IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION and SANOFI-AVENTIS U.S. LLC, Plaintiffs/Counterclaim-Defendants,	)	
Plaintiffs,	)	
v.	)	C.A. No. 13-1506-(GMS) Consolidated with C.A. No. 13-1508-(GMS)
DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC., Defendants/Counterclaim-Plaintiffs. and TEVA PHARMACEUTICALS USA, INC., Defendant/Counterclaim-Plaintiff.	)	

MEMORANDUM

I. INTRODUCTION

1. In this consolidated patent infringement action, plaintiffs Genzyme Corporation ("Genzyme") and Sanofi-Aventis US LLC ("Sanofi," and together with Genzyme, "the Plaintiffs") allege that pharmaceutical products proposed by defendants Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc. (collectively "DRL") and defendant Teva Pharmaceuticals USA, Inc. ("Teva") (collectively "the Defendants") infringe the asserted claims of the '590 patent and two other patents.[1] (D.I. 1.) The court held a four-day bench trial in this matter on November 9 through November 13, 2016. (D.I. 211-214.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of claim 19 of the '590 patent. (D.I.

[1] Plaintiffs alleged that two other Orange Book patents, U.S. Patent No. RE42,152 and U.S. Patent No. 6,987,102, were infringed. Pursuant to prior stipulations by the parties, these patents are no longer subject to this litigation. (D.I. 144, 185.) The parties have also stipulated to dismiss with prejudice claim 8 of the '590 patent. (D.I. 193.)

202, 204.) Also before the court are the Plaintiffs' Rule 52(c) motion for judgment on partial findings and accompanying brief and the Defendants' opposition. (D.I. 206-208.)[2]

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that the asserted claim of the patent-in-suit is not invalid due to obviousness. The court's findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[3]

A. The Parties

2. Plaintiff Genzyme Corporation ("Genzyme") is a corporation organized and existing under the laws of the State of Massachusetts, having its principal place of business at 500 Kendall Street, Cambridge, MA 02142.

3. Plaintiff Sanofi-Aventis US LLC ("Sanofi," and together with Genzyme, "Plaintiffs") is a Delaware corporation with its principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807.

4. Defendant Dr. Reddy's Laboratories, Ltd. is a company organized and existing under the laws of India having a place of business at 7-1-27, Ameerpet, Hyderabad, 500 016, Andhra Pradash, India.

5. Defendant Dr. Reddy's Laboratories, Inc. is a corporation organized and existing under the laws of New Jersey having a place of business at 107 College Road East, Princeton, NJ 08540.

6. Dr. Reddy's Laboratories, Inc. is a wholly owned subsidiary of Dr. Reddy's Laboratories, Ltd. (collectively, "DRL").

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[2] The court will not address the Rule 52(c) motion for judgment on partial findings and accompanying briefs (D.I. 206-208), which are rendered moot by the court's ruling on the parties' proposed findings of fact and conclusions of law.

[3] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 188, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, 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 the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

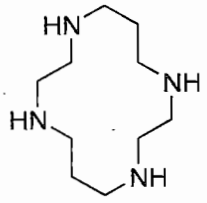
7. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware having a place of business at 1090 Horsham Road, North Wales, PA 19454.

8. The court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

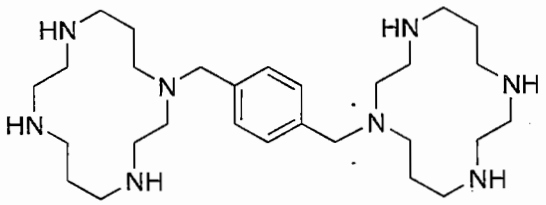
B. Background

9. Plerixafor 1,1'-[l,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane is a chemical name for plerixafor.

10. Cyclam (1,4,8,11-tetraazacyclotetradecane) is a macrocyclic compound having the following chemical structure:



11. Plerixafor has the following chemical structure:



12. Plerixafor is known as a "bicyclam" because it consists of two cyclams connected by a linker.

13. The compound plerixafor has also been referred to as AMD-3100, JM-3100, JM-2987, and SDZ-SID-791.

C. The Patent-in-Suit

14. Genzyme is the owner of U.S. Patent No. 7,897,590 ("the '590 patent"), which is listed in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation" (the "Orange Book") as being applicable to Genzyme's Mozobil® drug product. Genzyme is also the owner of other patents that are no longer in suit, but are also listed in the Orange Book as being applicable to Genzyme's Mozobil® drug product: U.S. Patent No. RE42,152 ("the '152 patent") and U.S. Patent No. 6,987,102 ("the '102 patent"). Sanofi is the exclusive licensee of the '152 patent, the '102 patent, and the '590 patent.

15. The '152 patent issued from U.S. Patent Application No. 12/192,704 ("the '704 application"), which was filed on August 15, 2008. The '152 patent is the reissue of U.S. Patent No. 5,583,131, which was filed on August 18, 1994, and issued on December 10, 1996. The '131 patent issued from U.S. Patent Application No. 08/244,863 ("the '863 application").

16. The '152 patent, entitled "Aromatic-Linked Polyamine Macrocyclic Compounds with Anti-HIV Activity," was issued on February 15, 2011 to inventors Gary J. Bridger, Sreenivasan Padmanabhan1, Renato Skerlj, and David M. Thornton.

17. Including patent term extension, the '152 patent will expire on December 10, 2018.

18. The rights to the invention claimed in the '152 patent were assigned from the inventors to Johnson Matthey PLC, which were then assigned to AnorMED, Inc., who assigned those rights to AnorMED Corp., which then assigned those rights to Genzyme in 2008.

19. The patent application that matured into the '102 patent was U.S. Application No. 10,209,001 ("the '001 application") filed July 30, 2002. The '102 patent claims priority to U.S. Provisional Application 60/309,196 ("the '196 application") filed July 31, 2001 and U.S. Provisional Application 60/382,155 ("the '155 application") filed May 20, 2002.

20. The '102 patent, entitled "Methods to Mobilize Progenitor/Stem Cells," was issued on January 17, 2006 to inventors Gary J. Bridger, Michael J. Abrams, Geoffrey W. Henson, Ronald Trevor MacFarland, Gary B. Calandra, Hal E. Broxmeyer, and David C. Dale.

21. The rights to the invention claimed in the '102 patent were assigned from the inventors to AnorMED, Inc., who assigned the rights to AnorMED Corp., which then assigned those rights to Genzyme in 2008.

