IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION and SANOFI-AVENTIS U.S. LLC Plaintiffs and Counter-Defendants v. ZYDUS PHARMACEUTICALS (USA) INC. Defendant and Counter-Claimant	C.A. No. 1:16-cv-00540 (KAJ)

FINAL JUDGMENT

This action came before the Court for a four-day bench trial held on March 26-27, 2018 and April 10-11, 2018 (D.I. 81-84). The issues have been tried and decisions have been rendered by the Court:

IT IS HEREBY ORDERED AND ADJUDGED that final judgment is entered in favor of:

1. Plaintiffs (GENZYME CORPORATION and SANOFI–AVENTIS U.S. LLC), and against Defendant (ZYDUS PHARMACEUTICALS (USA) INC.), finding that Defendant did not prove by clear and convincing evidence that claim 8 of U.S. Patent No. 6,987,102 ("the '102 patent") and claims 8 and 19 of U.S. Patent No. 7,897,590 ("the '590 patent") are invalid due to derivation (or anticipation), obviousness, or for reciting patent-ineligible subject matter for the reasons set forth in the Court's Post-Trial Findings of Fact and Conclusions of Law filed under seal (D.I. 105) and Order (D.I. 106).

2. Plaintiffs, and against Defendant, finding that because the Defendant stipulated that its proposed generic plerixafor ANDA product would infringe claim 8 of the '102 patent and claims 8 and 19 of the '590 patent, to the extent that those claims are valid and enforceable, and because this Court has found that Defendant did not prove that the claims are invalid or unenforceable, Plaintiffs are entitled to injunctive relief.

3. Defendant, and against Plaintiffs, finding that Plaintiffs are not entitled to attorney's fees under 35 U.S.C. § 285.

IT IS HEREBY ORDERED that, under 35 U.S.C. § 271(e)(4)(A), because Defendant stipulated that the submission of its ANDA infringes claim 8 of the '102 patent and claims 8 and 19 of the '590 patent, and the use, sale, or offer for sale of Defendant's proposed generic plerixafor ANDA product for the indication proposed in the ANDA in the United States, if approved by the FDA with its current proposed labeling or with labeling substantially identical to that currently proposed, would infringe claim 8 of the '102 patent and claims 8 and 19 of the '590 patent, and because those claims have not been found invalid or unenforceable, and have not expired, the effective date of approval of Defendant's ANDA No. 208980 shall not be prior to the expiration date of the '102 and '590 patents, except to the extent subsequently agreed between Plaintiffs and Defendant or ordered or otherwise permitted by this Court or other tribunal; and it is further

ORDERED that, under 35 U.S.C. § 27l(e)(4)(B), Defendant, as well as its officers, agents, servants, employees, attorneys, and those persons in active concert or participation with them, is permanently enjoined from manufacturing, using, selling, or offering to sell within the United States, or importing into the United States, its proposed generic plerixafor ANDA product, prior to the expiration date of the '102 and '590 patents, except to the extent

subsequently agreed between Plaintiffs and Defendant or ordered or otherwise permitted by this Court or other tribunal; and it is further

ORDERED that, within 14 working days from the date of entry of this Final Judgment, pursuant to 21 C.F.R. § 314.107(e), Defendant shall submit a copy of entry of this Final Judgment to the FDA Office of Generic Drugs; and it is further

ORDERED that the parties shall be responsible for their own attorney's fees.

Dated: August 21, 2018

KENT A. JORDAN, CIRCUIT JUDGE
SITTING BY DESIGNATION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION, and SANOFI-AVETIS U.S. LLC	)	
Plaintiffs and Counter-Defendants	)	Civil Action No. 16-540 (KAJ)
v.	)	
ZYDUS PHARMACEUTICALS (USA) INC.	)	
Defendant and Counter-Claimant.	)	

ORDER

This Order relates to a four-day bench trial held on March 26-27, 2018, and April 10-11, 2018 (D.I. 81-84), as well as Plaintiffs' Rule 52(c) motion for judgment on partial findings (D.I. 85). For the reasons set forth in the Post-Trial Findings of Fact and Conclusions of Law filed under seal today in this case, IT IS HEREBY ORDERED this 8th day of August, 2018, that:

(1) Zydus's proposed generic plerixafor ANDA product will infringe Claim 8 of U.S. Patent No. 6,987,102 ("the '102 Patent") and Claims 8 and 19 of U.S. Patent No. 7,897,590 ("the '590 Patent");

(2) Based on the evidence and arguments in this case, Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent are not invalid;

(3) The effective date of any approval of Zydus's ANDA No. 208980 shall not be earlier than the expiration date of the '102 and '590 Patents, pursuant to 35 U.S.C. § 271(e)(4)(A);

(4) Zydus is enjoined from commercially manufacturing, using, offering for sale, selling, or importing its proposed generic version of Plaintiffs' MOZOBIL® product before the expiration date of the '102 and '590 Patents, pursuant to 35 U.S.C. § 271(e)(4)(B);

(5) Plaintiffs' Rule 52(c) motion (D.I. 85) is DENIED as moot;

(6) Plaintiffs are not entitled to attorney's fees under 35 U.S.C. § 285;

(7) The parties are directed to provide, within 10 days of this Order, an agreed upon form of final judgment consistent with this Order and the aforementioned Findings and Conclusions; and

(8) The Findings and Conclusions shall remain under seal until August 15, 2018. On or before August 13, 2018, the parties shall provide any proposed redactions that they agree are necessary to maintain the confidentiality of any matters that were provided under seal and are referred to in the Findings and Conclusions.

KENT A. JORDAN, CIRCUIT JUDGE
SITTING BY DESIGNATION

Wilmington, Delaware

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENZYME CORPORATION, and SANOFI-AVETIS U.S. LLC Plaintiffs and Counter-Defendants v. ZYDUS PHARMACEUTICALS (USA) INC. Defendant and Counter-Claimant.	)	Civil Action No. 16-540 (KAJ) **FILED UNDER SEAL**

POST-TRIAL FINDINGS OF FACT AND CONCLUSIONS OF LAW

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August 8, 2018
Wilmington, Delaware

JORDAN, *Circuit Judge sitting by designation*

I. INTRODUCTION

This is a patent infringement case. More particularly, it is a case about the validity of two patents. Genzyme Corporation ("Genzyme") and sanofi-aventis US LLC ("Sanofi," and together with Genzyme, "Plaintiffs") have sued Zydus Pharmaceuticals (USA) Inc. ("Zydus"), in connection with Zydus's Abbreviated New Drug Application ("ANDA") and, upon FDA approval, Zydus's planned commercial manufacture, importation, use, offer to sell, or sale of its generic version of MOZOBIL®. MOZOBIL® is a 20 mg/mL plerixafor solution for subcutaneous injection indicated for use in combination with granulocyte-colony stimulating factor ("G-CSF") to mobilize hematopoietic stem cells. (Docket Index ("D.I.") 71, App. A at ¶¶ 26-27.) Plaintiffs allege infringement of U.S. Patent No. 6,987,102 ("the '102 Patent") and U.S. Patent No. 7,897,590 ("the '590 Patent"), both entitled "Methods to Mobilize Progenitor/Stem Cells," and seek a declaratory judgment of infringement of those patents. Zydus stipulates to infringement, but responds in counterclaims that the asserted claims of the patents-in-suit are invalid. A four-day bench trial was held on March 26-27, 2018, and April 10-11, 2018. The following, issued pursuant to Federal Rule of Civil Procedure 52(a), are my findings of fact and conclusions of law on the issues of the validity of the patents-in-suit and attorney's fees.[1]

[1] Throughout these Findings of Fact and Conclusions of Law, I may have adopted without attribution language suggested by one side or the other in this dispute. In all such instances, the finding or conclusion in question has become my own, based upon my

For the reasons that follow, I conclude that Zydus has infringed the asserted claims of the patents-in-suit and that those claims are valid. I also conclude that Plaintiffs have not carried their burden of establishing entitlement to attorney's fees.

II. FINDINGS OF FACT[2]

A. The Parties

1. Genzyme is a corporation organized and existing under the laws of the Commonwealth of Massachusetts, having its principal place of business at 500 Kendall Street, Cambridge, Massachusetts 02142. (D.I. 71, App. A at ¶ 1.) Though not a party, AnorMED is a company that played a critical role in the development of the pharmaceutical technology at issue in this case. Genzyme acquired AnorMED in 2006. (D.I. 82 at 371:15-23.) Sanofi is a limited liability company organized and existing under the laws of the State of Delaware with its principal place of business at 55 Corporate Drive, Bridgewater, New Jersey 08807. (D.I. 71, App. A at ¶ 2.) Zydus is a corporation organized and existing under the laws of the State of New Jersey, with a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534. (D.I. 71, App. A at ¶ 3.)

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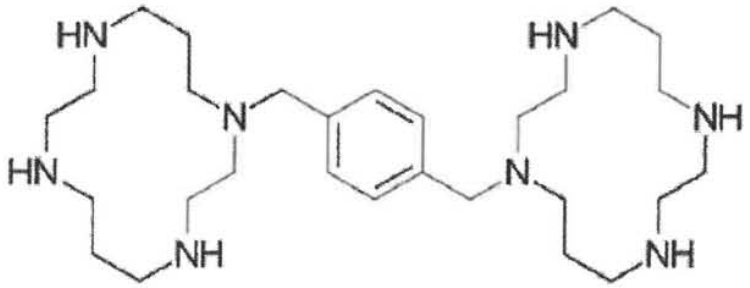
review of the evidence and the law. To the extent that any of my findings of fact may be considered conclusions of law, or vice versa, they should be considered as such.

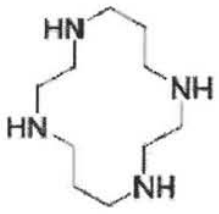
[2] As used in subsequent references within this document, "FOF" denotes findings of fact and "COL" refers to conclusions of law.

B. Plerixafor

2. 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane is the chemical name for plerixafor, and is pretty hard to spell. (D.I. 71, App. A at ¶ 20.) It has the following chemical structure:



(D.I. 71, App. A at ¶ 21.) Cyclam (1,4,8,11-tetraazacyclotetradecane) is a macrocyclic compound having the following chemical structure:



(D.I. 71, App. A at ¶ 22.) Plerixafor, sometimes referred to as AMD-3100,[3] is known as a "bicyclam" because it consists of two cyclams connected by a linker.[4] (D.I. 71, App. A

[3] AMD-3100 is the name AnorMED gave to plerixafor during its study. (D.I. 81 at 123:22-25.) Plerixafor was also given a number of other descriptors during various research and testing projects. (D.I. 71, App. A at ¶ 25.)

[4] Plerixafor is a compound of the following formula: Z-linker-Z', wherein Z is a cyclic polyamine containing 9–32 ring members of which 2–8 are nitrogen atoms, those nitrogen atoms being separated from each other by at least 2 carbon atoms, and wherein

at ¶¶ 23, 25.) It is not a naturally occurring compound (JTX-004 at 12; PTX-211; D.I. 82 at 307:3-308:14), and it was not invented by AnorMED (D.I. 82 at 307:10-13; D.I. 89 at ¶ 4; D.I. 98 at 1). It had been synthesized previously by an academic group, which published its findings in 1987. (PTX211; D.I. 82 at 307:10-308:14; D.I. 89 at ¶ 4; D.I. 98 at 1.) However, that publication did not describe the biological activity of plerixafor. (PTX211; D.I. 82 at 308:15-22.) I find that plerixafor is the active ingredient in a pharmaceutical composition with the anti-human immunodeficiency virus ("HIV") activity claimed in U.S. Patent No. 5,583,131 ("the '131 Patent"), which issued on December 10, 1996, and is currently owned by Plaintiffs. (PTX008 at 11; D.I. 89 at ¶ 7; D.I. 98 at ¶ 7.)

C. Stem Cells and Stem Cell Transplantation

3. The pharmaceutical technology at issue in this case has applications in the field of stem cell transplantation. (JTX-002 at 1; JTX-004 at 5.) Stem cells are undifferentiated and primitive cells in the blood system that give rise to all the other cells that develop later and form the body's blood. (D.I. 81 at 68:24-69:2.) Progenitor cells are slightly more mature and more differentiated cells that have a specialized function. (D.I. 81 at 69:3-19.) However, for purposes of this case, the parties agree that the term "stem cells" includes both stem cells and progenitor cells. (D.I. 81 at 11:18-21, 37:23-38:4, 69:20-22; D.I. 82 at 320:13-321:3.)

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the heterocycle may optionally contain additional heteroatoms besides nitrogen and/or may be fused to an additional ring system, Z' is defined by Z above and the linker comprises an aryl contained in an alkylene chain. (D.I. 71, App. A at ¶ 24.)

4. Stem cells normally reside in the bone marrow, but can be mobilized from the bone marrow into the peripheral blood stream. (D.I. 81 at 79:17-80:2, 170:16-23.) Stem cells express CD34 receptors, which are specific "site[s] or structure[s]" on stem cells that "combine[] with a drug or other biological to produce a specific alteration of cell function." *Receptor*, McGraw-Hill Dictionary of Scientific and Technical Terms (6th ed. 2003); (D.I. 81 at 82:14-83:5.) The presence of stem cells in the blood can be determined by testing for the CD34 marker that is present on the surface of the stem cells. (D.I. 81 at 82:22-24.)

5. Stem cell transplantation is a procedure used in the treatment of patients having certain blood cancers, such as non-Hodgkin's lymphoma and multiple myeloma. (D.I. 81 at 78:3-79:13.) Since before September 2000, the procedure has been used to help cancer patients (D.I. 81 at 82:8-10), and it can alleviate the negative side effects they experience due to intense chemotherapy and radiation therapy (D.I. 81 at 78:22-82:7). It involves "harvesting" stem cells from a cancer patient before a chemo- or radiation therapy session and then transplanting those cells back into the patient's blood stream after therapy. (D.I. 81 at 78:22-82:7.) "Mobilizing" stem cells from the bone marrow into the peripheral blood and then collecting or harvesting them from the body for future use is key to the success of the procedure. (D.I. 81 at 79:17-80:19, 170:16-23; D.I. 83 at 607:2-4.) Mobilizing regimens, which are combinations of chemical agents that can induce stem cell mobilization, are used to increase the number of stem cells in the blood to an amount sufficient to conduct a stem cell transplantation procedure. (D.I. 95 at

DDX-008; DTX-214 at 5; D.I. 81 at 90:20-93:10; D.I. 83 at 647:18-25; *see also, e.g.*, JTX-009 at 2.)

6. Harvested stem cells are stored while the patient undergoes chemotherapy or radiation therapy that simultaneously destroys both cancerous cells and healthy cells. (D.I. 81 at 80:20-81:6.) As just noted, after the therapy is completed, the harvested stem cells are then transplanted back into the patient, where they repopulate the bone marrow with healthy cells. (D.I. 81 at 81:7-82:7.) During stem cell transplantation, the stem cells "home" from the peripheral blood back to the bone marrow, and, ideally, they then "engraft" in the marrow by interacting with the bone marrow cells, proliferating, and producing progeny. (D.I. 81 at 81:7-22, 173:6-9.) Engraftment is essential to reconstituting the hematopoietic and immune systems in patients after transplantation. (D.I. 81 at 81:7-82:7, 112:24-113:17, 157:17-25; D.I. 83 at 753:11-19.) But if not enough stem cells are mobilized or harvested, stem cell transplantation cannot be performed on a patient. (D.I. 83 at 647:18-25, 649:12-20.) A successful stem cell transplantation requires successful mobilization, successful homing, and successful engraftment. (D.I. 84 at 743:11-744:11.)[5]

7. By September 2000, harvesting stem cells was a conventional procedure. (D.I. 81 at 80:5-19, 82:11-13; D.I. 83 at 628:23-629:13; D.I. 88 at ¶ 169; D.I. 100 at 37.) One method of harvesting them is known as apheresis. (D.I. 81 at 80:3-19.) During apheresis, the patient's blood is processed through a machine that concentrates the stem

[5] The transcript for Day 4 of the bench trial indicates that the proceedings occurred on Wednesday, April 21, 2018. That is a typographical error; the proceedings were on Wednesday, April 11, 2018.

cells and separates them from the other blood cells. (D.I. 81 at 80:3-19.) The non-stem cell fraction is reinfused into the patient, while the stem cells are retained outside the body. (D.I. 81 at 80:3-19.) The process of apheresis was known before September 2000. (D.I. 81 at 82:11-13.)

8. By September 2000, people researching in the field of blood chemistry had reported that the migration of stem cells out of (*i.e.*, mobilization) and into (*i.e.*, homing) the bone marrow might involve similar chemical actors. (DTX-214; D.I. 81 at 86:13-88:6.) Specifically, a person of ordinary skill in the art in September 2000 would have known of the theory that stem cell mobilization and homing "are likely to be 'mirror images' of each other, differentially utilizing similar classes of molecules and receptors" to achieve those respective ends. (DTX-214 at 6; *see also* D.I. 81 at 87:20-88:10; D.I. 83 at 697:24-698:17; D.I. 95 at DDX-116.) While uncertainty remained in understanding the complete, complex mechanisms supporting mobilization and homing, by September 2000, the hypothesis that those processes mirrored each other was known in the art.[6] (D.I. 83 at 578:12-578:17, 697:24-698:17.)

D. The Patents-In-Suit

9. Genzyme is the owner of the '102 and '590 Patents, which are listed in the United States Food & Drug Administration's ("FDA") publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") as being applicable to Genzyme's MOZOBIL® drug product. (D.I. 71, App. A at ¶ 5.) Sanofi is

[6] It is unnecessary to decide, and thus I do not make a finding with respect to, whether that "mirror image" hypothesis remains valid.

the exclusive licensee of the '102 Patent and the '590 Patent. (D.I. 71, App. A at ¶ 5.) The patent application that matured into the '102 Patent was U.S. Application No. 10/209,001 ("the '001 Application"), filed on July 30, 2002. (D.I. 71, App. A at ¶ 6.) The '102 Patent claims priority to U.S. Provisional Application 60/309,196 ("the '196 Application"), filed on July 31, 2001, and U.S. Provisional Application 60/382,155 ("the '155 Application"), filed on May 20, 2002. (D.I. 71, App. A at ¶ 6.) The '102 Patent, which, as already mentioned, is 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. (D.I. 71, App. A at ¶ 7.) The rights to the invention claimed in the '102 Patent were assigned by the inventors to AnorMED, Inc., which then assigned the rights to AnorMED Corp., which later assigned those rights to Genzyme in 2008. (D.I. 71, App. A at ¶ 8.) Including patent term adjustment, the '102 Patent will expire on July 22, 2023. (D.I. 71, App. A at ¶ 9.)

10. The application resulting in the '590 Patent, U.S. Application No. 11/841,837, filed on August 20, 2007, and is a continuation of U.S. Application No. 11/446,390, filed on June 2, 2006 (now abandoned), which is a divisional of U.S. Application No. 11/269,773, filed on November 8, 2005, which is a divisional of the '001 Application, filed on July 30, 2002, that matured into the '102 Patent, which claims priority to the '196 Application and to the '155 Application. (D.I. 71, App. A at ¶ 10.) The '590 Patent is also entitled "Methods to Mobilize Progenitor/Stem Cells." (D.I. 71, App. A at ¶ 11.) It 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. (D.I. 71, App. A at ¶ 11.) The rights to the invention claimed in the '590 Patent were assigned from the inventors to AnorMED, Inc., which assigned those rights to AnorMED Corp., which, again, assigned those rights to Genzyme in 2008. (D.I. 71, App. A at ¶ 12.) Including patent term adjustment, the '590 Patent will expire on July 22, 2023. (D.I. 71, App. A at ¶ 13.)

1. The Asserted Claims

11. The only claims at issue in this case are Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent. (D.I. 71, App. A at ¶¶ 14-16.)

Claim 8 of the '102 Patent recites (rewritten in independent form):

> 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 or prodrug form 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 by apheresis.

(JTX-002 at 16; *see also* D.I. 71, App. A at ¶ 17.)

Claim 8 of the '590 Patent recites (rewritten in independent form):

> 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.[7]

(JTX-004 at 18; *see also* D.I. 71, App. A at ¶ 18.)

Claim 19 of the '590 Patent recites:

> The method of [C]laim 8 which further comprises administering G-CSF to said subject prior to administering the [plerixafor] or a pharmaceutically acceptable salt thereof.[8]

(JTX-004 at 19; *see also* D.I. 71, App. A at ¶ 19.) Those asserted claims do not specify any threshold quantity of stem cells that must be mobilized to practice the claims. (D.I. 84 at 800:13-16.)

2. The Accused Products

a. *New Drug Application*

12. Genyzme is the holder of New Drug Application ("NDA") No. 022311, which relates to plerixafor solution 20 mg/mL for subcutaneous injection, marketed as MOZOBIL®. (D.I. 71, App. A at ¶ 26.) Genzyme and Sanofi share in the revenue from the sale of MOZOBIL®. (D.I. 71, App. A at ¶ 26.) On December 15, 2018, the FDA approved the plerixafor solution 20 mg/mL, as described in NDA No. 022311, for use in combination with G-CSF for mobilizing hematopoietic stem cells to the peripheral blood

[7] The only differences between Claim 8 of the '102 Patent and Claim 8 of the '590 Patent appear to be the alternative administration of a pharmaceutically acceptable prodrug form of plerixafor and the specificity that the stem cells must be harvested by apheresis, which are not relevant distinctions in this case. *See infra* FOF ¶ 33.

[8] G-CSF is a cytokine or protein that interacts with blood cells. (D.I. 71, App. A at ¶ 27; D.I. 81 at 88:22-89:10.)

for collection and subsequent autologous transplantation[9] in patients with non-Hodgkin's lymphoma and multiple myeloma. (D.I. 71, App. A at ¶ 27.) The FDA-approved use of MOZOBIL® as a mobilization agent in conjunction with G-CSF is covered by Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent. (D.I. 71, App. A at ¶ 28; D.I. 83 at 645:21-647:5.) 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." (D.I. 71, App. A at ¶ 29.) MOZOBIL® may be administered for "up to 4 consecutive days" at a dose of "0.24 mg/kg actual body weight." (D.I. 71, App. A at ¶ 29.) MOZOBIL® is administered "by subcutaneous injection approximately 11 hours prior to initiation of apheresis." (D.I. 71, App. A at ¶ 29.) Off-label use of MOZOBIL® as a stem cell mobilizing agent without G-CSF is also covered by Claim 8 of the'102 and '590 Patents. (D.I. 83 at 645:21-647:5.)

b. *Zydus's Abbreviated New Drug Application*

13. In December of 2015, Zydus submitted ANDA No. 208980 (the "Zydus ANDA") to the FDA under § 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 suitable for injection as a generic version of Genzyme's MOZOBIL® drug product as described in NDA No. 022311. (D.I. 71, App. A at ¶ 30.) The Zydus ANDA was submitted to obtain FDA approval to engage in the commercial

[9] An autologous transplantation is one in which the patient receives his or her own stem cells. (D.I. 83 at 686:12-15.)

manufacture, use, offer for sale, and/or sale of Zydus's plerixafor ANDA injection product ("Zydus's ANDA Product") prior to the expiration of the '102 and '590 Patents. (D.I. 71, App. A at ¶ 31.) Zydus's ANDA Product is a generic version of MOZOBIL®. (D.I. 71, App. A at ¶ 33.)

14. Zydus's ANDA Product is a pharmaceutical composition indicated in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. (D.I. 71, App. A at ¶ 47.) Exactly as with MOZOBIL®, the labeling for Zydus's ANDA product states that treatment with the product is to begin "after the patient has received G-CSF once daily for 4 days," and is to be administered "approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days" at a dose of "0.24 mg/kg body weight" by subcutaneous injection. (D.I. 71, App. A at ¶ 48.)

15. Zydus's ANDA was submitted with Paragraph IV certifications with respect to the '102 and '590 Patents. (D.I. 71, App. A at ¶ 32.) By letter dated May 17, 2016, which was received by Genzyme on May 18, 2016, and included the Paragraph IV certifications, Zydus notified Genzyme that Zydus had submitted its ANDA to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act. (D.I. 71, App. A at ¶ 33.) Plaintiffs then sued Zydus for infringing the '102 and '590 Patents. (D.I. 71, App. A at ¶ 36.)

E. Conception of the Claimed Subject Matter of the '102 and '590 Patents

16. Conception. The named inventors first synthesized plerixafor in 1991 using a known method published by an academic group that had previously made the molecule. (PTX-211; D.I. 82 at 307:3-308:14.) They were interested in it as an HIV treatment. (D.I. 82 at 306:9-307:5.) AnorMED's first clinical study of plerixafor, which is referred to as the 98-01 study, was a Phase I trial in healthy volunteers to test the safety and pharmacology of plerixafor to confirm that it was suitable for advancement into Phase II testing in HIV patients. (D.I. 312:20-314:15.) It was during that trial study that AnorMED observed an increase in the white blood cell count in all subjects. (DTX-109 at 3; D.I. 82 at 313:23-314:21; D.I. 435:8-12.) AnorMED originally hypothesized that the most likely cause of the increased white blood cell count was demargination, which is the release of cells from the endothelial lining of blood vessels. (D.I. 82 at 334:11-23, 337:4-7, 413:6-18, 436:2-10.) But, by October 9, 1999, it was also hypothesizing that the white blood cells may have been mobilized from the bone marrow. (DTX-109 at 5; JTX-064 at 1-2, 9; D.I. 82 at 318:17-319:19, 435:13-437:13.)

