatments. DTX-84.7; Tr. 435:15-436:19,

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for treatment of acute HAE attacks, Jerini was acquired by Shire for approximately $560 million. *Id.* at 305:17- 308:9, 308:11-310:3; PTX-36.1, 36.9-11. Icatibant was approved by the FDA in 2011 as a safe and effective treatment for acute attacks of HAE. Tr. 408:15-409:6; JTX-45. Icatibant's efficacy derives from its bradykinin antagonist activity, which—unlike any other acute treatment—directly blocks bradykinin, the molecule responsible for the swelling seen in an acute attack. *Id.* at 409:10- 410:22, 400:9-401:9; Tr. 801:1-25. Icatibant's safety profile is likewise intrinsic to the molecule and—unlike other acute HAE treatment—presents no risk of anaphylaxis. Tr. at 406:15-406:19, 410:24-411:13, 412:8-13; JTX-47.1; Tr. 802:5-15.

437:11-438:11; Tr. 796:8-797:5, 799:17-25, 802:16-23; DTX-120.8; (D.I. 111 at 22.) The court disagrees.

Evidence at trial demonstrated that Berinert's active ingredient is a C1 inhibitor. Tr. 404:18-22. While Berinert was approved for self-administration in 2011, the patient had to set up their own IV while experiencing a swelling-based attack. Tr. 406:7-11. Prior to 2011, the patient had to go to the doctor's office or the emergency room to have the IV setup. Tr. 405: 11022. Similarly, Kalbitor was approved in 2009 as the first subcutaneous drug to treat acute HAE attacks. Tr. 406:25-407:3. Kalbitor, however, could actually cause allergic reactions, including anaphylactic reactions. Tr. 407:4-8. Thus, there was a black box warning that the patient had to either have a health care professional come to their home to administer the drug or go to the health care provider. Tr. 407:9-19. Kalbitor has a black box warning and it cannot be self-administered. Tr. 32:25-33:5. By contrast, FIRAZYR® was the first acute HAE treatment that could be self-administered safely at the onset of an attack.

The clinical advantage of icatibant's safety, efficacy, and convenience is undisputed. Icatibant's safety profile allows for self-administration, unlike other acute treatments that require administration by a healthcare professional. Tr. 412:23-414:3; JTX-45.1. Icatibant's bioavailability allows subcutaneous injections, while other acute treatments require intravenous infusion. Tr. at 412:8-414:3; JTX-45.1. Testimony by Dr. Kaplan demonstrated that intravenous infusion is far less convenient—even if self-administered—than subcutaneous injection, particularly for a patient having an acute attack. Tr. 405:23-406:14, 440:10-442:13; JTX-21.3-4. Icatibant's stability allows it to be supplied as a pre-filled syringe stored at room temperature, unlike other acute treatments that require reconstitution or refrigeration. Tr. 410:24-412:7. Based on over forty years of experience treating HAE patients, Dr. Kaplan testified that faster treatment

leads to better clinical outcomes, *e.g.*, faster symptom relief. *Id.* at 414:5- 415:23, 439:17-440:9; PTX-227. Because icatibant is the fastest administered treatment, it offers clinical benefits over other acute treatments. *Id.* at 414:5-415:23, 439:17-440:9.

Because Icatibant is the only drug the patient can self-administer quickly and safely without requiring intervention by a healthcare professional, the court finds that long-felt need weighs against a finding of obviousness-type double patenting.

b. Commercial Success

"The commercial response to an invention is significant to determinations of obviousness, and is entitled to fair weight." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). Commercial success has been found where a patented compound achieves "significant sales in a relevant market." *UCB, Inc.*, 201 F. Supp. 3d at 539- 40; *Pfizer v. Mylan Pharm. Inc.*, 71 F. Supp. 3d 458, 476 (D. Del. 2014). The court finds that FIRAZYR® is a commercial success due to its safety, convenience, and efficacy, compared to other acute treatments, as evidenced by its sales, profitability, and share of the acute HAE market.