22. Including patent term adjustment, the '102 patent will expire July 22, 2023.

23. The application resulting in the '590 patent, U.S. Application No. 11/841,837 ("the '837 application"), filed August 20, 2007, is a continuation of U.S. Application No. 11/446,390 ("the '390 application"), filed June 2, 2006, which is a divisional of U.S. Application No. 11/269,773 filed November 8, 2005, which is a divisional of the '001 application filed July 30, 2002 which claims priority to the '196 application and to the '155 application.

24. The '590 patent, entitled "Methods to Mobilize Progenitor/Stem Cells," was issued on March 1, 2011 to inventors Gary J. Bridger, Michael J. Abrams, Geoffrey W. Henson, Ronald Trevor MacFarland, Gary B. Calandra, Hal E. Broxmeyer, and David C. Dale.

25. The rights to the invention claimed in the '590 patent were assigned from the inventors to AnorMED, Inc., who assigned those rights to AnorMED Corp., which then assigned those rights to Genzyme in 2008.

26. Including patent term adjustment, the '590 patent will expire on July 22, 2023.

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

27. Defendants allege that claim 19 of the '590 patent is invalid.

28. No other patent claims are at issue in these consolidated litigations.

ii. *'590 Patent, Claim 19*

29. Claim 19 of the '590 Patent reads: The method of claim 8 which further comprises administering G-CSF to said subject prior to administering the [plerixafor] or a pharmaceutically acceptable salt thereof.[4]

2. The Accused Products

i. *NDA No. 022311 Submitted by Genzyme*

30. Genzyme is the holder of New Drug Application ("NDA") No. 022311, which relates to plerixafor solution 20 mg/mL for subcutaneous injection, which is marketed as Mozobil®. Genzyme and Sanofi share in the revenue from the sale of Mozobil®.

31. On December 15, 2008, the FDA approved the plerixafor solution 20 mg/mL, as described in NDA No. 022311, for use in combination with granulocyte-colony stimulating factor ("G-CSF") for mobilizing hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

32. The FDA approved "Dosage and Administration" for Mozobil® is to "[i]nitiate Mozobil® treatment after the patient has received G-CSF once daily for 4 days." Mozobil® may be administered for "up to 4 consecutive days" at a dose of "0.24 mg/kg actual body weight." Mozobil® is administered "by subcutaneous injection approximately 11 hours prior to initiation of apheresis."

ii. *ANDA No. 205182 Submitted by DRL*

33. On or about December 15, 2012, DRL submitted ANDA No. 205182 to the FDA under section 505(j) of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking approval to engage in the commercial manufacture, importation, use, offer for sale, or sale within the United States, or importation into the United States, of 20 mg/mL Plerixafor injection as a generic version of Genzyme's Mozobil® drug product as described in NDA No. 022311 (the "DRL ANDA").

34. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. participated in the preparation and/or filing of ANDA No. 205182.

35. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. cooperated in providing a letter dated July 19, 2013, and received by Genzyme on July 22, 2013, containing "paragraph IV" certifications and notifying Genzyme that DRL had submitted ANDA No. 205182 to the FDA under

[4] Claim 8 of the '590 Patent reads (incorporating the elements of claim 1): A method to obtain progenitor and/or stem cells from a subject which method comprises (a) administering to said subject [plerixafor] or a pharmaceutically acceptable salt thereof; in an amount effective to mobilize said progenitor and/or stem cells into the peripheral blood of said subject; followed by (b) harvesting said progenitor and/or stem cells. (D.I. 1-2 at 19.)

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)), for Dr. Reddy's ANDA product, a drug product that is a generic version of Mozobil®. This letter satisfied all statutory and regulatory requirements.

36. DRL's ANDA was submitted to obtain FDA approval to engage in the commercial manufacture, importation, use, and sale of DRL's Plerixafor ANDA Injection Product ("DRL's ANDA Product") prior to the expiration of the '152 patent, the '102 patent, and the '590 patent.

37. DRL's ANDA does not seek approval to use plerixafor for the treatment of human immunodeficiency virus or HIV.

iii. *ANDA No. 205197 Submitted by Teva*

38. On or about December 15, 2012, Teva submitted ANDA No. 205197 to the FDA under section 505(j) of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 355(j)) seeking approval to engage in the commercial manufacture, importation, use, offer for sale, or sale within the United States, or importation into the United States, of 20 mg/mL Plerixafor injection as a generic version of Genzyme's Mozobil® drug product as described in NDA No. 022311 (the "Teva ANDA").

39. By letter dated July 16, 2013, and received by Genzyme on July 17, 2013, which included "paragraph IV" certifications, Teva notified Genzyme that Teva had submitted to the FDA ANDA No. 205197 under section 505(j) of the Federal Food Drug and Cosmetic Act (21 U.S.C. § 355(j)), for Teva's ANDA Product, a drug product that is a generic version of Mozobil®. This letter satisfied all statutory and regulatory requirements.

40. Teva submitted ANDA No. 205197 to FDA under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, offer for sale, and/or sale of Teva's Plerixafor ANDA Injection Product ("Teva's ANDA Product") prior to the expiration of the '152 patent, the '102 patent, and the '590 patent.

41. Teva's ANDA does not seek approval to use plerixafor for the treatment of human immunodeficiency virus or HIV.

3. Infringement of U.S. Patent No. 7,897,590

42. The parties previously stipulated that the submission of the DRL ANDA infringes claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(e)(2), to the extent those claims are valid and enforceable.

43. If DRL's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed for Section 1 Indication and Usage or Section 2.1 Recommended Dosage and Administration, the use of the DRL ANDA Product for the indication proposed in the ANDA in the United States would infringe claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(a), to the extent those claims are valid and enforceable.

44. If DRL's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed for Section 1 Indication and Usage or Section 2.1 Recommended Dosage and Administration, the sale or offer of sale of the DRL ANDA Product

would infringe claims 8 and 19 of the '590 patent in the United States under 35 U.S.C. § 271(b) and (c) by actively inducing and contributing to infringement by others, to the extent those claims are valid and enforceable.

45. The parties previously stipulated that the submission of the Teva ANDA infringes claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(e)(2), to the extent those claims are valid and enforceable.

46. If Teva's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed for Section 1 Indication and Usage or Section 2.1 Recommended Dosage and Administration, the use of the Teva ANDA Product for the indication proposed in the ANDA in the United States would infringe claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(a), to the extent those claims are valid and enforceable.

47. If Teva's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed for Section 1 Indication and Usage or Section 2.1 Recommended Dosage and Administration, the sale or offer of sale of the Teva ANDA Product in the United States would infringe claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(b) and (c) by actively inducing and contributing to infringement by others, to the extent those claims are valid and enforceable.