17. While still focused on HIV, AnorMED began discussing other possible clinical uses for plerixafor. (D.I. 82 at 314:16-315:9, 454:1-15.) A "Food for Thought" presentation from October 9, 1999, which was shared among the leading researchers at AnorMED, discussed the potential use of plerixafor both alone and with G-CSF to mobilize and harvest stem cells for transplantation. (JTX-064 at 1, 9-12; D.I. 82 at 319:20-320:4, 321:4-322:20, 323:2-22, 325:8-328:6, 328:19-329:21, 330:23-331:16, 444:11-446:21.) In late 1999, AnorMED approached Dr. Paul Kubes at the University of

Calgary about determining whether plerixafor was causing demargination. (D.I. 82 at 336:11-17, 337:1-13.) As a result of Dr. Kubes's final report in May 2000, demargination was ruled out as the cause of the white blood cell elevation.[10] (JTX-072 at 2-3; D.I. 82 at 337:14-20, 412:23-413:18.)

18. In December 1999, AnorMED approached Dr. Dale, one of the inventors later credited on the '102 and '590 Patents and a hematologist at the University of Washington with expertise in neutrophils and stem cells. (JTX-002 at 1; JTX-004 at 1; D.I. 82 at 336:18-23.) AnorMED wanted to discuss the possibility of conducting another clinical study of plerixafor in healthy volunteers. (D.I. 82 at 336:18-23, 337:21-338:10, 338:23-339:20; D.I. 83 at 490:16-492:4, 493:3-494:19.) By June 2000, AnorMED had decided to pursue such a clinical trial to determine if plerixafor mobilized stem cells. (JTX-061I; D.I. 82 at 338:23-339:20; D.I. 83 at 496:1-499:10.) Dr. Dale drafted a Human Study application and an accompanying protocol for a Phase I trial to administer plerixafor to healthy volunteers to determine whether plerixafor would mobilize hematopoietic progenitor cells into the blood. (JTX-061H; PTX-874 at 4, 8; PTX-875 at 1, 3-5; D.I. 83 at 500:5-502:13, 506:15-507:3, 513:21-514:3, 514:10-515:2, 515:23-516:11, 517:12-18.) That draft application noted that mobilization and harvesting of progenitor cells is a common practice for stem cell transplantation in connection with intensive chemotherapy for cancer. (PTX-874 at 8; D.I. 83 at 507:4-509:2.) Dr. Dale signed the Human Study application on August 10, 2000, and it was received by the

[10] Dr. Kubes's study did not address whether plerixafor was mobilizing stem cells and his data was not publicly available. (D.I. 82 at 338:7-10, 338:18-22, 414:14-18.)

University's Investigational Review Board by August 18, 2000. (PTX-796 at 2; D.I. 83 at 502:1-13, 513:1-17.)

19. In May 2000, AnorMED approached Dr. Broxmeyer, another inventor listed on the '102 and '590 Patents and a recognized expert in the field of progenitor cell studies. (JTX-002 at 1; JTX-004 at 1; D.I. 82 at 336:18-25, 340:2-15, 456:6-11.) AnorMED wanted him to perform in vivo animal studies to determine if plerixafor was mobilizing stem cells. (D.I. 82 at 340:16-21.) In June 2000, Dr. Broxmeyer submitted a Compound Request Form to AnorMED requesting plerixafor for the purpose of administering it to mice, alone and after G-CSF treatment, to determine whether plerixafor mobilized stem cells into the blood. (JTX-008 at 1, 3; JTX-061I; Broxmeyer Dep. Tr. Direct Q4, 6-8, 11, 13, 15, 17, 19; D.I. 82 at 402:16-403:2, 421:24-422:20, D.I. 83 at 497:8-499:10, 631:20-634:17, 636:5-638:3.) In that request, Dr. Broxmeyer also proposed harvesting any mobilized cells using a density cut procedure.[11] (JTX-008 at 3; Broxmeyer Dep. Tr. Direct Q20-23; D.I. 83 at 639:11-640:12.)

20. By September 2000, the named inventors had a reasonable expectation that plerixafor, either alone or in combination with G-CSF, would mobilize stem cells. In March 2000, Dr. Dale agreed with Dr. MacFarland's prediction that plerixafor could block the interaction between stromal cell-derived factor 1 ("SDF-1") and C-X-C chemokine receptor type 4 ("CXCR4") and lead to elevated levels of stem cells in the

[11] A density cut procedure is a method of harvesting stem cells that involves separating the low density blood cells rich in progenitor and stem cells from the higher density blood cells. (D.I. 83 at 640:7-12.)

peripheral blood.[12] (JTX-061B at 1; *see also* D.I. 83 at 538:13-539:7.) Dr. Dale testified that he expected to mobilize some stem cells using plerixafor and even more stem cells using G-CSF and plerixafor together. (D.I. 83 at 560:24-562:11; *see also* D.I. 83 at 514:15-515:22.) Moreover, Dr. Henson predicted that plerixafor, because of its ability to block CXCR4, would mobilize stem cells, although he was unsure whether those cells would be suitable for homing and engraftment. (D.I. 83 at 451:16-22.)

21. Drs. Bridger, Abrams, Henson, MacFarland, Calandra, Dale, and Broxmeyer all participated in preparing a protocol for a Phase I clinical trial (referred to as AMD3100-1002) in healthy volunteers to determine whether plerixafor mobilized stem cells. (JTX-067 at 1, 8-9; D.I. 71, App. A at ¶ 53; D.I. 82 at 415:3-5, 415:8-13, 416:3-21; D.I. 83 at 631:20-634:17.) Version 1.1 of the AMD3100-1002 protocol is dated September 27, 2000. (JTX-067 at 1; D.I. 71, App. A at ¶ 54.) One of the aims of the AMD3100-1002 study, among other things, was to test whether administration of plerixafor could mobilize stem cells, which could then be harvested for stem cell transplantation.[13] (JTX-067 at 7-8; D.I. 82 at 346:11-347:10, 419:14-420:14.) That protocol called for stem cells to be detected using tests generally used by transplanters. (JTX-067 at 7-8, 19-20; D.I. 82 at 416:22-417:17, 419:9-23; D.I. 83 at 522:10-523:19.) Mobilized stem cells were to be harvested using a density cut procedure. (JTX-008 at 3;

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[12] *See infra* FOF ¶¶ 70, 79-92 for a detailed discussion of the interaction between SDF-1 and CXCR4.

[13] Harvesting by apheresis was not part of the study because apheresis was a standard procedure for harvesting stem cells and the inventors knew, through prior work with G-CSF, the threshold number of stem cells needed to achieve a successful harvest. (D.I. 81 at 82:11-13; D.I. 83 at 508:17-511:13, 629:15-630:5, 705:15-18.)

Broxmeyer Dep. Tr. Direct Q16-17, 19; D.I. 83 at 629:4-630:5, 639:11-640:12; D.I. 84 at 797:9-24.)

22. Another version of the protocol followed. Version 1.2 of the AMD3100-1002 protocol is dated October 16, 2000. (D.I. 71, App. A at ¶ 55.) AnorMED submitted that version of the clinical study protocol to the FDA. (JTX-037 at 1-5; D.I. 82 at 343:17-344:20; D.I. 83 at 635:24-636:4.) Insofar as Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent are implicated, there are no substantive differences between Version 1.1 and Version 1.2 of the AMD3100-1002 protocol. (D.I. 71, App. A at ¶ 56.) Version 1.2 of the AMD3100-1002 protocol included the same administration of plerixafor, the same test endpoints, the same purpose, and the same consideration of transplantation as Version 1.1 of the protocol. (*Compare* JTX-037 at 11, 15-16, 25-26, *with* JTX-067 at 7-9, 18-20; *see also* D.I. 82 at 344:21-346:10, 346:24-348:11; D.I. 83 at 634:18-635:9.)

23. Reduction to Practice. There is no dispute that the named inventors diligently reduced the invention to practice following conception. (D.I. 88 at ¶ 28; D.I. 100 at 5.) In the spring of 2001, Dr. Broxmeyer reported to AnorMED that his mouse studies demonstrated that plerixafor alone mobilized stem cells and that plerixafor mobilized an even greater number of stem cells when combined with G-CSF. (JTX-007; JTX-028; JTX-056; JTX-057; JTX-058; Broxmeyer Dep. Tr. Direct Q16, 28, 31-39, 41, 43-48, 50, 52-60, 62-63, 65-66; Broxmeyer Dep. Tr. Cross Q13; D.I. 82 at 342:13-343:10, 352:9-353:10, 354:17-356:2, 360:24-362:2.) By May 2001, AnorMED received data on the first five subjects in the AMD3100-1002 clinical trial, which showed that

plerixafor mobilized stem cells. (JTX-007; JTX-008; JTX-015 at 10; JTX-027; JTX-028 at 2; JTX-057; JTX-058; Broxmeyer Dep. Tr. Direct Q16-17, 19, 31, 33-35, 43-47, 52-59; D.I. 82 at 349:7-18, 350:6-351:16, 359:13-362:2; D.I. 83 at 527:8-19.) On July 31, 2001, AnorMED filed its first stem cell mobilization patent application. (JTX-004 at 1; D.I. 71, App. A at ¶¶ 6, 10; D.I. 82 at 362:7-22.) The results from Dr. Dale's human volunteer study are included in Tables 3 and 4 of the '102 and '590 Patents. (JTX-002 at 13; JTX-004 at 14-15; D.I. 83 at 525:15-526:19.) The results of Dr. Broxmeyer's mouse studies are reported in Figure 1 and Tables 1-3, 6, 7, and 9-12 of the '102 and '590 Patents. (JTX-002 at 2, 12-15; JTX-004 at 4, 14-17; Broxmeyer Dep. Tr. Cross Q23; D.I. 83 at 526:20-527:7, 527:20-528:14.)

24. Following the positive results of the AMD3100-1002 study, AnorMED continued developing plerixafor for use as a stem cell mobilizer. (JTX-033 at 32, 34, 36; D.I. 82 at 363:14-24, 364:6-13, 364:20-367:12, 368:13-369:15, 369:22-371:4.) No significant obstacles or issues arose during the Phase II and Phase III clinical trials of plerixafor leading to FDA approval. (D.I. 82 at 372:8-11, 420:16-25.)

F. Procedural History

1. Previous MOZOBIL® Litigations

25. In 2013, Plaintiffs sued Dr. Reddy's Laboratories Ltd. and Dr. Reddy's Laboratories Inc. (collectively, "DRL"), Sandoz Inc., and Teva Pharmaceuticals USA, Inc., for infringement of the '102 Patent, the '590 Patent, and U.S. Patent No. RE42,152

("the '152 Patent").[14] *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, Nos. 13-1506, 13-1507, & 13-1508 (consolidated) (the "Prior Related MOZOBIL® Litigations"). (D.I. 71, App. A at ¶ 94.) In those consolidated cases, Plaintiffs and Sandoz stipulated to the dismissal of the parties' claims and counterclaims. (D.I. 71, App. A at ¶ 95.) Plaintiffs, DRL, and Teva stipulated that DRL and Teva infringed Claim 19 of the '590 Patent to the extent the claim is valid and enforceable, and Plaintiffs, DRL, and Teva dismissed their claims and counterclaims as to the other asserted claims of the '102, '152, and '590 Patents. (D.I. 71, App. A at ¶ 96.)

26. On May 11, 2016, following a bench trial at which another judge skillfully presided, this Court concluded that Claim 19 of the '590 Patent was not invalid. *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, Nos. 13-1506 & 13-1508, 2016 WL 2757689 (D. Del. May 11, 2016) (Sleet, J.). (D.I. 71, App. A at ¶ 97.) DRL and Teva appealed that judgment to the United States Court of Appeals for the Federal Circuit, and, on December 18, 2017, the Federal Circuit affirmed. *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, 716 F. App'x 1006 (Fed. Cir. 2017). (D.I. 71, App. A at ¶¶ 98-99.)

27. Zydus became aware of this Court's judgment in the Prior Related MOZOBIL® Litigation no later than May 16, 2016, before Zydus mailed its letter dated

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[14] The '131 Patent, which Plaintiffs own, reissued as the '152 Patent on February 15, 2011. (D.I. 89 at ¶ 8; D.I. 98 at 1.) The '152 Patent is another patent listed in the Orange Book as being applicable to MOZOBIL®. (D.I. 71, App. A at ¶ 34.) Including patent term adjustment, it will expire on December 10, 2018. (D.I. 71, App. A at ¶ 35.) The Zydus ANDA was submitted with a Paragraph III certification with respect to the '152 Patent. (D.I. 71, App. A at ¶ 34.) Zydus has requested that the FDA approve the Zydus ANDA after the expiration of that patent. (D.I. 71, App. A at ¶ 35.) Thus, the '152 Patent is not at issue in this case.

May 17, 2016, to Genzyme, which purported to be notice pursuant to 21 U.S.C. § 355(j)(2)(B).[15] (D.I. 71, App. A at ¶¶ 99-100.) As of December 2016, Zydus knew that third parties were expecting "the district court's previous decision … [in the Prior Related MOZOBIL® Litigation to] … be upheld on appeal[.]" (PTX-673 at 12; *see also* D.I. 82 at 471:4-472:23.)

2. The Current Litigation

28. Plaintiffs filed suit against Zydus on June 29, 2016, alleging infringement of the '102 and '590 Patents. (D.I. 1; D.I. 71, App. A at ¶ 36.) The lawsuit was filed within forty-five days of receiving Zydus's May 17, 2016, notice letter. (D.I. 71, App. A at ¶ 33.) November 18, 2018, is the thirty-month stay deadline, after which the FDA may make its approval of the Zydus ANDA effective, subject to potential court-ordered adjustment. (D.I. 71, App. A at ¶ 4); *see* 21 U.S.C. § 355(j).

29. Plaintiffs alleged that Zydus's submission of the Zydus ANDA to the FDA constitutes infringement of one or more claims of the '102 Patent, including, but not limited to, Claims 1-8, 12-13, 15-16, and 21-22, as well as one or more claims of the '590 Patent, including, but not limited to, Claims 1-8, 16-19, and 21-22, under 35 U.S.C. § 271(e)(2)(A). (D.I. 71, App. A at ¶¶ 37, 39.) They also alleged that, upon FDA approval, Zydus's commercial manufacture, importation, use, offer to sell, or sale of its

[15] That notice is required by statute to be given by the applicant to "each owner of the patent that is the subject of [a certification challenging the validity of the patent] … and … the holder of the [FDA-]approved application … for the drug that is claimed by the patent or a use of which is claimed by the patent[.]" 21 U.S.C. § 355(j)(2)(B)(iii). The notice is meant to inform those intended recipients of the abbreviated new drug application and "the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." *Id.* § 355(j)(2)(B)(iv).

plerixafor ANDA injection product in/into the United States prior to the expiration of the '102 and '590 Patents would infringe those same claims under 35 U.S.C. § 271(a), (b), and/or (c). (D.I. 71, App. A at ¶¶ 38, 40.)

30. Zydus answered Plaintiffs' complaint on July 20, 2016, pleading noninfringement and invalidity defenses. (D.I. 10 at 7.) It also counterclaimed for a declaration under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, that Zydus's ANDA Product does not infringe any valid claims of the '102 and '590 Patents. (D.I. 10 at 9-10.) It sought declaratory relief under the Declaratory Judgment Act that each claim of the '102 and '590 Patents asserted against it by Plaintiffs is invalid for failure to comply with one or more of the conditions or requirements for patentability under 35 U.S.C. §§ 101-103 and/or 112. (D.I. 10 at 10-12.) Plaintiffs answered those counterclaims on August 15, 2016. (D.I. 14.)

31. On June 30, 2017, the Court entered the parties' stipulation in which Plaintiffs dismissed with prejudice their assertions that Zydus infringed Claims 1-7, 12-13, 15-16, and 21-22 of the '102 Patent and Claims 1-7, 16-18, and 21-22 of the '590 Patent. (D.I. 55; D.I. 71, App. A at ¶ 44.) That left remaining only their allegations that Zydus infringed or would infringe Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent. In that same stipulation entered June 30, 2017, Zydus dismissed with prejudice its counterclaims for declaratory judgment of noninfringement with respect to the '102 and '590 Patents, as well as its counterclaims for declaratory judgment of invalidity with respect to all the claims of the '102 and '590 Patents, except for Claim 8

of the '102 Patent and Claims 8 and 19 of the '590 Patent. (D.I. 55; D.I. 71, App. A at ¶¶ 45-46.)

32. The parties previously stipulated that the submission of the Zydus ANDA infringes Claim 8 of the '102 Patent and 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. (D.I. 71, App. A at ¶ 41.) If Zydus's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed, the use of Zydus's ANDA Product for the indication proposed in the ANDA in the United States would infringe Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent under 35 U.S.C. § 271(a), to the extent those claims are valid and enforceable. (D.I. 71, App. A at ¶ 42.) Additionally, if Zydus's ANDA Product is approved with its current proposed labeling or with labeling substantially identical to that currently proposed, the sale or offer for sale of Zydus's ANDA Product in the United States would infringe Claim 8 of the '102 Patent and 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. (D.I. 71, App. A at ¶ 43.)

33. The parties agreed not to litigate Claim 8 of the '102 Patent in this case, and, instead, agreed that any judgment relating to the validity of Claim 8 of the '590 Patent will apply equally to Claim 8 of the '102 Patent. (D.I. 76, App. A at ¶ 3; D.I. 81 at 5:19-22.) Neither party proposed claim terms for construction, which rendered a Markman hearing unnecessary. (D.I. 23.)

3. Witnesses

34. There are two expert witnesses in this case. Dr. Michael Andreeff, the expert witness retained by Zydus, is a professor of medicine in the Department of Stem Cell Transplantation and Cell Therapy at the University of Texas, MD Anderson Cancer Center. (D.I. 81 at 66:18-21.) He received an M.D. degree from the University of Heidelberg and a Ph.D. in cell biology from the University of Heidelberg Medical School. (D.I. 81 at 66:11-14.) He is an expert in hematology, hematopoiesis, and stem and progenitor cell transplantation. (D.I. 81 at 73:7-12.)

35. Dr. Mohamad Mohty, the expert witness retained by Plaintiffs, is a professor of clinical hematology and head of the Clinical Hematology and Cellular Therapy Department at the Saint-Antoine Hospital of Pierre & Marie Curie University in Paris, France. (D.I. 83 at 568:23-569:16.) He received an M.D. degree from the University of Montpellier in France in 2000, a Ph.D. in 2003, and a Habilitation to Direct Research degree in 2005. (PTX-674A at 1; D.I. 83 at 567:19-568:12.) He is an expert in hematology, stem cell mobilization, and stem cell transplantation. (D.I. 83 at 573:25-574:5.)

36. Plaintiffs also relied upon the testimony of several additional witnesses. Dr. Michael Abrams was the head of biomedical research at Johnson Matthey, and later, for ten years, was the President and CEO of AnorMED, which he co-founded. (D.I. 82 at 305:7-11, 310:22-311:10.) He is a named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1.)

37. Dr. David Dale is a professor of medicine at the University of Washington, where he has accumulated over forty years of work experience as a researcher, clinician, and teacher. (PTX-093; D.I. 83 at 486:20-487:23.) He was among the earliest investigators of G-CSF and its effect on white blood cells, and he worked with AnorMED on its plerixafor project in December 1999. (D.I. 83 at 488:5-491:3.) As already mentioned, Dr. Dale is a named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1.)

38. Dr. Gary Bridger worked at Johnson Matthey until 1996, at which time he became Vice President of Research and Chief Scientific Officer of AnorMED, of which he is another co-founder. (D.I. 82 at 409:20-410:16.) He, too, is a named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1).

39. Dr. Hal Broxmeyer is a Distinguished Professor, Professor of Medicine, and Professor Emeritus of microbiology and immunology at Indiana University. (D.I. 82 at 475:5-7.) Again, he is a named inventor of the '102 and '590 Patents and contributed data to its specification. (JTX-002 at 1; JTX-004 at 1; Broxmeyer Dep. Tr. Cross Q23; D.I. 82 at 475:5-8.)

40. Dr. Gary Calandra was Vice President of Clinical Development at AnorMED starting in September 2000. (D.I. 82 at 452:3-11; D.I. 88 at xii; D.I. 89 at xii.) He, too, is a named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1.)

41. Dr. Geoffrey Henson co-founded AnorMED and served as its Chief Operating Officer from 1996 to 2003. (D.I. 82 at 446:25-447:6; D.I. 88 at xii; D.I. 89 at

xii.) He is also a named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1.)

42. Dr. Ronald MacFarland worked at AnorMED starting in 1998 and was involved in the nonclinical safety side effects and initial clinical studies of plerixafor as a stem cell mobilizing agent. (D.I. 82 at 430:11-20; D.I. 88 at xiii; D.I. 89 at xii.) He is another named inventor of the '102 and '590 Patents. (JTX-002 at 1; JTX-004 at 1.)

43. Mr. Kevin Campbell is Senior Director of U.S. Marketing for Hematology and Transplant at Sanofi. (D.I. 82 at 458:23-459:1; D.I. 88 at xiii; D.I. 89 at xii.)

44. Zydus also relies upon the testimony of one additional witness. Ms. Elizabeth Purcell is Senior Director of Marketing and Portfolio Management at Zydus. (D.I. 82 at 463:13-15; D.I. 89 at xiii.)

G. Asserted Prior Art

1. The Andreeff Letter

45. The document I will be referring to as "the Andreeff Letter" is dated October 5, 2000, which is before the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 57; DTX-029.) It was a private communication from Dr. Andreeff to Dr. Henson at AnorMED; it was not published and was not accessible to the public. (D.I. 71, App. A at ¶¶ 58-59; D.I. 81 at 130:12-20; D.I. 82 at 272:2-10.) In the letter, Dr. Andreeff proposed investigating whether use of plerixafor to block "CXCR4 during mobilization [would] increase the yield of [stem cell] collections, as homing of mobilized [stem cells] back to the marrow stroma is blocked." (DTX-029 at 1; *see also* D.I. 81 at 132:16-21, 291:22-25; D.I. 83 at 733:8-17.) Zydus

concedes that the Andreeff Letter is not prior art if the named inventors conceived of the invention before October 5, 2000. (D.I. 84 at 871:17-872:4.)

2. Other Prior Art References

46. As of July 31, 2000, it was publicly known that CXCR4 is a shorthand designation for C-X-C chemokine receptor type 4 and that SDF-1 is a shorthand designation for stromal cell-derived factor 1. (D.I. 71, App. A at ¶¶ 60-61.) By that time, SDF-1 was the only publicly known natural ligand for CXCR4.[16] (D.I. 71, App. A at ¶ 62.) Moreover, by July 31, 2000, plerixafor had been publicly disclosed as the active compound in a pharmaceutical composition used in anti-HIV clinical trials. (D.I. 71, App. A at ¶ 63.)

47. Konopleva *et al.*, *G-SCF Induces CXCR4 Expression on CD34+38- Peripheral Blood Progenitor Cells In Vivo*, Blood, 94(10) 322b: Abstract 4663 (1999) ("Konopleva"), was published in November 1999, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 64.) Konopleva is an abstract published in advance of the 1999 American Society of Hematology ("ASH") annual meeting. (D.I. 71, App. A at ¶ 65.) Konopleva was selected for "Publication Only," which means that the abstract was published in an abstract book for the 1999 ASH annual meeting, but was not otherwise selected for presentation at the meeting. (D.I. 71, App. A at ¶ 66.) Konopleva is not cited on the face

[16] A ligand is "[t]he molecule, ion, or group bound to the central atom in a chelate or a coordination compound[.]" *Ligand*, McGraw-Hill Dictionary of Scientific and Technical Terms (6th ed. 2003). In this case, it is the molecule, ion, or group that "binds to CXCR4." (D.I. 81 at 84:3-8.)

of either the '102 Patent or the '590 Patent. (D.I. 71, App. A at ¶ 67.) Dr. Andreeff is a co-author of the Konopleva abstract. (DTX-142 at 4; D.I. 81 at 103:19-104:5.)

48. Lapidot et al., A Single Dose of Human G-CSF Inhibited Production of SDF-1 in the Bone Marrow and Upregulated CXCR4 Expression on Immature and Mature Hematopoietic Cells Prior to their Mobilization, Blood, 94(10): 606a, Abstract 2695 (1999) ("Lapidot"), was published in November 1999, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 68.) Lapidot is an abstract published in advance of the 1999 ASH annual meeting. (D.I. 71, App. A at ¶ 69.) Lapidot is not cited on the face of either the '102 Patent or the '590 Patent. (D.I. 71, App. A at ¶ 70.)

49. Hendrix *et al.*, *Pharmacokinetics and Safety of AMD-3100, a Novel Antagonist of the CXCR-4 Chemokine Receptor, in Human Volunteers*, Antimicrobial Agents & Chemotherapy, 44(6):1667-73 (2000) ("Hendrix"), reports results from a clinical trial testing the safety of plerixafor in healthy human volunteers. (D.I. 71, App. A at ¶ 49.) Hendrix reported results from the clinical trial that AnorMED internally identified as Study Number 98-01. (D.I. 71, App. A at ¶ 50.) Hendrix was published in June 2000, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 71.) Hendrix is cited on the face of both the '102 Patent and the '590 Patent. (D.I. 71, App. A at ¶ 72.)