Defendant asserts that FIRAZYR® is not commercially successful because there are only a few thousand people undergoing treatment for HAE and third-party payers dedicate few resources to negotiating prices, allowing Plaintiffs to charge a high price. JTX-12.25; Tr. 809:14-810:11, 810:20-811:2. Specifically, Defendant argues that in 2016, the average FIRAZYR® patient spent over $200,000 on their supply of the drug. Tr. 679:1-3. Further, argues Defendant, fewer than a hundred patients are responsible for 40% of FIRAZYR® sales, and approximately 16-20 patients each individually consume over $3,000,000 of FIRAZYR® per year. Tr. 812:10-813:4; DTX-298.56. According to Defendant, over 80% of FIRAZYR® profits were realized after Plaintiffs

gained control over the leading brands in both acute and prophylactic treatment of HAE. Tr. 680:4-23.

The evidence adduced at trial stands in stark contrast to Defendant's assertions. Contrary to Defendant's contention, Plaintiffs' expert in economics and strategy in the life sciences industry, Dr. Gregory K. Bell, testified on cross-examination that for the entire time FIRAZYR® has been on the market, it has been priced $1,000 to $3,000 less than competing treatments per attack. Tr. 651:1-5, 675:16-676:16, 813:12-24; PTX-92. Sales of FIRAZYR® have increased every year since its launch, exceeding industry expectations and even Plaintiffs' own forecasts. Tr. 652:3-656:8; PTX-081.1; PTX-082.1. There is no dispute that FIRAZYR® has been profitable, generating $1.2 billion in global operating income with a roughly 74 percent profit margin as of 2016. Tr. 656:9-658:3. It is undisputed that FIRAZYR® has outperformed other acute HAE treatments. Tr. 820:10-20, 821:7-13. After its first year on the market, FIRAZYR® accounted for the majority of sales revenue among products indicated for acute attacks of HAE. Tr. 658:4-659:5, 660:1-12; PTX-088. FIRAZYR® achieved this majority share when it was Shire's only HAE product. Tr. 658:4-659:5, 820:24-821:13, 828:4-15. Moreover, icatibant is in its own therapeutic class: no other bradykinin antagonist has been found safe and effective for treating HAE, or for any other indication. Tr. 826:4-828:3. Because of icatibant, FIRAZYR® is the only acute treatment that may be self-administered subcutaneously. Tr. 825:2-21, 412:8-414:3, 410:24-412:7, 660:17-663:22. Third-party analysts have praised the unique properties of FIRAZYR® as the "holy grail for acute HAE treatment" and a "treatment paradigm shift." Tr. 667:24-668:18, 663:4-667:20; JTX-13.1; PTX-155.1, 155.5-6. Unrebutted testimony by Dr. Kaplan echoes this sentiment. FF ¶ 35. Documents relied on by both parties' experts affirm the importance of fast and effective treatment to

physicians, patients, and healthcare payors. Tr. 688:8-689:19; Tr. 821:21-824:2; PTX-141.57; JTX-43.28, 32.

The court finds that Defendant has not established that FIRAZYR®'s commercial success is due to factors other than the safety, efficacy, and convenience afforded by icatibant. Defendant's witness, Mr. Hofmann, did not explain how "dynamics" specific to the HAE market account for FIRAZYR®'s outperformance of other orphan drugs within that same market and subject to the same "dynamics." Tr. 813:5-11, 819:20-820:20. Additionally, there is no indication in the market research that price is a primary reason cited by physicians for prescribing FIRAZYR® over other acute treatments. Tr. 688:8-689:19; PTX-141.57; (D.I. 112 at 17.)[19] The court, therefore, finds that the commercial success of FIRAZRY® weighs against a finding of obviousness-type double patenting and the invalidation of Claim 14 of the '333 Patent.