48. The labeling for DRL's ANDA Product states that treatment with DRL's product is to begin "after the patient has received G-CSF once daily for 4 days;" DRL's ANDA Product is to be administered "approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days" and at a dose of "0.24 mg/kg body weight by subcutaneous (sc) injection."

49. Teva's ANDA Product is a pharmaceutical composition indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with nonHodgkin's lymphoma and multiple myeloma.

50. The labeling for Teva's ANDA product states that treatment with Teva's product is to begin "after the patient has received G-CSF once daily for 4 days," Teva's ANDA Product is to be administered "approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days" and at a dose of "0.24 mg/kg body weight by subcutaneous (sc) injection."

i. *Clinical Trials*

51. Hendrix et al., Pharmacokinetics and Safety of AMD-3100, a Novel Antagonist of the CXCR-4 Chemokine Receptor, in Human Volunteers, Antimicrobial Agents and Chemotherapy, 44(6):1667-1673 (2000) ("Hendrix") reports results from a clinical trial testing the safety of plerixafor in healthy human volunteers.

52. The clinical trial for which results were reported in the Hendrix (2000) article was internally identified by AnorMED as Study Number 98-01.

53. Hendrix et al., Safety, pharmacokinetics, and antiviral activity of AMD3100, a selective CXCR-4 receptor inhibitor, in HIV-1 infection, J. Acquir. Immune Defic. Syndr. 37:1253-1262

(2004) ("Hendrix (2004)") reports results from a clinical trial testing the safety and efficacy of plerixafor in HIV patients.

54. Fransen et al., Suppression of dualtropic Human Immunodeficiency Virus Type 1 by the CXCR-4 antagonist AMD3100 is associated with efficiency of CXCR-4 use and baseline virus composition, Antimicrobial Agents and Chemotherapy, 52:2608-2615 (2008) ("Fransen (2008)") reports additional testing on the viruses harbored in the 14 patients that participated in the clinical trial described in the Hendrix (2004) paper and who harbored dual/mixed (DM)-tropic HIV.

55. The clinical trial for which results were reported in the Hendrix (2004) and Fransen (2008) articles was internally identified by AnorMED as Study Number AMD3100-2001.

ii. Conception of the Claimed Subject Matter of the '590 Patent

56. The inventors memorialized their conception of the subject matter claimed in the '590 patent by October 2000.

57. The relevant date for determining whether a reference is prior art to the '590 patent under 35 U.S.C. §§ 102 et seq. is October 2000.

iii. Prior Art

58. By July 31, 2000, it was publicly known that CXCR-4 was a shorthand designation for CX-C chemokine receptor type 4.

59. By July 31, 2000, it was publicly known that SDF-1 was a shorthand designation for stromal cell-derived factor 1.

60. By July 31, 2000, SDF-1 was the only publicly known natural ligand for CXCR-4.

61. By July 31, 2000, the compound plerixafor had been publicly disclosed as the active compound in a pharmaceutical composition used in clinical trials.

62. By July 31, 2000, it was publicly known that plerixafor was a CXCR-4 antagonist.

63. By July 31, 2000, it was publicly known that stem cells could be mobilized to the peripheral blood and collected via a process known as apheresis.

64. Demirer et al., Optimization of Peripheral Blood Stem Cell Mobilization, Stem Cells, 14:106-116 (1996) ("Demirer 1 (1996)"), was published in January 1996, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

65. Demirer 1 (1996) is not cited on the face of the '590 patent.

66. Demirer et al., Factors Influencing Collection of Peripheral Blood Stem Cells in Patients with Multiple Myeloma, Bone Marrow Transplant, 17(6):973-941 (1996) ("Demirer 2 (1996)"),

was published in 1996, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

67. Demirer 2 (1996) is not cited on the face of the '590 patent.

68. Auiti et al., The Chemokine SDF-1 Is a Chemoattractant for Human CD34+ Hematopoietic Progenitor Cells and Provides a New Mechanism to Explain the Mobilization of CD34+ Progenitors to Peripheral Blood, 185 J. Exp. Med 111-120 (1997) ("Aiuti (1997)") was published January 1, 1997, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

69. Aiuti (1997) is cited on the face of the '590 patent.

70. Schols et al., Inhibition of T-Tropic HIV Strains by Selective Antagonization of the Chemokine Receptor CXCR-4, J. Exp. Med. 168(8): 1383-1388 (1997) ("Schols (1997)"), was published on October 20, 1997, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

71. Schols (1997) is not cited on the face of the '590 patent.

72. Körbling et al., Peripheral Blood Stem Cell: A Novel Source for Allogeneic Transplantation, The Oncologist, 1997; 2:104-113 ("Korbling (1997)"), was published in April 1997, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

73. Korbling (1997) is not cited on the face of the '590 patent.

74. There was prescribing information for Neupogen® dated April 2, 1998 ("Prescribing Information for Neupogen® (1998)"), more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

75. The Prescribing Information for Neupogen® (1998) is not cited on the face of the '590 patent.

76. Möhle et al., The Chemokine Receptor CXCR-4 is Expressed on CD34+ Hematopoietic Progenitors and Leukemic Cells and Mediates Transendothelial Migration Induced by Stromal Cell-Derived Factor-1, Blood, 91(12):4523-4530 (1998) ("Möhle (1998)") was published on June 15, 1998, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

77. Möhle (1998) is not cited on the face of the '590 patent.

78. Papayannopoulou, Peripheralization of Hematopoietic Stem Cells, U.S. Patent No. 5,824,304 ("the '304 patent"), was issued on October 20, 1998, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

79. The '304 patent is not cited on the face of the '590 patent.

80. Peled et al., Dependence of Human Stem Cell Engraftment and Repopulation of NOD/SCID Mice on CXCR-4, Science 283:845-848 (1999) ("Peled (1999)"), was published on February 5, 1999, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

81. Peled (1999) is cited on the face of the '590 patent.

82. Ma et al., The Chemokine Receptor CXCR-4 is Required for the Retention of B lineage and Granulocytic Precursors within the Bone Marrow Microenvironment, Immunity, 10:463-471(1999) ("Ma (1999)"), was published on April 1, 1999, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

83. Ma (1999) is cited on the face of the '590 patent.

84. Demirer et al., Peripheral Blood Stem Cell Mobilization for High-Dose Chemotherapy, Journal of Hematotherapy, 8:103-113 (1999) ("Demirer (1999)"), was published in April 1999, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

85. Demirer (1999) is not cited on the face of the '590 patent.

86. Hendrix et al., Pharmacokinetics and Safety of AMD-3100, a Novel Antagonist of the CXCR-4 Chemokine Receptor, in Human Volunteers, Antimicrobial Agents and Chemotherapy, 44(6): 1667-1673 (2000) ("Hendrix (2000)"), was published in June 2000, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

87. Hendrix (2000) is cited on the face of the '590 patent.

88. Gianni, Human Growth Hormone to Stimulate Mobilization of Pluripotent Hematopoietic Stem Cells, EP 1 016 413 ("EP '413"), was issued on May 7, 2000, more than one year prior to the earliest U.S. filing date to which the '590 patent claims priority.