50. MacFarland *et al.*, Methods and Composition to Enhance WBC Count, is a World Intellectual Property Organization ("WO") patent bearing the publication number WO 00/45814 ("WO '814"). (DTX-216; D.I. 71, App. A at ¶ 51.) It describes results

from clinical trials testing plerixafor in humans. (D.I. 71, App. A at ¶ 51.) WO '814 was published on August 10, 2000, prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 73.) WO '814 is cited on the face of both the '102 Patent and the '590 Patent. (D.I. 71, App. A at ¶ 74.)

51. Neupogen® is the brand name under which G-CSF is marketed. (D.I. 81 at 89:11-12.) There was prescribing information for Neupogen® dated April 2, 1998 ("Prescribing Information for Neupogen®"), more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 75.) The Prescribing Information for Neupogen® is not cited on the face of either the '102 Patent or the '590 Patent. (D.I. 71, App. A at ¶ 76.)

52. van Os *et al.*, *The CXCR4 Receptor Antagonist AMD3100 Does Not Prevent Homing and Engraftment of Murine Syngeneic Bone Marrow Cells*, Blood, 96 308(b): Abstract 5074 (2000) ("van Os"), describes results from a study in mice transplanted with either untreated or plerixafor-pre-treated bone marrow cells. (D.I. 71, App. A at ¶ 52.) van Os was published in November 2000, prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 77.) It is an abstract published in advance of the 2000 ASH annual meeting. (D.I. 71, App. A at ¶ 78.) van Os was selected for "Publication Only," which, again, means that the abstract was published in the abstract book for the 2000 ASH annual meeting but was not otherwise selected for presentation at the meeting. (D.I. 71, App. A at ¶ 79.) It is cited on the face of the '590 Patent, but not on the face of the '102 Patent. (D.I. 71, App. A at

¶ 80.) van Os is not prior art, however, if the named inventors conceived of the invention before November 16, 2000. (D.I. 81 at 265:4-18.)

53. 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 $CX34^+$ Progenitors to Peripheral Blood, 185 J. Ex. Med. 111-120 (1997) ("Auiti"), was published on January 1, 1997, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 81.) Auiti is cited on the face of the '590 Patent, but not on the face of the '102 Patent. (D.I. 71, App. A at ¶ 82.)

54. 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"), was published on June 15, 1998, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 83.) Möhle is not cited on the face of either the '102 Patent or the '590 Patent. (D.I. 71, App. A at ¶ 84.)

55. Peled *et al.*, *Dependence of Human Stem Cell Engraftment and Repopulation of NOD/SCID Mice on CXCR4*, Science 283:845-848 (1999) ("Peled"), was published on February 5, 1999, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 85.) Peled is cited on the face of the '590 Patent, but not the '102 Patent. (D.I. 71, App. A at ¶ 86.)

56. Whetton *et al.*, *Homing and* Mobilization *in the Stem Cell Niche*, Cell Biology, 9:233-238 (1999) ("Whetton"), was published in 1999, more than one year prior to the earliest U.S. filing date to which the '102 and '590 Patents claim priority. (D.I. 71, App. A at ¶ 87.) Whetton is not cited on the face of either the '102 Patent or the '590 Patent. (D.I. 71, App. A at ¶ 88.)

H. Level of Ordinary Skill in the Art

57. Plaintiffs contend that a person of ordinary skill in the art with respect to the patents-in-suit at the time of the claimed invention would have held a Ph.D. in cellular molecular biology, with several years of post-doctoral experience in the science of stem cell biology or hematopoiesis, or would have held an M.D. with an interest in the science of stem cell transplantation and with several years of training in stem cell transplantation, or would have held both. (D.I. 83 at 574:9-18; D.I. 88 at ¶ 6; D.I. 98 at ¶ 12.)

58. Zydus asserts that a person of ordinary skill in the art at the time of the claimed invention would have possessed a Ph.D. in cellular biology, molecular biology, immunology, or a related field with at least two or three years of experience in the science of stem cell biology or hematopoiesis, and/or an M.D. with an interest in the science of stem cell transplantation, with two to three years of experience in stem cell transplantation. (D.I. 81 at 76:2-14; D.I. 89 at ¶ 12.) Furthermore, such a person would have an appreciation of the commercial development of pharmacological products and would have worked or collaborated with others. (D.I. 81 at 76:2-14; D.I. 89 at ¶ 12.)

59. The opinions of Dr. Andreeff and Dr. Mohty regarding what would be known by one of ordinary skill in the art are unaffected by how I define the person of ordinary skill in the art. (D.I. 81 at 77:22-25; D.I. 83 at 575:3-7.)

60. I find that a person of ordinary skill in the art at the time of the claimed invention would have held (i) a Ph.D. in cellular biology, molecular biology, immunology, or a related field, with at least two years of experience in the science of stem cell biology or hematopoiesis, or (ii) an M.D. with an interest in the science of stem cell transplantation and at least two years of experience in stem cell transplantation, or (iii) both. (D.I. 81 at 76:2-11; D.I. 88 at ¶ 6; D.I. 89 at ¶ 12.) Both Dr. Andreeff and Dr. Mohty qualify under that definition as persons of at least ordinary skill in the art and have an understanding of what would be known by such a person during the relevant time. (D.I. 81 at 76:22-24; D.I. 83 at 575:8-14.)

I. Facts Bearing on the Patentability of the Asserted Claims

1. The Need for a Stem Cell Mobilizer Better Than G-CSF

61. In September 2000, the cytokine G-CSF was considered the "gold standard" stem cell mobilizing agent. (D.I. 81 at 109:3-20; D.I. 84 at 734:7-12.) It has been an FDA-approved stem cell mobilizer since December 1995. (DTX-025 at 24; PTX-649 at 1; D.I. 83 at 700:25-701:7.) Despite having had that "gold standard" status, G-CSF has its limitations. A person of ordinary skill in the art would have known that G-CSF acts slowly in mobilizing stem cells, and that it must be administered for a number of days before performing apheresis. (DTX-025 at 24; D.I. 81 at 91:1-10; D.I. 83 at 705:8-11.) Additional shortcomings of G-CSF included its inability to work effectively

in all subjects, the need for multiple doses before mobilization, and the need for many patients to undergo multiple apheresis sessions to achieve the minimum number of stem cells required for a stem cell transplant. (JTX-009 at 2; D.I. 81 at 95:5-18, 150:9-151:10.) As a result, Dr. Andreeff and Dr. Mohty agree that a person of ordinary skill in the art would have seen a need for a stem cell mobilizing regimen that, with minimal toxicity, could mobilize a greater number of stem cells in fewer apheresis sessions than the existing mobilizing agents, including G-CSF. (D.I. 81 at 95:5-18, 150:9-151:10; D.I. 83 at 647:18-648:18, 651:16-652:9.)

62. That need had been identified by September 2000. (D.I. 81 at 218:14-220:16; D.I. 83 at 652:1-7; JTX-009 at 2.) In fact, a person of ordinary skill in the art would have recognized the need to improve upon G-CSF by at least 1994. There was an increase in the use of peripheral blood stem cell transplantation in the early 1990s (PTX-649; PTX-977 at 3), and there may have been off-label use of G-CSF to mobilize stem cells before Neupogen® was approved by the FDA in December 1995 (D.I. 83 at 653:20-654:21). Dr. Mohty testified that "the need started very early" for a better stem cell mobilizing agent than G-CSF (D.I. 83 at 656:23-657:7), and that is confirmed by prior art references showing that researchers had begun studying other potential stem cell mobilizers by 1994 (*see, e.g.*, DTX-070 at 4-6, 10 (discussing research of stem cell mobilization regimens involving cyclophosphamide, GM-CSF, IL-3, PIXY321, SCF, and flk2/flt3 protein, with reference to SCF and PIXY321 studies as early as 1994)).

63. The need for an improved mobilizing agent existed across all populations, which included subjects who did not mobilize stem cells (the non-mobilizable patients),[17] those who did not mobilize an optimal number of stem cells for transplantation (the hard-to-mobilize patients), and those who readily mobilized at least the minimum number of stem cells necessary for transplantation (the easy-to-mobilize patients). (PTX-404 at 1; D.I. 83 at 649:9-651:3.) The need within the non-mobilizing and hard-to-mobilize populations was particularly urgent because patients in those groups did not have other therapeutic options; it was a matter of life and death. (D.I. 83 at 649:12-650:1.) One researcher stated that "[a] conservative estimate of the number of patients who failed mobilization annually [prior to plerixafor] … is 5000-10[,]000 each year. Poor mobilization has significant consequences for the patient with potential loss of the transplant as a treatment option." (JTX-053 at 1.) Approximately 15-25% of patients were known not to mobilize enough stem cells with G-CSF alone to complete a successful stem cell transplantation. (D.I. 81 at 91:20-92:4; D.I. 82 at 325:20-326:19.)

64. Experts in the field also recognized the desirability of mobilizing a higher, optimal level of stem cells. (JTX-009 at 2-3; DTX-070 at 1.) The mobilization of more stem cells during the transplantation process has many significant benefits for patients,

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[17] Although there is evidence in the record suggesting that non-mobilizers may be able to mobilize some number of stem cells (*see* PTX-404 at 1 ("The non-mobilizable patient: a patient who, after repeated aphereses, does not reach the minimum cell dose of 1 x 10^6 $CD34^+$/kg.")), I think that is consistent with Dr. Mohty's characterization of non-mobilizers as those who are "not able to mobilize stem cells" and are thus unable to proceed with a stem cell transplantation (D.I. 83 at 649:12-650:1). I interpret the "minimum cell dose" to be a negligible number that effectively represents an inability to mobilize stem cells under the circumstances.

including faster hematopoietic recoveries, shorter hospitalizations, fewer blood transfusions, reduced use of antibiotics, and diminished rates of infection. (D.I. 83 at 649:12-650:12, 664:4-665:6.) It also results in fewer apheresis sessions, which improves the quality of life for the patients and benefits the healthcare system by freeing up apheresis machines for other patients' use. (D.I. 83 at 650:23-651:11, 664:4-665:6.) Chemical agents that could mobilize more stem cells than the prior art agents might allow the hard-to-mobilize and non-mobilizer populations to reach the optimal number of stem cells, and allow the collection of enough stem cells in the easy-to-mobilize population to perform two transplants. (D.I. 83 at 649:12-650:22; PTX-236 at 6.)

65. I find that the need for new mobilizing agents with minimal toxicity was important for all patients, especially in light of the toxicity or negative side effects of other mobilizing agents that were in use or had been tested. (D.I. 81 at 207:23-208:8, 209:4-11; D.I. 83 at 651:12-652:09, 658:18-659:7; JTX-023 at 7; PTX-232 at 1; PTX-677 at 6.)

2. Failed Efforts in the Art

66. Before September 2000, more than a dozen candidates had been investigated during the search for a stem cell mobilizer that was better than existing agents. (D.I. 81 at 206:4-11, 207:23-216:22; D.I. 83 at 641:21-642:9, 644:4-13.) Like G-CSF, most of those candidates were cytokines or growth factors. (D.I. 83 at 641:21-642:6, 657:8-23, 658:10-12; DTX-190 at 15.) Although some investigators looked to antibodies and other molecules, many turned to cytokines or growth factors because, as

Dr. Mohty explained, there is a tendency "to rely on something that worked." (D.I. 83 at 657:8-658:12.)

67. Those investigations into other chemical agents spanned nearly a decade. The alternatives to G-CSF that were tested included granulocyte-macrophage colony-stimulating factor ("GM-CSF"), stem cell factor ("SCF"), flk2/flt3 ligand, interleukin-1 ("IL-1"), interleukin-3 ("IL-3"), interleukin-6 ("IL-6"), interleukin-8 ("IL-8"), PIXY321 – a GM-CSF/IL-3 fusion protein, macrophage inflammatory protein-1α ("MIP-1α"), anti-VLA-4 antibodies, anti-LFA-1 antibodies, and anti-CD44 antibodies. All of them either failed to demonstrate sufficient clinical efficacy, or exhibited undesirable side effects, or both.[18] (JTX-009 at 1-2; JTX-023 at 7; PTX-232 at 1; PTX-415 at 2-6; PTX-619; DTX-070 at 6; D.I. 81 at 207:23-216:22; D.I. 83 at 640:16-22, 641:11-642:9, 644:4-13, 653:2-18, 656:23-659:7.) Many of those failures were well documented in the literature by September 2000. (JTX-023 at 7; JTX-009 at 2.) Dr. Andreeff admitted that a person of ordinary skill in the art would have been well aware of those failures by September 2000.[19] (D.I. 81 at 206:4-7.)

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[18] Zydus disputes "that there is evidence of all the cited agent's clinical efficacy or undesirable side effects[.]" (D.I. 100 at 11.) The evidence demonstrates, however, that all of those stem cell mobilizing agent candidates were considered and tested before September 2000, and ultimately none (other than GM-CSF) was approved by the FDA.

[19] Zydus argues against the finding that the potential mobilizing agents "failed" because, as Zydus defines success, those agents all succeeded in mobilizing stem cells or progenitor cells in amounts that could be harvested. (D.I. 100 at 10-11; D.I. 84 at 801:18-803:8.) Zydus is correct that, technically and by definition, a stem cell mobilizer succeeds in some sense if it is capable of mobilizing stem cells in any amount. But the success a person of ordinary skill in the art would care about in this case is clinical success compared to G-CSF. (*See supra* FOF ¶¶ 61-65 (framing the need as one for a

3. The Mechanisms of Stem Cell Mobilization Were Poorly Understood

68. As of September 2000, there was uncertainty and unanswered questions about the mechanisms of stem cell mobilization. (D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2.) The mechanisms were described as "poorly understood" and "unclear." (DTX-148 at 4; DTX-214 at 5; *see also* D.I. 81 at 197:9-16.) Dr. Andreeff acknowledged that, while "we are … starting to understand parts of these systems[,]" the complexity in the field of stem cell mobilization remained "enormous" (D.I. 81 at 203:6-205:10), and Dr. Mohty agreed (D.I. 83 at 575:20-576:3).

69. Dr. Andreeff acknowledged that the best way to gauge the state of the art as of September 2000, including the level of uncertainty, is to look at the literature that existed as of and before September 2000. (D.I. 81 at 174:8-20.) The literature in the record reflects significant uncertainty in and leading up to 2000 about the mechanisms for stem cell mobilization. In 1997, in what Dr. Andreeff described as "a very important publication" (D.I. 81 at 115:5-13), Auiti reported that "[t]he mechanisms and specific molecules involved in the experimental mobilization" of stem cells from the bone marrow into the peripheral blood is "still unclear" (DTX-012 at 1). In 1999, the same author again reported that "little is known about the mechanisms and molecules that regulate the homing, retention, and emigration of progenitor cells in hematopoietic

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stem cell mobilizer better than G-CSF).) Given that the search was for a stem cell mobilizer that *improved* upon G-CSF, there is little reason to think an investigator would have found "success" in testing an agent that failed that benchmark.

organs."[20] (PTX-600 at 1; *see also* D.I. 83 at 576:4-13.) In 1998, a well-regarded researcher at the top of the stem cell field stated that "little is known about the types of molecular interactions that hold hematopoietic stem cells in the marrow environment in vivo."[21] (DTX-190 at 15; *see also* D.I. 81 at 187:23-188:11; D.I. 83 at 577:12-13.) Dr. Andreeff agreed with that assessment of the state of the art. (D.I. 81 at 188:12-21.) That same top researcher reported in 2000 that "the mechanism(s) of stem-progenitor-cell mobilization has remained elusive" and, "[a]lthough the chemokine SDF-1 plays a critical role in … migration and homing[,] … its involvement in mobilization remains uncertain." (PTX-354 at 2-3; *see also* D.I. 83 at 577:3-13.) In 1999, "one of the stars in stem cell research" stated that "[t]he mobilization of [stem cells] and mature hematopoietic cells from the bone marrow into the blood circulation involve[s] a complex interplay between cytokines, chemokines and adhesion molecules, though details of this regulatory system are poorly understood." (DTX-148 at 4; D.I. 81 at 189:12-16, 190:5-7; *see also* D.I. 83 at 576:23-24.) Dr. Andreeff and Dr. Mohty agreed with that statement.

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[20] Zydus disputes that the prior art reflected uncertainty about the mechanisms of stem cell mobilization as of September 2000. (D.I. 100 at 12.) Dr. Andreeff testified that "[e]very single paper" has "boilerplate" language about uncertainty. (D.I. 81 at 176:8-177:23.) To Zydus, such language in the literature is perfunctory and "does not accurately reflect the state of the art as of September 2000." (D.I. 100 at 12.) I disagree. Although any given scientific phenomenon may be simultaneously understood in some respects and uncertain in others, that does not mean that statements in the literature about how much is known with respect to that phenomenon are meaningless boilerplate. If the mechanisms of stem cell mobilization were clearly understood as of September 2000, including the molecules involved in its facilitation, then the literature would not have been reporting the opposite. (D.I. 83 at 577:17-578:8.)

[21] "In vivo" denotes that the experiments were conducted in a living organism. (D.I. 81 at 99:10-12.) That is in contrast with the phrase "in vitro," which means that the experiments were conducted outside of a living organism. (D.I. 81 at 99:1-4.)

(D.I. 81 at 189:17-190:14; D.I. 83 at 576:14-577:2.) Finally, Dr. Andreeff endorsed a statement in a 1999 state-of-the-art review that said "little [was] known" of the mechanisms regulating stem cell mobilization and that the process was "unclear" and "understood poorly" at that time.[22] (DTX214 at 5; *see also* D.I. 81 at 190:19-191:3, 194:25-195:9, 197:9-198:5.)

70. Nevertheless, that is not to say that nothing was known about stem cell mobilization as of September 2000. It was known that SDF-1 is a protein that is highly concentrated in the bone marrow, that it is produced and secreted by bone marrow cells, and that it appears in very low levels in the peripheral blood. (D.I. 81 at 83:12-24; D.I. 83 at 720:12-14.) It was known that SDF-1 binds to CXCR4, which is a receptor frequently expressed on the surface of many types of cells, including stem cells, and that SDF-1 and CXCR4 are "monogamous" because they only attract each other. (DTX-214 at 3; *see also* DTX-109 at 5; D.I. 81 at 84:3-85:2, 86:9-12, 98:16-25; D.I. 83 at 624:15-19, 697:3-23.) As of 2000, it was known that SDF-1 was "a general stem cell chemoattractant" for cells expressing the CXCR4 receptor, and thus, because of the monogamous relationship between SDF-1 and CXCR4, it was "clear that CXCR4 is the receptor responsible for the stem cell chemoattraction." (DTX-214 at 3; *see also* D.I. 81 at 85:3-86:12; D.I. 83 at 720:9-20.) But it was less clear at that time what was

[22] Zydus argues that, even though the mechanism by which G-CSF mobilized stem cells was unknown at the time the 1999 state-of-the-art review was written, findings reported by Lapidot months later resolved G-CSF's mechanism of action. (D.I. 100 at 13.) Again, I disagree. The Lapidot abstract published in 1999 suggested that SDF-1 and CXCR4 played a role in the mobilization of stem cells but did not propose or purport to resolve the mechanisms by which stem cells are mobilized.

responsible for keeping those stem cells in the bone marrow, given that a number of interactions were thought to be present "between the stem cell and the various cellular and molecular components of the stem cell niche." (DTX-214 at 4 & fig. 3.) For example, although some suggested as early as 1997 that the interaction of SDF-1 with receptors on the surface of stem cells may be associated with stem cell migration, including both homing and mobilization (DTX-012 at 1-2; DTX-161 at 1-2, 5-6; D.I. 82 at 443:1-15), others noted that "[t]he hematopoietic microenvironment of the bone marrow is extremely complex" and theorized that receptors other than CXCR4 that are expressed on the stem cell surface may play a role in adhering those stem cells within the niche (DTX-214 at 4-5 & fig. 4).

4. Stem Cell Mobilization and Homing Inform Each Other

71. As a reminder, stem cell mobilization involves moving cells from the bone marrow into the peripheral blood (D.I. 81 at 79:17-24, 170:16-23; D.I. 83 at 607:2-4), and stem cell homing describes the process by which stem cells move in the opposite direction, from the peripheral blood back into the bone marrow (D.I. 81 at 173:6-9). The parties dispute whether the two processes –mobilization and homing – are "mirror images." (D.I. 88 at ¶¶ 66-68; D.I. 100 at 14-15.)

72. Zydus relies on a statement by Whetton in 1999 for its argument that they are mirror images. Whetton said:

> Impacting on the bone marrow … are a number of agents capable of altering the proliferative-differentiative balance of the stem cell pool and additionally of mobilizing stem cells into the periphery. The complex array of cytokines, chemokines and adhesive molecules regulating these various process[es] helps to define the stem cell niche, and thus an understanding of

> these agents and their interactions is central to our overall understanding of bone marrow haemopoiesis. We have attempted to review here the emerging evidence implicating a range of such regulators in important aspects of stem cell homing to, and mobilization from, this stem cell niche. *While much currently remains to be explained, it seems that these processes are likely to be "mirror images" of each other, differentially utilizing similar classes of molecules and receptors to these respective ends.* The understanding of these regulatory activities might allow valuable therapeutic intervention in these processes. This is currently a routine practice with G-CSF in the context of mobilization; however, our poor knowledge of the role for G-CSF in this context has undermined attempts at improving this treatment option.

(DTX-214 at 6 (emphasis added); *see also* D.I. 89 at ¶ 28.) Dr. Andreeff testified that a person of ordinary skill in the art would have understood in September 2000, based on Whetton, that homing and mobilization "are related mechanisms using the same or identical or related molecules." (D.I. 81 at 87:15-88:10.) He explained that homing and mobilization were considered to involve "the same or very similar mechanisms." (D.I. 82 at 299:14-23.)

73. Plaintiffs respond that Zydus is taking the "mirror image" statement "out-of-context," and that Dr. Andreeff is ignoring other relevant parts of Whetton's article that acknowledge the continuing uncertainty surrounding the homing and mobilization processes. (D.I. 88 at ¶ 68 & n.10.) They cite Dr. Mohty's testimony for support, in which he explained that, due to the "complex" nature of the stem cell homing and mobilization processes, "the uncertainties[,] and the little information that was available" in 2000, "it would [have been] very difficult to conclude with certainty that they are mirror images." (D.I. 83 at 578:12-579:4.) Dr. Mohty characterized the "mirror image" theory as "very controversial" in 2000 because "homing and mobilization could use some

common pathways, but they are not necessarily the same process." (D.I. 83 at 697:24-698:13.) He said other authors were suggesting that homing and mobilization were not mirror images during this time, and, according to Dr. Mohty, we now know today that, in fact, they are not mirror image processes. (D.I. 83 at 697:24-698:13.) Nevertheless, Dr. Mohty acknowledged that some in the field thought that the processes were likely to be mirror images. (D.I. 83 at 698:14-17.)

74. I find that, although the complexity and incomplete understanding of the mechanisms and molecules involved in those processes precluded certainty (DTX-214 at 6; D.I. 83 at 578:15-579:17, 697:24-698:13), a person of ordinary skill in the art as of September 2000 would have understood that stem cell homing and stem cell mobilization were thought by some in the field to be mirror image processes (DTX-214 at 6; D.I. 81 at 87:20-88:10; D.I. 83 at 579:10-17, 698:14-17).

5. A Person of Ordinary Skill in the Art Would Have Pursued a Panoply of Stem Cell Mobilizer Candidates

75. The parties dispute the chemical agents that a person of ordinary skill in the art would have pursued as potential stem cell mobilizers. (D.I. 88 at ¶¶ 69-73; D.I. 100 at 15.) Plaintiffs contend that a person of ordinary skill in the art in September 2000 would have, as a first choice, pursued cytokines and growth factor cytokines as potential stem cell mobilizer candidates because G-CSF and GM-CSF, both growth factor cytokines, were the only two FDA-approved stem cell mobilizers at that time. (D.I. 88 at ¶¶ 69-72.) They admit that some researchers had pursued adhesion molecule receptors, but they contend that the literature did not support looking for molecules that may target the

interaction between SDF-1 and the CXCR4 receptor. (D.I. 88 at ¶¶ 73.) Zydus counters that a person of ordinary skill in the art in September 2000 would have looked beyond cytokines, growth factor cytokines, and adhesion molecule receptors, because the literature identified CXCR4 blockers as a source of investigation as stem cell mobilizers. (D.I. 100 at 15.)

76. I find that a person of ordinary skill in the art in September 2000 would certainly have studied cytokines and growth factors because the only two FDA-approved stem cell mobilizers at that time, G-CSF and GM-CSF, were both growth factor cytokines. (D.I. 83 at 657:8-23, 658:10-12.) The literature leading up to September 2000 recommended evaluating cytokines and growth factors in the search for an improvement upon G-CSF as a stem cell mobilizer, noting that the focus should be on "new cytokines or combinations" that mobilize a sufficient number of stem cells for transplantation (DTX-070 at 6), and that, "in addition to GM-CSF, other cytokines, including macrophage colony-stimulating factor (M-CSF), [G-CSF], erythropoietin, interleukins-1, -2, -3, -4, and -6, and various interferons and tumor necrosis factors have enormous potential" to mobilize stem cells (DTX-190 at 15). Dr. Mohty also testified that a person of ordinary skill in the art would look for a stem cell mobilizer that improved upon G-CSF – "the gold standard" at the time – by focusing on what was already known to work: "growth factors and cytokines." (D.I. 81 at 109:3-20; D.I. 83 at 657:8-23, 658:10-12, 734:7-12.)