c. Simultaneous Invention

Plaintiffs argue that there has been no showing of near-simultaneous invention. (D.I. 112 at 34.) "In some *rare* instances, the secondary consideration of simultaneous invention might also supply 'indicia of 'obviousness.'" *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) (citations omitted). Without more, Dr. Burch's uncorroborated twenty-five years old recollection that Nova developed icatibant cannot support an allegation of near-simultaneous invention. (D.I. 112 ¶ 42.) Moreover, where a distinct compound is alleged to be a near-simultaneous invention of the asserted compound, this evidence should be disregarded. *Endo Pharm. Inc. v. Amneal Pharm.*, LLC, 224 F. Supp. 3d 368, 381 (D. Del. 2016). Because NPC 16731 and icatibant are two different peptides, NPC 16731 cannot demonstrate near-simultaneous invention. "The tendency of simultaneous invention to weigh in favor of

[19] Mr. Hofmann did not rely on any documented evidence that patients, physicians, or healthcare payors prefer FIRAZYR® on the basis of its per-attack price. Tr. 813:12-814:4; PTX-092.1.

obviousness" is "negated if the purported simultaneous invention was not made independently of the claimed invention." *Trs. of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015). Here, NPC 16731 was "derived from" the sequence of icatibant. (D.I. 112, ¶ 43.)

Defendant's only argument with regard to this factor is that Nova was working on bradykinin antagonists within the scope of the '333 Patent during Plaintiffs' alleged period of delay and that Nova scientists independently synthesized their peptide NPC 16731. (D.I. 111 at 36); Tr. 232:10-235:16, 618:6-619:23, 629:11-632:4; JTX-9 at 3-4. Nova had licensed bradykinin antagonist peptides from Dr. Stewart in the 1980s. Tr. 219:2-12. Nova altered the amino acid sequence of earlier peptides in an effort to develop bradykinin peptides that were more resistant to enzymatic degradation. Tr. 220:3-20, 228:17-229:14, 621:9-624:6. NPC 16731 became Nova's "standard peptide," and despite budgetary constraints and interest in other projects, Nova continued to work on this and other bradykinin antagonist peptides until at least 1993, which is during the period of Plaintiffs' alleged prosecution delay. Tr. 216:7-22, 238:16-239:5, 616:10-20; JTX-41; JTX-9. Hoechst was aware of Nova's work on bradykinin antagonists and communicated with Nova about it. Tr. 750:6-9; PTX58.

Nova's disclosure of NPC 16731 came, however, after the publication of icatibant, and Nova was aware of Hoechst's work before it submitted data on NPC 16731. (D.I. 112 at 25-26.) Evidence of near-simultaneous invention that comes after the first invention has been publicized has little probative force. *Eli Lilly Co. v. Teva Pharms.*, No. IP 02-0512-C-B/S, 2004 WL 1724632 at n.23 (S.D. Ind. July 29, 2004), *aff'd*, No. 05-1044, 2005 WL 1635262 (Fed. Cir. July 13, 2005) (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 n. 4 (Fed. Cir. 1986).

The court, therefore, finds that the secondary considerations weigh against a finding of obviousness-type double patenting.

B. Prosecution Laches

Next, Plaintiffs assert that in view of the Supreme Court case law and 35 U.S.C. § 282(b), prosecution laches is no longer a defense. *SCA Hygiene Prods. Aktiebolag v. First Quality Baby Prods., LLC,* 137 S. Ct. 954, 967 (2017). The court, however, recognizes that prosecution laches is different from the affirmative defense of laches recognized by the Federal Rules of Civil Procedure and will, therefore, decide the issue on the substantive merits.[20] FED. R. CIV. P. 8(c)(1).

