IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK; NEW YORK UNIVERSITY; GALDERMA LABORATORIES, INC.; GALDERMA LABORATORIES, L.P.; and SUPERNUS PHARMACEUTICALS	:	
Plaintiffs	:	
v.	:	Civ. No. 09-184-LPS
MYLAN PHARMACEUTICALS INC.,	:	
Defendants.	:	
MYLAN PHARMACEUTICALS INC.,	:	
Plaintiffs	:	
v.	:	Civ. No. 10-892-LPS
THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK; NEW YORK UNIVERSITY; GALDERMA LABORATORIES, INC.; GALDERMA LABORATORIES, L.P.; and SUPERNUS PHARMACEUTICALS	:	
Defendants.	:	

OPINION

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August 26, 2011
Wilmington, DE

Stark, U.S. District Judge:

In July 2011, the Court held a four-day bench trial in this patent infringement action brought pursuant to the Hatch-Waxman Act. The case arises from Defendant's efforts to bring to market a generic version of Plaintiffs' Oracea® drug product, a once-daily 40 milligram (mg) administration of doxycycline indicated for the treatment of acne rosacea. Plaintiffs assert that claims of five separate patents are infringed. Defendants contend that all five patents are invalid.[1] As explained below, the Court concludes that the asserted claims of one patent-in-suit are infringed and valid. The preliminary injunction entered in July 2010 will remain in effect pending the Court's receipt and review of supplemental briefing as to an appropriate permanent remedy.[2]

FINDINGS OF FACT

I. PARTIES

1. Plaintiff The Research Foundation of State University of New York ("RF SUNY") is a private, non-profit corporation organized and existing under the laws of the State of New York, having a principal place of business in Albany, New York. (Statement of Uncontested Facts (C.A. 09-184-LPS D.I. 257-1[3]) ("SUF") ¶ 1)

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[1]There are five patents-in-suit. The "Ashley Patents" are U.S. Patent No. 7,211,267 ("the '267 patent") (PTX 1) and U.S. Patent No. 7,232,572 ("the '572 patent") (PTX 2). The "Amin Patents" are U.S. Patent No. 5,789,395 ("the '395 patent") (PTX 3) and U.S. Patent No. 5,919,775 ("the '775 patent") (PTX 4). Finally, the "Chang Patent" is U.S. Patent No. 7,749,532 ("the '532 patent"). (PTX 5)

[2]This opinion constitutes the Court's findings of fact and conclusions of law pursuant to Fed. R. Civ. Proc. 52(a).

[3]All citations to Docket Index ("D.I.") entries are to C.A. 09-184-LPS, unless otherwise noted.

2. Plaintiff New York University ("NYU") is a private, non-profit corporation organized and existing under the laws of the State of New York, having a place of business in New York, New York. (SUF ¶ 2)

3. Plaintiff Galderma Laboratories Inc. ("GLI") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business in Fort Worth, Texas. (SUF ¶ 3)

4. Plaintiff Galderma Laboratories, L.P. ("GLLP") is a privately held partnership registered in the State of Texas, having a principal place of business in Fort Worth, Texas. (SUF ¶ 4)

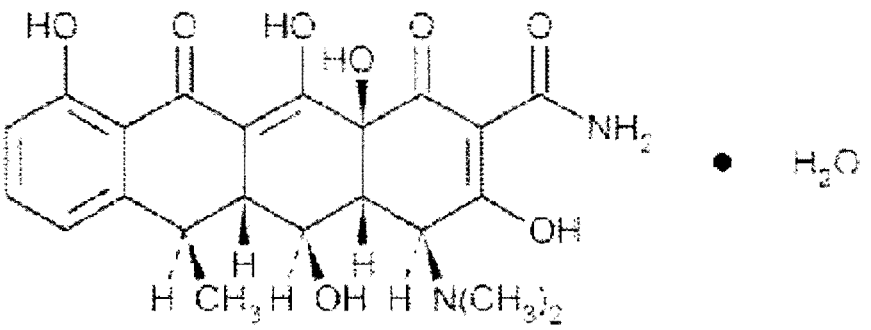
5. Plaintiff Supernus Pharmaceuticals, Inc. ("Supernus") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business in Rockville, Maryland. (SUF ¶ 5)[4]

6. Defendant Mylan Pharmaceuticals Inc. ("Mylan") is a corporation organized and existing under the laws of the State of West Virginia, having a principal place of business in Morgantown, West Virginia. (SUF ¶ 6)

II. DOXYCYCLINE

7. The structural formula of doxycycline monohydrate is:

[4]Plaintiffs RF, SUNY, NYU, GLI, GLLP, and Supernus are referred to collectively throughout this Opinion as "Plaintiffs" or "Galderma."



(SUF ¶ 41)

8. Doxycycline is a member of the tetracycline class of antibacterial drugs. (SUF ¶ 42)

9. Doxycycline is an antibiotic tetracycline compound. (SUF ¶ 44)

10. There are two general categories of antibiotics: bacteriostatic agents, which inhibit bacterial growth; and bactericidal agents, which kill bacteria. (SUF ¶ 45)

11. Generic doxycycline is commercially available in at least 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg dosage forms. (SUF ¶ 46)

12. Periostat® is a 20 mg dose of doxycycline administered twice-daily to a human and is indicated for treatment of periodontal disease. (SUF ¶ 47)

13. According to its approved label, Periostat® has a steady state C_{max} of 0.790 µg/ml. (SUF ¶ 48)

III. ROSACEA AND ITS TREATMENT

14. Rosacea is a long-lasting, chronic inflammatory disorder. (Tr. 71)[5]

15. Historically, rosacea has been treated by oral administration of antibiotics in antibiotic dosages and/or administration of topical gels and creams to treat the signs and symptoms of the disease. (PTX 209 at 1249; Tr. 75, 534-36)

16. The most common oral treatments for rosacea prior to the launch of Oracea® were antibiotic doses of tetracyclines. (PTX 209 at 1249; Tr. 534-36)

IV. Oracea®

17. Plaintiff GLLP currently holds New Drug Application ("NDA") 50-805 on Oracea® brand doxycycline capsules ("Oracea®"), which was approved by the U.S. Food and Drug Administration ("FDA") on May 26, 2006. (SUF ¶ 49)

18. GLLP is the exclusive distributor of Oracea® in the United States. (SUF ¶ 50)

19. The active ingredient in Oracea® is doxycycline monohydrate. (SUF ¶ 51)

20. Oracea® is a capsule dosage form for oral administration. (SUF ¶ 52)

21. The dosage strength of Oracea® is 40 mg. (SUF ¶ 53)

22. Oracea® is an oral pharmaceutical composition of doxycycline to be administered once-daily. (SUF ¶ 54)

23. Oracea® is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. (SUF ¶ 56)

24. Oracea® is a hard shell gelatin capsule filled with two types of doxycycline beads,

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[5]The trial transcript is docketed at D.I. 270, 271, 272, and 273. All references to the trial transcript are in the format "Tr." followed by the page number.

30 mg immediate-release ("IR") beads and 10 mg delayed-release ("DR") beads (coated with an enteric polymer). (SUF ¶¶ 57-58)

25. Oracea® does not contain a bisphosphonate compound. (SUF ¶ 59)

26. Oracea® contains one or more pharmaceutical excipients. (SUF ¶ 60)

27. Oracea® is the first and only orally administered, systemically delivered drug approved by the FDA for the treatment of rosacea. (PTX 426 at GAL 0229992; Tr. 540)

28. Oracea® treats rosacea in a human. (PTX 426 at GAL 0229992; PTX 381 at GAL 0240969-70; Tr. 73, 129-30)

29. Oracea®, when administered once-daily, is administered in an amount that reduces lesion count and an amount that is effective to treat the papules and pustules of rosacea. (PTX 426 at GAL 0229996-97; PTX 381 at GAL 0240969-70; Tr. 73, 287-88, 727)

30. Oracea® is administered long-term, i.e., over a period of time longer than eight to ten days. (PTX 426 at GAL 0229993, -96-97; SUF ¶ 38)

31. Oracea® is administered by "sustained release," i.e., a method of drug delivery to achieve a certain level of the drug over a particular period of time. (PTX 426 at GAL 0229993, -95, -96)

32. Oracea®, when administered once daily, is administered in an amount that results in no reduction of skin microflora during a six-month treatment. (PTX 426 at GAL 0229996; PTX 394; 459, 612-15)

33. *In vivo* microbiological studies utilizing a similar drug exposure to Oracea® for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina. (PTX 426 at GAL 0229996; PTX 394; PTX 413; PTX

200; PTX 201)

34. Oracea® should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. (PTX 426 at GAL 0229996)

35. Patients should not take Oracea® to treat infections caused by bacteria germs or viruses. (PTX 426 at GAL 0229998)

V. MYLAN'S GENERIC PRODUCT

36. Defendant Mylan submitted Abbreviated New Drug Application ("ANDA") 90-855 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), seeking FDA approval for the commercial manufacture, use, and sale of a generic version of Oracea® ("Mylan's Generic Product" or "Mylan's ANDA Product") before the expiration of the '267 patent, the '572 patent, the '395 patent, and the '775 patent. (SUF ¶ 61)

37. ANDA 90-855 identifies Mylan as the manufacturer of Mylan's Generic Product. (SUF ¶ 62)

38. The FDA approved ANDA 90-855 on July 1, 2010. (SUF ¶ 63)

39. Mylan's Generic Product will contain the package insert approved by the FDA for Mylan's Generic Product ("Mylan's Label," "Mylan Label," or "Label"). (SUF ¶ 64)

40. The active ingredient in Mylan's Generic Product is doxycycline. (SUF ¶ 65)

41. The dosage strength of Mylan's Generic Product is 40 mg. (SUF ¶ 66)

42. Mylan's Generic Product is a hard shell gelatin capsule filled with two types of doxycycline beads, 30 mg IR and 10 mg DR. (SUF ¶ 67)

43. Mylan's Generic Product does not contain a bisphosphonate compound. (SUF ¶

68)

44. FDA has found Mylan's Generic Product to be bioequivalent to Oracea®. (SUF ¶ 69)

45. The statements in the approved package insert for Mylan's Generic Product are true. (Memorandum Opinion granting Preliminary Injunction (D.I. 177) at 9; *see also* 18 U.S.C. § 1001; 21 U.S.C. §§ 355b(a)(1), 355c(a); Tr. 323)

46. The doxycycline in Mylan's Generic Product is doxycycline monohydrate. (DTX 2091 at MYL-D118692-93; DTX 2267 at MYL-D000206; Tr. 98-99)

47. Mylan's Label instructs doctors and patients that one doxycycline capsule (40 mg) of Mylan's Generic Product should be taken once-daily by oral administration. (DTX 2091 at MYL-D118686-87; DTX 2267 at MYL-D000220; Tr. 83, 100-01)

48. Mylan's Generic Product is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. (DTX 2091 at MYL-D118686-87; Tr. 82)

49. Mylan's Label instructs doctors and patients to use Mylan's Generic Product to treat rosacea in a human. (DTX 2091 at MYL-D118686-87, -97; Tr. 82)

50. Mylan's Generic Product, when administered once-daily in accordance with Mylan's Label, is administered in an amount that reduces lesion count and that is effective to treat the papules and pustules of rosacea. (DTX 2091 at MYL-D118695-96; Tr. 82-83)

51. Mylan's Generic Product is administered long-term, i.e., over a period of time longer than eight to ten days. (DTX 2091 at MYL-D118687, -95-96; Tr. 84)

VI. PATENTS-IN-SUIT

A. The Ashley Patents

1. Ashley '267 Patent

52. U.S. Application Number 10/117,709, from which the '267 patent issued, was filed on April 5, 2002. (SUF ¶ 7)

53. The '267 patent issued on May 1, 2007, naming Robert A. Ashley as the sole inventor and listing CollaGenex Pharmaceuticals, Inc. as assignee. (SUF ¶ 8) The '267 patent is entitled "Methods of Treating Acne." (PTX 1)

54. GLI is the current assignee of the '267 patent. (SUF ¶ 9)

55. The '267 patent claims priority from provisional application no. 60/325,489, filed September 26, 2001 and provisional application no. 60/281,916, filed April 5, 2001. (SUF ¶ 10)