77. But a person of ordinary skill in the art would not have focused exclusively on cytokines and growth factors in the search for stem cell mobilizing agents. First and

foremost, as already noted at ¶¶ 66-67, many cytokines and growth factors had been tested and failed to improve upon the stem cell mobilizing abilities of G-CSF. (JTX-009 at 1-2; JTX-023 at 7; PTX-232 at 1; PTX-415 at 2-6; D.I. 81 at 207:23-216:22; D.I. 83 at 640:16-22, 641:11-642:9, 644:4-13, 656:23-659:7.) That could have been enough impetus to lead some researchers in the field to look elsewhere. Furthermore, as of September 2000, the literature demonstrated that some researchers were pursuing adhesion molecule receptors as potential mobilizing agents, including VLA-4, MIP-1α, and growth hormones. (DTX-214 at 4-6; D.I. 83 at 657:24-658:9.) At that time, other researchers in the field were also recommending focusing on molecules that interfere with the interaction between the chemokine SDF-1 and the CXCR4 receptor to induce stem cell mobilization. (D.I. 81 at 94:22-95:4, 127:11-21; D.I. 82 at 298:21-299:23.) For example, Konopleva proposed that "blocking the CXCR4/SDF-1 interaction could increase the cytokine-induced mobilization of CXCR4-expressing stem cells with high engraftment capability" (DTX-142 at 4; D.I. 81 at 106:15-23; D.I. 84 at 768:24-769:5), and Lapidot stated that his group's research "demonstrate[d] a major role for SDF-1 and CXCR4 in the initial stages of bone marrow mobilization by G-CSF and suggest[ed] that G-CSF, SDF-1 and CXCR4 also participate in the daily migration of maturing hematopoietic cells from the bone marrow into the blood circulation" (DTX-148 at 4; *see also* D.I. 81 at 97:3-7; D.I. 83 at 704:20-22).

78. Thus, a person of ordinary skill in the art in September 2000 would have pursued a panoply of potential stem cell mobilizing agents in an effort to improve upon G-CSF, including, but not necessarily limited to, cytokines, growth factors, adhesion

molecule receptors, and agents that may interfere with the interaction between SDF-1 and CXCR4.

6. Studying CXCR4 Blockers

a. *There Was Some Motivation to Investigate SDF-1 and CXCR4, Including CXCR4 Blockers, as of September 2000*

79. As of September 2000, the role of SDF-1 and CXCR4 in the mobilization of stem cells was under study but not definitively resolved. (DTX-142 at 4; DTX-148 at 4; D.I. 81 at 127:17-21, 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2.) At that time, some had already proposed looking at SDF-1 or CXCR4 blocking agents as potential stem cell mobilizers (DTX-142 at 4), and a person of ordinary skill in the art would have known both that G-CSF was an agent that mobilizes stem cells *in vivo* and that G-CSF impacted the interaction between SDF-1 and CXCR4 (D.I. 83 at 700:25-704:22).[23]

[23] To the extent that Dr. Mohty testified that "there was no information as of September 2000 that [a] SDF-1/CXCR4 agent could mobilize stem cells in vivo" (D.I. 83 at 644:20-645:1), I do not deem that testimony credible because it conflicts with his other testimony confirming that, as of September 2000, a person of ordinary skill in the art "would know that G-CSF is an agent that causes stem cells to mobilize" and that G-CSF was known to "affect[] the CXCR4/SDF-1 interaction" (D.I. 83 at 700:25-701:17, 704:6-22). Plaintiffs suggest that the knowledge of a person of ordinary skill in the art as of September 2000 that G-CSF impacts the interaction between SDF-1 and CXCR4 is of little value because the literature did not establish a "causal role of SDF-1 and CXCR4 in stem cell mobilization[.]" (D.I. 98 at 5.) I find, however, that the most likely reason that the literature discussed the impact of mobilizing agents on the SDF-1/CXCR4 axis was for the purpose of suggesting that it may play some causal role in the mechanism by which those agents induce stem cell mobilization. In other words, although correlation does not equal causation, the existence of a correlation may nevertheless suggest the potential existence of a causal link. (*See, e.g.*, DTX-142 at 4 ("Correlation between baseline CXCR4 expression levels and the percentage of $CD34^{+}38^{-}$ cells at the peak of G-

80. The motivation to investigate potential mobilizing agents by looking to candidates that will block the interaction between SDF-1 and CXCR4 derives from a number of articles published in the years leading up to September 2000. In 1997, Aiuti identified SDF-1 as "a [n]ew [m]echanism to [e]xplain the [m]obilization of [stem cells into the] [p]eripheral [b]lood." (DTX-012 at 1; *see also* D.I. 81 at 115:5-13.) It disclosed that stem cells from the peripheral blood are less attracted to SDF-1 than are stem cells from the bone marrow, "suggesting that an altered response to SDF-1 may be associated with [stem cell] mobilization." (D.I. 81 at 115:14-23; *see also* DTX-012 at 2.) Aiuti said that, although, at the time of the publication, "we do not know what the relevance is in vivo of SDF-1 in the homing of $CD34^+$ to the marrow after transplantation or its involvement in the experimental mobilization of $CD34^+$ cells," recent experiments suggested that SDF-1 may "play[] a critical role in the migration of [stem cells] … in vivo" and that "manipulation of SDF-1 may offer promising ways to improve both transplantation and mobilization of hematopoietic cells."[24] (DTX-012 at 8.) Then, in 1998, Möhle disclosed that SDF-1 and the CXCR4 receptor "are likely to be involved in the trafficking of hematopoietic progenitor and stem cells, as suggested by the … chemotactic effect of SDF-1 on $CD34^+$ progenitor cells."[25] (DTX-161 at 1; *see also* D.I.

CSF priming suggests a role of CXCR4 in a G-induced mobilization of peripheral blood progenitor cells.").)

[24] $CD34^+$ indicates that the stem cell is positive for, or expresses, the CD34 receptor. (D.I. 81 at 82:14-83:5.)

[25] The "trafficking" of stem cells includes both stem cell mobilizing and homing. (D.I. 81 at 118:23-119:2, 171:1-173:3.)

81 at 117:16-118:22.) It also highlighted that the SDF-1/CXCR4 axis may be "critical" to stem cell homing in vivo because experiments demonstrated that stem cells exposed to an anti-CXCR4 antibody in vitro exhibited reduced migration to SDF-1.[26] (DTX-161 at 5, 6; *see also* D.I. 81 at 119:8-16.) Moreover, in 1999, Peled disclosed that "SDF-1 probably affects [stem cell] engraftment by mediating chemotaxis to the bone marrow[,]" and the article "link[ed] migration to SDF-1 in vitro to human stem cell function in vivo." (DTX-172 at 3; *see also* D.I. 81 at 120:23-121:3, 122:4-25; D.I. 83 at 585:5-586:7.)

81. Also in 1999, Lapidot conducted in vivo experiments focused on the effects of G-CSF on SDF-1 and CXCR4 expression. (DTX-148 at 4; D.I. 97:3-98:15, 99:10-20; D.I. 83 at 587:10-24, 701:8-17, 702:3-9, 704:20-22.) In those experiments, samples were taken directly from patients' bone marrow following administration of G-CSF. (DTX-148 at 4; D.I. 83 at 587:10-24, 723:16-724:12.) The results from Lapidot's experiments demonstrated that stem cells with higher CXCR4 expression exhibited increased migration to a fixed concentration of SDF-1 in vitro. (DTX-148 at 4; D.I. 81 at 100:21-101:8.) They also showed that in vivo administration of G-CSF increases CXCR4 expression on stem cells, while in vitro application of G-CSF has no effect on stem cell CXCR4 expression. (DTX-148 at 4; D.I. 83 at 99:5-20.) Thus, Lapidot concluded that G-CSF indirectly increases the CXCR4 expression of bone marrow stem cells in vivo. (DTX-148 at 4; D.I. 81 at 99:15-20; D.I. 83 at 715:9-11.) Unexpectedly, however, Lapidot's results also demonstrated that G-CSF inhibits the production of SDF-1 in the

[26] Like "trafficking," the "migration" of stem cells also includes both stem cell mobilizing and homing. (D.I. 81 at 118:23-119:2, 173:4-5; D.I. 83 at 698:18-23.)

bone marrow. (DTX-148 at 4; D.I. 97:3-98:15; D.I. 83 at 587:10-24.) I find that a person of ordinary skill in the art would understand, based on Lapidot's teachings, that G-CSF may operate to mobilize stem cells by reducing SDF-1 in the bone marrow. Since SDF-1 was a chemokine known to attract stem cells into the bone marrow, reducing it meant fewer tethers preventing stem cells from mobilizing into the bloodstream. (DTX-214 at 4 & fig. 3; D.I. 97:20-98:15, 99:23-100:6, 102:10-103:1.) That person of ordinary skill would also understand that CXCR4 may have "a role … in the mobilization process." (DTX-148 at 4; *see also* D.I. 81 at 98:16-99:20, 100:7-20.)

82. Finally, Konopleva, which is another publication from 1999, reported in vivo experimental data involving human subjects that underwent peripheral blood stem cell transplantation and provided insight into the effects of G-CSF administration on CXCR4 expression on stem cells in the peripheral blood. (DTX-142 at 4; D.I. 81 at 105:13-106:14, 145:16-146:8; D.I. 83 at 708:4-18.) Consistent with Lapidot's results, Konopleva found that G-CSF increases CXCR4 expression on peripheral blood stem cells. (DTX-142 at 4; D.I. 81 at 105:13-106:14, 109:3-20; D.I. 83 at 721:4-12.) Konopleva also noted "[a] strong positive correlation … between baseline expression of CXCR4 on [stem] cells … and the percentage of [stem] cells … after G-CSF mobilization[.]" (DTX-142 at 4.) A person of ordinary skill in the art would consider Konopleva together with Lapidot because they were published together and relate to the same topic (DTX-142 at 1; DTX-148 at 1; D.I. 83 at 722:2-723:5), and I find that the correlation between mobilization induced by G-CSF and increased CXCR4 expression on peripheral blood stem cells would have led a person of ordinary skill in the art to

hypothesize that G-CSF mobilization may operate by interfering with the interaction between SDF-1 and CXCR4 (D.I. 81 at 109:3-110:6, 111:2-14).[27]

83. Konopleva ultimately "propose[d] that blocking the CXCR4/SDF-1 interaction could increase the cytokine-induced mobilization of CXCR4-expressing stem cells with high engraftment capability" (DTX-142 at 4), and both Dr. Andreeff and Dr. Mohty agree that "cytokine-induced mobilization" refers to G-CSF-induced mobilization (D.I. 81 at 112:10-23; D.I. 83 at 709:2-7). A person of ordinary skill in the art would have understood that conclusion to be a proposal to administer some agent other than G-CSF, which blocks the interaction between SDF-1 and CXCR4, to improve upon the stem cell mobilization results obtained by administering G-CSF alone. (D.I. 81 at 112:2-23; D.I. 83 at 709:12-710:3.) While Konopleva does not expressly teach a method for, or any agents capable of, blocking CXCR4, a person of ordinary skill in the art would have understood that administering a CXCR4 antagonist is one way to block CXCR4 and satisfy the proposal in Konopleva. (DTX-142 at 4; D.I. 81 at 151:23-152:13; D.I. 83 at 709:12-710:3.)

84. On the whole, that body of literature would have been enough to motivate a person of ordinary skill in the art to investigate SDF-1 and the CXCR4 receptor.

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[27] Zydus urges me to find that a person of ordinary skill in the art would understand that the increase in CXCR4 expression after G-CSF administration would result in "some cells left over in the bone marrow that are not mobilized" and that stem cell mobilization induced by G-CSF "is incomplete[.]" (D.I. 89 at ¶¶ 61-62; *see also* D.I. 81 at 109:21-110:6.) But that is not necessarily what a person of ordinary skill in the art would have understood at the time. There is no evidence that such a person would have gleaned that understanding from Lapidot and Konopleva because those prior art publications do not disclose any data regarding the number of stem cells left in the bone marrow following G-CSF-induced mobilization. (DTX-142 at 4; DTX-148 at 4.)

85. Plaintiffs give three main reasons for their assertion that I should not find that motivation. First, they would have me completely discount the value of any known studies of SDF-1 or CXCR4 blocking agents because they largely involved in vitro experimentation, and none studied in vivo the manipulation of either CXCR4 or SDF-1 to mobilize stem cells. (D.I. 88 at ¶¶ 74-75; *see also* D.I. 83 at 644:20-645:5; DTX-012 at 2-3; DTX-161 at 2-3; DTX-172 at 2-4.) The distinction between in vitro and in vivo experimentation is important because stem cell mobilization is inherently an in vivo process without an in vitro counterpart. (D.I. 82 at 346:11-16; D.I. 83 at 582:20-583:2.) As Dr. Mohty explained, "you cannot mimic the bone marrow, and you cannot mimic the peripheral blood," which is why in vivo data on the effects of potential mobilizing agents would obviously be valuable to a person of ordinary skill in the art. (D.I. 83 at 582:20-583:12; *see also* D.I. 83 at 733:24-734:6.) But I find that a person of ordinary skill in the art would not ignore in vitro data. While it is not uncommon for in vitro and in vivo studies to yield different results (D.I. 82 at 264:15-20; *see, e.g.*, DTX-148 at 4), that does not mean that they always produce different outcomes or, even when different, outcomes without relevance to one another. I thus do not accept Plaintiffs' invitation to pass over the import of prior art because it involved in vitro, rather than in vivo, studies. And I do not totally discount the value of the disclosures in Aiuti, Möhle, and Peled simply because they did not report in vivo experimental data relating to the manipulation of CXCR4 or SDF-1 to mobilize stem cells from the bone marrow into the peripheral blood. (D.I. 88 at ¶ 75; D.I. 100 at 16-17.)

86. Second, Plaintiffs contend that, even though Konopleva may have proposed blocking the interaction between SDF-1 and CXCR4 to improve upon G-CSF-induced stem cell mobilization, other prior art references pointed away from blocking CXCR4. (D.I. 88 at ¶¶ 76-82.) For example, Peled taught that SCF and IL-6, both of which were known to have at least modest effects on stem cell mobilization (D.I. 81 at 209:4-11; PTX-415 at 5-6), upregulated CXCR4 expression and increased stem cell engraftment in transplanted mice (DTX-172 at 4-5; D.I. 83 at 591:16-592:3). And Lapidot taught that inducing stem cell mobilization using G-CSF also indirectly increased CXCR4 expression on stem cells, as well as reduced SDF-1 levels in the bone marrow. (DTX-148 at 4.) Konopleva confirmed the upregulation of CXCR4 expression when G-CSF is used as a stem cell mobilizer. (DTX-142 at 4; D.I. 81 at 105:13-106:14, 109:3-20; D.I. 83 at 721:4-12.) Plaintiffs therefore argue that, when read together, a person of ordinary skill in the art would have been encouraged by the prior art to increase CXCR4 expression, rather than decrease, block, or otherwise interfere with it, to achieve stem cell mobilization. (D.I. 88 at ¶ 78; D.I. 82 at 249:15-24; D.I. 83 at 588:8-589:5, 591:16-592:11, 598:16-599:2, 722:2-723:5.)

87. But Plaintiffs have identified nothing in the prior art expressly telling skilled artisans *not* to block CXCR4, and in fact, Konopleva expressly proposed the opposite. (DTX-142 at 4; D.I. 88 at ¶¶ 76-82.) The mechanism by which G-CSF mobilized stem cells was admittedly uncertain as of September 2000. (PTX-354 at 3; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2.) There were multiple theories about mobilization mechanisms that were surfacing in the art at the

time, including that stem cell mobilization may be facilitated by: (1) perturbing the integrity of extracellular matrix components thought to be responsible for the release of hematopoietic cells (PTX-354 at 2-3; DTX-214 at 5 & fig.4); (2) inhibiting SDF-1 and increasing CXCR4 expression because those were the effects associated with G-CSF administration (D.I. 83 at 588:8-589:5); or (3) interfering with the SDF-1/CXCR4 axis by inhibiting SDF-1 and limiting CXCR4 expression because that axis was known to be critical to stem cell homing, which was hypothesized to be the "mirror image" of stem cell mobilization (DTX-214 at 2-3, 5-6; D.I. 81 at 84:19-86:24, 97:20-98:25; D.I. 82 at 298:6-299:23).[28] As a result, a person of ordinary skill in the art at that time would have been trying a lot of things. That person may have tried to increase CXCR4 expression because it was a known effect of mobilization using G-CSF, SCF, and IL-6. (DTX-142 at 4; DTX-148 at 4; DTX-172 at 4-5.) That person may also have tried to reduce CXCR4 expression or block the CXCR4 receptor because it was known that SDF-1 attracted stem cells from the peripheral blood to the bone marrow through the CXCR4 receptor on the surface of those stem cells and thus CXCR4 expression may simply be a tether keeping stem cells in the bone marrow through its interaction with SDF-1. (PTX-600 at 8; DTX-142 at 4; D.I. 81 at 109:3-113:17.) Consistent with my earlier finding, then, that a person of ordinary skill in the art would have been motivated to investigate SDF-1 and the CXCR4 receptor as a general matter, I also find that such a person in September 2000 would have been motivated to study potential mobilizing agents that increase CXCR4

[28] In fact, even today, the mechanism by which G-CSF mobilizes stem cells is not fully understood. (D.I. 83 at 705:12-14.)

expression as well as ones that block the CXCR4 receptor. (DTX-142 at 4; D.I. 81 at 109:3-110:6, 112:10-113:10; D.I. 83 at 588:8-589:5.)

88. Third, Plaintiffs argue that the conclusions in Konopleva are "inconsistent" with, or "contradict[ory]" to, its own experimental data as well as the data reported in the articles it cites, and thus any motivations that could be derived from that abstract should be discounted. (D.I. 88 at ¶¶ 79-80.) Specifically, Plaintiffs contend that the proposal to block the interaction between SDF-1 and CXCR4 to achieve "stem cells with high engraftment capability" is inconsistent with the reported lack of correlation after G-CSF administration between CXCR4 expression on stem cells and time to granulocyte recovery. (DTX-142 at 4; D.I. 88 at ¶ 80.) Dr. Mohty testified that the proposal contradicted the data because "[g]ranulocyte recovery and engraftment are the same." (D.I. 83 at 594:20-595:22; *see also* D.I. 83 at 593:12-19, 597:20-598:7, 712:21-713:14.) But Dr. Andreeff, a co-author of the Konopleva abstract, testified that a person of ordinary skill in the art would have read that sentence with the previous one, which reports that "[n]o correlation was found between pre-/post-CXCR4 expression and [white blood cell]/absolute granulocyte count[,]" and thus would have understood that the CXCR4 expression was on white blood cells rather than $CD34^{+}CD38^{-}$ cells.[29] (DTX-142 at 4; D.I. 81 at 240:19-241:22.) And granulocytes, which are a subset of white blood cells, are not stem cells. (D.I. 82 at 249:6-11, 274:21-275:4.) Therefore, based on Dr.

[29] Like CD34, CD38 is a receptor found on the surface of progenitor cells. $CD38^{-}$ indicates that the cell is negative for, or does not express, the CD38 receptor. Stem cells are "negative or only very low positive for CD38," and progenitor cells are positive for that receptor. (D.I. 81 at 82:14-83:5.)

Andreeff's testimony, it appears that the reported lack of correlation was between CXCR4 expression on white blood cells and time to granulocyte recovery, which is a sign of engraftment, and not between CXCR4 expression on stem cells and time to granulocyte recovery. (DTX-142 at 4; D.I. 81 at 240:19-241:25; D.I. 82 at 249:6-14.) Accepting Dr. Andreeff's version of what a person of ordinary skill in the art would have understood, I find that the data in the abstract is not inconsistent with the proposal.

89. Plaintiffs set forth a stronger argument, however, that the Peled article cited in Konopleva contradicts the suggestion that blocking the interaction between SDF-1 and CXCR4 could result in "stem cells with high engraftment capability" because the data in Peled demonstrated that two different CXCR4 antibody blocking agents reduced engraftment of stem cells. (DTX-142 at 4; DTX-172 at 3; D.I. 82 at 249:15-20; D.I. 88 at ¶ 79.) Although stem cell engraftment and stem cell mobilization are different processes, both are important to the success of a transplantation procedure. (D.I. 84 at 743:11-744:11.) To put the issue in simpler terms, the problem is that, even if a CXCR4 blocking agent could mobilize stem cells from the bone marrow into the peripheral blood, that inhibition of the CXCR4 receptor could significantly decrease the ability of those stem cells to home back into the bone marrow and engraft during the final steps of the transplantation process. The question thus becomes whether, based on that understanding, a person of ordinary skill in the art as of September 2000 would have had the foresight to look for a very temporary, rather than longer-lasting, blocking agent. I

find that such a person would not have had that foresight. Any contrary conclusion, I believe, is nothing more than impermissible hindsight bias.[30]

90. The evidence adduced at trial does not support finding that a person of ordinary skill the art in September 2000 would have distinguished between temporary and longer-lasting blocking agents or otherwise would have recognized the need to consider the temporal aspect of CXCR4 blockers. The Konopleva abstract does not say anything about "temporarily" blocking the interaction between SDF-1 and CXCR4. (DTX-142 at 4; D.I. 83 at 598:8-15.) And none of the other prior art references supporting Zydus's motivation argument, including Aiuti, Möhle, Peled, and Lapidot, teaches temporarily blocking the CXCR4 receptor to capitalize on both stem cell mobilization and later stem cell homing and engraftment. (*See generally* DTX-012; DTX-148; DTX-161; DTX-172; D.I. 89 at ¶¶ 36-72.) Nor does van Os, which was published later in November 2000 and concluded that stem cell homing and engraftment is not compromised by blocking CXCR4 on transplanted cells using plerixafor, help Zydus. (DTX-208 at 4; D.I. 89 at ¶¶ 80-81.) Dr. Andreeff testified that van Os tested the hypothesis that one would achieve "very little engraftment" by "effectively permanently

[30] Zydus attempts to explain away the apparent discrepancy between the proposal in Konopleva and the data in Peled by asserting that Peled discussed antibodies rather than small molecules, and a person of ordinary skill in the art would have understood that antibodies persist for a long period of time and thus would not have used them as potential blocking agents. (D.I. 81 at 156:3-22, 226:9-228:3; D.I. 82 at 263:8-264:3; D.I. 100 at 18.) But the critical knowledge a person of ordinary skill in the art would have needed was not simply that antibodies are different from small molecules, but rather that there was a temporal aspect to achieving both stem cell mobilization and stem cell homing using a CXCR4 blocking agent, which would then prompt one to look to small molecules over antibodies.

block[ing] the [CXCR4] receptor[,]" and found that the CXCR4 antagonist plerixafor made "no difference in engraftment" of treated stem cells versus untreated stem cells "[b]ecause plerixafor is short-acting." (D.I. 81 at 143:6-25.) In short, Dr. Andreeff said van Os showed "that plerixafor, because of its [short half-life] properties, does not prevent engraftment of mobilized cells." (D.I. 81 at 143:6-25.) But van Os provides no indication that the authors considered the temporary nature of the tested CXCR4 blocking agent. (DTX-208 at 4; D.I. 83 at 610:20-22.) For example, nowhere does that publication use the words "temporary," "short duration," "short-acting," or "short half-life," and it makes no suggestion that the authors assessed CXCR4 expression over the course of their experiments to test the purported short-term effects of plerixafor. (DTX-208 at 4; D.I. 83 at 610:20-22.) In sum, Zydus has not identified any record evidence other than Dr. Andreeff's say so that a person of ordinary skill in the art in September 2000 would have specifically known to look for a short-term rather than a long-lasting blocker. (D.I. 89 at ¶¶ 80-81; D.I. 100 at 18.)

91. Nevertheless, that does not mean, as Plaintiffs suggest, that there would have been no motivation at that time for a person of ordinary skill in the art to pursue a CXCR4 blocker as a potential stem cell mobilizing agent. The complexity and uncertainty in the art, coupled with the known facilitators of stem cell homing, and the fact that homing was hypothesized to be a "mirror image" process of stem cell mobilization, may have encouraged a person of ordinary skill in the art to at least try CXCR4 blockers despite possible misgivings. (DTX-214 at 6; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2, 578:12-578:17, 697:24-698:17.)

The difficulties a blocker might present to stem cell homing and engraftment would not have completely undermined the evidence already discussed that would encourage a person of ordinary skill in the art in September 2000 to pursue CXCR4 blocking agents as potential stem cell mobilizers.