89. EP '413 is cited on the face of the '590 patent.

90. MacFarland et al., Methods and Composition to Enhance WBC Count, WO 00/45814 ("WO '814"), was published August 10, 2000, prior to the time the inventors memorialized their conception of the subject matter claimed in the '590 patent. WO '814 is cited on the face of the '590 patent.

iv. Mozobil® and Other Mobilizing Agents

91. Mozobil® had net U.S. sales of 62 and 56 million euros in 2014 and 2013, respectively.

92. Plerixafor in combination with G-CSF is an accepted standard of care for a patient who fails to mobilize the minimum number of stem and/or progenitor cells needed for transplant.

93. There has been an improvement in the care of patients who are poor mobilizers because of the availability of Mozobil®.

94. In 2011, the Spanish version of Mozobil® was awarded the Prix Galien Award in Spain for Best Pharmaceutical of the Year, but Mozobil® has not been given a comparable award in the United States.

95. In 2013, the Greek version of Mozobil® was awarded the Prix Galien Award in Greece for Best Pharmaceutical of the Year, but Mozobil® has not been given a comparable award in the United States.

96. The U.K. version of Mozobil® was selected as a finalist in the competition for the 2010 Prix Galien Award in the UK in the orphan drug category for the U.K. market, but the U.S. version of Mozobil® has not received a comparable award for the U.S. market.

D. Procedural History

97. The Plaintiffs filed suit against defendant DRL (D.I. 1) on August 29, 2013 asserting infringement of the '590 patent and two other patents. The suit was filed within forty-five days of receiving defendant DRL's July 19, 2013 notice letter.

98. The Plaintiffs filed suit against defendant Teva (Civil Action No. 1:13-cv-01508-GMS, D.I. 1) on August 29, 2013 asserting infringement of the '590 patent and two other patents. The suit was filed forty-five days of receiving defendant Teva's July 16, 2013 notice letter.

99. The thirty-month stay deadline is June 15, 2016.

100. Defendant DRL answered the complaint on October 16, 2013, (D.I. 19) pleading affirmative defenses of noninfringement and invalidity, and declaratory judgment counterclaims.

101. Plaintiffs answered those counterclaims on November 12, 2013. (D.I. 21.)

102. Defendant Teva answered the complaint on October 11, 2013, pleading affirmative defenses of noninfringement and invalidity. (Civil Action No. 1:13-cv-01508-GMS, D.I. 13.)

103. Defendant Teva filed an amended answer on May 15, 2014, pleading affirmative defenses of noninfringement and invalidity, and declaratory judgment counterclaims. (D.I. 60.)

104. Plaintiffs answered those counterclaims on May 28, 2014. (D.I. 66.)

105. On November 26, 2013, the court granted the parties' Motion to Consolidate for the purposes of fact and expert discovery. (D.I. 23.)

106. On January 27, 2015, the court entered the parties' Stipulation that the submissions of the DRL ANDA and the Teva ANDA infringe, inter alia, claims 8 and 19 of the '590 patent under 35 U.S.C. § 271(e)(2), to the extent those claims are valid and enforceable, but for purposes of 35 U.S.C. §271(a), (b), and (c), only to the extent the Defendants' respective ANDA Products are approved with their current proposed labeling or with labeling substantially identical to that currently proposed for Section 1 Indication and Usage or Section 2.1 Recommended Dosage and Administration. (D.I. 144.)

107. On July 30, 2015, the court entered the parties' Stipulation, in which: (a) the Plaintiffs dismissed with prejudice their assertions of infringement against the Defendants regarding all claims of the '152 and '102 patents, and all claims of the '590 patent, except claims 8 and 19; (b) Teva dismissed with prejudice (i) its First Counterclaim for Declaratory Judgment of Invalidity with respect to all claims of the '152 patent, all claims of the '102 patent, and all claims of the '590 patent, with the exception of claims 8 and 19 and (ii) its Second Counterclaim for Declaratory Judgment of Non-infringement with respect to the '152, '102, and '590 patents; and (c) DRL dismissed with prejudice (i) its First Counterclaim for Declaratory Judgment of Invalidity with respect to all claims of the '152 patent, all claims of the '102 patent, and all claims of the '590 patent, with the exception of claims 8 and 19 and (ii) its Second Counterclaim for Declaratory Judgment of Non-infringement with respect to the '152, '102, and '590 patents. (D.I. 185.)

108. On November 4, 2015, the Court entered the parties' Stipulation, in which: (a) the Plaintiffs dismissed with prejudice their assertions of infringement against the Defendants regarding claim 8 of the '590 patent; (b) Teva dismissed with prejudice (i) its First Counterclaim for Declaratory Judgment of Invalidity with respect to all claims of the '590 patent, with the exception of claim 19 and (ii) all remaining counterclaims with respect to claim 8 of the '590 patent; (c) DRL dismissed with prejudice (i) its First Counterclaim for Declaratory Judgment of Invalidity with respect to all claims of the '590 patent, with the exception of claim 19; and (ii) any and all remaining counterclaims with respect to claim 8 of the '590 patent. (D.I. 193.)

109. The court held a four-day bench trial in this matter on November 9 through November 13, 2015. (D.I. 211-214.)

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202. The Defendants challenge the validity of the claim 19 of the '590 Patent as obvious in light of the prior art. 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 Defendants have not established by clear and convincing evidence that the asserted claim of the patent-in-suit is invalid due to obviousness. The court's reasoning follows.

A. The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a).

Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[5] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 1356-57.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed.