56. The '267 patent is set to expire on April 5, 2022. (SUF ¶ 11)

2 Ashley '572 Patent

57. U.S. Application Number 11/061,866, from which the '572 patent issued, was filed on February 18, 2005. (SUF ¶ 12)

58. The '572 patent issued on June 19, 2007, naming Robert A. Ashley as the sole inventor and listing CollaGenex Pharmaceuticals, Inc. as assignee. (SUF ¶ 13) The '572 patent is entitled, "Methods of Treating Rosacea." (PTX 2)

59. GLI is the current assignee of the '572 patent. (SUF ¶ 14)

60. The '572 patent is a continuation of application no. 10/272,499, filed on October 15, 2002, and issued as U.S. Patent No. 7,014,858, which is a continuation of application no. 10/117,709, which issued as the '267 patent. (SUF ¶ 15)

61. The '572 patent claims priority from provisional application no. 60/281,916, filed April 5, 2001 and provisional application no. 60/325,489, filed September 26, 2001. (SUF ¶ 16)

62. The '572 patent is set to expire on April 5, 2022. (SUF ¶ 17)

3. Facts relating to infringement and validity of Ashley Patents

63. Dr. Webster, who was called at trial by Galderma, is an expert in the field of clinical dermatology and microbiology. (Tr. 70; PTX 248)[6]

64. Dr. Chambers, who was called at trial by Mylan, is an expert in the field of infectious diseases and antimicrobial agents, including antibiotic resistance and the pharmacokinetics and pharmacodynamics of antimicrobial agents. (Tr. 552; DTX 2102)

65. Dr. Randall Stafford, who was called at trial by Mylan, is an expert in the field of clinical epidemiology, including the use prescription patterns generated by IMS Health. (Tr. 416; DTX 2208)

66. Dr. Barbara Gilchrest, who was called at trial by Mylan, is an expert in the field of clinical dermatology with a specific focus in the treatment of acne and rosacea. (Tr. 449; DTX 2135)

67. A microorganism is a single cellular life form or sub-life form, including a bacterium, a virus, a yeast, or protozoan. (Tr. 557)

68. Microorganisms live everywhere on and in our bodies. (Tr. 557)

69. Approximately 100,000,000,000,000 bacterial cells inhabit the human body. (Tr. 149-50, 557)

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[6]There is no dispute that each of the experts who testified at trial is a person having at least ordinary skill in the art with respect to the patents about which that expert testified.

70. In our bodies, the number of bacterial cells is greater than the number of human cells by a factor of 10. (Tr. 557)

71. Doxycycline is among the most potent known antimicrobial agents. (Tr. 558)

72. Doxycycline is "broad spectrum," which means that it affects a large number of organisms. (Tr. 558)

73. Doxycycline is a protein synthesis inhibitor that inhibits the growth of microorganisms by paralyzing their protein machinery. (Tr. 559)

74. When administered orally, doxycycline is absorbed into the bloodstream and travels wherever blood goes in the body. (Tr. 558-59)

75. The inhibitory effect caused by doxycycline can be measured in several ways, including reduction in count of an organism and the emergence of organisms resistant to doxycycline. (Tr. 559-60, 562-66)

76. *In vivo* microbiological studies utilizing a similar drug exposure to Mylan's Generic Product for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina. (DTX 2091 at MYL-D118694; PTX 394; PTX 413; PTX 200; PTX 201; Tr. 90-95, 325-26, 608-09, 612-14, 616-17, 620, 621-25)

77. Mylan's Generic Product, when administered as 40 mg of doxycycline once a day, is administered in an amount that results in no reduction of skin microflora during a six-month treatment. (DTX 2091 at MYL-D118694; PTX 394; Tr. 88-93, 326, 459, 612-15)

78. The assessment of whether an antibiotic substance has activity against microorganisms should not be limited to examining only certain types of categories of bacteria. (Tr. 151)

79. The purpose of the Haffajee study was to examine subgingival microbiological changes in human subjects with periodontitis. (DTX 2097 at 148; Tr. 561)

80. Patients in the Haffajee study received one of four treatments: 1) scaling and root planning ("SRP") alone; 2) SRP and doxycycline (20 mg twice-daily for 3 months); 3) SRP and metronidazole (150 mg thrice-daily for 14 days); and 4) SRP and azithromycin (500 mg once-daily for 3 days). (DTX 2097 at 149; Tr. 561-62)

81. Samples of subgingival plaque and saliva were taken at baseline, two weeks, three months, nine months and twelve months. (DTX 2097 at 150; Tr. 561)

82. Each sample was measured for the percentage of total isolates that were resistant to 4 μg/ml of doxycycline at each time point. (DTX 2097 at 152 (Figure 3); Tr. 566-67)

83. Figure 3 in the Haffajee study is a graphic representation of the percentage of total isolates resistant to 4 μg/ml of doxycycline at each time point in both the doxycycline group and placebo group. (DTX 2097 at 152 (Figure 3); Tr. 562-63, 566-70)

84. At time zero (i.e., prior to administration of drug), the percentage of total isolates resistant to 4 μg/ml of doxycycline are virtually identical in both the doxycycline and placebo groups – approximately 10% of the isolates are resistant. (DTX 2097 at 152 (Figure 3); Tr. 567-68)

85. At the two week time point, the percentage of resistant isolates in the doxycycline group spiked from 10% to approximately 45%, whereas in the placebo group, the two week data indicated virtually no change in the percentage of isolates resistant to doxycycline. (DTX 2097 at 152 (Figure 3); Tr. 568)

86. The spike in percentage of resistant isolates in the doxycycline group at the two

week time period is due to significant inhibition of growth caused by exposure to doxycycline. (DTX 2097 at 152 (Figure 3); Tr. 562-66, 568)

87. The significant inhibition of growth of microorganisms susceptible to doxycycline allowed microorganisms resistant to doxycycline to increase in numbers. (DTX 2097 at 152 (Figure 3); Tr. 562-66, 568)

88. The statistical analysis included in the Haffajee study confirms that there is virtually no chance that the data in Figure 3 resulted from random occurrence. (DTX 2097 at 152 (Figure 3); Tr. 568)

89. The data in Figure 3 of the Haffajee study provides conclusive evidence that Mylan's Generic Product will significantly inhibit the growth of microorganisms in the oral cavity. (DTX 2097 at 152 (Figure 3); Tr. 568-70)

90. The Haffajee study did not detect any long-term effect of 40 mg dose of doxycycline. (DTX 2097 at 152 (Figure 3); Tr. 568-69)

91. The purpose of the Thomas study was to assess whether doxycycline changes antibiotic susceptibility of the oral microflora in adults with periodontitis. (DTX 2121 at 1472; Tr. 571-72)

92. Patients in the Thomas study received one of the following treatments: 20 mg doxycycline twice daily, 20 mg doxycycline once daily, 10 mg of doxycycline once daily or placebo. (DTX 2121 at 1473 (Table 1); Tr. 571-72)

93. Samples of subgingival plaque were taken at baseline, twelve months, fifteen-to-eighteen months, and twenty-one to twenty-four months. (DTX 2121 at 1473 (Table 1); Tr. 571-72)

94. The Thomas study measured the doxycycline MIC50 values for Actinomyces species isolates at each sample period. (DTX 2121 at 1477 (Figure 2A); Tr. 572)

95. An increase in MIC50 values in the presence of an antibiotic indicates emergence of drug resistant cells due to inhibition of susceptible cells. (DTX 2121 at 1477 (Figure 2A); Tr. 572)

96. Figure 2A in the Thomas study is a graphic representation of the MIC50 data for Actinomyces species isolates at each sample period. (DTX 2121 at 1477 (Figure 2A); Tr. 572-73)

97. At baseline, the MIC50 values of all four groups are at or near 1. (DTX 2121 at 1477 (Figure 2A); Tr. 572-73)

98. At twelve months, the MIC50 values in the 20 mg twice daily and 20 mg once daily groups jumped to 32, while the placebo group remained relatively constant. (DTX 2121 at 1477 (Figure 2A); Tr. 572-73)

99. The difference between the baseline and twelve month data is due to the significant inhibition of growth of microorganisms susceptible to doxycycline, which facilitates growth of microorganisms resistant to doxycycline. (DTX 2121 at 1477 (Figure 2A); Tr. 573)

100. The Thomas study reflects the same results as the Haffajee study – administration of a 40 mg daily dose of doxycycline caused an increase in the number of microorganisms resistant to doxycycline. (DTX 2121 at 1477 (Figure 2A); Tr. 573-74)

101. The Thomas study did not detect any long term effect of a 40 mg dose of doxycycline. (DTX 2121 at 1477 (Figure 2A); Tr. 574)

102. The purpose of the Walker 2000 study was to determine whether treatment with a

40 mg daily dose of doxycycline exerted an antimicrobial effect on the microflora associated with adult periodontitis. (DTX 2120 at 1465; Tr. 575-76)

103. Patients in the Walker 2000 study received one of the following treatments: 20 mg doxycycline twice-daily or placebo. (DTX 2120 at 1466; Tr. 575-76)

104. Each patient also received scaling and root planning in half of their mouth; thus, there were effectively 4 treatment groups: SRP-placebo, SRP-doxycycline, placebo, and doxycycline. (DTX 2120 at 1466; Tr. 575-76)

105. Samples of subgingival plaque were taken at baseline, three months, six months, nine months, and twelve months. (DTX 2120 at 1466; Tr. 575-76)

106. The Walker 2000 study measured the mean percentage of spirochetes (a type of microorganism) relative to the total microscopic flora at each sampling period. (DTX 2120 at 1467-68 (Tables 1, 2 & 3); Tr. 576-77)

107. The mean percentage of spirochetes data, which appears in Tables 1-3, shows that a 40 mg daily-dose of doxycycline significantly inhibited the growth of microorganisms. (DTX 2120 at 1467-68 (Tables 1, 2 & 3); Tr. 576-77, 579)

108. Table 1 provides data regarding small spirochetes. (DTX 2120 at 1467 (Table 1); Tr. 577)

109. In Table 1, at baseline, the mean percentage of small spirochetes in the SRP-doxycycline and SRP-placebo groups is nearly identical – approximately 10.35%. (DTX 2120 at 1467 (Table 1); Tr. 577-78)

110. At three months, the number of small spirochetes was significantly reduced in the doxycycline group to 4.32%, whereas the percentage in the placebo group was relatively

unchanged at 9.59%. (DTX 2120 at 1467 (Table 1); Tr. 578)

111. According to the statistical analysis in Walker 2000, that difference is statistically significant – i.e., very unlikely to be the result of random chance. (DTX 2120 at 1467 (Table 1); Tr. 578)

112. The significant reduction in the mean percentage of small spirochetes was due to the exposure of doxycycline and resulting significant inhibition of growth. (DTX 2120 at 1467 (Table 1); Tr. 578)

113. Table 2 (data regarding reduction of large spirochetes) and Table 3 (data regarding reduction of intermediate spirochetes) also show significant inhibition of growth. (DTX 2120 at 1467-68 (Tables 2 & 3); Tr. 579)

114. The Walker 2000 study did not detect any long term effect of 40 mg dose of doxycycline. DTX 2120 at 1467 (Table 1); Tr. 578-79.