92. In the end, a person of ordinary skill in the art who pursued CXCR4 blocking agents would have had mixed success depending on the type of agent used. Many antibodies to CXCR4 would have decreased, rather than increased, stem cell mobilization. (DTX-172 at 3, 5; DTX 161 at 2-3, 5; JTX-051 at 1, 4-6; D.I. 82 at 251:19-252:21, 255:8-260:13, 263:8-15, 295:9-16.) But other CXCR4 blocking molecules, such as plerixafor, would have augmented stem cell mobilization. (D.I. 83 at 712:2-17.) I find that a person of ordinary skill in the art would have been motivated to pursue, among other things, a CXCR4 blocker as a potential stem cell mobilizer.

b. *No Reasonable Expectation That a CXCR4 Blocker Would Succeed*

93. Plaintiffs contend that, even if there was sufficient motivation to seek out CXCR4 blockers, a person of ordinary skill in the art would not have had a reasonable expectation that such blockers would succeed in mobilizing stem cells. (D.I. 88 at ¶¶ 83-88.) Zydus, of course, disagrees. (D.I. 100 at 19-20.) Dr. Andreeff and Dr. Mohty hold different opinions about whether a person of ordinary skill in the art would have had a reasonable expectation of success in September 2000. (D.I. 81 at 153:25-155:8; D.I. 83 at 692:19-693:20.) I find that, based on the uncertainties regarding the mechanisms of stem cell mobilization, the known complexity in the art, and the fact that G-CSF, SCF,

and IL-6 were known stem cell mobilizers that increased CXCR4 expression, a person of ordinary skill in the art would not have had a reasonable expectation of success in September 2000. (DTX-142 at 4; DTX-148 at 4; DTX-172 at 3-5; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5, 203:6-205:10; D.I. 82 at 249:15-20; D.I. 83 at 576:14-577:2, 692:19-693:20.) But, of course, that does not mean that such a person would not have been motivated to pursue or try CXCR4 blocking agents, as researchers in fact did in 2000 and continued to do into 2002. (DTX-172 at 3; JTX-051 at 1, 4-6.); *see also* Mark A. Lemley, *Expecting the Unexpected*, 92 Notre Dame L. Rev. 1369, 1374-75, 1388 (2017) (differentiating between the motivation to try something and the reasonable expectation that it will succeed).

7. Pursuing Plerixafor, Which Is a CXCR4 Blocker, as a Stem Cell Mobilizer

a. *There Was Motivation to Study Plerixafor as a Stem Cell Mobilizing Agent*

94. Zydus nevertheless argues that, as of September 2000, a person of ordinary skill in the art would have known that plerixafor was a CXCR4 antagonist and would have pursued it as a potential stem cell mobilizer with a reasonable expectation that it would succeed in mobilizing stem cells. (D.I. 89 at ¶¶73-97.)

95. The prior art suggested a potential link between plerixafor and mobilization through manipulation of the SDF-1/CXCR4 axis. By September 2000, it was known that plerixafor completely inhibits the binding of SDF-1 to CXCR4. (DTX-109 at 5; D.I. 83 at 700:8-14.) Hendrix and WO '814, both published before September 2000, disclose the safe administration of 10-80 μg/kg of plerixafor to human subjects and teach that

plerixafor is a CXCR4 antagonist that blocks the CXCR4 receptor. (DTX-109 at 1, 5; DTX-216 at 1, 9, 11; D.I. 81 at 123:5-124:18, 155:9-23; D.I. 83 at 699:24-700:17.) Hendrix and WO '814 disclose that administering plerixafor to human subjects increases the presence of white blood cells, which are known to have CXCR4 receptors, in the peripheral blood. (DTX-109 at 1; DTX-216 at 11; D.I. 81 at 123:5-11, 124:8-18, 126:14-25; D.I. 83 at 700:15-17.) Hendrix notes that the increase in white blood cell count is "consistent with a demargination effect in which [white blood cells] are released from attachment to the endothelial cell surface into the central circulation[,]" but also recognizes that "reports … suggest an increase in [white blood cells] may be CXCR4 mediated." (DTX-109 at 5; D.I. 81 at 126:1-25; D.I. 83 at 616:11-617:5.) Hendrix even went so far as to "suggest that binding of [plerixafor] to CXCR4 may inhibit the chemotactic effects of SDF-1α, causing release of [white blood cells] from the endothelium and/or stem cells from bone marrow." (DTX-109 at 5 (citations omitted).) Thus, Hendrix hypothesized that plerixafor may mobilize stem cells. (DTX-109 at 5; D.I. 81 at 126:18-25.)

96. A person of ordinary skill in the art would have extended Hendrix's teaching with respect to the effect of plerixafor on white blood cells to that chemical's potential effect on stem cells. As of September 2000, a person of ordinary skill in the art would have thought that, although not always true, an increase in white blood cell count could be a sign of an increase in stem cell count.[31] (D.I. 81 at 127:1-10; D.I. 82 at

[31] Dr. Mohty testified that an increase in white blood cells is "not connected" to an increase in stem cells. (D.I. 83 at 620:5-12.) But his testimony did not suggest that

275:18-276:7.) And because both white blood cells and stem cells express CXCR4, such a person could have hypothesized that an agent capable of mobilizing white blood cells through the CXCR4 receptor may also mobilize stem cells through that same receptor.[32] (D.I. 81 at 126:1-127:10.) It follows then that, based on Hendrix, a person of ordinary skill in the art would have understood that plerixafor may mobilize stem cells from the bone marrow into the peripheral blood by blocking the CXCR4 receptor. (DTX-109 at 5; D.I. 81 at 126:20-127:21, 155:9-23.)

97. Zydus would go even further, arguing that a person of ordinary skill in the art would have looked to plerixafor as a potential stem cell mobilizer because of its short duration of action. (D.I. 89 at ¶¶ 77-81.) Without a doubt, Hendrix discloses that plerixafor has a half-life of 3.6 hours and found that the white blood cell count peaks at 6

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there was no possible correlation between the two phenomena, only that they are not necessarily correlated. (*See* D.I. 83 at 620:5-10 (stating that "[t]here are several situations where your white blood cells can increase without any increase of your stem cells"), 621:2-6 (noting that "it was clear that white blood cells are not a good indicator for stem cell mobilization"), 621:10-12 ("[F]rom my own personal experience in the clinic, … when you have a lot of white blood cells, it may not be a good mobilization procedure.").) To the extent that Dr. Mohty suggested otherwise (*see* D.I. 83 at 621:7-9 ("So there's no correlation between $CD34^+$ cells and white blood cells when it comes to stem cell mobilization.")), I do not find that credible based on the other evidence in the record (DTX-109 at 5; D.I. 81 at 127:1-10; D.I. 82 at 275:18-276:7, 387:11-25; D.I. 83 at 555:11-17).

[32] Zydus asserts that a person of ordinary skill in the art would have known even more: "that white blood cells and stem cells are mobilized via the same mechanism." (D.I. 89 at ¶ 83.) Although Dr. Andreeff testified that "white blood [cell] mobilization and stem cell mobilization" involve "the same mechanism[,]" there is insufficient support for that contention elsewhere in the record. (D.I. 81 at 127:1-10.) Many agents that increased the white blood cell count were known not to similarly increase the stem cell count, which suggests that the mobilization mechanisms may not have been understood to be identical. (DTX-190 at 21; D.I. 83 at 555:11-15, 621:10-12.) I thus do not adopt Zydus's assertion.

hours, which aligns with a similar disclosure in WO '814 that plerixafor increases white blood cell counts over a 5- to 10-hour period after dosing. (DTX-109 at 1, 3; DTX-216 at 11; D.I. 81 at 124:19-125:6.) Hendrix and WO '814 also disclose that plerixafor is a short-acting drug with little to no effect after 24 hours. (DTX-109 at 3; DTX-216 at 11; D.I. 81 at 125:16-25.) But I find that none of those disclosures would have been meaningful in encouraging a person of ordinary skill in the art in September 2000 to use plerixafor as a stem cell mobilizer because, as already stated, such a person would not yet have recognized the need to consider the temporal aspect of CXCR4 blockers.[33]

98. Plaintiffs, on the other hand, proffer several reasons for discounting the weight a person of ordinary skill in the art would have given to Hendrix's suggestion that the increased white blood cell count may have been mediated by blocking CXCR4. (D.I. 88 at ¶¶ 92-95.) First, they say, a person of ordinary skill in the art would have understood that band cells are released with stem cells during mobilization and that bone pain is a common side effect of stem cell mobilization induced by G-CSF. (DTX-025 at 21; D.I. 83 at 617:6-618:2, 622:6-623:20; D.I. 84 at 778:20-779:5.) Hendrix noted, however, that plerixafor did not cause an increase in band cells or bone pain in the patients. (DTX-109 at 3; D.I. 83 at 617:6-19, 621:20-622:5.) Plaintiffs contend then that

[33] Zydus also encourages me to find a slew of facts to further support its motivation-to-pursue-plerixafor argument, including that plerixafor is a small molecule that does not suffer from the same known pharmaceutical disadvantages as proteins and peptides. (DTX-216 at 3; D.I. 89 at ¶¶ 85-87.) I do not make any of those findings, however, because Zydus does not point to any evidence corroborating Dr. Andreeff's suggestion that a person of ordinary skill in the art would have pursued plerixafor simply because plerixafor was a small molecule rather than a protein or peptide. (D.I. 81 at 133:22-134:12, 152:14-153:3; D.I. 89 at ¶¶ 85-87.)

a person of ordinary skill in the art would have read Hendrix to suggest that the increased white blood cell count following administration of plerixafor was due to demargination rather than CXCR4 inhibition because a correlated increase in the stem cell count should have caused an increase in band cells and bone pain. (D.I. 88 at ¶ 94; D.I. 98 at 9; D.I. 83 at 617:6-618:16.)

99. But Dr. Mohty confirmed that "it's not always true that you can see band cells when stem cells are mobilized" (D.I. 84 at 778:20-779:5), and that band cells are the last of many stages in the development of a stem cell into a mature white blood cell and express lower levels of CXCR4 than stem cells, which means a person of ordinary skill in the art would have understood that the effect of blocking CXCR4 on band cells may not have had the same effect as blocking CXCR4 on stem cells (D.I. 84 at 780:6-20, 784:6-11, 784:20-785:6, 785:16-25). Furthermore, bone pain is thought to be caused by the proliferation of white blood cells in the bone marrow that puts pressure on the bones following G-CSF administration, and the record evidence does not suggest that plerixafor was known in 2000 to cause a similar proliferation of stem cells in the bone marrow. (D.I. 83 at 617:20-618:2; D.I. 84 at 786:1-787:9, 787:10-13.) Thus, a person of ordinary skill in the art may not have expected plerixafor to cause bone pain. In addition, blocking the CXCR4 receptor, which was a known function of plerixafor, was not understood in the art to be associated with bone pain. (D.I. 84 at 788:17-20; D.I. 89 at ¶ 198; D.I. 98 at 29.)

100. Second, Plaintiffs point out that another publication from 2001 written by a research group at the National Institutes of Health cited Hendrix and only adopted its

demargination explanation as the cause for an increase in the white blood cell count. (PTX-595 at 9-10; D.I. 83 at 626:2-627:10.) But just because that later group of researchers selectively interpreted the data and theories reported in Hendrix does not erase or otherwise limit the alternative theory of CXCR4-mediated mobilization that would have been understood by a person of ordinary skill in the art.[34] (DTX-109 at 5; D.I. 81 at 126:1-25; D.I. 83 at 616:11-617:5.)

101. Third, Plaintiffs state that demargination has nothing to do with stem cells and that Hendrix provides no data on stem cells or any possible clinical use related to stem cells. (DTX-109; D.I. 82 at 333:9-16, 333:24-334:10, 335:7-9; D.I. 83 at 615:21-616:1, 617:6-14, 627:11-628:2.) That may be true, but it would not cause a person of ordinary skill in the art to ignore the stem cell hypothesis. (DTX-109 at 5; D.I. 81 at 126:1-25; D.I. 83 at 616:11-617:5.)

102. Finally, Plaintiffs argue that a person of ordinary skill in the art at the time Hendrix was published would have understood that platelets also express CXCR4, yet Hendrix did not report elevated platelet levels in the peripheral blood. (PTX-731 at 1; DTX-109 at 5; D.I. 83 at 618:3-12, 623:24-625:6.) Plaintiffs thus contend that a person of ordinary skill in the art would have connected the increased white blood cell count to demargination rather than the blocking of CXCR4. (D.I. 83 at 618:13-16, 627:11-24; D.I. 88 at ¶ 95.) But Hendrix does not address platelet levels at all. (DTX-109; D.I. 84 at 791:14-16.) It makes little sense to say that something unaddressed in the article – and as

[34] The same is true of Plaintiffs' argument that the authors of Hendrix "favored the demargination theory" merely because they reiterated that theory in their conclusion. (D.I. 88 at ¶ 92; *see also* DTX-109 at 6.)

to which there is nothing to suggest it should have been addressed – is a basis for discounting what is addressed in the article.[35]

b. *Hendrix Is Analogous Art*

103. Plaintiffs also contend that Hendrix should not simply be discounted but should not be considered at all. They say the Hendrix reference is irrelevant to the obviousness analysis in this case because it is not analogous art.[36] (D.I. 88 at ¶¶ 102-08.) A reference must be analogous to the claimed invention to be prior art for purposes of obviousness. *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015). Whether a reference is analogous art is a question of fact. *Id.* "Prior art is analogous if it is from the same field of endeavor or if it is reasonably pertinent to the particular problem the inventor is trying to solve." *Id.* Even though "familiar items may have obvious uses beyond their primary purposes," *id.* (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007)), a disputed prior art "reference is only reasonably pertinent when it 'logically would have commended itself to an inventor's attention in considering his problem,'" *id.* (quoting *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992)). That makes "the purposes of both the invention and the prior art" important to understanding the pertinence of a reference. *Clay*, 966 F.2d at 659. Whether a reference is reasonably pertinent "as a

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[35] Plaintiffs attempt to diminish the import of WO '814 for many of the same reasons they give for limiting the disclosure in Hendrix, including that WO '814 never mentions stem cells or stem cell mobilization, it only reports that plerixafor elevates total white blood cell count, and there is no link between the increased presence of white blood cells and the possible presence of stem cells. (D.I. 88 at ¶ 96.) That attempt by Plaintiffs meets the same fate as the attempt to discount Hendrix, and for the same reasons.

[36] The parties do not dispute that Aiuti, Möhle, Peled, Whetton, Lapidot, Konopleva, and WO '814 are analogous prior art. (D.I. 89 at ¶ 139; D.I. 98 at ¶ 139.)

source of solution to the inventor's problem" is something that "must be recognizable with the foresight of a person of ordinary skill, not with the hindsight of the inventor's successful achievement." *Sci. Plastic Prods., Inc. v. Biotage AB*, 766 F.3d 1355, 1359 (Fed. Cir. 2014).

104. Hendrix and the claims of the '590 Patent pertain to different fields of endeavor and are focused on different problems because, while the purpose of Hendrix was to test the safety and pharmacology of plerixafor for use as an HIV treatment, the purpose of Claims 8 and 19 of the '590 Patent is to use plerixafor to mobilize and harvest stem cells. (DTX-109 at 1; D.I. 71, App. A at ¶¶ 18-19, 49; D.I. 81 at 74:17-75:3; D.I. 82 at 313:16-22, 314:13-15, 331:24-332:3.) Dr. Mohty testified that the fields of anti-HIV agents and stem cell mobilizing agents are different (D.I. 83 at 612:21-613:2), and Dr. Andreeff noted that plerixafor was developed to block CXCR4 in the HIV context, which he described as "an entirely different context" (D.I. 81 at 124:19-125:6). Furthermore, Hendrix was published in Antimicrobial Agents and Chemotherapy, a journal focused on infectious diseases and anti-infective chemotherapeutic agents rather than anti-cancer chemotherapeutic agents. (DTX-109 at 1; D.I. 82 at 332:18-333:5; D.I. 83 at 612:7-15.) Exemplifying that articles in the journal were generally unrelated to the field of stem cell mobilization, Dr. Mohty testified that he never published in the journal and could not recall ever having consulted the journal before this case. (D.I. 83 at 612:16-20.) Thus, Hendrix is not from the same field of art as the invention, and it is only analogous art if it would have been reasonably pertinent to the particular problem facing the inventors. *See Circuit Check*, 795 F.3d at 1335 (stating that "the disputed prior art can be analogous

only if it is reasonably pertinent to the particular problem solved by the inventor" because it "is not part of the [invention's] field [of art]").

105. Hendrix was placed before the Examiner at the USPTO during the prosecution of the '590 Patent (JTX-003A at 465; JTX-004 at 2; D.I. 82 at 399:3-24), and the Examiner concluded that Hendrix was not analogous art (PTX-777 at 3). The Examiner said that Hendrix, which it described as "[t]he closest prior art," teaches that plerixafor "selectively blocks CXCR-4 receptor mediated entry of HIV-1 into $CD4^+$ T-cells[;] however it does not suggest the use as instantly claimed – harvesting progenitor and/or stem cells from peripheral blood." (PTX-777 at 3.) The Examiner went on to conclude that, "while the art teaches generation/harvesting of stem/progenitor cells from blood using CXCR4 antagonists (e.g. TUDAN), one would not have looked to the HIV therapeutic art in order to find a suitable antagonist for collection of stem/progenitor cells." (PTX-777 at 3.)

106. In the Prior Related MOZOBIL® Litigations, this Court concluded similarly and found that, "a POSA would [not] have pursued CXCR-4 over the proven field of cytokines and other possible stem cell mobilizers," and that, "[w]ithout a specific focus on CXCR-4, *Hendrix* would not have been reasonably pertinent to a [person of ordinary skill in the art] focused on harvesting stem cells." *Genzyme Corp.*, 2016 WL 2757689, at *11. This Court said that it "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." *Id.* (internal quotation marks and citation omitted).

107. Zydus counters, however, that Hendrix qualifies as analogous prior art. As of September 2000, researchers were studying the role of SDF-1 and CXCR4 in stem cell migration (DTX-012; DTX-161; DTX-172; DTX-142; DTX-148; D.I. 81 at 109:3-111:14), and a person of ordinary skill in the art would have wanted to familiarize himself or herself with the available CXCR4 blocking agents (D.I. 81 at 152:9-11; D.I. 83 at 775:14-18). Specifically, the proposal in Konopleva to block the interaction between SDF-1 and CXCR4 to increase stem cell mobilization may have led such a person to look for a CXCR4 blocker. (DTX-142 at 4; D.I. 81 at 151:16-152:11; D.I. 83 at 709:12-710:3.) It follows, then, that scientific literature disclosing CXCR4 blockers would have been reasonably pertinent to a person of ordinary skill in the art interested in new agents to improve stem cell mobilization as of September 2000 through a potential CXCR4-inhibiting mechanism. (D.I. 81 at 128:4-9; D.I. 84 at 775:14-18.) Hendrix disclosed in its title and in its body that plerixafor is a CXCR4 blocker. (DTX-109 at 1.) Thus, Hendrix would have logically commended itself to a person of ordinary skill in the art to carry out Konopleva's proposed method of mobilizing stem cells. (D.I. 81 at 127:16-128:9.)

108. Although Plaintiffs make much of the fact that the purpose in Hendrix was to conduct an HIV-related, rather than stem cell mobilization-related, study (D.I. 88 at ¶¶ 104, 108), that argument is undercut by another HIV-related article that a person of ordinary skill in the art would have known about. Doranz *et al.*, *A Small-molecule Inhibitor Directed against the Chemokine Receptor CXCR4 Prevents its Use as an HIV-1 Coreceptor*, Journal of Experimental Methods, 186(8):1395-1400 (1997), is a publication

from 1997 that concerned a polypeptide known as ALX40-4C, which inhibited CXCR4 expression. (PTX-240; D.I. 84 at 776:7-13, 777:3-21.) Doranz is directed to HIV research and does not address whether ALX40-4C might also mobilize stem cells. (PTX-240; D.I. 84 at 776:5-6, 776:17-21.) Nevertheless, despite the fact that Doranz is directed to HIV research, Dr. Mohty admitted that a person of ordinary skill in the art would have been aware of that publication as of September 2000. (D.I. 84 at 775:19-21.) Therefore, based on facts I have already found, including that the problem facing the inventors was identifying a stem cell mobilizer that improved upon G-CSF, that a person of ordinary skill in the art would have been motivated to at least try blocking CXCR4 to reach that goal, and that such a person would want to familiarize himself or herself with CXCR4 blockers such as the ALX40-4C drug discussed in Doranz, it follows that the discussion of plerixafor in Hendrix as a CXCR4 inhibitor would have been reasonably pertinent to a person of ordinary skill in the art.[37] (D.I. 81 at 128:4-9; D.I. 84 at 775:14-21.)

109. Although the Examiner of the application that ultimately resulted in the '590 Patent and this Court in the Prior Related MOZOBIL® Litigations reached a different conclusion, neither had before it all the evidence presented here. Specifically,

[37] Plaintiffs contend that Doranz would have commanded more attention from a person of ordinary skill in the art than Hendrix because, unlike Hendrix, which was published in a "specialized anti-infective journal[,]" Doranz was published "in a general purpose scientific journal" called the Journal of Experimental Medicine. (D.I. 98 at ¶ 148; *see also* PTX-240; D.I. 83 at 612:7-15; D.I. 84 at 775:22-776:4.) But Plaintiffs do not explain why the search by a person of ordinary skill in the art for a CXCR4 blocker would be so limited, *see Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1001 (Fed. Cir. 2016) ("The field of endeavor of a patent is not limited to the specific point of novelty, the narrowest possible conception of the field, or the particular focus within a given field."), especially in the age of broad-based computer searches. Therefore, I do not think that the distinction identified by Plaintiffs undercuts the pertinence of Hendrix.

although the goal remains the same (*i.e.*, identifying a stem cell mobilizer that improves upon G-CSF), Lapidot and Konopleva were neither placed before the Examiner nor this Court in the Prior Related MOZOBIL® Litigations to allow them to consider whether a person of ordinary skill in the art may have been motivated to at least try CXCR4 blockers to achieve that goal. (JTX-003A at 465-66; PTX-777 at 3); *see also Genzyme Corp.*, 2016 WL 2757689, at *6-7, *10-11. For those reasons, I find that Hendrix would have been reasonably pertinent in September 2000 to a person of ordinary skill in the art investigating new stem cell mobilizing agents that improve upon G-CSF (D.I. 81 at 128:4-9), and thus Hendrix is analogous prior art.[38]

c. *Closest Prior Art*

110. The parties dispute the closest prior art at the time of invention. Plaintiffs contend that G-CSF, either with or without chemotherapy, is the closest prior art. (D.I. 88 at ¶ 119.) But Zydus disagrees and argues that Konopleva is closer.[39] (D.I. 89 at

[38] Although not dispositive of the pertinence of Hendrix as prior art, the fact that the named inventors of the '590 Patent disclosed Hendrix to the PTO during the prosecution of that patent supports my conclusion because it suggests that they too thought it may have been pertinent to their invention. *See Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1279 (Fed. Cir. 2003) ("[W]ith the mere listing of references in an [Information Disclosure Statement], the applicant has admitted no more than that the references in the disclosure may be material to prosecution of the pending claims."); (*see also* JTX-003A at 465; D.I. 82 at 398:14-17, 399:7-24).

[39] Zydus argues alternatively that Konopleva "in combination with either Hendrix or WO '814" is the closest prior art. (D.I. 89 at ¶ 223; *see also* D.I. 100 at 28.) Although there does not appear to be much guidance from the Federal Circuit on determining the closest prior art, a dated case from the Court of Customs and Patent Appeals suggested that the closest prior art is a single reference. *See In re Merchant*, 575 F.2d 865, 868 (C.C.P.A. 1978) (focusing on "the closest single prior art reference" in its search for the closest prior art); *cf.* European Patent Office, Guidelines for Examination, pt. G, ch. VII,

¶ 223; D.I. 100 at 28.) I agree with Plaintiffs. G-CSF was the most widely used mobilization agent in September 2000, and, as I found earlier, both experts in this case recognized that it was the "gold standard" for stem cell mobilization at that time. (D.I. 83 at 734:7-12; *see also* D.I. 81 at 109:3-20; D.I. 83 at 683:9-14.) Moreover, Dr. Mohty testified that G-CSF, with or without chemotherapy, is the closest prior art (D.I. 83 at 683:9-12), and Dr. Andreeff never stated an opinion on what a person of ordinary skill in the art would have understood the closest prior art to be at the time of invention. Therefore, there is practically no support in the record for Zydus's position that Konopleva is the closest prior art, and, as a result, I find otherwise. G-CSF is the closest prior art.

d. *Plerixafor Ultimately Fulfilled the Need for an Improved Stem Cell Mobilizer*

111. As noted earlier, plerixafor is a molecule that a person of ordinary skill in the art may have turned to in improving upon stem cell mobilization with G-CSF through the proposed CXCR4-blocking mechanism. As of September 2000, a person of ordinary skill in the art could well have been motivated to combine Konopleva's express proposal that blocking the CXCR4 receptor on stem cells may improve upon G-CSF-induced mobilization with Hendrix's suggestion that plerixafor, which mobilizes white blood

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§ 5.1 (Nov. 2017), *available at* http://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vii_5_1.htm ("The closest prior art is that which in *one single reference* discloses the combination of features which constitutes the most promising starting point for a development leading to the invention." (emphasis added)). *But see Sanofi-Aventis Deutschland Gmbh v. Glenmark Pharm. Inc., USA*, No. 07-5855, 2011 WL 383861, at *8 (D.N.J. Feb. 3, 2011) ("[T]he 'closest prior art' does not mean only the single, closest reference, but rather refers to … all the prior art used by the Patent Office or by a challenger in a suit challenging the patent's validity.").

cells, may also mobilize stem cells. (DTX-109 at 5; DTX-142 at 4; D.I. 81 at 151:16-152:11; D.I. 83 at 709:12-710:3.) Plerixafor would have been one compound worth trying because it was known to block the CXCR4 interaction with SDF-1 (DTX-109 at 5; D.I. 83 at 700:8-14); it was known to increase white blood cell counts, which could be a sign of an increase in stem cell count (DTX-109 at 5; D.I. 81 at 127:1-10; D.I. 82 at 275:18-276:7); it had already been proven to be safe and well tolerated in humans at a dosage range shown to increase white blood cell counts (DTX-109; DTX-216 at 11; D.I. 81 at 133:14-134:12); and Hendrix hypothesized that it may mobilize stem cells (DTX-109 at 5).