1. The Legal Standard

"The doctrine [of prosecution laches] 'may render a patent unenforceable when it has issued only after an unreasonable and unexplained delay in prosecution' that constitutes an egregious misuse of the statutory patent system under the totality of the circumstances." *Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724, 728 (Fed. Cir. 2010) (quoting *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found.*, 422 F.3d 1378, 1385-86 (Fed. Cir. 2005)). It also requires a showing of prejudice, which in turn requires "evidence of intervening rights, *i.e.*, that either the accused infringer or others invested in, worked on, or used the claimed technology during the period of delay." *Id.* at 729. "[T]here are no strict time limitations for determining whether continued refiling of patent applications is a legitimate utilization of statutory provisions or an abuse of those provisions. The matter is to be decided as a matter of equity, subject to the discretion of [the] district court . . . . " *Symbol Techs.*, 422 F.3d at 1385. Prosecution laches is an "equitable defense to a charge of patent infringement." *Cancer Research*, 625 F.3d at 729. An unreasonable

[20] The court finds it important to point out that prosecution laches, which is a delay in filing a patent, differs from laches, which is a delay in filing suit. Since *SCA Hygene*, courts have still recognized prosecution laches as an affirmative defense to patent infringement. *In re Lantus Direct Purchaser Antitrust Litig.*, 284 F. Supp. 3d 91, 101 (D. Mass. 2018); *Finjan, Inc. v. ESET, LLC*, 2017 WL 4358128, at *3 (S.D. Cal. Oct. 2, 2017); *Sonos, Inc. v. D&M Holdings Inc.*, 2017 WL 4969330, at *2 (D. Del. Nov. 1, 2017) (Bryson, J.) (recognizing affirmative defense, but dismissing it as it was no longer asserted in the case).

and inexcusable delay is required to successfully assert a defense of prosecution laches. *Id.*; *Cordance Corp. v. Amazon.com, Inc.*, 631 F. Supp. 2d 484, 489 (D. Del. Jun. 30, 2009); *Sonos, Inc. v. D&M Holdings Inc.*, No. CV 14-1330-RGA-MPT, 2016 WL 4249493, at *7 (D. Del. Aug. 10, 2016), *report and rec. adopted*, 2016 WL 4581078 (D. Del. Sept. 1, 2016).

2. Unreasonable or Unexplained Delay

Defendant primarily argues that Plaintiffs' four year delay in prosecuting the patent between 1991 and 1995 was unreasonable and unexplained because, during that time, applicants failed to provide a substantive response to the PTO. (D.I. 111 at 31.) Specifically, Defendant asserts that Plaintiffs failed to provide the Patent Office with the *in vivo* data requested to support utility of the '162 application and, instead, argued the *in vitro* data was sufficient, which delayed prosecution. (D.I. 111 at 32.) Defendant argues Plaintiffs had the *in vivo* data related to icatibant, as early as March 1989 prior to the original '162 application filing date. Tr. 360:14-361:2, 369:18-370:19, 454:6-18, 472:9-474:6, 474:12-476:9, 763:18-764:2; (D.I. 111 at 33.) On August 17, 1990, the first office action in the '162 application rejected genus Claims 1-6, among other rejections, for lack of utility. JTX-6A.152-159.[21] On February 19, 1991, applicants responded with an amendment and remarks, including deleting Claims 1-4, amending Claims 5-6, and adding claims 7-13. JTX-6A.221-242. Newly-added Claim 13 was to icatibant. Tr. 372:11-373:1; JTX-6A.229. Applicants argued that the *in vitro* data for the 25 peptides in the specification "established sufficient statutory utility for the compounds of the instant invention as set forth in M.P.E.P. § 608.01(p)." Tr. 723:8-21; JTX-6A.233. At the time, however, contrary to Defendant's

[21] The rejection stated "[t]he specification does not support the asserted utility of the claimed method of treating the broad pathological disorders" and it seemed to request *in vivo* data to support the utility of the claimed compounds. JTX-6A at 154-55. Both parties' experts agreed the '162 application contained 164 examples of specific peptides, *in vitro* data of antagonist activity for 25 of those peptides, and 6 genus claims. JTX-6A at 27-28, 31-59. Dr. Raines testified that genus Claim 1 of the '162 application covered millions of compounds. Tr. 368:5-370:19; JTX-6A at 121-24.