115. The FDA reviewed the clinical microbiology studies described in PTX 394 ("Skidmore"), PTX 413 ("Walker 2005"), PTX 200 ("Walker 2000"), and PTX 201 ("Thomas") during the approval process for Oracea®, and Mylan's Label relies on these studies. (Tr. 90-95, 612-13, 615-16, 622-23, 626)

116. Mylan is unaware of any *in vivo* microbiology studies of Mylan's Generic Product or a product with similar drug exposure that demonstrate a detectable long-term effect on bacterial flora of the oral cavity, skin, intestinal tract, or vagina. (Tr. 325-26)

117. Mylan is unaware of any *in vivo* microbiology studies of Mylan's Generic Product or a product with similar drug exposure that demonstrate a detectable long-term effect on the bacterial flora at any site in the human body other than the oral cavity, skin, intestinal tract, and

vagina. (Tr. 326)

118. Neither Mylan nor any of its experts has tested Mylan's Generic Product, Oracea®, or a product with a similar drug exposure to determine whether it will significantly inhibit the growth of microorganisms, e.g., bacteria. (Tr. 328, 659-60)

119. Mylan's Generic Product should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease. (DTX 2091 at MYL-D118687, -94; Tr. 89, 324-25, 606-07, 608)

120. When administered once daily in accordance with Mylan's Label, the plasma concentrations of doxycycline achieved with Mylan's Generic Product during administration are less than the concentration required to treat bacterial diseases. (DTX 2091 at MYL-D118694; Tr. 89-90, 607)

121. Mylan's Generic Product should not be used for the treatment of infections. (DTX 2091 at MYL-D118682, -97, Tr. 606-07)

122. Patients should not take Mylan's Generic Product to treat infections caused by bacterial germs or viruses. (DTX 2091 at MYL-D118683, -99)

123. Exceeding the recommended dosage for Mylan's Generic Product may result in an increased incidence of side effects including the development of resistant organisms. (DTX 2091 at MYL-D118687)

124. Nothing in Mylan's Label instructs doctors or patients to administer Mylan's Generic Product with a bisphosphonate compound. (DTX 2091; Tr. 84-85)

125. The doxycycline in Mylan's Generic Product is administered by "sustained

release," i.e., a method of drug delivery to achieve a certain level of the drug over a particular period of time. (DTX 2091 at MYL-D118687, -93; Tr. 100)

126. Both of the Ashley Patents identify Periostat® as "an especially preferred embodiment" of the inventions. (SUF ¶ 70; PTX1, 2; Tr. 457, 460)

127. Periostat® is an oral antibiotic tetracycline compound that provides a 40 milligram daily dose of doxycycline (20 mg BID). (PTX 1 at col. 5 lines 63-67; Tr. 143)

128. Dr. Lawrence Feldman is a physician who specializes in dermatology, including the treatment of patients with rosacea. (Tr. 333, 335-37)

129. Dr. Feldman is afflicted with rosacea, including the papules and pustules of rosacea. (Tr. 344, 408-09)

130. In October 1998 or 1999, Dr. Feldman attended a dermatology meeting in Las Vegas, Nevada. (Tr. 338-40)

131. At the convention, Dr. Feldman learned "new[] ideas," including "Periostat as being a treatment for rosacea." (Tr. 341-42)

132. Dr. Feldman learned that use of Periostat® to treat rosacea was a "new kind of idea in dermatology where an antibiotic could work as anti-inflammatory and not kill bacteria and it was just the dawn of that whole idea." (Tr. 403)

133. While taking Periostat® for his gingivitis, the Periostat® improved Dr. Feldman's rosacea. (Tr. 344-45, 408-09)

134. In January 2000, Dr. Feldman contacted CollaGenex and requested "professional courtesy samples of Periostat" to continue his use. (Tr. 366-67)

135. CollaGenex provided Dr. Feldman with 300-400 professional courtesy samples of

Periostat®. (Tr. 367)

136. In late January or early February 2000, Dr. Feldman used the professional courtesy samples of Periostat® to treat his rosacea. (Tr. 409-10)

137. Periostat® reduced Dr. Feldman's pustules. (Tr. 344-45, 409)

138. On February 19, 2000, Dr. Feldman diagnosed a patient as suffering from rosacea, including rosacea pustules. (DTX 1559; Tr. 356)

139. On February 19, 2000, Dr. Feldman gave his patient a three month prescription for Periostat®, and one three month refill. (DTX 1559; Tr. 359)

140. Dr. Feldman prescribed "Periostat 20 BID [twice daily] due to its anti-inflammatory effect with decreased risk of side effects." (DTX 1559; Tr. 357)

141. Dr. Feldman's personal use of Periostat® led him to anticipate that Periostat® would improve his patient's condition. (Tr. 345, 362-63; DTX 1559)

142. Dr. Feldman did not prescribe a bisphosphonate compound to his patient. (Tr. 408; DTX 1559)

143. In 2004, Dr. Feldman saw his patient again, at which time he did not notice anything about her rosacea and the patient did not say anything about her rosacea. (Tr. 365-66)

144. Dr. Feldman was free to discuss, publicly or privately, his own personal use of Periostat® to treat rosacea, including the specific dosage regimen he used. (Tr. 408)

145. Dr. Feldman's patient was free to discuss, publicly or privately, her use of Periostat® to treat rosacea, including the specific dosage regimen she used. (Tr. 159, 408)

146. Apart from this litigation, Dr. Feldman has never disclosed the Feldman patient record to anyone else. (Tr. 348-49, 405, 504)

147. Dr. Feldman stored the original of the Feldman patient record in a secure, locked storage facility. (Tr. 348-49, 405, 504)

148. Mylan has not identified Dr. Feldman's patient.

149. Mylan has not produced any testimony from Dr. Feldman's patient.

150. Mylan has not produced the prescription of Periostat® to Dr. Feldman's patient.

151. Dr. Feldman never published, publicly presented, or in any other way made public his prescribing of Periostat® to his patient, or his own personal use of Periostat®. (Tr. 399-400, 410, 500-02, 505-06)

152. Dr. Feldman never (1) attempted to sell the idea of using Periostat® to treat rosacea, (2) informed CollaGenex that Periostat® could be used to treat rosacea, or (3) considered submitting a patent application for the use of Periostat® to treat rosacea. (Tr. 400, 506)

153. Prior to February 19, 2000, Dr. Feldman was not personally aware of anyone who had prescribed Periostat® for the treatment of rosacea. (Tr. 403)

154. Periostat® is FDA-approved for the treatment of periodontitis, and has off-label uses other than the treatment of rosacea. (Tr. 418, 442)

155. The IMS Health Periostat® data demonstrates that Dr. Feldman prescribed a patient Periostat®, a prescription which was actually dispensed at a pharmacy. (Tr. 432; DTX 2211)

156. The IMS Data does not provide any patient-identifying information. (Tr. 435, 440-41)

157. The IMS Data does not provide patient diagnosis information, and the word

"rosacea" does not appear anywhere in the IMS Data. (Tr. 435, 441-42)

158. None of DTX 1764 ("Murphy"); DTX 1484 ("Cotterill"); DTX 1901 ("Sneddon"); DTX 2067 ("Wereide"); DTX 1703 ("Marmion"); DTX 1418 ("Bartholomew") (collectively, "the six Gilchrest References") discloses the administration of any antibiotic tetracycline compound in a sub-antibacterial amount or an amount that has substantially no antibiotic activity (i.e., an amount that does not significantly inhibit the growth of microorganisms, e.g., bacteria). (Tr. 518-19)

159. None of the six Gilchrest References discloses the administration of (1) doxycycline in any amount, (2) any antibiotic tetracycline compound in an amount of less than 100 mg/day, or (3) Periostat® or 20 mg doxycycline twice-daily. (Tr. 521-22)

160. Murphy, a clinical study conducted in 1962, followed 85 moderate to severe acne patients administered 125 mg oxytetracycline for 6-12 months. (Tr. 481; DTX 1764)

161. Cotterill, a study from 1971, administered 250 mg of oxytetracycline to 42 acne patients for 3 months. (DTX 1484)

162. Sneddon, a clinical study from 1966, administered a controlling dose of 100 mg tetracycline to severe rosacea patients. (Tr. 486; DTX 1901)

163. Wereide, a study from 1969, administered 250 mg oral tetracycline to reduce the papules and pustules of rosacea. (Tr. 487; DTX 2067)

164. Marmion, another study from 1969, treated ocular and cutaneous rosacea patients with 300 mg oxytetracycline. (Tr. 486; DTX 1703)

165. Bartholomew, a study from 1982, administered 500 mg oxytetracycline to treat both ocular and cutaneous rosacea. (Tr. 487; DTX 1418)

166. According to the '267 patent, 50 or 100 mg of doxycycline is an antibacterial effective amount. (PTX 1 at col. 5 lines 47-49)

167. None of the six Gilchrest references discloses the administration of doxycycline by "sustained release," i.e., by a method of drug delivery to achieve a certain level of the drug over a particular period of time. (DTX 1764; DTX 1484; DTX 1901; DTX 2067; DTX 1703; DTX 1418)

168. Prior to the invention of the Ashley Patents, no one developed a doxycycline treatment for rosacea at any dose lower than 50 mg per day. (Tr. 523)

169. None of DTX 1640 ("Hussar"), DTX 1694 ("Maibach"), DTX 1996 ("the '836 patent"), DTX 2005 ("the '065 patent"), DTX 1840 ("Plewig & Kligman"), DTX 1838 ("Plewig & Schopf"), DTX 1436 ("Braun-Falco"), DTX 1897 ("Smith & Mortimer"), or DTX 1493 ("Cunliffe") discloses the treatment of acne or the papules and pustules of rosacea with an antibiotic tetracycline compound administered in a sub-antibacterial amount. (Tr. 115-16, 536-40)

170. Plewig & Kligman and Plewig & Schopf were both considered by the United States Patent and Trademark Office ("PTO") during examination of the Ashley Patents. (PTX 1 at GAL 0037676; PTX 2 at GAL 0037655-56; Tr. 536-37, 538-39)

171. The authors of Plewig & Kligman stated that "beyond doubt . . . it is the antibiotic activity of antibiotics that accounts for therapeutic benefits" in treating acne. (DTX 1840 at MYL-D098330-31, Tr. 538)

172. Plewig & Schopf reported use of an antibiotic dose of tetracycline (1000-1500 mg per day) to treat inflammatory pustules induced by potassium iodide; and Braun-Falco instructed

that the initial dose of tetracyclines to treat rosacea is an antibacterial dose (1000-1500 mg, divided in two to three doses a day) until there is significant clinical improvement. (DTX 1838 at MYL-D119127; DTX 1436 at MYL-D098730; Tr. 539-40)

173. Smith & Mortimer and Cunliffe report studies of 250 mg tetracycline administered once-daily or more frequently, which according to Wereide is an antibacterial amount that may alter the intestinal flora and lead to growth of yeast or emergence of resistant strains of bacteria in the intestine. (DTX 1897 at MYL-D098386; DTX 1493 at MYL-D098304; DTX 2067 at MYL-D094936-37)

174. DTX 1045 (U.S. Patent No. 6,455,583) ("Pflugfelder") was considered by the PTO during the prosecution of the '572 patent, and the patent examiner for the '572 patent noted that its claims were patentable over Pflugfelder. (PTX 478 at GAL 0037966; Tr. 104-05, 524)

175. Pflugfelder does not disclose (1) a method of treating acne or acne rosacea, (2) a method for treating the papules and pustules of rosacea, (3) administration of an antibiotic tetracycline compound in a sub-antibacterial amount that reduces lesion count wherein the lesions are papules and pustules, or (4) administration of an antibiotic tetracycline compound in an amount that is effective to treat the papules and pustules of rosacea. (Tr. 103-04, 523-24)

176. Up to 50% of patients with cutaneous or facial rosacea also have symptoms of ocular rosacea. (Tr. 140, 492-93; DTX 2059 at MYL-D098660)

177. Facial rosacea and meibomian gland disease are distinct disease states, and patients with meibomian gland disease do not necessarily have acne, acne (facial) rosacea, or papules and pustules of rosacea. (PTX 478 at GAL 0037966; DTX 1045 at col. 1 lines 9-12; Tr. 102-03, 524-25)

B. The Amin Patents

1. Amin '395 Patent

178. U.S. Application Number 08/697,815, from which the '395 patent issued, was filed on August 30, 1996. (SUF ¶ 18)

179. The '395 patent issued on August 4, 1998, naming Ashok R. Amin, Steven B. Abramson, Lorne M. Golub, Nungavaram S. Ramamurthy, Thomas F. McNamara, Robert A. Greenwald, and Howard Trachtman as inventors, and RF SUNY and the Hospital for Joint Diseases as assignees. (SUF ¶ 19) The '395 patent is entitled, "Method of Using Tetracycline Compounds for Inhibition of Endogenous Nitric Oxide Production." (PTX 3)