112. But it should not be lost on those of us looking back to September 2000 that a person of ordinary skill in the art would not have had a reasonable expectation that using plerixafor as a stem cell mobilizer would succeed. Again, based on the uncertainties regarding the mechanisms of stem cell mobilization, the known complexity in the art, and the fact that G-CSF, SCF, and IL-6 were known stem cell mobilizers that increased CXCR4 expression, even if a person of ordinary skill in the art may have given plerixafor a try, that does not mean that such a person could, at that time, have reasonably expected it would succeed in mobilizing stem cells.[40] (DTX-142 at 4; DTX-148 at 4;

[40] Zydus's reliance on testimony from Drs. Henson, Dale, MacFarland, and Abrams to support its contention that a person of ordinary skill in the art would have reasonably expected plerixafor to mobilize stem cells is unhelpful because there is no evidence in the record that those named inventors are persons of ordinary skill in the art, rather than having above-ordinary skill. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material."); *Bausch & Lomb, Inc. v. Barnes-*

DTX-172 at 3-5; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2, 692:19-693:20.) Furthermore, although the ability of plerixafor to completely inhibit the CXCR4/SDF-1 interaction would have supported the purported mobilization theory at that time, it also would have suggested to a person of ordinary skill in the art that the affected stem cells would not home or engraft well, which are capacities essential to the overall stem cell transplantation process. (DTX-214 at 3; D.I. 81 at 85:3-86:12; D.I. 83 at 720:9-20; D.I. 84 at 743:11-744:11.)

113. Nevertheless, the use of plerixafor in stem cell transplantation was ultimately a success story. The need for a stem cell mobilizer better than G-CSF was finally fulfilled in December 2008 when MOZOBIL® was approved for use in the United States. (D.I. 83 at 653:13-18, 659:8-12.) It was the first and only CXCR4 blocker approved by the FDA for such purposes, and the FDA has not approved any other stem cell mobilizing agents to join it and G-CSF. (D.I. 83 at 691:10-20.)

114. Plerixafor is successful at increasing stem cell mobilization in a broad range of subjects, including mice, macaques, healthy human subjects, and, most importantly, cancer patients. (JTX-018 at 2; JTX-019 at 2; JTX-028 at 2; JTX-033 at 36; PTX-238 at 2, 10; D.I. 82 at 352:19-353:16, 354:17-355:8, 368:16-369:15.) In the first Phase II clinical trial, plerixafor in combination with G-CSF mobilized more stem cells than using G-CSF alone, including in patients who failed to reach the minimum target using G-CSF alone. (JTX-033 at 32, 34; D.I. 82 at 364:20-368:12.). The Phase III trials

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Hind/Hydrocurve, Inc., 796 F.2d 443, 448 (Fed. Cir. 1986) (concluding that it was error for a district court to substitute an inventor's opinion for the knowledge a hypothetical person of ordinary skill would have had).

further demonstrated the advantages of administering plerixafor in combination with G-CSF, because it was well-tolerated by the patients and resulted in a significantly higher proportion of patients achieving the optimal stem cell collection target in fewer apheresis sessions in comparison to patients treated with G-CSF alone. (PTX-235 at 1; PTX-236 at 1; D.I. 83 at 673:10-25, 674:25-675:14.) Therefore, administration of plerixafor, both alone and in combination with G-CSF, has the unnatural effect of amplifying the natural phenomenon of stem cell mobilization. (JTX-004 at 14; D.I. 81 at 88:11-21, 95:5-18; D.I. 83 at 659:8-21, 798:2-800:3.)

115. The combination of plerixafor and G-CSF has been shown to mobilize more stem cells and exhibit less toxicity than G-CSF combined with chemotherapy. (PTX-686 at 1-2, 5.) That has led to "a strong case for preferring plerixafor+G-CSF to chemotherapy+G-CSF for first line [mobilization] of lymphoma and myeloma patients requiring [stem cell transplant]" (PTX-686 at 2), and "for first-line plerixafor as the standard of care for [stem cell mobilization]" in patients with multiple myeloma or non-Hodgkin's lymphoma (PTX-686 at 5; *see also* D.I. 83 at 665:7-666:13).

116. MOZOBIL® was the first agent to satisfy each of the outstanding needs, including increased numbers of stem cells in the peripheral blood, fewer apheresis sessions, and minimal toxicity. (D.I. 83 at 659:8-23.) Its large impact on stem cell transplantation is exemplified by the many peer-reviewed publications discussing the drug, including thirty-nine stem cell transplantation experts' stated belief in 2009 that plerixafor would "likely change the current standards for stem cell transplantation and mobilization" (PTX-269 at 6; *see also* D.I. 83 at 659:24-661:6), and a 2012 report that

"[w]ith the availability of plerixafor for stem cell mobilization, most patients are now able to yield stem cells successfully" (PTX-177 at 1; *see also* D.I. 83 at 676:1-23). Another publication from 2011 described plerixafor as a "new and important agent for mobilization." (JTX-053 at 1; *see also* D.I. 83 at 661:7-662:22.) Today, plerixafor is very clearly part of the standard of care for stem cell mobilization. (D.I. 83 at 685:6-9.)

117. Therefore, the methods claimed in Claims 8 and 19 of the '590 Patent, which embody the FDA approved use of MOZOBIL® as a stem cell mobilizer in combination with G-CSF (D.I. 71, App. A at ¶ 28), provide significant medical benefit by "decreas[ing] the number of patients who fail to collect the minimum number of $CD34^+$ stem cells necessary for transplantation" and by lowering the number of "patients [who] will be transplanted with suboptimal numbers of [stem cells]," which may allow avoidance of delayed hematopoietic recovery, augmented need for blood transfusions, higher rates of infection, and longer hospital stays (PTX-381 at 11; *see also* D.I. 83 at 663:5-665:6).

118. MOZOBIL® also has the unexpected benefit of improving the quality of harvested stem cells in comparison to those cells mobilized using G-CSF alone. (JTX-021 at 8; PTX-238 at 10-12; PTX-261 at 1; D.I. 83 at 679:19-680:2.) Using G-CSF and plerixafor together mobilizes more Severe Combined Immunodeficiency ("SCID") Repopulating Cells[41] than either G-CSF or plerixafor alone, which is an indication of the

[41] Dr. Andreeff testified that Severe Combined Immunodeficiency ("SCID") Repopulating Cells are stem cells in immunodeficient mice models (D.I. 81 at 120:23-122:10), and Dr. Mohty testified that they are "a good measurement of the strength of your engraftment" and they "highlight the quality of the cells" (D.I. 83 at 679:9-16).

presence of higher quality stem cells.[42] (JTX-021 at 8; PTX-238 at 10-12; PTX-261 at 1, 8; D.I. 83 at 677:15-681:13.) Furthermore, an additional unexpected benefit of MOZOBIL® is its ability to rapidly mobilize stem cells in just a few hours compared with the slower-acting nature of G-CSF, which takes four to six days to cause mobilization. (PTX-177 at 1, 4; PTX-216 at 14-15; D.I. 83 at 681:15-682:15, 683:4-14, 705:8-11.)

119. Plerixafor has been praised by experts as a "new and important agent" and "major advance" that has "strongly impacted" the field of stem cell transplantation. (JTX-053 at 1; PTX-181 at 7; PTX-285 at 1; *see also* D.I. 83 at 688:6-12, 689:10-19, 690:16-24.) Many publications have praised the use of plerixafor in combination with G-CSF for stem cell mobilization. (PTX-177 at 1; PTX-216 at 8; PTX-238 at 10; *see also* D.I. 83 at 670:9-671:10.) The American Society for Blood and Marrow Transplantation concluded in its guidelines for peripheral blood stem cell mobilization that "[p]lerixafor plus G-CSF (without chemotherapy) results in the highest success when used in the standard manner and is the preferred approach[.]" (PTX-248 at 8; *see also* D.I. 83 at 684:21-685:4.) Moreover, researchers at Washington University indicated that, "like

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[42] Zydus disagrees that the improved quality of stem cells harvested following administration of G-CSF and plerixafor was unexpected as of September 2000 because Konopleva predicted that blocking CXCR4 would mobilize stem cells with "high engraftment capability." (DTX-142 at 4; D.I. 100 at 30.) I have already noted, however, that the Peled article cited in Konopleva contradicts the suggestion that blocking the interaction between SDF-1 and CXCR4 could result in "stem cells with high engraftment capability" because the data in Peled demonstrated that two different CXCR4 antibody blocking agents reduced engraftment of stem cells. (DTX-142 at 4; *see also* DTX-172 at 3; D.I. 82 at 249:15-20; D.I. 88 at ¶ 79.) Furthermore, the publications Plaintiffs cite suggest that the mechanism was not clearly understood even as of 2009 and that enhanced homing of those stem cells may not be the answer. (JTX-021 at 10; PTX-261 at 8.)

many others," their institution uniformly administers plerixafor for autologous stem cell transplantation in all multiple myeloma and non-Hodgkin's lymphoma patients. (PTX-682 at 13; *see also* D.I. 83 at 686:4-687:7.)

120. Notably, the drug has also received numerous awards. In 2010, the U.K. version of MOZOBIL® was selected as a finalist in the competition for the Prix Galien Award in the U.K. in the orphan drug category for the U.K. market. (D.I. 71, App. A at ¶ 93.) In 2011, the Spanish version of MOZOBIL® was awarded the Prix Galien Award in Spain for Best Pharmaceutical of the Year. (D.I. 71, App. A at ¶ 91; D.I. 83 at 691:21-692:3.) In 2013, the Greek version of MOZOBIL® was awarded the Prix Galien Award in Greece for Best Pharmaceutical of the Year. (D.I. 71, App. A at ¶ 92; D.I. 83 at 691:21-692:3.) While the U.S. version of MOZOBIL® has not received a comparable award to those Prix Galien Awards, (D.I. 71, App. A at ¶¶ 91-93), Zydus does not dispute that MOZOBIL® has received a great deal of industry praise.[43] (D.I. 100 at 32.)

e. *The Presence of Blocking Patents*

121. AnorMED controlled access to plerixafor through September 2000. (D.I. 81 at 134:13-15; D.I. 82 at 294:5-10.) The '131 Patent, which reissued as the '152 Patent, blocked researchers from using plerixafor beginning in December 1996. (PTX-008; PTX-006; D.I. 81 at 134:13-15, 294:5-10.) Plaintiffs acquired ownership of the '131 Patent and rights to the '152 Patent when it acquired AnorMED. (PTX-127 at ¶ 19;

[43] Plaintiffs contend that a bidding war between Genzyme and Millennium for AnorMED further demonstrates the praise and value of MOZOBIL®. (D.I. 82 at 371:15-23; D.I. 88 at ¶ 136.) But there is no evidence to corroborate Dr. Abrams's suggestion that the bidding war was due primarily to an interest in plerixafor or rights to the '102 and '590 Patents.

D.I. 82 at 371:15-23.) The fact that Plaintiffs held those blocking patents leading up to September 2000 is significant because it may impact the relevance of some secondary considerations in the obviousness analysis, such as long-felt but unsolved need and the failure of others. *See infra* COL ¶¶ 47, 49.

122. Plaintiffs argue that the '131 and '152 Patents did not block researchers from using plerixafor because AnorMED had a system for allowing researchers interested in using a compound like plerixafor to submit a compound request form. (D.I. 98 at ¶ 212; D.I. 82 at 421:24-422:17.) But the Federal Circuit has defined a "blocking patent" as "an earlier patent that must be licensed in order to practice a later patent." *Prima Tek II, L.L.C. v. A-Roo Co.*, 222 F.3d 1372, 1379 n.2 (Fed. Cir. 2000). There is no indication in the case law that a patent is no longer a blocking one merely because the patentees may allow the claimed invention to be practiced or otherwise used. The point is that the patentees controlled access to the technology.

III. DISCUSSION AND CONCLUSIONS OF LAW

1. The Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Zydus does not contest personal jurisdiction. *See Burger King Corp. v. Rudzewicz*, 471 U.S. 462, 472 n.14 (1985) ("[T]he personal jurisdiction requirement is a waivable right[.]"); (*see also* D.I. 10 at ¶¶ 7-8 ("Zydus does not contest personal jurisdiction in this Court solely for purposes of Genzyme's claims against Zydus in this case.")). Venue is proper under 28 U.S.C. §§ 1391 and 1400(b).

2. After considering the substantial evidence in the entire record, the parties' post-trial submissions, and the applicable law, I draw six main conclusions. First, the

inventors of the '590 Patent conceived of the invention as of September 27, 2000.[44] Second, the Andreeff Letter does not invalidate Claims 8 and 19 of the '590 Patent under 35 U.S.C. §§ 102(f). Third, those claims are not obvious under 35 U.S.C. § 103 in light of Konopleva, Hendrix, WO '814, the Andreeff Letter, or any combination of those or other prior art references noted by the parties. Fourth, Claims 8 and 19 of the '590 Patent do not recite patent ineligible subject matter pursuant to 35 U.S.C. § 101. Fifth, Plaintiffs are entitled to injunctive relief. Finally, Plaintiffs are not entitled to attorneys' fees. My reasoning follows.

A. Conception

3. I begin by identifying the date of conception of the invention embodied in the '590 Patent. "Conception is the touchstone of invention[.]" *In re VerHoef*, 888 F.3d 1362, 1366 (Fed. Cir. 2018) (quoting *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1227-28 (Fed. Cir. 1994)). It "defines the legally operative moment of invention[.]" *Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052, 1063 (Fed. Cir. 2005). It "is 'the formation, in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.'" *REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016) (citation and emphasis omitted). Conception is a legal question based on underlying factual findings. *Id.* at 958. It involves a subjective rather than objective inquiry. Conception is not based on "whether one skilled in the art could have thought of the invention, but

[44] I reiterate that the analysis herein is directed to Claims 8 and 19 of the '590 Patent because Zydus has acknowledged that the conclusions with respect to Claim 8 of that patent are fully applicable to Claim 8 of the '102 Patent. *See supra* FOF ¶ 33.

[rather it depends on] whether the alleged inventors actually had in their minds the required definite and permanent idea." *Dawson v. Dawson*, 710 F.3d 1347, 1356 (Fed. Cir. 2013) (quoting *Burroughs*, 40 F.3d at 1232).

4. A bare idea will not suffice. *Burroughs*, 40 F.3d at 1229. Instead, conception requires a three-part showing. *Id.* at 1228-30. First, the idea must be definite and permanent, which means the inventors must have had "a specific, settled idea, a particular solution to the problem at hand, [and] not just a general goal or research plan [they] hope[d] to pursue." *Id.* at 1228. Second, the idea "must also be sufficiently precise that a skilled artisan could carry out the invention without undue experimentation." *Id.* at 1230. Finally, "of course, the alleged conception must be supported by corroborating evidence." *Id.* Because conception is "keyed to the *claimed* invention[,]" it "must encompass all limitations of the claimed invention." *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1218 (Fed. Cir. 2017) (citation omitted).

5. Those three requirements were satisfied here as of September 27, 2000. As of that date, written documentation confirms that the named inventors had a specific and settled idea of improving stem cell mobilization by administering plerixafor, both alone and in combination with G-CSF. Well before September 2000, AnorMED had conducted clinical study 98-01, in which it observed an increase in the white blood cell count in all subjects. (DTX-109 at 3; D.I. 82 at 312:20-314:21, 435:8-12.) Although AnorMED originally hypothesized that the most likely cause of that increase was demargination (D.I. 82 at 334:11-23, 337:4-7, 413:6-18, 436:2-10), Dr. Kubes's final report helped it

reject that theory before September 2000 in favor of the hypothesis that the white blood cells were being mobilized from the bone marrow (DTX-109 at 5; JTX-064 at 1-2, 9; JTX-072 at 2-3; D.I. 82 at 318:17-319:19, 337:14-20, 412:23-413:18, 435:13-437:13). And that hypothesis had implications for potentially using plerixafor to mobilize stem cells because, as of September 2000, a person of ordinary skill in the art would have thought that, although not always true, an increase in white blood cell count could be a sign of an increase in stem cell count. (D.I. 81 at 127:1-10; D.I. 82 at 275:18-276:7.) The AnorMED scientists had such skill, and the evidence shows they had that thought.

6. The corroborating evidence proves that. A "Food for Thought" presentation from October 9, 1999, which was shared among the leading researchers at AnorMED, noted the potential use of plerixafor both alone and with G-CSF to mobilize and harvest stem cells for stem cell transplant. (JTX-064 at 1, 9-12; D.I. 82 at 319:20-320:4, 321:4-322:20, 323:2-22, 325:8-328:6, 328:19-329:21, 330:23-331:16, 444:11-446:21.) Drs. Bridger, Abrams, Henson, MacFarland, Calandra, Dale, and Broxmeyer all participated in preparing Version 1.1 of the protocol for the AMD3100-1002 Phase I clinical trial, which is dated September 27, 2000, and included as one of its aims testing whether administration of plerixafor could mobilize stem cells in healthy volunteers suitable for harvesting and use in stem cell transplantation.[45] (JTX-067 at 1, 7-9; D.I. 71, App. A at ¶¶ 53-54; D.I. 82 at 346:11-347:10, 415:3-5, 415:8-13, 416:3-21, 419:14-

[45] A definite and permanent idea of the other limitations of Claims 8 and 19 of the '590 Patent were also documented in that protocol. Specifically, mobilized stem cells were to be harvested using a density cut procedure. (JTX-008 at 3; Broxmeyer Dep. Tr. Direct Q16-17, 19; D.I. 83 at 629:4-630:5, 639:11-640:12; D.I. 84 at 797:9-24.)

420:14; D.I. 83 at 631:20-634:17.) Thus, the named inventors had a definite and permanent idea for mobilizing stem cells using plerixafor; it was not just a bare hope or general goal or research plan.

7. But, as Zydus sees it, that is not enough to prove conception of the claimed invention. Zydus relies largely on the Federal Circuit's decision in *Hitzeman v. Rutter*, 243 F.3d 1345 (Fed. Cir. 2001), to argue that conception of the invention claimed in Claims 8 and 19 of the '590 Patent also requires showing that the inventors had a reasonable expectation of success. Plaintiffs disagree, emphasizing the Federal Circuit's decision in *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, 40 F.3d 1223 (Fed. Cir. 1994), for the proposition that conception does not require such a showing.

8. In *Burroughs*, the plaintiff had six patents covering methods of using a drug to treat persons infected with HIV or acquired immunodeficiency syndrome ("AIDS"), including five patents interpreted as covering methods of using an effective amount of that drug to treat persons who have contracted HIV or AIDS and a sixth patent covering a method of using an effective amount of that drug to increase the number of T-lymphocytes in a person infected with HIV.[46] 40 F.3d at 1225 & nn.1, 3-4. The parties

[46] Five of the patents included claims such as "[a] method of treating a human having acquired immunodeficiency syndrome comprising the oral administration of an effective acquired immunodeficiency syndrome treatment amount of 3'-azido-3'-deoxythymidine to said human[,]" and "[a] method of treating a human having an HTLV III virus infection comprising administering to said human an effective HTLV III virus treatment amount of 3'-azido-3'-deoxythymidine." *Burroughs*, 40 F.3d at 1225 n.3 (first and third alteration in original). Although two of those five patents claimed pharmaceutical compositions, the court nevertheless adopted the district court's and parties' treatment of those claims as covering a particular use of the drug to treat HIV or AIDS. *Id.* at 1225 n.1. The sixth patent claimed "[a] method of increasing the number of

disputed whether "the inventor's definite and permanent idea must include a reasonable expectation that the invention will work for its intended purpose." *Id.* at 1228. The Federal Circuit held that it does not because "[a]n inventor's belief that his invention will work or his reasons for choosing a particular approach are irrelevant to conception." *Id.* It repeated that "an inventor need not know that his invention will work for conception to be complete" and that all he needs to show is "that he had the idea[.]" *Id.* The court said that "the discovery that an invention actually works is part of its reduction to practice." *Id.*

9. Applying that rule to the facts in the case before it, the Federal Circuit held that the district court correctly concluded that, by the critical date, the inventors had conceived of the invention of the first five patents claiming methods of using an effective amount of the drug to treat persons with HIV and AIDS. *Id.* at 1230. Documentation demonstrated that, at that time, the inventors had drafted a patent application that expressly disclosed the intended use of the drug to treat AIDS, including details for preparing a pharmaceutical formulation of the drug and ways to use it to treat patients infected with HIV. *Id.* That the operability of the drug in treating patients having HIV or AIDS was not confirmed until later did not eliminate the inventors' conception of the first five patented inventions. *Id.* at 1230-31.

T-lymphocytes in a human infected with the HTLV III virus comprising administering to said human an effective amount of 3'-azido-3'-deoxythymidine or a pharmaceutically acceptable alkali metal, alkaline earth or ammonium salt thereof." *Id.* at 1225 n.4 (alteration in original).

10. With respect to the sixth patent, however, which involved a claimed method of using an effective amount of the drug to increase the number of T-lymphocytes in a person infected with HIV, the Federal Circuit held that there was insufficient record evidence to conclude whether the inventors had conceived of that claimed invention by the critical date. *Id.* at 1231-32. There was an open question whether the inventors had conceived of the invention in the sixth patent only after it learned the results of a study showing that the drug increased a person's T-lymphocytes. *Id.* at 1232.

11. In *Hitzeman*, the Federal Circuit expanded upon the distinction it drew in *Burroughs* between the proof required to show conception of the inventions in the first five patents and that required to show conception of the invention in the sixth patent. *Hitzeman* involved a patent interference proceeding for determining which of two sets of inventors was the first to conceive of claims directed to producing a hepatitis B vaccine using genetically altered yeast to obtain surface antigen in a particle form having a specific particle size and sedimentation rate. *Hitzeman*, 243 F.3d at 1348-52. The Federal Circuit held that the junior parties had not conceived of the claimed invention before the senior parties. *Id.* at 1358. According to the Court, while the junior parties "claimed the specific result of a biological process[,]" they "failed to show that [they] had a reasonable expectation that the claimed result of the biological process would occur[.]" *Id.* The court reasoned that, because they "chose to claim the invention by reciting the particular result of an intracellular process, *i.e.*, the production of [surface antigen particles of a specific size] in yeast that had been transformed with a vector containing [a

specific] gene[,]" they had to show that they had "a 'definite and permanent idea of the complete and operative invention,' including that yeast would express the [specific] gene, and that the expressed [protein] would be assumed into … particles [of the specifically claimed size]." *Id.* at 1356 (quoting *Gunter v. Stream*, 573 F.2d 77, 80 (C.C.P.A. 1978)). Despite evidence that the junior parties hoped to obtain the results at the time of disputed conception, that hope did not complete the conception because they did not reasonably expect at that time that the claimed limitations would actually be met. *Id.* at 1357.

12. The Federal Circuit said that its holding in *Hitzeman* was consistent with its holding in *Burroughs*. *Id.* at 1358. It explained that, unlike the first five patents at issue in *Burroughs* in which the inventor claimed a method of using a drug "without reciting details of how the human body would react to the drug[,]" the claims at issue in *Hitzeman* included limitations directed at the specific result of a biological process. *Id.* It analogized the claims in *Hitzeman* to the claims of the sixth patent at issue in *Burroughs*, which "recited details of an anticipated immune response to [a] drug[,]" and said that, under those circumstances, inventors have conceived of their claimed invention only if they had a reasonable expectation that they would produce the specified result. *Id.*

13. Thus, it would appear, the language chosen for a claim determines whether conception requires the inventors to have "had a reasonable expectation that they would produce the claimed invention."[47] *Hitzeman*, 243 F.3d at 1358. Conception does not

[47] While I think this is the conclusion to be drawn from *Hitzeman*, I confess some confusion. It makes sense that the evidence necessary to prove conception of a claimed invention depends on what is claimed, but it seems strange that the *test* for establishing the historical fact of conception should change depending on nuances in the claim

require "the inventor[s] [to have] had a reasonable expectation that the [claimed invention], once completed, would work for its intended purpose" so long as that intended purpose is not a limitation stated in the claims. *Id.* Once that purpose is stated in a claim, however, conception cannot be held to have existed unless the inventors had a reasonable expectation that the invention would work for that purpose.[48] *Id.*

14. Here, looking at the specific language in Claims 8 and 19 of the '590 Patent, those claims expressly recite, in relevant part, methods of obtaining stem cells from a subject by administering plerixafor, or plerixafor in combination with G-CSF, "in an amount effective to mobilize said … stem cells into the peripheral blood of said

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language that a patent drafter later chooses. Shouldn't there be only one test for conception, regardless of the claim language?

[48] Plaintiffs argue for a different point of distinction between *Hitzeman* and *Burroughs*. They contend that the "reasonable expectation" rule from *Hitzeman* only applies to claims directed at devices or novel compositions, not methods of using known compositions, such as those at issue in *Burroughs*. (D.I. 99 at 15-16.) That is an interesting argument, but it is difficult to square with the Federal Circuit's characterization of the claims of the sixth patent at issue in *Burroughs* as a method claim requiring proof of "a reasonable expectation that the claimed result of the biological process would occur," *id.*, as well as the fact that one of the claims at issue in *Hitzeman* was a method claim, *id.* at 1352 n.2.