[5] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

B. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the patent-in-suit would have: a Ph.D., M.D., or Ph.D./M.D.; training and experience in bone marrow or hematopoietic stem cell transplantation; and expertise in mammalian hematopoiesis and the underlying science thereof.[6]

C. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

(1) A POSA Would Not Have Been Motivated to Practice the Method of Claim 19 Based on *Hendrix*

As an initial matter, the Plaintiffs argue that *Hendrix* is not analogous art and therefore not relevant to the obviousness determination. (D.I. 202 at 16.) *See In re Klein*, 647 F.3d 1343, 1348 (Fed. Cir. 2011) (a reference must be analogous to the claimed invention to be prior art for purposes of obviousness.) To establish that *Hendrix* was analogous, the Defendants must prove that *Hendrix* is from "the same field of endeavor" or is "reasonably pertinent" to the problem the

[6] Both sides agree on the level of ordinary skill of a POSA. Identification of a person of ordinary skill in the art is derived from Drs. Scadden and Mohty. Tr. 104:7-105:22 (Scadden); Tr. 574:17-575:7 (Mohty). The number of years of experience required to qualify as a POSA would depend on the nature of the person's experience and training. Tr. 182:4-12 (Scadden). According to the Defendants, a POSA must have at least three years of training and experience in bone marrow or hematopoietic stem cell transplantation. Tr. 104:7-105:10, 181:14-183:1 (Scadden); Tr. 574:12-575:7 (Mohty).

inventor is trying to solve. *In re Clay*, 966 F.2d 656, 658-59 (Fed. Cir. 1992). A reference is reasonably pertinent if it "logically would have commended itself to an inventor's attention in considering" the problem addressed by the patent. *Id.* at 659.

The Plaintiffs argue that a POSA would not logically consider *Hendrix*, which focused on evaluating the safety and pharmacology of plerixafor, a drug for treating HIV. (D.I. 202 at 17); UF 52; DTX94.1; Tr. 378:2-7 (Scadden). The Plaintiffs also point out the USPTO Examiner considered *Hendrix* and concluded that it was a non-analogous art in the context of the subject matter claimed in the patents at issue. (D.I. 202 at 18.) The Defendants respond that although the PTO found that *Hendrix* was non-analogous art, it did so without the benefit of testimony from hematologists in HIV-related research with respect to the CXCR-4 receptor. (D.I. 204 at 15 n.7.)

Both parties agree that a POSA would have been aware of the need for a better stem cell mobilizing regimen. (D.I. at 202 at 6; D.I. 204 at 19); *see also* FOF 15-18. The parties disagree about the likelihood that CXCR-4 would become the object of research as a stem cell mobilizing agent. Defendants rely on papers by Aiuti, Möhle, Peled, and Ma relating to CXCR-4 or SDF-1 to support their position that CXCR-4 was the target of stem cell transplantation ("SCT") research at the time. (D.I. 204 at 7-10.) The Defendants also rely on the testimony of Dr. Scadden to argue that a POSA would have been motivated to study any art that addressed CXCR-4 antigens. (D.I. 204 at 15.) According to the Defendants, a POSA would have been particularly interested in CXCR-4's importance in hematology and HIV. (*Id.* at 16.)

The Plaintiffs argue that instead of CXCR-4, a POSA's first choice for evaluation of potential stem cell mobilizers would have been cytokines and growth factor cytokines because the only two FDA-approved stem cell mobilizers as of October 2000 were G-CSF and GM-CSF. (D.I. 202 at 10.) Tr. 85:4-12, 234:21-24, 235:14-16, 241:14-22 (Scadden); *see also* FOF 24. The

Plaintiffs point out that none of the papers on CXCR-4 or SDF-1 that the Defendants cite reported any *in vivo* experiments demonstrating that manipulation of either CXCR-4 or SDF-1 mobilizes stem cells. (D.I. 202 at 12); Tr. 233:8-19, 255:6-18 (Scadden); Tr. 619:13-15 (Mohty). This lack of *in vivo* data would have been important to a POSA because mobilization is an *in vivo* process. Tr. 483:24-484:2 (Abrams); *see also* FOF 73.

The court finds that Defendants have not shown that a POSA would have pursued CXCR-4 over the proven field of cytokines and other possible stem cell mobilizers. Dr. Scadden's rationale for a POSA focusing on SDF-1 or CXCR-4 over other options was based on his own decision at the time to investigate a modified form of SDF-1. Tr. 166:6-10, 253:24-255:18, 769:24-770:24 (Scadden). In other words, Dr. Scadden improperly based his opinion on his own experiments, Tr. 770:7-8 (Scadden), not prior art.

Without a specific focus on CXCR-4, *Hendrix* would not have been reasonably pertinent to a POSA focused on harvesting stem cells.[7] The purpose of *Hendrix* was to evaluate the safety and pharmacology of plerixafor, a drug for treating HIV. UF 52; DTX94.1; Tr. 378:2-7 (Scadden). It is not logical that a POSA would have focused in particular on plerixafor, known at the time only as an HIV drug, Tr. 101:8-15 (Scadden), as a potential stem cell mobilizer for subsequent harvest and transplantation. Nor would a POSA have even read *Hendrix*, which was published in the Antimicrobial Agents and Chemotherapy journal. DTX94.1; Tr. 689:2-3 (Mohty). Indeed, Dr. Scadden was conducting research on a modified form of SDF-1 when *Hendrix* was published, but did not remember reading *Hendrix* when it was published. Tr. 377:3-18 (Scadden). While from today's perspective the relationship between *Hendrix* and claim 19 may seem clear, the court finds that the Defendants' relevance analysis is colored by hindsight.

[7] The Defendants argue that "The POSA's interest in the SDF-1/CXCR-4 axis, and search for CXCR-4 antagonists would have led the POSA to Hendrix ..." (D.I. 204 at 20.)

Moreover, the USPTO Examiner thoroughly considered *Hendrix* and concluded that it was non-analogous art: "[O]ne would not have looked to the HIV therapeutic art in order to find a suitable antagonist for collection of stem/progenitor cells." JTX3 at 1447, 787-812, 1115-33 (using *Hendrix* to reject the claims). There is a presumption that decisions made by the PTO Examiner are valid. These decisions are particularly pertinent because they were made contemporaneously with full view of the art at the time and not tainted by hindsight. In light of the foregoing evidence, the court simply cannot conclude that the *Hendrix* reference "logically would have commended itself to an inventor's attention in considering" the problem of stem cell harvesting. *In re Clay,* 966 F.2d 656, 658 (Fed. Cir. 1992).