180. RF SUNY and NYU are the current assignees of the '395 patent. (SUF ¶ 20)

181. GLI is the licensee of the '395 patent. (SUF ¶ 21)

182. The '395 patent is set to expire on August 30, 2016. (SUF ¶ 22)

2. Amin '775 Patent

183. U.S. Application Number 09/061,286, from which the '775 patent issued, was filed on April 16, 1998. (SUF ¶ 23)

184. The '775 patent issued on July 6, 1999, naming Ashok R. Amin, Steven B. Abramson, Lorne M. Golub, Nungavaram S. Ramamurthy, Thomas F. McNamara, Robert A. Greenwald, and Howard Trachtman as inventors, and RF SUNY and the Hospital for Joint Diseases as assignees. (SUF ¶ 24) The '775 patent is entitled, "Method for Inhibiting Expression of Inducible Nitric Oxide Synthase with Tetracycline." (PTX 4)

185. The '775 patent is a division of and claims priority from Application No. 08/697,815, filed August 30, 1996, which issued as the '395 patent. (SUF ¶ 25)

186. The '775 patent is set to expire on August 30, 2016. (SUF ¶ 26)

187. RF SUNY and NYU are the current assignees of the '775 patent. (SUF ¶ 27)

188. GLI is the licensee of the '775 patent. (SUF ¶ 28)

3. Facts relating to infringement and validity of Amin Patents

189. Nitric Oxide ("NO") is a chemical compound (a free radical gas) made up of one nitrogen atom and one oxygen atom. (SUF ¶ 73)

190. The first biological functions of NO were discovered in the 1980s. (SUF ¶ 75)

191. NO research immediately received a great deal of attention. In 1992, NO was named "molecule of the year" by the U.S. journal *Science*. (SUF ¶ 76)

192. NO is a short-lived molecule that rapidly decomposes into nitrate and nitrite. (SUF ¶ 78)

193. In mammalian cells, endogenous NO is synthesized by a group of enzymes known as "nitric oxide synthases" ("NOS"). (SUF ¶ 79)

194. NOS are expressed in a wide variety of mammalian cells, and can generally be categorized into three different types, or "isoforms." (SUF ¶ 80)

195. The production of large amounts of NO associated with inflammatory responses is generated by inducible nitric oxide synthase ("iNOS"). (SUF ¶ 81)

196. Expression of the gene coding for iNOS in cells and tissue involved in the inflammatory response leads to increased NO levels. (SUF ¶ 82)

197. Increased NO production has numerous downstream effects, e.g., vasodilation, increased vascular permeability, altered white blood cell function, and tissue damage. (SUF ¶ 83)

198. The expression of the iNOS gene is modulated by signaling cytokines that are activated in response to inflammatory stimuli. (SUF ¶ 84)

199. NO production can be reduced by inhibiting expression of the iNOS gene. (SUF ¶ 85)

200. Doxycycline decreases NO production from iNOS by destabilizing iNOS mRNA. (SUF ¶ 86)

201. Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as the presence of pathogens (e.g., bacteria) or compounds (e.g., bacterial endotoxin). (SUF ¶ 87)

202. Dr. Richard Robbins, who testified on behalf of Mylan with respect to the Amin Patents, has extensive education and experience in the area of NO and iNOS, as well as the inflammatory effects of antibiotics, including doxycycline, on NO and iNOS. (DTX 2168; Tr. 672-676)

203. Dr. Robbins is recognized as an expert in the area of NO and iNOS as well as the inflammatory effects of antibiotics, including doxycycline, on NO and iNOS. (Tr. 676)

204. Dr. Matthew Grisham, who testified on behalf of Galderma with respect to the Amin Patents, has extensive education and experience in the area of NO and iNOS, as well as acute and chronic inflammation and NO. Dr. Grisham is recognized as an expert in molecular and cellular physiology particularly as it relates to the biological functions of nitric oxide. (Tr. 261; PTX 245)

205. Claims 1, 2, 4, 11, 13, 14, and 16 of the '395 patent and claims 1, 2, 4, 5, and 9 of the '775 patent require administration of a tetracycline in an amount sufficient to decrease or

inhibit endogenously produced NO or inhibit the expression of iNOS. (PTX 3 at col. 21 line 48-col. 24 line 9; PTX 4 at col. 21 line 47- col. 22 line 63)

206. There are no tests, studies, or other experimental data showing that a 40 mg dose of doxycycline administered daily decreases NO production or inhibits iNOS expression. (Tr. 289-90, 291, 687-88)

207. There is no quantitative data showing a decrease of NO production or inhibition of iNOS expression when a 40 mg dose of doxycycline is administered daily. (Tr. 292)

208. According to the Oracea® package insert, a 40 mg daily dose of doxycycline achieves a steady state C_{max} blood concentration of 0.6 μg/ml. (PTX 426 at GAL 0229996; Tr. 293, 681-82)

209. There is no evidence that the 0.6 μg/ml steady state C_{max} blood concentration achieved by a 40 mg daily administration of doxycycline has an effect on endogenous NO production or iNOS expression. (Tr. 294, 680-90)

210. Examples 2 and 3 in the Amin Patents provide data regarding the effect of doxycycline on endogenous NO production and iNOS expression observed as part of *in vitro* experiments. (PTX 3 at col. 11 line 22-col. 12 line 67; Tr. 682-83)

211. Figures 1A, 1B, and 1C of the Amin Patents present graphical data regarding the effect of doxycycline and minocycline on endogenous NO production and iNOS expression in the study discussed in Example 2 of the Amin Patents. (PTX 3 at FIG-1A, FIG-1B, FIG-1C; *see also* Tr. 683-84)

212. To determine the effect of doxycycline and minocycline on endogenous NO production and iNOS expression in the studies discussed in Examples 2 and 3 of the Amin

Patents, nitrite, a stable-end product of the decomposition of NO, was measured in the mediums treated with doxycycline and minocycline. (PTX 3 at col. 11 line 22-col. 12 line 67; Tr. 683)

213. As shown in Figures 1A, 1B, and 1C of the Amin Patents, doxycycline does not appear to have a dose-dependent inhibition of nitrite below 10 μg/ml doxycycline. (PTX 3 at FIG-1A, FIG-1B, FIG-1C; *see also* Tr. 684-85)

214. The 0.6 μg/ml C_{max} steady state blood concentration achieved by the 40 mg doxycycline in Oracea® administered daily is "far below" what one would expect to be required to decrease NO production. (Tr. 687-88)

215. As shown in Figures 2A and 2B, doxycycline appears to have a dose-dependent inhibition of nitrite at concentrations of doxycycline much higher than 0.6 μg/ml doxycycline. (PTX 3 at FIG-2A, FIG-2B; Tr. 687-88)

216. The results of the experiments performed in Dr. Robbins' laboratory regarding the *in vitro* effect of doxycycline on nitrite production, NO production, and iNOS protein expression are published in Hoyt *et al.*, "Doxycycline Modulates Nitric Oxide Production in Murine Lung Epithelial Cells," *J. Immun.* (2006) 176:567-72. (DTX 1627; Tr. 688)

217. In experiments conducted in Dr. Robbins' laboratory, doxycycline showed an inhibition of iNOS expression and NO production at a concentration of 30 μg/ml, but not at 10 μg/ml and lower. (Tr. 688-690; DTX 1627)

218. The data from Dr. Robbins' research shows that the maximal blood concentration obtained with the 40 mg per day dosage of doxycycline is insufficient to cause inhibition of iNOS expression or NO production. (Tr. 689-90)

219. CollaGenex, the predecessor in interest to Galderma, proposed that the FDA

approve the following language for the Oracea® label: "[Oracea®] has been shown *in vitro* to suppress pro-inflammatory processes such as neutrophil activation, inhibition of matrix metalloproteases, endogenous nitric oxide release, and expression of inducible nitric oxide synthase." (DTX 1340 at GAL 0034431)

220. The FDA rejected CollaGenex's proposed language, requiring the label to read instead: "The mechanism of action of Oracea® in the treatment of inflammatory lesions of rosacea is unknown." (PTX 426 at GAL 0229996)

221. Dr. Grisham disagrees with the FDA that "[t]he mechanism of action of Oracea® in the treatment of inflammatory lesions of rosacea is unknown." (Tr. 297-99; PTX 426 at GAL 0229996)

222. Gürer *et al.*, "The seroprevalence of *Helicobacter pylori* and nitric oxide in acne rosacea," published in *Int'l J. Dermatol.* (2002) 41:768-770 ("Gürer"), is cited within one of the review articles upon which Dr. Grisham relies in support of his opinion that NO and iNOS are involved in the mechanism of action of acne rosacea. (Tr. 270-71)

223. Gürer concluded that "the inflammatory species NO . . . has no role in the inflammatory mechanism of acne rosacea." (DTX 2180 at 770)

224. Another of Galderma's experts, Dr. Webster, testified that "[w]e still don't know convincingly what the cause of rosacea is." (Tr. 136)

225. Robert Ashley, the named inventor on the Ashley Patents, testified that he did not "think causality has ever been proven one way or the other" with respect to acne rosacea. (Tr. 670)

226. Mylan's expert, Dr. Robbins, testified that "there is no evidence that nitric oxide

is involved in the pathogenesis of rosacea." (Tr. 692)

227. The Amin Patents list more than thirty different chronic inflammatory conditions. (PTX 3 col. 7 line 58- col. 8 line 3; PTX 4 col. 7 line 53-col. 8 line 8)

228. The word "rosacea" does not appear anywhere in the Amin Patents. (PTX 3; PTX 4; Tr. 691-92)

229. The Amin Patents contain the first disclosure that tetracycline compounds inhibit iNOS expression and NO production. (Tr. 740-41)

230. Prior to August 1996, there were no literature reports in which tetracyclines were reported to have any effect on NO or iNOS. (Tr. 740)

231. None of the eight prior art references relied on by Mylan's Dr. Robbins ("Robbins References") disclose, explicitly or inherently, NO or iNOS. (DTX 2183; DTX 2181; DTX 2182; DTX 2184; DTX 2188; DTX 1603; DTX 2186; DTX 2187; *see also* Tr. 730-37)

232. None of the eight Robbins References disclose, explicitly or inherently, using any tetracycline compounds in methods of decreasing NO production or inhibiting iNOS expression. (DTX 2183; DTX 2181; DTX 2182; DTX 2184; DTX 2188; DTX 1603; DTX 2186; DTX 2187; *see also* Tr. 730-33, 735-39)

233. None of the eight Robbins References disclose, explicitly or inherently, whether the patients in those studies experienced elevated levels of NO production or iNOS expression. (DTX 2183; DTX 2181; DTX 2182; DTX 2184; DTX 2188; DTX 1603; DTX 2186; DTX 2187; *see also* Tr. 730-33, 735-39)

234. Dr. Robbins did not form an opinion as to whether 20 mg of doxycycline administered twice a day decreases iNOS expression or NO production in humans with

periodontitits or inhibits endogenous production of NO or expression of iNOS in patients with rheumatoid arthritis. (Tr. 730, 734-35)

235. Dependent claims 2 and 14 of the '395 patent and claim 2 of the '775 patent add the limitation that the administered tetracycline compound have substantially no antimicrobial activity. (PTX 3 at col. 21 lines 54-56; *id.* at col 23 lines 8-10; PTX 4 at col. 21 lines 53-55)

236. Dependent claims 2 and 14 of the '395 patent and claim 2 of the '775 patent require a dose of tetracycline sufficient to reduce endogenous NO production or inhibit iNOS expression. (PTX 3 at col. 21 lines 49-56; *id.* at col. 22 line 67- col. 23 line 3; *id.* at col. 23 lines 8-10; PTX 4 at col. 21 lines 48-55)

237. The lowest concentration of doxycycline and minocycline used in the studies that are the subject of Examples 2 and 3 of the Amin Patents is 5 μg/ml. (PTX 3 at col. 11 line 22-col. 12 line 67, FIG-1A, FIG-1B, FIG-1C, FIG-2A, FIG-2B; Tr. 720-21)

238. The Amin Patents do not teach that 5 μg/ml is a concentration that has substantially no antimicrobial activity. (PTX 3; PTX 4; Tr. 720-21)

239. The Amin Patents do not provide any teaching or description to allow one of ordinary skill in the art to make or use a dose of a tetracycline that is both sufficient to reduce endogenous NO or inhibit iNOS expression and has substantially no antimicrobial activity. (Tr. 719-21)