Plaintiffs also argue that the Federal Circuit's decision in *University of Pittsburgh of Commonwealth System of Higher Education v. Hedrick*, 573 F.3d 1290 (Fed. Cir. 2009), confirms that *Burroughs*, not *Hitzeman*, articulates best the current state of the law. In that case, the Federal Circuit rejected the argument that inventors are "required to 'know' that the invention contained every limitation of each claim at the time of conception[.]" *Id.* at 1299. It said that "[k]nowledge in the context of a possessed, isolated biological construct does not mean proof to a scientific certainty that the construct is exactly what a scientist believes it is" and that "[p]roof that the invention works to a scientific certainty is reduction to practice" rather than conception. *Id.* The court said "it is immaterial that [the inventors'] knowledge was not scientifically certain[.]" *Id.* But no one argues here that conception requires scientific certainty or knowledge that each claim limitation will be achieved, only that the inventors must have had a reasonable expectation of meeting each claim limitation.

subject[.]" (JTX-004 at 18.) Thus, Claims 8 and 19 "recite[] details of an anticipated … response" to plerixafor (*i.e.*, mobilization of stem cells into the peripheral blood) and "claim[] the specific result of a biological process" by claiming an intended use (*i.e.*, obtaining stem cells in part by mobilizing them into the peripheral blood). *Hitzeman*, 243 at 1358. Conception of those claims, then, requires proof that the inventors "had a reasonable expectation that the claimed result of the biological process would occur," or the reasonable expectation that an effective amount of plerixafor would mobilize stem cells into the peripheral blood. *Id.*

15. Interestingly, Plaintiffs believe that the record evidence does not support a finding that the named inventors had a reasonable expectation that plerixafor would mobilize stem cells. (D.I. 88 at ¶¶ 26-27.) But I see the record differently and interpret their position as a precautionary measure to avoid conflict with their obviousness arguments, in which they assert that a person of ordinary skill in the art would not have reasonably expected plerixafor to mobilize stem cells as of the date of invention. (D.I. 86 at 9.) They have fallen into an unnecessary defensive crouch. Whether the named inventors had a reasonable expectation of success for purposes of a conception analysis involves a subjective inquiry that is wholly distinct from the objective question of whether a person of ordinary skill in the art would have had a similar expectation for purposes of an obviousness analysis. *See Burroughs*, 40 F.3d at 1231-32 (differentiating between the legal standards for obviousness and conception).

16. In fact, in this case, the evidence in the record does support the conclusion that the named inventors had a reasonable expectation as of September 27, 2000, that

plerixafor would mobilize stem cells. Zydus, equally eager to protect its own obviousness arguments, actually assists in identifying support in the record for the conclusion that the named inventors had a reasonable expectation of success. (D.I. 89 at ¶¶ 160, 181-84; D.I. 100 at 4-5.) In March 2000, Dr. Dale and Dr. MacFarland predicted that plerixafor could block the interaction between SDF-1 and CXCR4 and lead to elevated levels of stem cells in the peripheral blood. (JTX-061B at 1; *see also* D.I. 83 at 538:13-539:7.) Dr. Dale expected to mobilize some stem cells using plerixafor and even more stem cells using G-CSF and plerixafor together. (D.I. 83 at 560:24-562:11; *see also* D.I. 83 at 514:15-515:22.) Moreover, Dr. Henson predicted that plerixafor, because of its ability to block CXCR4, would mobilize stem cells. (D.I. 83 at 451:16-22.) Thus, as of late September 2000, the named inventors had a reasonable expectation that plerixafor, either alone or in combination with G-CSF, would mobilize stem cells.

17. That is what Claims 8 and 19 require. But Zydus argues that the named inventors were required to have a reasonable expectation that plerixafor would mobilize enough stem cells to be therapeutically effective for purposes of stem cell transplantation or would mobilize more stem cells than G-CSF alone. That is wrong. Both *Hitzeman* and *Burroughs* stand for the proposition that it is "immaterial that the inventors lacked a 'reasonable expectation' as to how non-claimed aspects of the drug would work[.]" *Hitzeman*, 243 F.3d at 1358. Use of plerixafor to improve upon G-CSF's stem cell mobilization abilities in the stem cell transplantation process is a non-claimed intended application for the method of mobilizing stem cells using plerixafor, or plerixafor in combination with G-CSF, which does not have to be supported by the inventors'

reasonable expectation of success. Zydus's attempt to raise the bar for conception even higher fails.

18. I conclude that the named inventors of the '590 Patent conceived of the claimed invention by September 27, 2000.

B. Derivation

19. Zydus argues that the Andreeff Letter, dated October 5, 2000, invalidates Claims 8 and 19 of the '590 Patent under 35 U.S.C. § 102(f) because the inventors derived the invention from that letter. (D.I. 87 at 29-34, *see also* D.I. 71, App. A at ¶ 57; DTX-029.) To prove derivation under § 102(f), the party challenging the patent must show "both prior conception of the invention by another and communication of that conception to the patentee." *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011) (citation omitted). Zydus admits, however, that its derivation argument fails as matter of law if the date of conception of the invention claimed in the '590 Patent is determined to predate the Andreeff Letter. (D.I. 84 at 871:17-872:4.) Because I have concluded that the named inventors of the '590 Patent conceived of their invention by September 27, 2000, I also conclude that the Andreeff Letter cannot invalidate Claims 8 and 19 of the '590 Patent under § 102(f).

C. Obviousness

20. Zydus next argues that Claims 8 and 19 of the '590 Patent are invalid as obvious in light of Konopleva and either Hendrix or WO '814.[49] (D.I. 87 at 3-25.)

[49] Zydus also argues that the asserted claims are invalid as obvious in light of the Andreeff Letter. (D.I. 87 at 34.) However, because I concluded that the date of

Plaintiffs naturally disagree, (D.I. 86 at 3-9), and they have the better of the argument. Zydus has not met its burden of proving by clear and convincing evidence that the asserted claims are obvious over the prior art provided in this case.

21. A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art. 35 U.S.C. § 103; *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 13 (1966). Whether the claimed subject matter would have been obvious is a question of law based on several underlying facts: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) any relevant secondary considerations, such as commercial success, long felt but unsolved need, and failure of others.[50] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Graham*, 383 U.S. at 17-18.

22. Patents are presumed to be valid. 35 U.S.C. § 282(a). As a result, the party seeking to invalidate a patent as obvious "must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citation omitted). Clear and

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conception predates the Andreeff Letter, it is not prior art and cannot render the asserted claims obvious.

[50] Those underlying factual findings were made above, *see supra* FOF ¶¶ 2-15, 45-122, and are incorporated into the legal analysis herein as necessary.

convincing evidence requires "an abiding conviction that the truth of [the] factual contentions are highly probable." *Id.* (alteration in original) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

23. One reason an invention may be obvious under § 103 is because it may have been obvious to try. The Supreme Court has explained that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. If the anticipated success stems from that, "it is likely the product not of innovation but of ordinary skill and common sense." *Id.* But the Federal Circuit has cautioned that there is "an important distinction between combining known options into 'a finite number of identified, predictable solutions,'" *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *KSR*, 550 U.S. at 421), and "'merely throwing metaphorical darts at a board' in hopes of arriving at a successful result," *id.* (citation omitted).

24. A claimed invention is not rendered obvious "when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009). "When 'what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful' an invention would not have been obvious." *Id.* (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Moreover, "an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution." *Id.* Obviousness does not exist where the identified solutions are not predictable, such as "where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it[,]" despite the obviousness of attempting "to explore a new technology or general approach that seemed to be a promising field of experimentation[.]" *Id.*

25. Finally, the Federal Circuit has cautioned that "[o]bviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all facets of the legal test." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (citation omitted). Each case "must necessarily be decided upon its own facts." *Id.* (citation omitted). Courts are instructed to avoid "[u]ndue dependence on mechanical application of a few maxims of law, such as 'obvious to try,' that have no bearing on the facts[.]" *Id.* At bottom, "decisions on obviousness must be narrowly tailored to the facts of each individual case." *Id.*

26. At the start, I assume without deciding that the prior art, on the whole, discloses all of the limitations of Claims 8 and 19 of the '590 Patent. Thus, I assume that there are no differences between the scope and content of the prior art and the asserted claims. If a combination of prior art references discloses all of the claim elements, then the factfinder should "consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015). Since Zydus's obviousness

argument centers on Konopleva as combined with either Hendrix or WO '814, I turn to assessing the motivation to make either of those combinations.

1. Motivation to Combine Prior Art References

27. Zydus argues that a person of ordinary skill in the art would have been motivated to combine Konopleva with either Hendrix or WO '814. Plaintiffs disagree but, based on my analysis of the record, I conclude that Zydus's position is more persuasive, at least as to combining Konopleva and Hendrix.[51] There is substantial evidence that a person of ordinary skill in the art would have been motivated to combine those references.

28. Whether there would have been a motivation to combine prior art references is not determined using "[r]igid preventative rules that deny factfinders recourse to common sense[.]" *In re Van Os*, 844 F.3d 1359, 1361 (Fed. Cir. 2017) (first alteration in original) (quoting *KSR*, 550 U.S. at 421). Instead, the proper analysis "credits the common sense and creativity of a skilled artisan to assess whether there would have been a motivation to combine elements from prior art references in the manner claimed." *Id.* Teachings in the prior art itself, design needs, market pressures, or other motivations can also "provide a suggestion or motivation to combine prior art elements[.]" *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1333 (Fed. Cir. 2015).

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[51] Based on that conclusion, it is not necessary for me to decide whether a person of ordinary skill in the art would have also been motivated to combine Konopleva with WO '814.

29. As of September 2000, a person of ordinary skill in the art would have been motivated to investigate potential mobilizing agents by looking for candidates that would block the interaction between SDF-1 and CXCR4. *See supra* FOF ¶¶ 79-92. Aiuti said that SDF-1 may "play[] a critical role in the migration of [stem cells] … in vivo" and that "manipulation of SDF-1 may offer promising ways to improve both transplantation and mobilization of hematopoietic cells." (DTX-012 at 8.) Möhle disclosed that SDF-1 and the CXCR4 receptor "are likely to be involved in the trafficking of hematopoietic progenitor and stem cells, as suggested by the … chemotactic effect of SDF-1 on $CD34^+$ progenitor cells" (DTX-161 at 1), and highlighted that the SDF-1/CXCR4 axis may be "critical" to stem cell homing in vivo because experiments had demonstrated that stem cells exposed to an anti-CXCR4 antibody in vitro exhibited reduced migration to SDF-1 (DTX-161 at 5, 6). Peled disclosed that "SDF-1 probably affects [stem cell] engraftment by mediating chemotaxis to the bone marrow" and "link[ed] migration to SDF-1 in vitro to human stem cell function in vivo." (DTX-172 at 3.) Those prior art disclosures would have been important for a person of ordinary skill in the art focused on stem cell mobilization because that person also would have known that some in the field thought that the stem cell mobilization and homing processes "are likely to be 'mirror images' of each other, differentially utilizing similar classes of molecules and receptors" to achieve those respective ends. (DTX-214 at 6; *see also* D.I. 81 at 87:20-88:10; D.I. 83 at 697:24-698:17; D.I. 95 at DDX-116.)

30. Furthermore, based on the experimental results and conclusions drawn in Lapidot, which suggested that G-CSF inhibits the production of SDF-1 in the bone

marrow and indirectly increases CXCR4 expression of bone marrow stem cells in vivo (DTX-148 at 4; D.I. 81 at 97:3-98:15, 99:15-20; D.I. 83 at 587:10-24, 715:9-11), a person of ordinary skill in the art would have understood that G-CSF may operate to mobilize stem cells by reducing SDF-1 in the bone marrow, SDF-1 being a chemokine known to attract stem cells into the bone marrow, so that one fewer tether would exist to prevent stem cells from mobilizing into the bloodstream (DTX-214 at 4 & fig. 3; D.I. 97:20-98:15, 99:23-100:6, 102:10-103:1). All of that has led me to find that a person of ordinary skill in the art would have understood that CXCR4 may have "a role … in the mobilization process." (DTX-148 at 4; *see also* D.I. 81 at 98:16-99:20, 100:7-20.)

31. Finally, a person of ordinary skill in the art would have considered Konopleva together with Lapidot because they were published together and relate to the same topic (DTX-142 at 1; DTX-148 at 1; D.I. 83 at 722:2-723:5), and I found that the correlation between mobilization induced by G-CSF and increased CXCR4 expression on peripheral blood stem cells taught by Konopleva would have led a person of ordinary skill in the art to hypothesize that G-CSF mobilization may operate by interfering with the interaction between SDF-1 and CXCR4 (D.I. 81 at 109:3-110:6, 111:2-14). Konopleva ultimately "propose[d] that blocking the CXCR4/SDF-1 interaction could increase the cytokine-induced mobilization of CXCR4-expressing stem cells with high engraftment capability" (DTX-142 at 4), and both Dr. Andreeff and Dr. Mohty agree "cytokine-induced mobilization" refers to G-CSF-induced mobilization (D.I. 81 at 112:10-23; D.I. 83 at 709:2-7). While Konopleva does not expressly teach a method for, or any chemical agents capable of, blocking CXCR4, a person of ordinary skill in the art

would have understood that administering a CXCR4 antagonist is one way to block CXCR4 and achieve what Konopleva proposed. (DTX-142 at 4; D.I. 81 at 151:23-152:13; D.I. 83 at 709:12-710:3.) Thus, Konopleva would have sent a person of ordinary skill in the art, who was hunting for a stem cell mobilizer that improves upon G-CSF, on a search for a CXCR4 blocker. *See supra* FOF ¶¶ 82-83, 85-88, 91-92.

32. Such a person in September 2000 would have been motivated to combine Konopleva's proposal that a CXCR4 blocker may mobilize stem cells with the teachings in Hendrix that plerixafor blocks the CXCR4 receptor. Hendrix disclosed that 10-80 μg/kg of plerixafor could be safely administered to human subjects and worked as a CXCR4 antagonist that blocks the CXCR4 receptor. (DTX-109 at 1, 5; D.I. 81 at 123:5-124:18, 155:9-23; D.I. 83 at 699:24-700:17.) Hendrix also disclosed that administering plerixafor to human subjects increases the presence of white blood cells, which are known to have CXCR4 receptors, in the peripheral blood. (DTX-109 at 1; D.I. 81 at 123:5-11, 124:8-18, 126:14-25; D.I. 83 at 700:15-17.) That would have been significant to a person of ordinary skill in the art searching for a CXCR4 blocker in the stem cell mobilization context because such a person would have thought that, although not always true, an increase in white blood cell count could be a sign of an increase in stem cell count. (D.I. 81 at 127:1-10; D.I. 82 at 275:18-276:7.) And because both white blood cells and stem cells express CXCR4, such a person may have hypothesized that an agent capable of mobilizing white blood cells by manipulating the CXCR4 receptor may also mobilize stem cells by the same means. (D.I. 81 at 126:1-127:10.)

33. Perhaps even more significantly, though, Hendrix went so far as to "suggest that binding of [plerixafor] to CXCR4 may inhibit the chemotactic effects of SDF-1α, causing release of [white blood cells] from the endothelium and/or stem cells from bone marrow." (DTX-109 at 5 (citations omitted).) Hendrix thus hypothesized that plerixafor may mobilize stem cells. (DTX-109 at 5; D.I. 81 at 126:18-25.) It follows then that, based on the hypotheses in Hendrix, a person of ordinary skill in the art would have understood that plerixafor may mobilize stem cells from the bone marrow into the peripheral blood by inhibiting the CXCR4 receptor. (DTX-109 at 5; D.I. 81 at 126:20-127:21, 155:9-23); *see supra* FOF ¶¶ 95-96, 98-102.

34. Those facts would have been enough, in my judgment, to motivate a person of ordinary skill in the art, who was looking for potential stem cell mobilizing agents in September 2000, to combine Konopleva, which proposed searching for a CXCR4 blocker to mobilize stem cells, with Hendrix, which taught that plerixafor is a CXCR4 blocker that can be safely administered to human subjects and is possibly capable of mobilizing stem cells from the bone marrow into the peripheral blood.

35. Plaintiffs numerous attempts to discount the weight of the prior art or the motivation to combine Konopleva and Hendrix to use plerixafor as a CXCR4 blocker potentially capable of mobilizing stem cells are not persuasive. The value of the disclosures in Aiuti, Möhle, and Peled does not evaporate because they did not report in vivo experimental data relating to the manipulation of CXCR4 or SDF-1 to mobilize stem cells. A person of ordinary skill in the art would not ignore in vitro experiments simply because they sometimes yield different results than in vivo studies. *See supra* FOF ¶ 85.

Nor would a person of ordinary skill in the art necessarily be turned away by suggestions in the prior art that some CXCR4 antagonists did not mobilize enough stem cells to improve upon G-CSF because such a person would have been motivated to try a lot of things in September 2000. *See supra* FOF ¶¶ 86-87. Moreover, I found that the data in the Konopleva abstract is not inconsistent with its proposal of using a CXCR4 blocker to increase stem cell mobilization. *See supra* FOF ¶ 88. Although I found that a person of ordinary skill in the art may not have credited Konopleva's suggestion that a CXCR4 blocker could mobilize "stem cells with high engraftment capability" to the extent it conflicts with Peled's teaching that two different CXCR4 antibody blocking agents reduced engraftment of stem cells (DTX-142 at 4; *see also* DTX-172 at 3; D.I. 82 at 249:15-20; D.I. 88 at ¶ 79), I also found that that does not mean there would have been no motivation at that time for a person of ordinary skill in the art to pursue a CXCR4 blocker as a potential stem cell mobilizing agent, *see supra* FOF ¶¶ 89-92. The complexity and uncertainty in the art, coupled with the additional known facilitators of stem cell homing, which was hypothesized to be a "mirror image" process of stem cell mobilization, may have encouraged a person of ordinary skill in the art to at least try CXCR4 blockers, despite potential misgivings. (DTX-214 at 6; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5; D.I. 83 at 576:14-577:2, 578:12-578:17, 697:24-698:17.)

36. Furthermore, Hendrix is analogous art because it would have been reasonably pertinent in September 2000 to a person of ordinary skill in the art investigating new stem cell mobilizing agents that improve upon G-CSF. (D.I. 81 at 128:4-9); *see also supra* FOF ¶¶ 103-09. And Hendrix would not have been ignored

merely because it noted that plerixafor did not cause an increase in band cells or bone pain in patients, it did not report elevated levels of platelets, it did not expressly recite experimental data related to stem cell counts, and it had been cited by a research group at the National Institutes of Health for its demargination theory of elevated white blood cell count rather than the alternative CXCR4-mediated mobilization theory. *See supra* FOF ¶¶ 98-102.

37. Having found a motivation to combine Konopleva and Hendrix, I now consider whether, as of September 2000, a person of ordinary skill in the art would have had a reasonable expectation that the research path emanating from that combination of references would succeed in mobilizing stem cells.

2. No Reasonable Expectation of Success

38. Zydus contends that, as of September 2000, a person of ordinary skill in the art would have had a reasonable expectation that combining Konopleva and Hendrix, which together teach using plerixafor as a CXCR4 blocker that might mobilize stem cells, would succeed. (D.I. 87 at 10-22.) Plaintiffs argue that such a person would not have had a reasonable expectation of success. (D.I. 86 at 3-9.) On this critical point, Plaintiffs have the stronger argument, which is supported by substantial evidence in the record.

39. The reasonable expectation of success gauges "the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). As stated earlier with respect to the law surrounding the obvious-to-try theory, "[t]o have a reasonable expectation of success, one must be motivated to do more than merely to vary

all parameters or try each of numerous possible choices until one possibly arrived at a successful result." *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007)).

40. Although a person of ordinary skill in the art would have been motivated to try CXCR4 blocking agents, and to combine Konopleva and Hendrix in pursuit of that goal, such a person would not have had a reasonable expectation that a CXCR4 antagonist, including plerixafor, would succeed in mobilizing harvestable stem cells. *See supra* FOF ¶¶ 93, 112. I noted that Dr. Andreeff and Dr. Mohty hold different opinions about whether a person of ordinary skill in the art in September 2000 would have had a reasonable expectation of success in achieving the claimed invention by combining Konopleva and Hendrix. (D.I. 81 at 153:25-155:8; D.I. 83 at 692:19-693:20.) The evidence in the record supports Dr. Mohty's expert opinion that, for persons of ordinary skill in the art, "there was no reasonable expectation of success" in reaching the claimed invention at that time. (D.I. 83 at 693:16-20.)

41. The evidence in support of that determination is three-fold. First, the evidence is clear that everyone, including Drs. Andreeff and Mohty, viewed the mechanisms of stem cell mobilization to be uncertain and complex. *See supra* FOF ¶¶ 68-70. That would have made it difficult to predict with any degree of certainty how blocking CXCR4 expression would impact other interactions that may have been necessary for mobilizing stem cells. It would have been particularly difficult to predict how manipulation of one variable would affect the overall mobilization process, given the complex state of the art. Indeed, a person of ordinary skill in the art at the time of the

invention would have known that experts in the field had been attempting to improve upon G-CSF-induced mobilization for years and failed to find an efficacious, nontoxic agent that could serve as an improvement. *See supra* FOF ¶¶ 66-67. Second, as Dr. Mohty testified, a person having ordinary skill in the art would have focused on what was already known to work, which was G-CSF. (D.I. 83 at 657:8-658:12). Known stem cell mobilizers had been shown to increase CXCR4 expression, which put into serious question whether an agent that blocks the CXCR4 receptor would prompt mobilization in a successful way. Because G-CSF, SCF, and IL-6 were all known stem cell mobilizers that were reported to increase CXCR4 expression (DTX-142 at 4; DTX-148 at 4; DTX-172 at 4-5), a person having ordinary skill in the art would not have reasonably expected something that blocks CXCR4, and thus counteracts CXCR4 expression, to succeed. Finally, the prior art suggested that, even if CXCR4 blockers succeeded in mobilizing stem cells, those blockers would have made the mobilized cells perhaps inefficacious in the remainder of the stem cell transplantation process, because both Peled and Möhle reported that antibodies to CXCR4 decreased rather than increased stem cell engraftment. (DTX-161 at 2-3, 5; DTX-172 at 3, 5; D.I. 82 at 251:19-252:21.); *see also Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) ("[P]rior art need not explicitly 'teach away' to be relevant to the obviousness determination. Implicit in our discussion of the 'degree' of teaching away is an understanding that some references may discourage more than others." (citation omitted)). That would have put a damper on a person of ordinary skill in the art's reasonable expectation of mobilizing

useful stem cells because stem cell transplantation requires successful mobilization, homing, and engraftment. *See supra* FOF ¶ 6.

42. Just because one potential pathway to mobilizing stem cells may have been obvious to try does not mean that the claimed invention was therefore obvious. For a given invention, there may be many different pathways suggested in the art at any given time that are encouraging enough for a person of ordinary skill in that art to pursue. But just because each pathway may have been obvious to try on its own does not mean that such a skilled person pursuing each of those pathways would have reasonably expected success at every turn. Some pathways may have been more promising than others, and, indeed, that is the very reason scientists conduct research and experiments. Perhaps even a 1% chance of success may be enough motivation for a researcher to pursue a given pathway that may ultimately lead to a multi-million dollar drug, but no one would say a 1% chance of success is sufficient, ex ante and without the benefit of hindsight, to constitute a reasonable expectation that that pathway would succeed in producing the invention. *See Leo Pharm. Prods.*, 726 F.3d at 1357 (concluding that, "even if it was obvious to experiment with [known] options, 'there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed … .' There is no indication in the prior art which of [the known] possible formulations would be the most promising to try." (citation omitted)).

43. In sum, the uncertainties regarding the mechanisms of stem cell mobilization, the known complexity in the art, the fact that chemical agents known to mobilize stem cells increased rather than decreased CXCR4 expression, and evidence that

CXCR4 blockers reduced the engraftment capabilities of mobilized stem cells all would have prevented a person of ordinary skill in the art from having a reasonable expectation of meeting the limitations in Claims 8 and 19 of the '590 Patent in September 2000. (DTX-142 at 4; DTX-148 at 4; DTX-172 at 3-5; D.I. 81 at 179:12-21, 189:17-190:14, 197:9-198:5, 203:6-205:10; D.I. 82 at 249:15-20; D.I. 83 at 576:14-577:2, 692:19-693:20.)

3. Secondary Considerations

44. Before concluding the obviousness analysis, I must also consider any objective indicia of nonobviousness. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered" in an obviousness inquiry. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). Secondary considerations are "an important component of the obviousness inquiry because" it "may often be the most probative and cogent evidence in the record." *Id.* (quoting *Stratoflex*, 713 F.2d at 1538). Secondary considerations include commercial success, long-felt but unsolved need, failure of others, unexpected results, industry praise, industry skepticism, copying, and licensing. *Id.* at 1349-54; *accord Graham*, 383 U.S. at 17-18. I will explore the considerations for which the parties have proffered evidence.

a. *Long-Felt but Unsolved Need*

45. Evidence of a long-felt but unsolved need that is met by the claimed invention supports its nonobviousness. *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862

F.3d 1356, 1369 (Fed. Cir. 2017). The shortcomings of existing pharmaceuticals can highlight needs that are long-felt and unmet. *Cf. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082-83 (Fed. Cir. 2012) (concluding that a long-felt need existed for the pharmaceutical invention at issue). Plaintiffs argue that, starting in the early 1990s, there was a plain need for a mobilizing agent that improved upon G-CSF. (D.I. 88 at ¶¶ 109-16.) Zydus disagrees, but not cogently. (D.I. 100 at ¶¶ 109-16.)