Even if *Hendrix* were considered prior art, *Hendrix* would not render claim 19 obvious to a POSA. The Defendants argue that *Hendrix* taught that plerixafor may cause stem cell mobilization. (D.I. 204 at 15.) Relying on the testimony of Drs. Scadden and Mohty, however, the Plaintiffs argue that the primary speculation in *Hendrix* for the cause of the elevated WBC counts was demargination. (D.I. 202 at 21); Tr. 383:3-24 (Scadden). The Plaintiffs also cite the 2001 Suzuki article to demonstrate what *Hendrix* would have taught a POSA: "when CXCR-4 receptors were blocked by AMD3100, a 'demargination' effect occurred . . ." (D.I. 204 at 23); Tr. 396:11-398:1 (Scadden). Furthermore, the Plaintiffs assert that a POSA also would have known that bone pain is a common side effect of G-CSF and GM-CSF, Tr. 584:4-8 (Mohty); Tr. 395:11-18, 396:5-10 (Scadden), yet no volunteer in the *Hendrix* study reported any bone pain after receiving plerixafor. DTX94.3 (Table 1); Tr. 583:11-584:3 (Mohty); Tr. 395:5-10 (Scadden). Thus, according to the Plaintiffs, a POSA would believe the lack of any observed bone pain indicated that plerixafor was not causing the release of stem cells from the bone marrow. Tr. 582:24-583:10, 584:9-14 (Mohty). The Defendants respond that a POSA would not have expected to see the same side effects as G-

CSF because it was not believed to use the same mechanism for proliferation as G-CSF. (D.I. 204 at 17.) The Defendants' argument demonstrates the limitations on what a POSA would know with certainty when reading *Hendrix*. Ultimately, the court finds that even if *Hendrix* were relevant art, it would not have rendered claim 19 obvious.

(2) A POSA Would Not Have Been Motivated to Practice the Method of Claim 19 Based on the '304 Patent

Next, the Defendants argue that a POSA would have been motivated to practice the method of claim 19 based on the '304 patent. (D.I. 204 at 12); DTX279. The invention of the '304 patent includes a method for increasing the number of stem cells in the peripheral blood by administering a blocking agent of VLA-4 antigens. Tr. 117:22-118:3, 119:15-120:1 (Scadden); Tr. 630:1-5 (Mohty). Thus, the Defendants argue, based upon the '304 patent, a POSA would have been motivated to look for blocking agents to combine with G-CSF to mobilize stem cells. (D.I. 204 at 12.) This motivation would lead a POSA to plerixafor as "an analogous blocking agent that similarly disrupts the tether between CXCR-3 and SDF-1." (*Id.* at 11.) Essentially, Defendants argue that plerixafor would be expected to disrupt the tether between CXCR-4 and SDF-1 in the same way that VLA-4 antigens disrupt the tether between VLA-4 and VCAM-1, thereby causing stem cell mobilization. The Plaintiffs respond that the '304 Patent's discussion of mobilization by blocking of VLA-4 would not have led a POSA to SDF-1 or CXCR-4 because neither is specifically mentioned in the '304 Patent. (D.I. 204 at 15.) The Plaintiffs also point out that CXCR-4 is in a completely different family of receptors than VLA-4. (D.I. 204 at 14); Tr. 763:5-6 (Scadden); Tr. 598:13-14 (Mohty).

The court agrees with the Plaintiffs that the '304 Patent's discussion of VLA-4 antibody blocking agents would not have rendered obvious claim 19, which covers CXCR-4 and not VLA-

4. In addition, the court notes that the Defendants' argument is based on combining the teachings of the '304 Patent with *Hendrix* in order for a POSA to focus on the plerixafor blocking agent. (D.I. 204 at 19). As previously discussed, *Hendrix* is not analogous art and therefore cannot be considered as part of the Defendants' obviousness argument. The Defendants' argument is based on too many faulty assumptions to support a finding of obviousness.

(3) A POSA Would Not Have Been Motivated to Practice the Method of Claim 19 Based on the WO '814 Patent

The Defendants next argue that based on the WO '814 Patent, and the understanding in the art that manipulation of the SDF-1/CXCR-4 axis could result in mobilization of stem cells, a POSA would have understood that plerixafor's antagonism of CXCR-4 could cause mobilization of stem cells. (D.I. 204 at 26); FOF ¶¶ 33-34, 52; DTX212.12; Tr. 158:25-159:9 (Scadden). Again, the Defendants argue that, in the way the anti-VLA-4 antibody causes mobilization by blocking the interaction between VCAM-1 and VLA-4, WO '814 would have motivated a POSA to use plerixafor to block CXCR-4's interaction with SDF-1 in order to mobilize stem cells for harvesting. (*Id.* at 17-18.) At the outset, the court notes that WO '814 does not disclose information about using plerixafor to mobilize stem cells, but instead reveals the relationship between plerixafor and white blood cell elevation. Thus, the Defendants' argument depends upon the assumption that a POSA would have known that white blood cells are a proxy for stems cells and that successful stem cell mobilization and harvesting could occur through CXCR-4 antagonists because the '304 patent taught mobilization through the analogous VLA-4 antibody. As previously discussed, the court is not persuaded by Defendants' arguments that the '304 patent would teach a POSA to use plerixafor as a CXCR-4 blocking agent, simply because plerixafor is as an agent like an anti-VLA-4 blocking agent. Thus, the court also rejects the argument that a

POSA would read the '304 patent for the proposition that plerixafor's antagonism of CXCR-4 could cause mobilization of stem cells and then apply this concept in combination with the WO '814 to practice claim 19. In addition, the patent examiner considered WO '814 and determined that claim 19 was not obvious in light of WO '814. (D.I. 202 at 18 n.8.) The court agrees that the evidence on the record supports this conclusion.

(4) A POSA Would Not Have Had a Reasonable Expectation of Success

The Defendants contend that it was reasonably predictable in October 2000 that plerixafor would mobilize stem cells in sufficient numbers for harvesting and transplantation. (D.I. 204 at 26.) The court rejects this position. Dr. Dale explained he had a "hope," but not an expectation, that the first clinical trial of plerixafor would show an elevation of stem cells. Tr. 371:22-372:24 (Dale). As he testified "the release of stem cells is complicated, and I reviewed work by very fine investigators over the years about things that have failed, because it is more complicated than we realize." Tr. 372:14-17 (Dale). Even Dr. Scadden testified that, before October 2000, more than a dozen candidates had been investigated in the search for a stem cell mobilization agent better than existing agents. Tr. 234:2-239:23 (Scadden); *see also* Tr. 577:7-578:19 (Mohty). The history of failure in the field demonstrates that a POSA would not have a reasonable expectation of success about the practice of claim 19. *See KSR*, 550 U.S. at 421. As previously discussed, there were many different cytokines and growth factors that were the subject of research for a POSA looking for a better stem cell mobilizer. In short, the complexity and incomplete understanding of stem cell mobilization made it a highly unpredictable field in October 2000. Tr. 576:7-18, 580:22-581:3 (Mohty). In light of the foregoing evidence, Defendants have failed to make a clear and convincing showing that claim 19 of the '590 Patent would have been *prima facie* obvious. *See Sanofi–Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008) (upholding the district court's finding

of non-obviousness where there were a "wide range of possible outcomes" and a "relative unlikelihood" that the desired results would be obtained).