C. The Chang Patent

1. Chang '532 Patent

240. U.S. Application Number 10/819,620, from which the '532 patent issued, was filed on April 7, 2004. (SUF ¶ 29)

241. The '532 patent issued on July 6, 2010, naming Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee. (SUF ¶ 30) The '532 patent is entitled, "Once Daily Formulations of Tetracyclines." (PTX 5)

242. Supernus is the current assignee of the '532 patent. (SUF ¶ 31)

243. The '532 patent is set to expire on December 19, 2027. (SUF ¶ 32)

244. GLI is the licensee of the '532 patent. (SUF ¶ 33)

2. Facts relating to infringement and validity of Chang Patent

245. Dr. Edward Rudnic, who testified on behalf of Galderma, is an expert in the field of pharmaceutical drug development and formulation. (Tr. 174)

246. Dr. David Friend, who testified on behalf of Mylan, is an expert in the field of designing and developing controlled release drug delivery systems. (Tr. 782)

247. Dr. Werner Rubas, who testified on behalf of Mylan, is an expert in the area of pharmacokinetics and pharmacokinetic modeling. (Tr. 753)

248. Mylan admits that its Generic Product infringes claims 1-3, 5, 7-9, 13-17, and 19-21 of the '532 patent. (D.I. 103 (C.A. No. 10-892))

249. Mylan's Generic Product contains an amount of doxycycline that, when administered once-daily in accordance with Mylan's Label, will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. (PTX 5, claims 1, 15, 20; PTX 464 at GAL 0004365-66; DTX 2091 at MYL-D118693; Tr. 182-83)

250. Mylan's Generic Product contains an amount of doxycycline that, when administered once-daily in accordance with Mylan's Label, will give steady state blood levels of doxycycline of between 0.3 μg/ml to 0.8 μg/ml. (PTX 5, claims 4 and 18; PTX 464 at GAL

0004365-66; DTX 2091 at MYL-D118693; Tr. 183, 640)

251. Mylan's Generic Product is bioequivalent to Oracea® and Mylan relied on Galderma's pivotal pharmacokinetic study of Oracea® in seeking FDA approval for Mylan's Generic Product. (Tr. 288; SUF ¶ 69)

252. The pivotal pharmacokinetic study demonstrates that 30 of 31 subjects have steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. (PTX 464 at GAL 0004365-66; DTX 1305; Tr. 183)

253. The pivotal pharmacokinetic study demonstrates that the majority of subjects will have steady state blood levels of doxycycline of between 0.3 μg/ml to 0.8 μg/ml at the majority of time points. (PTX 464 at GAL 0004365-66; Tr. 183)

254. Mylan's expert, Dr. Friend, testified that the Ashley CR References[7] and the Ashley Rosacea Reference[8] are the closest prior art to the Chang patent. (Tr. 832)

255. None of the references Mylan relies on expressly discloses once-daily doses of doxycycline. (Tr. 191-96, 831-33, 844, 853)

256. None of the references Mylan relies on expressly discloses formulations with a 30 mg IR portion and a 10 mg DR portion. (Tr. 829-34, 839, 844, 849-50)

257. None of the references Mylan relies on expressly discloses formulations that result

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[7]The "Ashley CR References" are DTX 1008 (Provisional Application No. 60/281,854 ("the '854 application")) and DTX 1067 (International Application WO 02/083,106 ("the '106 application")), and may also be referred to as "the Ashley Patent Applications."

[8]The "Ashley Rosacea Reference" is International Application WO 02/080932 ("the '932 application"), and may also be referred to as the "Ashley Method of Use Application." (DTX 2111) Collectively, the Ashley Rosacea Reference, the Ashley CR References, and the Ashley '267 and '572 patents may also be referred to as the "Ashley References."

in steady state blood levels of a minimum of 0.1 μg/ml to a maximum of 1.0 μg/ml. (Tr. 831-34, 845-46, 850)

258. None of the references Mylan relies on expressly discloses formulations that result in steady state blood levels of between 0.3 μg/ml to 0.8 μg/ml. (Tr. 190-91, 195-98, 200-01, 850)

259. The Ashley CR References do not disclose any examples of any formulations. (Tr. 191, 194-95, 833; DTX 1008)

260. The inventor of the Ashley CR References did not make any formulations of doxycycline. (Tr. 191, 194-95, 833, 869-70; DTX 1008)

261. The Ashley CR References do not disclose, teach, or suggest the use of an IR/DR formulation. (Tr. 192; DTX 1008)

262. The Ashley CR References do not disclose, teach, or suggest any composition that contains a 30 mg IR component or any composition that contains a 10 mg DR component. (Tr. 192, 194-95, 834, 839; DTX 1008)

263. The Ashley Rosacea Reference does not disclose any examples of any formulations. (Tr. 195, 831)

264. The Ashley Rosacea Reference does not disclose, teach, or suggest any composition that contains a 30 mg IR component or any composition that contains a 10 mg DR component. (Tr. 195-96, 829, 832)

265. The Ashley Rosacea Reference does not disclose, teach, or suggest any formulation that will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. (Tr. 831)

266. The disclosure of the '304 patent[9] is not as close to the Chang Patent claims as the disclosures in the Ashley References. (Tr. 844)

267. The '304 patent does not disclose, teach, or suggest the use of doses of doxycycline that do not have an antibiotic effect or doses with a maximum plasma concentration of 1.0 μg/ml. (Tr. 200-01, 845-47; DTX 2119)

268. The '304 patent teaches away from the inventions of the Chang Patent because the '304 patent discloses and claims formulations in which both the IR and DR components are independently therapeutic and antibiotic doses. (DTX 2119 at col. 5 line 42-col. 6 line 49; *see also* Tr. 200-01)

269. Mylan's expert, Dr. Friend, testified that one of ordinary skill in the art would not look to a patent relating to amphetamine drugs, such as the '819 patent,[10] for guidance in formulating a once daily doxycycline product. (Tr. 848-49, 196-98, 925-27)

270. The physical and chemical characteristics of doxycycline and amphetamines are different. (Tr. 196-98, 849, 925-27)

271. The '819 patent teaches away from the inventions of the Chang Patent because the '819 patent teaches formulations that result in continually increasing plasma concentration levels of the drug. (Tr. 196-97, 849-50, 925-27)

272. The '819 patent does not mention doxycycline. (DTX 2116; *see also* Tr. 197-98)

273. The '819 patent does not disclose, teach, or suggest any composition that contains

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[9]The '304 patent is entitled "Pulsatile Once-a-Day Delivery Systems for Minocycline." (DTX 2119)

[10]The '819 patent is entitled "Oral Pulsed Dose Drug Delivery System" and is directed to a pulsed delivery of amphetamine salts. (DTX 2116)

a 30 mg IR component or any composition that contains a 10 mg DR component. (Tr. 197-98, 850)

274. The '819 patent does not disclose, teach, or suggest any method of treating rosacea. (Tr. 197-98, 850-51)

275. The '819 patent teaches away from the invention of the Chang Patent because it teaches formulations that result in C_{max} levels greater than 1.0 μg/ml. (Tr. 850)

276. Neither the '932 application, the '106 application, nor the '819 patent provide any motivation to combine their teachings. (Tr. 207-08)

277. Robert Ashley did not invent the inventions claimed in the Chang Patent and had no idea how to create any formulations that met the steady state blood levels claimed. (Tr. 869-70, 961-62, 966-67)

278. CollaGenex had "no meaningful idea what composition might achieve" a once-daily doxycycline product without antibiotic effect or if it was even possible to do so because CollaGenex lacked formulation expertise. (Tr. 869; *see also* Tr. 217-18, 913-16, 964-67)

279. Dr. Richard Chang and the other named inventors of the Chang Patent took the target blood level provided by CollaGenex and gave it "meaning." (Tr. 915-16)

280. The named inventors of the Chang Patent conceived of and proposed the IR and DR combination and the claimed IR:DR bead ratio of 75:25 to CollaGenex. (Tr. 914-15, 938, 896-97, 910-11, 917-18, 964-65, 967-68)

281. Microtrol® technology is a marketing term used for business development purposes to broadly describe the general concept of having beads in a capsule and is not actually a fixed technology. (Tr. 892, 942)

282. As of the time of the invention of the Chang Patent, the inventors were in possession of data that demonstrated that the formulations of doxycycline claimed in the Chang Patent will give steady state blood levels of doxycycline of between 0.3 μg/ml to 0.8 μg/ml. (PTX 5, claims 4 and 18; DTX 1305; Tr. 184)

VII. OBJECTIVE CONSIDERATIONS OF NON-OBVIOUSNESS

283. In 1998, CollaGenex attempted, in partnership with FH Faulding & Co. Limited ("Faulding"), to develop a once-daily controlled-release formulation of doxycycline for the treatment of rosacea. (Tr. 214-15, 944)

284. Faulding formulated three 40 mg doxycycline drug products intended for once-daily administration. (PTX 530; PTX 95; PTX 96; Tr. 214-15, 964-65)

285. Formulations developed by Faulding were not successful in achieving once daily administration of doxycycline because bioavailability was significantly compromised. (PTX 530; PTX 95; PTX 96; PTX 510; Tr. 215-17, 238, 944, 969-70)

286. It was unexpected that a therapeutic, controlled-release, once-daily dosage form which provided steady state plasma concentrations of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml could be achieved. (Tr. 214)

287. Despite already marketing several different doses of doxycycline, including 50 mg, 100 mg, and 150 mg doses of doxycycline immediate-release tablets, Mylan still seeks to market a generic formulation of Oracea®. (Tr. 327-28, 498)

288. Oracea® is a commercial success. (Tr. 129, 214, 542)

289. According to IMS sales data maintained by Mylan, Oracea®'s sales (i.e., "brand dollars") for the period of January 2007 through December 2007 were approximately $43.0

million. (DTX 2243 at MYL-D118537) Oracea®'s brand dollars for the period of January 2008 through December 2008 were approximately $80.4 million. (*Id.* at MYL-D118540) Oracea®'s brand dollars for the period of January 2009 through December 2009 were approximately $155.3 million. (*Id.*)

290. Mylan projected that Oracea®'s brand dollars for the period of January 2010 through December 2010 would be approximately $236.7 million. (DTX 2243 at MYL-D118540) Mylan projected that Oracea®'s brand dollars for the period of January 2011 through December 2011 would be approximately $258.1 million. (*Id.*)

291. Prior to Oracea®, there was a long-felt, unmet need for an effective, long-term oral treatment for rosacea without the side effects associated with long-term administration of antibiotics (*e.g.*, gastrointestinal upset and phototoxicity). (Tr. 75-76, 540-43)

292. Oracea® is an effective, long-term oral treatment that does not have the undesirable side effects of traditional dose antibiotics. (PTX 426; Tr. 75-76, 128-30, 184, 540)

293. Prior to Oracea®, there was a long-felt, unmet need for a rosacea treatment without antibiotic effect that could be administered as a once-daily formulation of doxycycline to increase patient compliance and therapeutic outcome. (PTX 5 at col. 2 lines 1-4; DTX 1640 at MYL-D098594; Tr. 214, 456, 785)

PROCEDURAL BACKGROUND

On March 19, 2009, Plaintiffs initiated a patent infringement lawsuit against Mylan pursuant to 35 U.S.C. § 271(e)(2)(A).[11] (D.I. 1) In the complaint, Galderma asserts that Mylan's

[11]The statute provides, in relevant part, "It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a

ANDA, through which Mylan seeks to market a generic version of Oracea®, infringes Galderma's rights in the Ashley Patents and the Amin Patents. (D.I. 1 at 5-8) On April 2, 2010, Galderma filed a motion for preliminary injunction and for a temporary restraining order. (D.I. 87) On June 28, 2010, the Court granted Galderma's motion and entered a preliminary injunction. (D.I. 176; D.I. 188)

The Chang Patent issued on July 6, 2010. (PTX 5) Mylan subsequently brought suit against Galderma, seeking a declaratory judgment that its Generic Product does not infringe any claims of the Chang Patent and that the Chang Patent is invalid. (Civ. No. 10-892-LPS, D.I. 1) On December 1, 2010, the Court consolidated Mylan's declaratory judgment action with Galderma's ANDA action. (D.I. 239) The parties entered into a stipulation and order on March 11, 2011, in which Mylan conceded that its Generic Product infringes all asserted claims of the Chang Patent except claims 4 and 18. (D.I. 103)

The Court held a consolidated bench trial from July 5-9, 2011, addressing infringement and invalidity of the Ashley Patents, the Amin Patents, and the Chang Patent. (D.I. 270; D.I. 271; D.I. 272; D.I. 273) The parties completed post-trial briefing on July 29, 2011. (D.I. 265; D.I. 267; D.I. 274; D.I. 275)

DISCUSSION

I. THE ASHLEY PATENTS

A. Infringement

Galderma asserts that Mylan has infringed and/or will infringe (i) claims 1, 22, 23, 26, 28, and 30 of the '267 patent and (ii) claims 1, 12-15, 20, 21, 23, 24, and 26 of the '572 patent.