46. By September 2000, it had become very clear indeed that there was a need for a stem cell mobilizing regimen that, with minimal toxicity, could mobilize a greater number of stem cells in fewer apheresis sessions than the existing options, including G-CSF. *See supra* FOF ¶¶ 61-65. That need was felt across all populations of patients (PTX-404 at 1; D.I. 83 at 649:9-651:3), but was particularly acute for non-mobilizing and hard-to-mobilize populations because they did not have other therapeutic options (D.I. 83 at 649:12-650:1). There was an increase in the use of stem cell transplantation in the early 1990s (PTX-649; PTX-977 at 3), and expert testimony that "the need started very early" for a better stem cell mobilizing agent than G-CSF (D.I. 83 at 656:23-657:7). The prior art demonstrates that researchers had started studying other potential stem cell mobilizers by 1994. (*See, e.g.*, DTX-070 at 4-6, 10 (discussing research of stem cell mobilization regimens involving cyclophosphamide, GM-CSF, IL-3, PIXY321, SCF, and flk2/flt3 protein, with reference to SCF and PIXY321 studies as early as 1994).) That clinical need remained unmet until the invention at issue here in September 2000, which did not become a product capable of clinical use until MOZOBIL® was approved by the

FDA at the end of 2008. (D.I. 83 at 653:13-18, 659:8-12.) There was, therefore, a long-felt but unsolved need.

47. Zydus argues that any evidence of a long-felt but unsolved need has minimal value because the '131 and '152 Patents blocked use of plerixafor by others. (D.I. 100 at ¶¶ 110-11, 116.) I found that those patents, which were held by Plaintiffs or their predecessor in September 2000, blocked the use of plerixafor beginning in December 1996. *See supra* FOF ¶¶ 121-22. It is thus possible that the need for an improved stem cell mobilizing agent "remained unmet *despite* the *obviousness* of the [method] claimed in the ['590 Patent]." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 14-882, 2017 WL 1199767, at *40 (D. Del. Mar. 31, 2017). It is speculative, however, that the need would have been solved any sooner had those blocking patents not existed, given the complex and uncertain state of the art in September 2000. *See supra* FOF ¶¶ 68-70. Many options were being tried, and it was not until October 2000, after the date of invention, that Dr. Andreeff, an expert in the field, sent a letter to AnorMED proposing to test the effect of plerixafor in the stem cell transplantation context. (DTX-029.) Thus, the blocking patents do little to limit the value of the strong evidence demonstrating a long-felt but unsolved need.

b. *Failure of Others*

48. Evidence of the failure of others to solve the problem answered by the claimed invention can be another source of nonobviousness. That is because it may "show 'indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.'"

Cyclobenzaprine, 676 F.3d at 1082 (citation omitted). Plaintiffs argue that there were numerous failed attempts to identify mobilizing agents that improved upon G-CSF before September 2000. (D.I. 88 at ¶¶ 56-57.) Though Zydus disagrees (D.I. 100 at ¶¶ 56-57), the Plaintiffs are correct in asserting that the evidence shows others tested potential stem cell mobilizers and failed to identify one that improved upon existing agents. *See supra* FOF ¶¶ 66-67. Before September 2000, more than a dozen candidates had been investigated during the search for a stem cell mobilizer that was better than existing agents. (D.I. 81 at 206:4-11, 207:23-216:22; D.I. 83 at 641:21-642:9, 644:4-13.) Those investigations into other mobilizing agent candidates spanned nearly a decade and were largely unsuccessful because the alternatives to G-CSF, including granulocyte-macrophage colony-stimulating factor ("GM-CSF"), stem cell factor ("SCF"), flk2/flt3 ligand, interleukin-1 ("IL-1"), interleukin-3 ("IL-3"), interleukin-6 ("IL-6"), interleukin-8 ("IL-8"), PIXY321 – a GM-CSF/IL-3 fusion protein, macrophage inflammatory protein-1α ("MIP-1α"), anti-VLA-4 antibodies, anti-LFA-1 antibodies, and anti-CD44 antibodies, all either failed to demonstrate sufficient clinical efficacy, exhibited undesirable side effects, or both. (JTX-009 at 1-2; JTX-023 at 7; PTX-232 at 1; PTX-415 at 2-6; PTX-619; DTX-070 at 6; D.I. 81 at 207:23-216:22; D.I. 83 at 640:16-22, 641:11-642:9, 644:4-13, 653:2-18, 656:23-659:7.) While Zydus is also correct that those agents technically succeeded in mobilizing some amount of stem cells, they were still failures because they did not exhibit clinical success compared to G-CSF. *See* discussion *supra* note 19.

49. Zydus again contends that the evidence must be discounted because of the blocking patents that cover the use of plerixafor. (D.I. 100 at ¶¶ 110-11, 116.) It argues

that, because the '131 and '152 Patents effectively prevented the use of plerixafor by others starting in 1996, the widespread failure of others "is not particularly probative of a 'gap' in the prior art that would render non-obvious the invention" of the '590 patent. *Acorda Therapeutics*, 2017 WL 1199767, at *39. That argument is not persuasive on the facts of this case. While an argument can be made that the invention may have been discovered sooner had the blocking patents not existed, it does not alter the historical fact that others in the art tried various avenues for improving upon G-CSF-induced mobilization and failed for nearly a decade. *See supra* FOF ¶¶ 66-67. Nor, as alluded to earlier, *see supra* COL ¶¶ 37 (noting motivation to combine Konopleva and Hendrix, the latter of which did not appear until 2000), 47, does it change the fact that, even by Zydus's evidence, the motivation to combine references in the prior art and look to plerixafor as a mobilization candidate did not arise until late in the game. Therefore, the blocking patents do not significantly limit the value of the evidence in this case of the failure of others.

c. *Unexpected Results*

50. Even if Zydus had made a prima facie showing of obviousness, which it has not, Plaintiffs "may rebut based on 'unexpected results' by demonstrating 'that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.'" *Proctor & Gamble*, 566 F.3d at 994 (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)). Put differently, something that "would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *Soni*, 54 F.3d at 750. Unexpected results can include

unexpected, desirable clinical properties, *see In re Alfuzosin Hydrochloride Patent Litig.*, No. 08-1941, 2010 WL 1956287, at *7 (D. Del. May 14, 2010), and evidence of unexpected results may come from evidence post-dating the patent's filing or issue date, *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011). The results must be unexpected compared to the closest prior art. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

51. The use of plerixafor, both alone and in combination with G-CSF, to mobilize stem cells provided at least three unexpected results. (D.I. 83 at 666:14-19.) Because a person of ordinary skill in the art would have known at the time of invention that the closest prior art, G-CSF, increased CXCR4 expression and that various CXCR4 antagonists decreased stem cell mobilization compared to G-CSF, it was likely unexpected that plerixafor would mobilize stem cells even in patients who failed to mobilize a sufficient number using G-CSF. (DTX-148 at 4; DTX-172 at 3; JTX-019 at 2; JTX-033 at 32, 34; JTX-051 at 1, 4-6; D.I. 82 at 364:20-368:12; D.I. 83 at 667:2-668:25.) Furthermore, it was unexpected that plerixafor would mobilize high quality stem cells, given that it is a CXCR4 blocker and CXCR4 was known to be integral to the homing and engraftment processes necessary for a successful stem cell transplantation.[52] (JTX-021 at 8; DTX-109 at 1; DTX-214 at 3; PTX-238 at 10-12; PTX-261 at 1; D.I. 81 at 85:3-86:12, 143:6-25; D.I. 83 at 679:19-680:2, 720:9-20; D.I. 84 at 743:11-744:11.) Finally,

[52] The statement in Konopleva that a CXCR4 blocker would mobilize "stem cells with high engraftment capability" is not evidence to the contrary because, as I have already found, a person of ordinary skill in the art would have been critical of that part of the proposal. (DTX-142 at 4); *see* discussion *supra* note 42.

there was no reason to expect that plerixafor would rapidly mobilize stem cells in just a few hours compared to G-CSF, which took several days to cause mobilization. (PTX-177 at 1, 4; PTX-216 at 14-15; D.I. 82 at 451:17-22; D.I. 83 at 681:15-682:15, 683:4-14, 705:8-11.) Thus, evidence of unexpected results supports the nonobviousness of the claimed invention.

d. *Industry Praise*

52. Industry praise for "a claimed invention or product that embodies the patent claims" is evidence of the nonobviousness of the claimed invention. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016). "Industry participants … are not likely to praise an obvious advance over the known art." *Id.* Substantial evidence demonstrates that use of plerixafor to mobilize stem cells has received widespread industry praise. Zydus does not dispute that conclusion. (D.I. 100 at ¶ 137.)

53. Plerixafor has been praised by experts as a "new and important agent" and "major advance" that has "strongly impacted" the field of stem cell transplantation. (JTX-053 at 1; PTX-181 at 7; PTX-285 at 1; *see also* D.I. 83 at 688:6-12, 689:10-19, 690:16-24.) Many publications have praised the use of plerixafor in combination with G-CSF for stem cell mobilization. (PTX-177 at 1; PTX-216 at 8; PTX-238 at 10; *see also* D.I. 83 at 670:9-671:10.) Moreover, plerixafor is now part of the standard of care for stem cell mobilization. (D.I. 83 at 685:6-9.)

54. The pharmaceutical has also received numerous awards. In 2010, the U.K. version of MOZOBIL® was selected as a finalist in the competition for the Prix Galien Award in the U.K. in the orphan drug category for the U.K. market. (D.I. 71, App. A at

¶ 93.) In 2011, the Spanish version of MOZOBIL® was awarded the Prix Galien Award in Spain for Best Pharmaceutical of the Year. (D.I. 71, App. A at ¶ 91; D.I. 83 at 691:21-692:3.) In 2013, the Greek version of MOZOBIL® was awarded the Prix Galien Award in Greece for Best Pharmaceutical of the Year. (D.I. 71, App. A at ¶ 92; D.I. 83 at 691:21-692:3); *see also supra* FOF ¶ 120. That evidence of industry praise supports the nonobviousness of the claimed invention.

e. *Nexus Between Secondary Considerations and the Claimed Invention*

55. Secondary considerations can only be given substantial weight if there is "a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis omitted) (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). A nexus to the merits of the claimed invention exists where the evidence of secondary considerations "actually results from something … both claimed and novel in the claim[.]" *Id.* (emphasis omitted). A nexus is presumed "when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Polaris Indus. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) (citation omitted). Once the patentee has established that presumption, the challenger may rebut it with evidence that the objective indicia of nonobviousness were caused by "extraneous factors other than the patented invention[.]" *Id.* (citation omitted).

56. The evidence of long-felt but unsolved need and the failure of others is tied to the merits of the claimed invention because MOZOBIL® succeeded in satisfying the

unmet need that others were unable to satisfy for nearly a decade. *See supra* FOF ¶¶ 66-67. Furthermore, Plaintiffs are entitled to a presumption that a nexus exists with respect to the evidence of unexpected results and industry praise. The FDA-approved use of MOZOBIL® as a mobilization agent in conjunction with G-CSF is covered by Claims 8 and 19 of the '590 Patent. (D.I. 71, App. A at ¶ 28; D.I. 83 at 645:21-647:5.) Off-label use of MOZOBIL® to mobilize stem cells, which includes administering plerixafor without G-CSF, is also covered by Claim 8. (D.I. 83 at 645:21-647:5.) The evidence of unexpected results and industry praise described above is directly tied to the use of plerixafor as a stem cell mobilizer, which is marketed in 20 mg/mL solution as MOZOBIL®. (D.I. 71, App. A at ¶ 26; D.I. 83 at 645:21-647:5, 692:4-18.) Thus, a nexus is presumed between the evidence of secondary considerations and the merits of the claimed invention.

57. Zydus does not identify any evidence of outside factors other than the invention claimed in the '590 Patent that may have led to the secondary consideration evidence I have credited.[53] Instead, Zydus argues that there is no nexus because "the failure to mobilize clinically relevant quantities of stem cells or the presence of side effects" are not required by Claims 8 and 19. (D.I. 87 at 24.) But it strains credulity to think that mobilizing a small number of stem cells using plerixafor would have constituted a patentable invention. The novel aspect of what is expressly claimed is that

[53] One caveat: Zydus does, of course, lean heavily on Plaintiff's blocking patents to explain away the secondary considerations of long-felt need and failure of others, but I have already addressed those points. *See supra* COL ¶¶ 47, 49.

plerixafor mobilizes a sufficient number of stem cells to conduct a harvest. (JTX-004 at 18-19.) Therefore, Zydus has not rebutted the presumption of nexus.

f. *No Evidence of Simultaneous Invention*

58. Finally, "[i]n some rare instances, the secondary consideration of simultaneous invention might also supply indicia of obviousness." *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) (citation and internal quotation marks omitted). "Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed [invention] 'was the product only of ordinary … skill.'" *Id.* at 1305 (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925)). Zydus argues that the Andreeff Letter and van Os are evidence of simultaneous invention of the methods claimed in the '590 Patent. (D.I. 87 at 22-23.) Plaintiffs rightly disagree. (D.I. 99 at 10-11.)

59. Neither is evidence of simultaneous invention, and they do not support the alleged obviousness of Claims 8 and 19 of the '590 Patent. The Andreeff letter does not disclose all of the elements of those claims because Dr. Andreeff proposed mobilizing stem cells into the peripheral blood using G-CSF and blocking homing of those stem cells back into the bone marrow using plerixafor, not mobilizing stem cells into the peripheral blood using plerixafor. (DTX-029 at 1; D.I. 81 at 136:6-20, 159:18-160:4; D.I. 82 at 291:22-25; D.I. 83 at 606:20-608:4; D.I. 84 at 737:4-738:6.) Furthermore, van Os does not discuss or contemplate stem cell mobilization, which is explicitly claimed in Claims 8 and 19, because its focus was on stem cell homing and engraftment. (DTX-208 at 4.)

60. In sum, a person of ordinary skill in the art would not have reasonably expected the claimed invention to succeed, the claimed invention fulfilled a long-felt but unmet need that others failed to satisfy for nearly a decade, the claimed invention produced unexpected benefits and exhibited unexpected properties, and the claimed invention has received industry praise. Zydus therefore has not proven by clear and convincing evidence that Claims 8 and 19 of the '590 Patent are invalid as obvious.

D. Patentable Subject Matter

61. The scope of patentable subject matter is broad and includes "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof[.]" 35 U.S.C. § 101. A limited set of subject matter is not patent eligible, however, including "[l]aws of nature, natural phenomena, and abstract ideas[.]" *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (citation omitted). The Supreme Court uses a two-step framework, known as the *Alice/Mayo* test, to assess whether claimed subject matter is patent eligible. *Id.* at 2355; *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 77 (2012). One must first ask "whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice*, 134 S. Ct. at 2355. If they are, then one must identify "additional elements" in each claim, "both individually and 'as an ordered combination[,]'" that "'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78-79). That second step has been described "as a search for an '"inventive concept[,]"'" which is "an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" *Vanda Pharm.*

Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1133 (Fed. Cir. 2018) (last alteration in original) (quoting *Alice*, 134 S. Ct. at 2355 (quoting *Mayo*, 566 U.S. at 72-73, 75-79)). Patent eligibility is a question of law that "may contain underlying issues of fact[,]" and it must be proven by the patent challenger with clear and convincing evidence. *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1365, 1368 (Fed. Cir. 2018). Zydus argues that the asserted claims of the '590 Patent are invalid under § 101 because they recite patent-ineligible subject matter (D.I. 87 at 34-40), but that argument is wholly unconvincing.

62. There is no need to proceed to step two in this case because Claims 8 and 19 of the '590 Patent are not directed to a patent-ineligible concept at step one. Both the Supreme Court and the Federal Circuit have "cautioned that 'too broad an interpretation of' ineligible subject matter 'could eviscerate patent law' because 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Vanda Pharm.*, 887 F.3d at 1134 (quoting *Mayo*, 566 U.S. at 71). It is for that reason that, "at step one, 'it is not enough to merely identify a patent-ineligible concept underlying the claim[.]'" *Id.* (quoting *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016)). Instead, the claim must be "directed to" that patent-ineligible concept. *Id.* (quoting *CellzDirect*, 827 F.3d at 1050). Claims 8 and 19 are "directed to the application of a drug to [achieve] a particular [result]" and cover "a new way of using an existing drug[.]" *Id.* at 1134-35. Specifically, they claim using plerixafor, itself a compound that does not naturally exist, to amplify a natural phenomenon – stem cell mobilization – in an unnatural way. (JTX-004 at 14; D.I. 81 at

88:11-21, 95:5-18; D.I. 83 at 659:8-21, 798:2-800:3.) Thus, Claims 8 and 19 of the '590 Patent are very plainly patent eligible.

63. But even if those claims were directed simply to the natural phenomenon of stem cell mobilization, they recite an "inventive concept" at step two of the *Alice/Mayo* test that would remove them from the sphere of patent ineligibility. *Alice*, 134 S. Ct. at 2355 (quoting *Mayo*, 566 U.S. at 72). At step two, a claim must recite more than "well-understood, routine, conventional activity already engaged in by the scientific community[.]" *CellzDirect*, 827 F.3d at 1051 (quoting *Mayo*, 566 U.S. at 79). Even if every element of the claim were well-understood, routine, or conventional, a new combination of those elements could still constitute patent-eligible subject matter. *Id.* Claims 8 and 19 contain an "inventive concept" because it was not understood, routine, or conventional at the time of the invention to use plerixafor to mobilize stem cells from the bone marrow into the peripheral blood. (Broxmeyer Dep. Tr. Cross. Q13.) Zydus therefore has failed to demonstrate by clear and convincing evidence that Claims 8 and 19 recite patent-ineligible subject matter.

64. Based on all of the foregoing, I conclude that Claims 8 and 19 of the '590 Patent have not been proven invalid by clear and convincing evidence under §§ 101, 102, or 103.[54]

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[54] Because the parties agreed that any judgment relating to the validity of Claim 8 of the '590 Patent will apply equally to Claim 8 of the '102 Patent, (D.I. 76, App. A at ¶ 3), I also conclude that Zydus has not proven by clear and convincing evidence that Claim 8 of the '102 Patent is invalid under §§ 101, 102, or 103. Moreover, because I conclude that Zydus has not proven any of its invalidity contentions, I will deny as moot Plaintiffs' Rule 52(c) motion for judgment on partial findings. (D.I. 85.)

E. Injunctive Relief

65. When a pharmaceutical is found to infringe a patent under 35 U.S.C. § 271(e)(2), "the court shall order the effective date of any [FDA] approval of the [infringing] drug … to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4)(A). Relief pursuant to § 271(e)(4)(A) is not discretionary under those circumstances. *See In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1367 (Fed. Cir. 2008) (stating that § 271(e)(2)(A) "requir[es] the district court" to issue such an order upon concluding that a valid patent is infringed); *Janssen Prods, L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 708 (D.N.J. 2014) (describing orders under § 271(e)(4)(A) as "mandatory upon a finding of infringement of a valid patent").

66. Zydus stipulated that the submission of the Zydus ANDA infringes Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent under 35 U.S.C. § 271(e)(2) (D.I. 71, App. A at ¶ 41), and that use, sale, or offer for sale of the Zydus ANDA Product for the indication proposed in the ANDA in the United States, if approved by the FDA with its current proposed labeling or with labeling substantially identical to that currently proposed, would infringe Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent under 35 U.S.C. § 271(a)-(c) (D.I. 71, App. A at ¶¶ 42-43). Because those claims are valid, enforceable, and have not expired, I will order that the effective date of any approval of Zydus's ANDA No. 208980 shall not be earlier than the July 22, 2023, expiration dates of the '102 and '590 Patents, including any extensions and exclusivities, pursuant to § 271(e)(4)(A).

67. Additionally, when a pharmaceutical is found to infringe a valid patent, the court may grant "injunctive relief … against [the] infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug[.]" 35 U.S.C. § 271(e)(4)(B). It would appear that, without FDA approval, there is no commercial use for Zydus's ANDA Product, which may make injunctive relief superfluous. Nevertheless, in cases such as this, where the defendant cannot receive FDA approval for its generic drug product before the expiration of various Orange Book patents, injunctive relief appears appropriate given the significant weight of the public interest. There is a strong public interest in avoiding the use or sale of pharmaceutical products before they are approved by the FDA. Furthermore, "the 'encouragement of investment-based risk is the fundamental purpose of the patent grant, and is based directly on the right to exclude.'" *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) (citation omitted).

68. Therefore, in the absence of any countervailing considerations and pursuant to § 271(e)(4)(B), I will also permanently enjoin Zydus from commercially manufacturing, using, offering for sale, selling, or importing its proposed generic version of MOZOBIL® before the expiration dates of the '102 and '590 Patents, including any extensions and exclusivities.

F. Attorneys' Fees

69. In exceptional cases, the court "may award reasonable attorney fees to the prevailing party." 35 U.S.C. § 285; *see also id.* § 271(e)(4). Plaintiffs argue this is such a case. I agree with Zydus, though, that it is not.

70. The Supreme Court has defined an "exceptional" case as "one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated." *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1756 (2014). Whether a case is exceptional is a case-by-case, totality-of-the-circumstances decision committed to the discretion of the district court. *Id.* A party must prove its entitlement to fees under § 285 by a preponderance of the evidence, *id.* at 1758, which Plaintiffs have not done here.

71. Zydus's Paragraph IV certification was not baseless and this case does not stand out from other ANDA cases. Although Zydus became aware of this Court's decision in the Prior Related MOZOBIL® Litigation before this suit began (D.I. 71, App. A at ¶¶ 99-100), and it knew that third parties were expecting "the district court's previous decision in favor of Sanofi [in the Prior Related MOZOBIL® Litigation to] … be upheld on appeal" (PTX-673 at 12; *see also* D.I. 82 at 471:4-472:23), it also relied upon different prior art references to prove its invalidity contentions, including Lapidot, Konopleva, and the Andreeff Letter. Zydus made colorable arguments supported by evidence in the record that a lot was going on in the complex art of stem cell mobilization as of the date of invention, and it identified one possible pathway of research known to persons of ordinary skill in the art as of September 2000 that could have led to the claimed invention and, thus, may have been worth pursuing. Although its argument ultimately fails to demonstrate by clear and convincing evidence that the claimed invention would have been obvious, it is not frivolous or wholly unfounded.

Furthermore, there is no evidence that Zydus acted in bad faith or that it litigated this case in an unreasonable manner. Even if the parties temporarily disputed the plain and ordinary meaning of some of the claim terms during the course of the litigation, despite neither party having sought claim construction (D.I. 88 at ¶¶ 192-94; D.I. 100 at ¶¶ 192-94), that is the fault of both parties for having foregone claim construction to resolve what each thought was the plain and ordinary meaning of the material claim terms.

72. Nor is there evidence that Zydus willfully infringed the '102 and '590 Patents. Willful infringement, where found, may support the conclusion that a case is exceptional, although exceptionality does not necessarily follow from willful infringement. *Stryker Corp. v. Zimmer, Inc.*, 837 F.3d 1268, 1279 (Fed. Cir. 2016). Willful infringement can be established by proving that the accused infringer acted despite an unjustifiably high risk of infringement of a valid and enforceable patent that was either actually known or so obvious that it should have been known. *Arctic Cat*, 876 F.3d at 1371. There is no evidence that Zydus knew there was a high likelihood that the asserted claims of the '102 and '590 Patents were not invalid, and this case was not so easy to decide that I think Zydus obviously should have known of the outcome I have ultimately reached.

73. Plaintiffs have not proven by a preponderance of the evidence that this is an exceptional case and, thus, are not entitled to attorney's fees under § 285.[55]

[55] I have considered the parties' other arguments on all the issues presented in this case and determine that they are either without merit or are unnecessary to resolve, in light of my other findings and conclusions.

IV. CONCLUSION

For the reasons set forth, Zydus's ANDA filing infringes Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent, and the manufacture, use, offer to sell, sale, and import of its generic 20 mg/mL plerixafor injection product would infringe those same claims. Zydus has not established by clear and convincing evidence that Claim 8 of the '102 Patent or Claims 8 and 19 of the '590 Patent are invalid as anticipated by or obvious in light of the Andreeff Letter, invalid as obvious in light of Konopleva and either Hendrix or WO '814, or invalid for reciting patent-ineligible subject matter. As a result, I will deny Plaintiffs' Rule 52(c) motion for judgment on partial findings as moot (D.I. 85). I will order, pursuant to § 271(e)(4)(A), that the effective date of any approval of Zydus's ANDA No. 208980 shall not be earlier than the July 22, 2023, expiration dates of the '102 and '590 Patents, including any extensions and exclusivities, and, pursuant to § 271(e)(4)(B), I will permanently enjoin Zydus from commercially manufacturing, using, offering for sale, selling, or importing its ANDA Product before the expiration dates of the '102 and '590 Patents, including any extensions and exclusivities. Plaintiffs are not entitled, however, to attorney's fees under 35 U.S.C. § 285. An appropriate order will follow.