D. Secondary Considerations

Even if the Defendants had successfully established a *prima facie* case, the evidence on several relevant secondary considerations weighs against a finding of obviousness. The Supreme Court has made clear that secondary considerations can include evidence of, among other factors, commercial success, long-felt but unsolved needs, and/or the failure of others. *See Graham*, 383 U.S. at 17-18. A plaintiff may also rebut obviousness by demonstrating that there were: unexpected results created by the claimed invention; unexpected properties of the claimed invention; licenses showing industry respect for the invention; and/or skepticism of skilled artisans before the invention. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). However, "[e]vidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

The Plaintiffs assert that the secondary considerations of fulfilment of long-felt need after repeated failure of others, unexpected results, praise, and skepticism sufficiently rebut a *prima facie* case. (D.I. 202 at 29-38). The Defendants argue there is no evidence of unexpected results, there was no failure of others, any fulfillment of a long-felt need was limited to the class of poor mobilizers, industry praise was not commensurate with claim 19, and skepticism does not support non-obviousness. (D.I. 204 at 28-34.) The Defendants also argue that because claim 19 sweeps much more broadly than Mozobil®'s use in practice, any asserted objective evidence of non-obviousness associated with that use is not commensurate with the scope of claim 19. The court addresses each secondary consideration that the Plaintiffs raise in turn.

(1) Fulfillment of Long-Felt Need after Repeated Failure by Others

The Plaintiffs argue that despite considerable efforts, researchers had failed to find a better mobilizer by the time of the invention. (D.I. 202 at 29-32); *see* FOF 21-23. According to the Plaintiffs, Mozobil® met this need because the method of claim 19 is successful at increasing the mobilization of stem cells in a broad range of subjects. (D.I. 202 at 33-36); Tr. 313:13- 314:2 (Dale); FOF 88-92, 103-105. Dr. Mohamad Mohty testified that Mozobil® allows approximately 90% of the former non-mobilizers and hard-to-mobilize subjects to mobilize and harvest sufficient numbers of stem cells for a successful stem cell transplant. Tr. 686:4-687:1 (Mohty); *see also* Tr. 665:11-19 (Mohty). The Plaintiffs also introduced evidence that Mozobil® has minimal toxicity, and a regimen of G-CSF and Mozobil® reduces the average number of apheresis sessions needed to harvest the stem cells. JTX52 at 36; Tr. 508:3-509:2 (Abrams); Tr. 599:5-14, 619:22-620:12 (Mohty); *see also* FOF 19-20. The Defendants respond that other mobilizing agents had been successfully combined with G-CSF prior to October 2000. (D.I. 204 at 31.) The Defendants also argue that plerixafor's benefits are only seen in poor mobilizers and therefore there is no nexus to claim 19. (*Id.* at 33.)

The court concludes that Plaintiffs have established that the claimed invention met a long-felt, but unmet need for a better stem cell mobilizing regimen. The need for an improved mobilizing agent was widely recognized. After the FDA approved Mozobil®, publications by experts in the field repeatedly discussed its positive impact on the non-mobilizers, poor mobilizers, and even the easy-to-mobilize subjects. *See* Tr. 601:3-607:1 (Mohty); JTX134 at 4-5; JTX183 at 1; JTX174 at 11; UF 108. Even Dr. Scadden admitted that he would recommend administration of Mozobil® with G-CSF for non- and sub-optimal mobilizers, and that this is the most common regimen for these patients. Tr. 761:13-762:7 (Scadden). While the Defendants

argue that there are some patients who do not mobilize sufficiently even with Mozobil®, (D.I. 204 at 33), this does not negate the benefits of the claimed invention. *See Pfizer Inc. v. Mylan Pharm.*, 71 F. Supp. 3d 458, 475 (D. Del. 2014), *aff'd*, No. 2015-1131, slip op. (Fed. Cir. Jan. 13, 2016).

(2) Unexpected Results

Unexpected results may be demonstrated by showing "that the claimed invention exhibits some superior property or advantage that a [POSA] in the relevant art would have found surprising or unexpected." *Procter & Gamble*, 566 F.3d at 994 (Fed. Cir. 2009). This comparison is made to the closest prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Here, the closest prior art is G-CSF in combination with chemomobilization. The Plaintiffs argue that the following unexpected results are associated with the method of claim 19: (1) increased number of mobilized stem cells; (2) rapidity of action of plerixafor; (3) increased quality of stem cells; and (4) synergy between plerixafor and G-CSF. (D.I. 202 at 29.) The Defendants claim that these results are either unproven or would have been expected. (D.I. 204 at 29.)

The court agrees with the Plaintiffs that a POSA would not have expected that the combination of Mozobil® and G-CSF would rapidly and predictably mobilize stem cells because the known mobilization agents were slow-acting and unpredictable. Tr. 614:24-615:20 (Mohty). This positive effect across so many patient populations would have been unexpected. Tr. 618:1-17 (Mohty); *see also* FOF 72-74. The evidence presented at trial also supports the conclusion that Mozobil® in combination with G-CSF unexpectedly mobilizes more cells in a range of patients. JTX52 at 36; Tr. 508:3-23, 511:2-5 (Abrams); FOF 88-92. The court finds that Mozobil® in combination with G-CSF also produces an unexpected rapid mobilization. Tr. 614:24-615:20

(Mohty); Tr. 115:4-23 (Scadden). Finally, the court finds that the combination of Mozobil® and G-CSF unexpectedly mobilizes better quality stem cells with a greater capacity to repopulate bone marrow in humans. JTX33 at 8, Fig. 5A; Tr. 613:10-614:7 (Mohty). The Defendants argue that plerixafor would have been expected to mobilize higher quality stem cells. (D.I. 204 at 30.) The court disagrees. In October 2000, it was not known with certainty whether a CXCR4 antagonist like Mozobil would mobilize stem cells at all. *See* FOF 31-41. As previously discussed, there was great uncertainty about the mechanism of mobilization in general and the role of SDF-1 or CXCR-4, if any, in the process. FOF 21-28, 31-41. Thus, the court is persuaded that the benefits discussed thus far were unexpected. While the defendants argue that there remains a need to develop improved mobilizing agents (D.I. 204 at 33), this does not undermine the benefits that Mozobil® offers.