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patent . . . ." 35 U.S.C. § 271(e)(2)(A) (2006).

Mylan counters that it does not infringe any of the asserted claims of the Ashley Patents, directly or indirectly, literally or under the doctrine of equivalents. The Court agrees with Mylan.

1. Galderma Failed To Prove That Mylan's Generic Product Contains An Amount Of Doxycycline That Does Not Significantly Inhibit The Growth Of Microorganisms

Each of the asserted claims of the '267 and '572 patents require the administration of an amount of doxycycline "that does not significantly inhibit the growth of microorganisms, e.g., bacteria."[12] Galderma failed to prove that Mylan's ANDA product does not significantly inhibit the growth of microorganisms. To the contrary, *in vivo* studies show that 40 mg doxycycline administered once-daily ***does*** significantly inhibit the growth of some microorganisms in some locations of some humans at some times. Galderma's contention that Mylan's Label acknowledges that Mylan's Generic Product will infringe is incorrect. Galderma's other arguments for infringement are also unpersuasive. Each of these conclusions is described further below.

a. *In vivo* studies

Nothing in the Court's construction of the "amount" terms limits the "no significant inhibition in growth of microorganisms" limitation to certain portions of the human body, or to long-term effects, or to certain humans or certain microorganisms. Hence, the "amount" limitation applies to all microorganisms found in all parts of the human body at all times. (*See*

[12]The '267 patent's asserted claims all require "a sub-antibacterial amount." The Court construed "sub-antibacterial amount" to mean "an amount that does not significantly inhibit the growth of microorganisms, e.g., bacteria." (D.I. 166 at 3) The '572 patent's asserted claims all require "an amount that . . . has substantially no antibiotic activity." The Court construed "an amount that . . . has substantially no antibiotic activity" as "an amount that is effective to treat the papules and pustules of rosacea but does not significantly inhibit the growth of microorganisms, e.g., bacteria." (*Id.*)

Tr. 142 (Galderma's Dr. Webster agreeing that Ashley Patents' claims are not limited to any type of microbe or any particular part of human body); *see also* Tr. 556 (Dr. Chambers agreeing)) As there are approximately 100,000,000,000,000 bacterial cells that inhabit a typical human body at any moment (Tr. 149, 557), it may be impossible to prove infringement of a claim that requires no significant inhibition in the growth of any of them. In any event, here Galderma failed to prove that Mylan's ANDA product will not significantly inhibit the growth of microorganisms.

To the contrary, although Mylan does not have a burden to show non-infringement, Mylan proved through *in vivo* studies that a 40 mg once-daily administration of doxycycline significantly inhibits the growth of microorganisms in the oral cavity over periods of two weeks, three months, and twelve months. (*See* Tr. 562-79; DTX2097 (Haffajee) at 152; DTX2121 (Thomas) at 1476-78; DTX2120 (Walker 2000) at 1466-67) As Mylan's expert, Dr. Chambers[13] testified: (a) Haffajee found a significant spike in the percentage of doxycycline-resistant microorganisms in the oral cavity following administration of 20 mg doxycycline twice-daily, which was explained by the killing of non-resistant microorganisms by the doxycycline; (b) Thomas found an increase in MIC50 values for certain species isolates, indicating emergence of drug resistant cells due to significant inhibition of susceptible cells, all resulting from administration of 20 mg doxycycline twice-daily; and (c) Walker 2000 found a statistically significant difference in the number of spirochetes between a group receiving 20 mg doxycycline

[13]Dr. Chambers was highly qualified to offer an opinion on the *in vivo* studies, having served as editor of the journal for the American Society of Microbiology, which publishes papers on drug resistance and antimicrobial therapy and antibiotics. (Tr. 550)

twice-daily as compared to a group receiving a placebo.[14]

Galderma's expert on infringement of the Ashley Patents, Dr. Webster, did not address the Haffajee, Thomas, or Walker 2000 studies. Dr. Webster did agree, however, that *in vivo* tests are how one measures for the effects of drugs on people. (Tr. 79) Galderma's efforts to argue away the impact of these *in vivo* studies fall flat. For example, Galderma emphasizes that Haffajee states: "The question as to whether the same strains of a given species were resistant pre- and post- therapy to the administered agents, or ***whether new, resistant strains*** or strains resistant to multiple antibiotics had emerged ***could not be determined***." (DTX 2097 at 155 (emphasis added); *see also* D.I. 267 at 9-10) However, as Mylan's expert, Dr. Chambers testified, "What they're [Haffajee] telling you is they do not know which species it is. . . . They're not saying there is no inhibition of growth." (Tr. 631-32; *see also* DTX2097 at 155 ("Not surprisingly, the percentage of resistant isolates increased in subjects receiving adjunctive agents immediately after taking these agents, primarily because of a decrease in susceptible species.")) The Court is likewise not persuaded by Galderma's arguments against reliance on Dr. Chambers' opinion of the impact of Thomas and Walker 2000.

b. Mylan Label

Galderma contends that the label for Mylan's Generic Product – which is identical, in all material respects, to the label for Oracea® – proves infringement. A careful reading of the Mylan Label, however, confirms Mylan's contrary position. The Mylan Label is accurate and truthful but does not address infringement.

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[14]Each of these studies involved administration of 20 mg twice daily doxycycline, as opposed to 40 mg once daily administration. Galderma failed to prove that this difference should affect the weight attributed to Mylan's *in vivo* studies in the infringement analysis.

Galderma relies on four portions of the Label to show infringement, but none of these portions (or any other portion of the Label to which the Court has been directed) do so. The first Label excerpt Galderma points to states: "*In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long term effects on bacterial flora of the oral cavity, skin, intestinal tract and vagina." (DTX2091 at MYL-D118694) As Mylan observes, this Label excerpt only "addresses ***long-term*** effects in only ***four*** parts of the body." (D.I. 265 at 3) (emphasis added) This Label excerpt tells one absolutely nothing about the effects of Mylan's Generic Product on any other part of the body, nor does it reveal anything about the immediate, short-term, or medium-term effects of Mylan's Generic Product even on the four parts of the body that are identified. Although the four parts of the body referenced in the Label excerpt are the body parts having the highest bacterial populations (Tr. 87), the Label simply does not address the full range of body parts in which antibacterial effects may occur. Nor does the Label excerpt address all time frames in which antibacterial effects may be observed.

The next two portions of the Mylan Label to which Galderma points support only the truthful statement that a 40 mg once-daily administration of doxycylcine is not an amount that is recommended for treatment of an infection. These portions of the Label state: "Doxycycline should not be used for treating bacterial infections, providing antibacterial prophylaxis or reducing the numbers or eliminating microorganisms associated with any bacterial disease" and "The plasma concentrations of doxycycline achieved with doxycycline during administration . . . are less than the concentration required to treat bacterial diseases." (DTX2091 at MYL-D118694) Neither of these excerpts states that Mylan's Generic Product does not significantly inhibit the growth of microorganisms, such as bacteria. Even Galderma's expert, Dr. Webster,

agreed that there is a difference between a therapeutic dose (i.e., enough doxycycline to treat an infection or eliminate microorganisms associated with bacterial disease) and a dose that causes significant inhibition in the growth of microorganisms. As Dr. Webster testified, "One dosage that reaches antimicrobial effect, while inadequate to treat infection, could still alter the normal flora and have changes induced therein." (Tr. 140; *see also* Tr. 590 (Mylan's Dr. Chambers agreeing "even at subtherapeutic doses, there can be significant growth inhibition in microorganisms"))

In its briefing, Galderma also highlights the following statement in Mylan's Label: "Exceeding the recommended dosage may result in an increased incidence of side effects including the development of resistant organisms." (DTX 2091 at MYL-D118687; D.I. 267 at 5) This excerpt is no more helpful to Galderma. It is true that administering a dosage greater than 40 mg once-daily may result in increased incidence of side effects and may even result in the development of antibiotic resistance. It does not follow, however, as a matter of logic or evidence, that a daily dose of 40 mg also does not significantly inhibit the growth of microorganisms.

Both parties have devoted a great deal of attention to drafts of the Label for Oracea® (which forms the basis for the Mylan Label). While the nature of the Label changes required by the FDA generally supports Mylan, the record does not establish with clarity precisely why the FDA required the changes it required. Certainly nothing in the back-and-forth between Galderma and the FDA supports a reading of Mylan's Label that is contrary to that adopted by the Court here, as described above.

c. Other arguments for infringement

Galderma also contends that the Court should find infringement based on statements made by Mylan and a Mylan expert in the course of this litigation. Galderma points to an "admission" by Mylan, in Mylan's opening post-trial brief, to the effect that Periostat® – a 20 mg twice-daily administration of doxycycline – is administered in a sub-antibacterial amount. (D.I. 274 at 3) (citing D.I. 264 at 10) Galderma also notes that Mylan's proposed findings of fact include a proposal that the Court find that Periostat® embodies the Ashley Patents, which requires that Periostat® be administered in a sub-antibiotic amount. (D.I. 274 at 3) (citing D.I. 266 (MFF) ¶ 218) Galderma adds that one of Mylan's experts, Dr. Barbara Gilchrest, "agrees that administration of 40 mg/day doxycycline is a sub-antibacterial amount." (D.I. 267 at 6; Tr. 459, 471)

The Court rejects Galderma's arguments. Each of the Mylan (or Mylan witness) statements identified by Galderma were made in the context of Mylan's invalidity case. Mylan's invalidity position is that prior art disclosures of 40 mg daily administration of doxycycline disclosed an amount meeting the "amount" limitations of the Ashley Patents. As explained further in connection with the analysis of invalidity, the Court rejects Mylan's invalidity position. For the reasons explained above, the Court has found that 40 mg daily administration of doxycycline does not meet the amount limitations (i.e., it ***does*** significantly inhibit the growth of microorganisms). Mylan's statements to the contrary do not persuade the Court otherwise.[15]

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[15]Given the Court's findings, it is not necessary to resolve the parties' additional dispute as to whether Galderma has proven that Mylan's Generic Product will satisfy the claim limitation of "without administering a bisphosphonate compound." (D.I. 265 at 4)

2. Indirect infringement

The analysis above explains how Galderma failed to prove that use of Mylan's Generic Product in a manner consistent with the Mylan Label would directly infringe the asserted claims of the Ashley Patents. Because there is no direct infringement, Mylan cannot be liable for indirect infringement, under theories of either induced or contributory infringement. *See Dynacore Holdings Corp. v. U.S. Phillips Corp.*, 363 F.3d 1263, 1272 (Fed. Cir. 2004) ("Indirect infringement, whether inducement to infringe or contributory infringement, can only arise in the presence of direct infringement, though the direct infringer is typically someone other than the defendant accused of indirect infringement.") (internal citations omitted).