argument, the utility guidelines stated: "[p]roof of utility under [M.P.E.P. § 608.01(p)] may be established by clinical or *in vivo* or *in vitro* data, or combinations." JTX-6A.233; Tr. 794:7-10; PTX-072.2. Regardless of the utility guidelines at the time, Defendant argues applicant's *in vivo* data—that Defendant's expert, Dr. Raines, agreed related to icatibant only—was not "responsive" to the Examiner's request. Tr. 354:1-8, 360:14-361:2, 369:18-370:19, 454:6-18; DTX-50. At trial, however, Dr. Wingefeld explained that it was uncommon to include *in vivo* data because the utility guidelines did not require it. Tr. 724:2-725:1.[22] Dr. Raines contends that Wirth 1991 "could have been responsive," but admits that he could not read the examiner's mind, did not know what the M.P.E.P. was, never asked if the utility rejection was proper, and never reviewed the utility guidelines relied on by applicants. Tr. 355:9-20, 357:11-13, 365:10-367:12, 370:4-10 .

"There are legitimate grounds for refiling a patent application which should not normally be grounds for a holding of laches, and the doctrine should be used sparingly lest statutory provisions be unjustifiably vitiated." *Symbol Techs*, 422 F.3d at 1385, *amended on reh'g in part*

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[22] There is further support for the continued prosecution of the patent between 1991 and 1995. A May 31, 1991 final office action rejected all claims on multiple grounds. JTX- 6A at.247-255. Genus claims 5-12 were rejected for lack of utility, but claim 13 to the icatibant species was not. *Id.* at 248-250. Dr. Raines agreed icatibant was not rejected for lack of utility, but still asserted that Wirth (1991) (only to icatibant) "could have been responsive." Tr. 375:6-14. On August 14, 1991, applicants responded by filing the '149 CIP application, which added peptide examples 165-195, additional *in vitro* data for 46 specific peptides, and Claims 14-17. Tr. 712:15-713:1, 725:2-726:6; JTX-6A. Applicants added *in vitro* data in the '149 CIP application to underline the utility of the invention. Tr. 727:4-11.

July 1, 1992 office action issued in the '149 CIP application. JTX-6A.468-479. The same Wirth (1991) publication that Dr. Raines asserts "could have been responsive" to the utility rejection became part of the record and was cited by the examiner as the basis to reject claims 5-17 under 35 U.S.C. § 102(f) for claiming an identical compound and method. Tr. 376:17-377:20, 728:1-19; JTX-6A.476. Only genus claims 5 and 6 were rejected for lack of utility—"[t]he specification fails to factually show that the claimed peptides used in the claimed method would treat all/or any of the pathological states." JTX-6A.470. A restriction requirement to icatibant was withdrawn and all species were examined. JTX-6A.153, 469. On November 25, 1992, applicants responded to the July 1, 1992 office action by filing the '052 application because they were considering how to respond to the OTDP rejections pending over the three groups (JTX-4.300, 301; JTX-5A.204; JTX-6A.474, 475). Tr. 713:2-6, 728:20-729:6; JTX-6A.491-496.

The '849 CIP application, filed less than three months after the '052 application and before an office action issued, overcame the OTDP rejections. JTX-6A.497. On May 3, 1993, applicants submitted an information disclosure statement that included Wirth (1991), which the examiner considered on November 1, 1993. JTX-7A.209-214. A November 3, 1993 office action rejected all genus and species Claims 1-34 for lack of utility, among other rejections, despite the examiner having again considered Wirth 1991. JTX-7A.217-232. Groups 2 and 3 had not been previously rejected for lack of utility. After filing the '018 application, on December 6, 1994, the USPTO issued an office action still rejecting all of the Claims 1-34 for lack of utility, among other reasons. Tr. 737:24-738:13; JTX-7A.246-260.