The court, however, cannot conclude that Mozobil® in combination with G-CSF unexpectedly acts synergistically with G-CSF. The Plaintiffs introduced testimony that Dr. Broxmeyer showed that in mice the increase in the number of stem cells mobilized with the combination of G-CSF and plerixafor was greater than the additive amount of the increase observed with either agent alone. JTX33 at 3, 5, 8, Figs. 2A, 2C, 3, and 5A; Tr. 608:22-614:1, 669:12-670:3, 670:13-17, 671:10-20 (Mohty). In addition, the Plaintiffs contend that Drs. Broxmeyer and Dale demonstrated in humans that, when normalized for patient weight, the number of stem cells mobilized by the combination of G-CSF and plerixafor was greater than the sum of the results with G-CSF alone and plerixafor alone. JTX152 at 3, Fig. 1D; Tr. 307:6-309:16 (Dale). The Defendants respond that the Plaintiffs did not demonstrate synergy because the experiment was not designed for this purpose and because the data is not statistically significant. (D.I. 204 at 80.) The Defendants depend on the testimony of Dr. Jessie Au who

opined that the data in *Broxmeyer* (JTX33) do not establish that the combination of G-CSF and plerixafor is synergistic because the study was not properly designed to test whether the two agents are synergistic in combination. Tr. 718:2-11, 722:6-17 (Au). The court found this testimony to be credible. The Plaintiffs failed to persuade the court that there is sufficient evidence of synergy in the face of Dr. Au's compelling drug interactivity analysis. In the end, regardless of whether there was synergy, the other evidence of unexpected results supports a finding of nonobvious in this case.

(3) Industry Praise

The Plaintiffs argue that Mozobil® has been praised as a "new and important agent" and "significant advance in stem cell mobilization." JTX183 at 1; JTX174 at11; *see also* FOF 91-92. Mozobil® was a finalist for the UK Prix Galien Award in 2010 and won the award in 2011 in Spain and 2013 in Greece. Tr. 617:10-22 (Mohty); Dep. Tr. 138:10-16 (Cheverton). The Defendants argue that, as Dr. Mohty testified, the European indication expressly limits use of the drug to poor or failed mobilizers. Tr. 685:5-17 (Mohty). Thus, according to Defendants, any award for the use of Mozobil® in Europe is not commensurate with the scope of claim 19, which is not limited to poor mobilizers. (D.I. 404 at 33.) The court rejects the Defendants' argument; the Plaintiffs have established that Mozobil® received widespread praise in the US and Europe and this weighs in favor of nonobviousness. *Vulcan Eng'g Co. v. Fata Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002) ("Appreciation by contemporaries skilled in the field of the invention is a useful indicator of whether the invention would have been obvious to such persons at the time it was made.").

(4) Skepticism about Testing Mozobil® and Surprise Regarding the Results

The Plaintiffs assert that POSAs expressed skepticism about experimentation with Mozobil® as a stem cell mobilizer. (D.I. 202 at 37.) In particular, the Plaintiffs depend on the testimony of Dr. Dale that he encountered skepticism from four of his colleagues while working on the invention. *Id.* Even after working in the field of stem cell transplantation for over a decade, Dr. Papayannopoulou was "so surprised" that Mozobil® "really work[ed]." Tr. 301:17-302:8 (Dale); *see* FOF 28. The Defendants respond that only Dr. Dale testified that Dr. Papayannopoulou was surprised regarding his work on plerixafor and this evidence was uncorroborated. (D.I. 204 at 34.) The Defendants also assert that Dr. Papayannopoulou was likely surprised that Dr. Dale had access to and was working on plerixafor, not that plerixafor could be used as a mobilizing agent. (*Id.*) The court disagrees with the Defendants' characterization of the evidence; the evidence at trial suggested skepticism related to how Dr. Dale was using plerixafor not that he was using it. Moreover, inventor testimony can be sufficient to show skepticism. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1352-53 (Fed. Cir. 2012). The evidence on the record supports a finding of skepticism in this case.

(5) The Objective Indicia Have a Nexus With and Are Reasonably Commensurate in Scope With Claim 19 of the '590 Patent

Finally, the Defendants argue that the objective indicia does not have a nexus that is reasonably commensurate in scope with claim 19. (D.I. 204 at 28.) The Plaintiffs respond that no evidence was presented that Mozobil®'s effects would not be observed in other subjects or at other doses. (D.I. 202 at 38-40.) Use of Mozobil® in combination with G-CSF according to its FDA-approved label falls within the scope of claim 19. *See* FOF at 5, 88. Plaintiffs have established that there is a nexus between the objective indicia and asserted claim 19 of the '590

Patent. Thus, the court concludes that objective indicia based on Mozobil®'s FDA-approved use weigh against a finding of obviousness.

E. Injunctive Relief

Because the Defendants have stipulated that their proposed generic plerixafor ANDA products will infringe claim 19 of the '590 Patent, and because that claim is valid, enforceable and has not expired, Plaintiffs request that the court order that the effective date of any approval of the Defendants' ANDA Nos. 205182 and 205197 shall not be earlier than the expiration date of the '590 Patent, including any associated extensions and exclusivities, pursuant to 35 U.S.C. § 271(e)(4)(A). (D.I. 202 at 40.) Having found that claim 19 is valid, the court will grant the Plaintiffs' request for injunctive relief.

IV. CONCLUSION

For the reasons stated above, the court finds that the Defendants have not established by clear and convincing evidence that the patent-in-suit is invalid as obvious. The Plaintiffs' Rule 52(c) motion (D.I. 202) is granted and the Defendants' Rule 52(c) motion (D.I. 204) is denied. An appropriate order will follow.

Dated: May 11, 2016

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION and SANOFI-AVENTIS U.S. LLC, Plaintiffs/Counterclaim-Defendants, Plaintiffs, v. DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC., Defendants/Counterclaim-Plaintiffs. and TEVA PHARMACEUTICALS USA, INC., Defendant/Counterclaim-Plaintiff.	C.A. No. 13-1506-(GMS) Consolidated with C.A. No. 13-1508-(GMS)

ORDER

At Wilmington this 11th day of May, 2016, IT IS HEREBY ORDERED THAT:

1. The asserted claim of the patent-in-suit is not invalid due to obviousness;

2. The plaintiffs' Rule 52(c) motion (D.I. 202) is GRANTED.

3. The defendants' Rule 52(c) motion (D.I. 204) is DENIED.

4. The defendants are enjoined from commercially manufacturing, using, offering for sale, selling or importing their proposed generic versions of plaintiffs' Mozobil® product prior to the expiration date of the '590 Patent pursuant to 35 U.S.C. § 271(e)(4)(B).

5. The Clerk of Court is directed to enter final judgment in favor of the plaintiffs and against the defendants.

UNITED STATES DISTRICT JUDGE