3. Preliminary injunction and preferred embodiments

In July 2010, the Court entered a preliminary injunction (D.I. 188), based on its finding that Galderma was likely to succeed on the merits of proving Mylan's Generic Product infringes claim 1 of the '267 and claim 1 of the '572 patents (D.I. 177 at 8). This finding was based, in part, on the Court's rejection of the relevance of the *in vitro* studies on which Mylan was then predicating its non-infringement position. The *in vivo* studies presented at trial (such as Haffajee, Thomas, and Walker 2000) were not part of the record at the preliminary injunction hearing. (*See* D.I. 177 at 10-11) ("In contending that Oracea® and Mylan's proposed generic version are administered in antibiotic amounts, Mylan relies on evidence consisting of *in vitro*, not *in vivo*, results. . . . The problem with Mylan's argument is that the serum concentration levels and minimum inhibitory concentrations that it reports are based solely on *in vitro* studies. That is, Mylan is relying on laboratory measurements to show that 40 mg of doxycycline has a significant antibiotic effect. The invention disclosed and claimed in the Ashley patents, however, requires

administration in a human. Thus, what matters for purposes of the infringement analysis is whether Mylan's proposed generic product will significantly inhibit the growth of bacteria in a human, that is *in vivo*.") Mylan's expert, Dr. Chambers, relied on *in vitro* studies at the preliminary injunction stage, but relied on *in vivo* studies at the trial. (*Compare* D.I. 106 at ¶¶ 22-29 with Tr. 661)

The Court's preliminary injunction ruling was also based on the Court's preliminary finding that the Mylan Label "expressly states that Mylan's generic product will not significantly inhibit the growth of bacteria." (D.I. 177 at 8; *see also id.* at 9 ("[T]he statements in Mylan's label . . . provide substantial evidence that Mylan's generic product will not significantly inhibit the growth of bacteria.") This preliminary finding does not withstand scrutiny following a full trial on the merits. *See generally Jack Guttman, Inc. v. Kopykake Enterprises, Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002) ("[A]ll findings of fact and conclusions of law at the preliminary injunction stage are subject to change upon the ultimate trial on the merits.") (internal quotation marks and citations omitted); *see also Wyrough & Loser, Inc. v. Pelmor Laboratories, Inc.*, 376 F.2d 543, 547-48 (3d Cir. 1967) (same).

The Court recognizes there is further tension between today's ruling and the following statement in the preliminary injunction opinion: "It follows that Mylan's argument is that Mr. Ashley, the inventor, expressly defined key claim terms in a manner that had the consequence of excluding from the scope of his patent the very embodiment of his invention that his employer intended to practice. There is no support in the record for this highly improbable contention." (D.I. 177 at 15) (citing *Dow Chem. Co. v. Sumitomo Chem. Co., Ltd.*, 257 F.3d 1364, 1378 (Fed. Cir. 2001)) ("[I]t is . . . well established that a claim construction that excluded a preferred

embodiment is rarely, if ever, correct. This is because it is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment, or that persons of skill in the field would read the specification in such a way.") (internal quotation marks and emphasis omitted); *see also Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1383 (Fed. Cir. 2008) (stating caselaw "generally counsels against interpreting a claim term in a way that excludes the preferred embodiment from the scope of the invention").

As the instant case proves, "highly improbable" does not mean "impossible." At trial, unlike at the preliminary injunction (or claim construction)[16] stage, Mylan presented a significant amount of evidence that demonstrated that a 40 mg daily administration of doxycycline – either 40 mg once-daily or 20 mg twice daily – does ***not*** not significantly inhibit the growth of microorganisms. It follows, then, that Oracea® and Periostat®, despite being identified as preferred and "especially preferred" embodiments of the Ashley Patents, respectively, are not actually embodiments of the asserted claims. Although unusual, this is the conclusion compelled by the record developed at trial.[17]

B. Validity

Mylan seeks to invalidate the Ashley Patents on the following grounds: (i) all asserted

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[16]At the claim construction hearing, Galderma effectively agreed to the constructions of the "amount" terms that the Court ultimately adopted and that are the key to the Court's findings on infringement. Specifically, at the time the Court made its recommended constructions of "the antibacterial effective amount" and "sub-antibacterial amount" in the '267 patent and "an amount that . . . has substantially no antibiotic activity" in the '572 patent, these constructions had been agreed upon by the parties. (D.I. 134 (R&R) at 16-17; *see also id.* at 3; D.I. 177 at 12) No objections were taken to the Court's R&R by either party. (D.I. 166)

[17]It is also worth noting that the claim term driving these unusual conclusions is a negative limitation.

claims of the '267 and '572 patents are invalid as anticipated under 35 U.S.C. § 102; (ii) all asserted claims of the '267 patent are invalid as anticipated under § 102(a) by Dr. Feldman's prior use of Periostat® to treat his rosacea; (iii) claims 1, 12, and 14 of the '572 patent are invalid as anticipated under § 102(a) by Dr. Feldman's prior use of Periostat® to treat his patient's rosacea; (iv) all asserted claims of the '267 patent and claims 1, 12, and 14 of the '572 patent are invalid as anticipated under § 102(b) by Dr. Feldman's public use of Periostat® to treat his rosacea; and (v) all asserted claims of the '267 and '572 patents are invalid as obvious under 35 U.S.C. § 103.

Galderma responds that, with respect to (i) anticipation, Mylan has not proven by clear and convincing evidence that any prior art reference asserted by Mylan (1) discloses each and every element, either expressly or inherently, of any of the asserted claims of the patents-in-suit, and (2) does so in a way that would have enabled a person of ordinary skill in the art to practice the claimed invention without undue experimentation as of the time of the invention. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) ("Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim."); *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation."). With respect to the other anticipation contentions (ii, iii, iv), Galderma responds that the use of Periostat® by Dr. Feldman personally and by his patient to treat their rosacea are not invalidating prior or public uses. Finally, as to obviousness (v),

Galderma contends that Mylan has not proven by clear and convincing evidence that the differences between the subject matter of any asserted claim of the Ashley Patents and any prior art references relied on by Mylan (alone or in combination) are such that any of the asserted claims would have been obvious to a person of ordinary skill in the art. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). Moreover, Galderma believes it has proven objective indicia of non-obviousness.

For reasons described more fully below, the Court concludes that Mylan has failed to prove by the requisite clear and convincing evidence that any claim of the Ashley Patents is invalid.

1. Anticipation by Dr. Feldman's personal use

The Court has found that Dr. Lawrence Feldman, a dermatologist in Maryland, used Periostat® – described in the Ashley Patents as an "especially preferred embodiment" – which Dr. Feldman was prescribed by his periodontist, to treat his own rosacea.[18] These findings, however, do not anticipate, and therefore invalidate, any of the claims of the Ashley Patents. This is because, first, the Court has found that Periostat® (like Oracea® and Mylan's Generic Product) is ***not*** an embodiment of the Ashley Patents, as it does not meet the claim limitation of not significantly inhibiting the growth of microorganisms. *See generally Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1325 (Fed. Cir. 2009) ("In order for a use to be public within

[18]The Court makes its invalidity findings based on clear and convincing evidence. *See Microsoft Corp. v. i4i L.P.*, 131 S.Ct. 2238, 2243 (2011) ("That burden is constant and never changes and is to convince the court of invalidity by clear evidence."); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 292 (Fed. Cir. 1985) ("Each fact forming the factual foundation upon which the court bases its ultimate conclusion regarding the obviousness of the claimed subject matter as a whole must be established by clear and convincing evidence.") (internal citations omitted))

the meaning of § 102(b), there must be a public use with all of the claim limitations.").[19]

Additionally, while the Court finds Dr. Feldman's testimony credible, it is nonetheless true that uncorroborated testimony of a witness regarding anticipation is insufficient as a matter of law to meet the clear and convincing standard necessary to prove invalidity. *See TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1159-60 (Fed. Cir. 2004) ("Corroboration is required of any witness whose testimony alone is asserted to invalidate a patent.") (internal quotation marks and citations omitted); *see also Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1370 (Fed. Cir. 1999) (explaining corroboration requirement); *Woodlawn Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1371 (Fed. Cir. 1998) (same). Here, there is no corroboration that Dr. Feldman was prescribed Periostat® by his periodontist or that he requested and obtained professional courtesy samples of it from CollaGenex. (Tr. 343, 366-67) There is no prescription record, no documents relating to a request for a sample, and nothing documenting Dr. Feldman's improvement in his rosacea while taking Periostat®.[20]

2. Anticipation by Dr. Feldman's treatment of a patient

Mylan further contends that Dr. Feldman's treatment of one of his patients' rosacea, around February 2000, with Periostat® (40 mg daily doxycycline) also renders the Ashley Patents invalid due to anticipation. The Court has found, by clear and convincing evidence, that Dr. Feldman did prescribe Periostat® to his patient for treatment of her rosacea. Dr. Feldman's testimony on these points is corroborated by his patient record and by IMS data, showing that a

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[19]As Mylan failed to make out a prima facie showing of prior or public use, Galderma does not bear a burden of production to counter Mylan's showing.

[20]Given the Court's findings, it is not necessary to resolve the parties' dispute as to conception date. (*See, e.g.*, D.I. 275 at 6)

Dr. Feldman prescription for Periostat® was filled in March 2000, just weeks after Dr. Feldman prescribed Periostat® for his patient's rosacea. (DTX 1559; DTX 1842) *See generally Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1374 (Fed. Cir. 2001) ("Although oral testimony asserted to invalidate a patent must be corroborated, as we have explained in a similar context, this court 'has not impose[d] an impossible standard of 'independence' on corroborative evidence by requiring that every point . . . be corroborated by evidence having a source totally independent of the [witness].' Rather, this court applies a 'rule of reason' analysis to determine whether the testimony introduced has been sufficiently corroborated.") (quoting *Knorr*, 671 F.2d at 1374).[21]

These findings, however, do not invalidate the claims of the Ashley Patents due to anticipation. As already explained, Periostat® is not an embodiment of the Ashley Patents; therefore, Dr. Feldman's patient's use of Periostat® does not anticipate the claims of the Ashley Patents. Additionally, the patient's use does not appear to have been "public," given that none of the activity relating to it occurred in public, there was no public access to the use, Dr. Feldman had a confidentiality obligation to his patient not to disclose her name and treatment, and Dr. Feldman did not commercially exploit his use of doxycycline to treat rosacea.

3. Invalidity due to obviousness: Feldman uses plus prior art

Mylan argues that the two Feldman uses of Periostat® – Dr. Feldman's treatment of himself and his patient – in combination with three prior art references – Maibach (DTX 1694),

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[21]The parties dispute whether the Federal Circuit permits a "rule of reason" and "totality of circumstances" analysis to determine if the Dr. Feldman patient record corroborates the Dr. Feldman prior uses as "public uses." *Compare, e.g.*, D.I. 265 at 8 *with* D.I. 274 at 7. It is not necessary for the Court to resolve this dispute.

U.S. Patent No. 5,188,836 (DTX 1996), and U.S. Patent No. 5,283,065 (DTX 2005) – invalidate claims 13, 15, 20, 21, 23, 24, and 26 of the '572 patent. Again, because Periostat® is not an embodiment of the Ashley Patents, and none of the three prior art references discloses an amount of doxycycline having substantially no antibiotic activity, Mylan has failed to invalidate the Ashley Patents as obvious. (*See also generally* D.I. 274 at 11 (Galderma stating, "Mylan's argument that Dr. Feldman would not have prescribed Periostat® to his patient but for the knowledge he gained from his personal use of Periostat® directly contradicts the obviousness of the inventions.") (internal citations and quotation marks omitted))

4. Invalidity due to obviousness: six Gilchrest References

Mylan contends that combinations of several prior art references disclosing "low dose" use of tetracycline compounds to treat acne and rosacea render the Ashley Patents invalid due to obviousness. The Court will refer to these prior art references collectively as the "six Gilchrest References," as they were identified by and testified to by Mylan's expert, Dr. Barbara Gilchrest.[22] No combination of the six Gilchrest References invalidates the Ashley Patents.