by, 429 F.3d 1051 (Fed. Cir. 2005). "Commonly, and justifiably, one might refile an application to add subject matter in order to attempt to support broader claims as the development of the invention progresses. . . ." *Id.* Moreover, an application may be refiled for any reason, "provided that such refiling is not unduly successive or repetitive." *Id.* The filing of multiple continuing applications is not *per se* unreasonable. *Novozymes A/S v. Genencor Int'l, Inc.*, 446 F. Supp. 2d 297, 333-34 (D. Del. 2006). "It is not enough for a defendant to show . . . refiling of rejected claims or the use of continuation applications to add new subject matter." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 529 F. Supp. 2d 106, 137 (D. Mass. 2007). An applicant's decision to file a continuation application instead of appealing a rejection does not constitute an unreasonable or unexplained delay in prosecution. *Ariad Pharm.*, 529 F. Supp. 2d at 137–38; *see Regents of the Univ. of Cal. v. Monsanto Co.*, 2005 WL 3454107, at *25 (N.D. Cal. Dec. 16, 2005).

In the instant case, the court finds Plaintiffs actively prosecuted without an unreasonable or unexplained delay. The '333 Patent resulted from German priority and U.S. applications of three distinct inventions. Tr. 702:14-704:8, 706:6-708:25. The applications of the '333 Patent were prosecuted in three different groups each directed towards bradykinin antagonist peptides. Tr. 326:25-328:9, 328:14-329:5; (D.I. 111 at 32.) The prosecution timeline is as follows:

- On June 30, 1989, the first U.S. application, the '162 application, was filed in Group 1 (Tr. 701:7-13; JTX-1.2; JTX-7A.294-295);
- On August 10, 1990, the '270 application was the first Group 2 application filed;
- On April 24, 1991, the '297 application was filed as the first in Group 3 (UF ¶ 6);
- The groups 1-3 were prosecuted separately, but concurrently not individually lengthening the prosecution time, until February 3, 1993 (Tr. 708:10-25, 710:2-16; JTX-1.2[63]; JTX-7A.294-295);

- On February 3, 1993, Groups 1-3 were consolidated into the '849 continuation-in-part ("CIP") application, only in the U.S., to overcome OTDP rejections over the separate groups and to expedite prosecution (Tr. 708:10-25, 709:10-16, 710:9-14, 711:13-16, 716:22-717:21, 737:4-23; JTX-7A.7-110, 197-199);

- The '849 CIP application contained over 200 examples of peptides and 34 claims and was the first U.S. application containing all the subject matter of the inventions of Groups 1-3 (Tr. 709:1-6; 734:23-735:14; JTX-7A.9, 48-109);

- On May 2, 1994, the '018 application was filed in the consolidated groups. (Tr. 718:1-5); and

- Then on June 7, 1995, the '442 application was filed and issued on July 15, 1997 as the '333 patent. JTX-1.2 at 11, 21, 22, 45.

The '333 Patent issued July 15, 1997 with claims from all three groups, eight years and half a month later from the June 30, 1989 filing date of the first U.S. application. JTX-1; Tr. at 705:20-23, 717:22-25. Defendant's expert testified that out of those eight years, only the four-year period from 1991 to 1995 account for the alleged delay. Tr. 357:14-358:17.

During prosecution, however, the applicants' goal was to have all filed claims allowed by the Patent Office. Tr. 703:19-22, 704:2-8. Dr. Renate Wingefeld, Ph.D., the lead prosecuting attorney, explained that filing CIP applications, like the '149 and '849 CIP applications in Group 1, and the '090 CIP application in Group 2, was common because it allowed the applicants to add matter and to add or amend claims. Tr. 699:12-17, 711:23-713:1. Similarly, filing continuation applications, like the '052 application in Group 1, the '766 and '523 applications in Group 3, and the '018 application was common because it allowed the applicants to maintain the priority date and continue prosecution. *Id.* at 713:2-24. As such, filing a continuing application avoided the lengthy appeal process and allowed the continuation of prosecuting the patents. *Id.* at 713:25-715:3. Applicants filed applications under Rule 62, like the '149 CIP, '052, '090 CIP, '766, '523, and '018 applications, because they believed that approach resulted in a faster response from the

USPTO. *Id.* at 726:20-727:3. Applicants never filed a CIP application that re-filed allowed claims. As demonstrated at trial, the applications in each group were initially prosecuted in parallel and were not prior art to each other. (D.I. 111 at 32); (D.I. 112 at 19.) Dr. Wingefeld, testified that at each stage the claims got a rejection from the Patent Office, in deciding how to proceed, it was easier, less expensive, and more efficient to begin a new application. Tr. 697:17-785:20.

Next, Defendant asserts that while Hoechst continued to argue that the *in vitro* data in should be sufficient throughout prosecution, Hoechst submitted a declaration from Dr. Schölkens, an inventor on the '333 Patent "to address the Examiner's specific concerns" about the predictive value of the bradykinin antagonists *in vivo*. Tr. 340:23-341:18, 764:3-765:17; JTX-7A at 298-302. The Schölkens declaration cited Wirth 1991 and 1993 to support the conclusion that "a compound that counteracts [the] effect of bradykinin *in vivo* in an animal model can be reasonably predicated to be effective *in vivo* in treating asthma," but it only studied the effects of icatibant. Tr. 741:8-742:5; JTX-7A.329-330. The declaration was, however, provided after the change in the Patent Office's Updated Utility Guidelines. In January 1995, Updated Utility Guidelines were noticed—to "address issues that may arise during examination of applications claiming protection for inventions in the field of *biotechnology* and *human therapy*"—in response to inconsistent utility rejections in the newly-formed USPTO biotechnology group. Tr. 794:20-795:17; PTX-73.2. The Updated Utility Guidelines made clear that applicants can rebut a lack of utility "by amending the claims, by providing reasoning or arguments, or by providing evidence." PTX-073.3. Examiners were reminded "that they must treat as true credible statements" made in the specification *or in a declaration. Id.* One week after conducting an Examiner interview, on June 6, 1995, the end of the alleged delay, applicants filed an amendment and remarks in the '018 application in response to all rejections. Tr. 738:20-739:2; JTX-7A.263-392. In compliance with the Updated Utility

Guidelines applicants submitted a declaration of inventor Schölkens. Tr. at 739:22-740:17, 794:1-2, 11-13; JTX-7A.299, 327-331; PTX-073.3. Dr. Raines admitted that he had not read and was not familiar with the Updated Utility Guidelines despite the applicants' citation to it. Tr. 379:21-381:2. In further support of utility, applicants submitted seven other publications from 1992-1994 that could not have been submitted earlier and attested to utility in treating a variety of pathological states. Tr. 740:18-741:7; JTX-7A.301-302. Dr. Raines agreed that it was not the Wirth 1991 publication alone that resulted in the utility rejection being withdrawn. Tr. 377:21-379:20.

In addition to the evidence adduced at trial, prosecution laches has not been applied to an alleged four-year-delay. *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 301 F. Supp. 2d 1147, 1155 (D. Nev. 2004), *aff'd*, 422 F.3d 1378, 1386 (Fed. Cir. 2005); *Medtronic*, 777 F. Supp. 2d at 782–83 (no unreasonable delay in 14-year prosecution); *Novozymes*, 446 F. Supp. 2d at 333-34 (no unreasonable delay for 10-year prosecution). Whether "the prosecution history of plaintiff's patents was typical of patents in that field or patents generally" is a relevant consideration in assessing unreasonable delay. *Regents*, 2005 WL 3454107, at *24. Filing the '442 patent application or June 6, 1995 office action response immediately prior to the enactment of GATT is *not* unreasonable or unexplained. *Ariad Pharm.*, 529 F. Supp. 2d at 139 ("[The patentee's] desire to obtain the maximum term for its patent grant, particularly when the rules were being changed, is neither unreasonable nor unexplained."). During prosecution, the patent office did not reject any of the applications on the grounds of prosecution laches nor did it reject the '333 patent. *In re Bogese*, 303 F.3d 1362, 1367 (Fed. Cir. 2002); (D.I. 112, ¶ 46.) The prosecution history of the '333 patent was explained to the Examiner and was typical of patent applications filed in the biotechnology field at the USPTO at the time. (D.I. 112 at 24.)

As is clear from a recitation of the prosecution history, there was no unreasonable or unexplained delay in prosecuting the '333 Patent.

3. Prejudice as a Result of Delay

To establish prejudice, Fresenius must show that the alleged delay in prosecution "adversely affected" the party with *intervening rights*. *Cancer Research*, 625 F.3d at 729-732; (D.I. 112 at 39.) To show that a party was "adversely affected," it must show that the holder of intervening rights would have either done something differently or experienced a change in economic position as a result of the alleged delay in issuance of the patent-in-suit. *Cancer Research*, 625 F.3d at 731. "[W]hen one considers the public interest, the public has benefitted by the fact that" a patentee develops and markets a drug induced by the protection of its patent. *Cancer Research*, 625 F.3d at 732. A patentee "should not lose [patent] protection because its patent issuance was delayed under circumstances where no one suffered prejudice." *Id.*

Plaintiffs argue that Defendant failed to show prejudice during and by the alleged delay. (D.I. 112 at 38.) Defendant argues that the extension of the '333 Patent term caused by Hoechst's alleged delay prevents earlier regulatory approval of Fresenius's ANDA. (D.I. 111 at 38.) The NDA for FIRAZYR® was approved on August 25, 2011. The FDA determined that FIRAZYR® was entitled to NCE until August 25, 2016. Fresenius filed its ANDA for a generic version of FIRAZYR® on the earliest possible date called the "NCE-1" date, which was August 25, 2015. (D.I. 94, ¶ 23.) Shire obtained the maximum patent term extension of five years for the '333 patent. JTX2.390-91. FIRAZYR® was also granted a 7-year period of Orphan Drug Exclusivity ("ODE") by the FDA, which expires August 25, 2018. The ODE expiration is the earliest date Fresenius's product can be approved. 21 C.F.R. § 316.31. Defendant asserts if it were not for the four year delay in prosecution of the '333 patent, which extended the term of the patent until July

15, 2019, the FDA could approve Fresenius's ANDA on August 25, 2018, and Fresenius could launch its product thereafter. (D.I. 111 at 38.) The court disagrees.

Defendant did not prove that the alleged delay adversely impacted or prejudiced it or Nova. Nova's alleged investment in NPC 16731 is based on evidence prior to the alleged delay, and, thus, cannot constitute intervening rights. Because prosecution laches does not apply "on the basis of claims that are not actually the subject of the litigation," it is only assessed in terms of Claim 14 of the '333 Patent. *Regents*, 2005 WL 3454107, at *24-26. It does not apply to Fresenius's allegations of intervening rights based only upon Nova's NPC 16731 in unasserted Claim 12. (D.I. 112, ¶¶ 81, 86.) Further, Fresenius did not invest in, work on, or use icatibant during the alleged four-year period of delay and it did not begin its icatibant project until 2014—nineteen years after the end of the alleged delay. Tr. 693:12-14, 694:13-695:8. Because icatibant is a new chemical entity, Fresenius could not have filed its ANDA any earlier than it did. (D.I.112 at 27.)

The court, therefore, finds that Defendant did not establish by clear and convincing evidence that there was an unreasonable and unexplained delay in the prosecution of the '333 Patent. Thus, Claim 14 of the '333 Patent is not invalid under the doctrine of prosecution laches.

IV. CONCLUSION

For the reasons stated above, the court concludes that the asserted claims of the patent-in-suit are not invalid under the doctrine of obviousness-type double patenting or prosecution laches.

Dated: June 5, 2018

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH Plaintiffs, v. FRESENIUS KABI USA, LLC, Defendant.	)	C.A. No. 15-1102-GMS

ORDER

At Wilmington this 5th day of June, 2018, IT IS HEREBY ORDERED THAT:

1. The '333 Patent is not invalid in light of the '7,803 Patent under the doctrine of obviousness-type double patenting;

2. The '333 Patent is not invalid due to prosecution laches; and

3. The Clerk of Court is directed to enter judgment in favor of the Plaintiffs and against the Defendant.

UNITED STATES DISTRICT JUDGE