The Court has found that a 40 mg once daily administration of doxycycline does not meet the "amount" limitations of the Ashley Patents. Each of the six Gilchrest References discloses an amount of tetracycline that exceeds 40 mg once-daily. (*See* Tr. 521, 523; DTX1764 (Murphy) (125 mg); DTX1901 (Sneddon) (100 mg); DTX1703 (Marmion) (300 mg); DTX2067 (Wereide) (150 mg); DTX1484 (Cotterill) (250 mg); DTX1418 (Bartholomew) (500 mg)) Nothing in the record supports a conclusion that a dose higher than 40 mg would fail to significantly inhibit the

[22]The Gilchrest References are: DTX1764 (Murphy), DTX1901 (Sneddon), DTX1703 (Marmion), DTX2067 (Wereide), DTX1484 (Cotterill), and DTX1418 (Bartholomew).

growth of microorganisms. Therefore, the six Gilchrest References do not render the Ashley Patent claims invalid due to obviousness.[23]

5. Invalidity due to obviousness: Pflugfelder

Mylan also cites as invalidating prior art U.S. Patent No. 6,455,583 to Pflugfelder, which discloses use of a tetracycline compound of "preferably about 20 to 80% of the normal antibiotic therapeutic dose" for treatment of ocular rosacea, a condition correlated with acne rosacea in many patients. (DTX1045 at col. 5 line 2-3) The PTO described Pflugfelder as "[t]he closest prior art" to the Ashley Patents. (PTX478 at 3) Nonetheless, the PTO found the Ashley Patents patentable over Pflugfelder, reasoning:

> Pflugfelder, teaches a method for treating meibomian gland disease associated with rosacea. Pflugfelder, however, does not explicitly teach a method for treating papules and pustules of rosacea by orally administering an antibiotic tetracycline compound in an amount of 10-80% of the antibiotic effective amount, which results in no reduction of skin microflora in long term treatment without administering a bisphosphonate compound.

(PTX478 at 3) Mylan did not meet the difficult burden of showing that this prior art that was considered and rejected by the PTO is, in actuality, invalidating. *See generally Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005) ("[A] challenger's burden to show

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[23]In its Answering Brief (D.I. 274 at 12 n.3), Galderma argues that other prior art references about which Dr. Gilchrest testified – Cunliffe (DTX1493) and Smith (DTX1897) – are outside the scope of Dr. Gilchrest's expert report and, therefore, her testimony about them is improper. Pursuant to the Court's procedures (*see* D.I. 262 at 10-11; *see also* Tr. 749), Galderma made this objection at trial, and the Court deferred ruling on it, unless and until it was renewed in post-trial briefing (Tr. 477-78). Galderma did not renew this objection in its opening post-trial brief; nor does Galderma anywhere offer any reasoning to support its objection. Accordingly, Galderma's objection is overruled. Likewise, as no other objections to testimony being beyond the scope of an expert's report were renewed post-trial by either party, they are deemed waived and are hereby overruled.

invalidity is more difficult to satisfy when prior art references have been presented to the PTO. . . . ") (internal citations omitted).

6. Secondary considerations of non-obviousness

Given the Court's findings regarding Mylan's invalidity evidence, it is not necessary to address Galderma's evidence of secondary considerations of non-obviousness.

II. THE AMIN PATENTS

A. Infringement

Galderma asserts that Mylan's Generic Product infringes claims 1, 2, 4, 11, 13, 14, and 16 of the '395 patent and claims 1, 2, 4, 5, and 9 of the '775 patent. The Court concludes that Galderma failed to prove any such infringement.

1. Galderma Failed to Prove Infringement of the Asserted Claims of the Amin Patents

a. Nitric Oxide production and inducible Nitric Oxide Synthase

Each of the asserted claims of the Amin Patents requires the administration of a tetracycline in an amount sufficient to decrease or inhibit endogenously produced Nitric Oxide ("NO") or inhibit the expression of inducible Nitric Oxide synthase ("iNOS").[24] (PTX 3 at col. 21 line 48 - col. 24 line 9; PTX 4 at col. 21 line 47 - col. 22 line 63) Thus, in order to prove infringement, Galderma must prove by a preponderance of the evidence that Mylan's Generic Product – a 40 mg dosage of doxycycline administered once-daily – will inhibit the production of endogenously produced NO or inhibit the expression of iNOS.

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[24]Both parties effectively concede that the central dispute for infringement of both of the Amin Patents is whether Oracea® and Mylan's Generic Product will inhibit NO and iNOS production. Each of the independent claims in both of the Amin Patents contains this limitation.

Galderma's expert, Dr. Matthew Grisham, acknowledged that there have been no empirical tests or studies showing that a once-daily 40 mg dose of doxycycline actually decreases endogenous NO or inhibits iNOS expression. (Tr. 289-91) Mylan's expert, Dr. Robbins, confirmed this fact. (Tr. 679-80) Dr. Robbins further testified that, based in part on experiments conducted in his laboratory, the serum concentrations achieved by a 40 mg/day dosage – including a C_{max} concentration of 0.6 μg/ml – were not high enough to inhibit NO production or iNOS expression. (Tr. 684-85, 689; DTX 1627) Dr. Robbins explained that nitrite production is inhibited when the serum concentration of doxycycline is much higher, such as 10 μg/ml. (Tr. 686-88) Hence, the plasma concentrations achieved by a 40 mg/day dosage of doxycycline are "far below" what Dr. Robbins would expect to inhibit NO and iNOS. (Tr. 688)

The Court concludes that Galderma has failed to prove through direct evidence that Mylan's Generic Product will inhibit the production of endogenously produced NO or inhibit the expression of iNOS.

b. Galderma's syllogism

Lacking any experimental data to show that Mylan's Generic Product infringes, Galderma pieces together several factual contentions that, taken together, it contends reveal that Mylan's Generic Product infringes. Galderma's theory of infringement is as follows: (a) NO and iNOS are upregulated in nearly all inflammatory conditions; (b) rosacea is an inflammatory condition and is therefore mediated or caused by the upregulation of NO and iNOS; (c) tetracyclines inhibit NO and iNOS; (d) Mylan's Generic Product effectively treats the papules and pustules of rosacea; so, therefore, (e) Mylan's Generic Product must inhibit NO and iNOS.

If any of the steps in Galderma's syllogism are not proven, Galderma's conclusion is not

supported. As explained below, while Galderma proved (or Mylan did not contest) steps (a), (c) and (d) of its syllogism, it failed to prove step (b). Therefore, Galderma failed to prove its conclusion, i.e., that Mylan's Generic Product infringes the Amin Patents.

i. steps (a), (c), and (d)

With respect to step (a) of its syllogism, Galderma has proven by a preponderance of the evidence that inflammatory conditions result in an expression of iNOS and an increase in the level of NO. (PTX 317 at 1; PTX 333 at 95-96) Inflammation is the body's physiological and protective response to fight infection and repair tissue injury. (Tr. 265-66) Inflammation is associated with the upregulation of iNOS and the overproduction of NO. (*Id.* at 267; *see also* PTX 333; PTX 317) An inflammatory stimulus induces iNOS expression and production of NO. (Tr. 679, 724) Two common examples of inflammatory diseases in which iNOS expression is increased are rheumatoid arthritis and periodontitis. (Tr. 679) NO is also associated with inflammation in skin diseases. (Tr. 269)

With respect to step (c), it is undisputed that tetracyclines, including doxycycline, decrease iNOS expression and NO production. (SUF ¶¶ 85-86) Both Dr. Grisham and Dr. Robbins testified that doxycycline can inhibit NO production. (Tr. 277, 280, 684-86, 718) Finally, as to step (d), Mylan essentially concedes that a 40 mg once-daily dosage of doxycycline is effective at treating the papules and pustules of rosacea. (SUF ¶¶ 53-58, 69; Tr. 287-88, 727)

ii. step (b): cause of rosacea

In step (b) of its syllogism, Galderma seeks to prove that rosacea is a chronic inflammatory condition and that the papules and pustules of rosacea are caused by an increase in NO production and iNOS expression. (Tr. 270) Galderma contends that the papules and

pustules of rosacea are formed by the infiltration of white blood cells, including neutrophils and macrophages, caused by an dysregulated immune response. (Tr. 270-73; *see also* PTX 372) Based on this data, Galderma contends the overproduction of NO and overexpression of iNOS is the pathological mechanism responsible for causing rosacea. (Tr. 273)

As already explained above, there are no studies showing that NO production and iNOS expression are associated with the papules and pustules of rosacea. Dr. Robbins testified on this point. (Tr. 679) Dr. Grisham, Galderma's expert, did not disagree, stating only that his opinion did not require quantitative data. (Tr. 319)

Consequently, part of Dr. Grisham's methodology is to rely on studies of other skin conditions besides acne rosacea. Even assuming that just because NO production and iNOS expression are associated with other skin conditions means that they are also associated with rosacea,[25] these studies of other skin conditions do not uniformly find the association Galderma posits. For example, Dr. Grisham relies on the Rowe article, which concludes: "We have so far found iNOS in three diverse inflammatory dermatoses ([atopic dermatitis, allergic contact dermatitis, and psoriasis]) where a number of factors . . . may be involved in its induction. . . . iNOS induction ***may not be a primary event*** in skin inflammation." (PTX 386 at GAL 0241035) (emphasis added) Dr. Grisham relied on a review article by Yamasaki and Gallo that, in turn, relied on the Gurer paper. (Tr. 695) The Gurer paper concluded that NO "has ***no role*** in the inflammatory mechanism of acne rosacea." (DTX 2180 at 768) (emphasis added) Similarly, another study on which Dr. Grisham relied concluded:

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[25]See generally Dr. Grisham's testimony about studies by Bruch-Gerharz (PTX 328, PTX 329, PTX 330) on psoriasis. (Tr. 320 ("iNOS is in fact upregulated in chronic skin diseases. . . . In fact, in a very close cousin of rosacea, in psoriasis, there is in fact upregulation . . . .")

> It is already apparent that NO can exert both antiinflammatory and proinflammatory properties, even in parallel, depending on the cellular context, and the type and phase of the inflammatory and cellular immune response. Consequently, further elucidation of the regulatory crosstalk between NO and other cutaneous inflammatory and immune mediators in the skin remains a daunting task.

(PTX 329 at GAL 0240605) Dr. Robbins explained why the remaining review articles upon which Dr. Grisham relied also were deficient. (Tr. 698-702)

Consistent with the results of these various studies, the witnesses at trial – with the exception of Dr. Grisham – did not conclude that NO production and iNOS expression are upregulated in rosacea. Mylan's expert, Dr. Robbins, did not form an opinion as to whether or not iNOS is upregulated in rosacea. (Tr. 721) Dr. Webster, Galderma's expert on the Ashley Patents, testified that "[w]e still don't know convincingly what the cause of rosacea is." (Tr. 136) Robert Ashley, the inventor of the Ashley Patents, added that he did not think that "causality has ever been proven one way or the other" with respect to rosacea. (Tr. 670) Dr. Ashley's belief was that in 2004, "[t]he general knowledge in the prior art was that acne was caused by bacteria." (Tr. 669-70)

The record contains further evidence that scientists uninvolved in this litigation are uncertain as to the cause of rosacea. For example, a study by McAleer and Powell indicates that while there appears to be a connection between a dysregulated immune system and rosacea, several other potential causes of rosacea also exist, including UV radiation, reactive oxygen species, microbes, and other environmental aggressors, such as the Demodex mite. (PTX 368 at GAL0241210-0241214) McAleer and Powell ultimately conclude that "[t]here are many questions about the cause of this disease [acne rosacea]" and that, while an "abberent (*sic*) innate

immune response" may be a hallmark of rosacea, the causes of this immune response are unknown. (*Id.* at GAL0241215) Likewise, the Millikan reference – while observing that antibiotic treatments for rosacea are "thought to be due more to anti-inflammatory rather than antibiotic effects" – concludes that "[t]he pathophysiology of rosacea is still a subject of controversy." (PTX 372 at GAL0240931; *see also* PTX 381 at GAL02400969 ("The pathogenesis of rosacea appears to be multifactorial . . . . The etiology of the disease remains speculative . . . .")) None of these studies demonstrates by a preponderance of the evidence that iNOS or NO are involved in the mediation of rosacea.

The Amin Patents themselves contain a lengthy list of conditions in which tetracyclines can be used to inhibit NO production and iNOS expression. (PTX 3 at col. 7 line 58-col. 8 line 3) No fewer than thirty-five conditions are listed, including serious illnesses such as malaria and diabetes as well as minor ailments such as sunburns and insect bites. (PTX 3 at col. 8 line 2-3) Rosacea is not included on the list. Additionally, CollaGenex, the predecessor in interest to Galderma, attempted to include in its labeling language to the effect that Oracea® "has been shown *in vitro* to suppress pro-inflammatory processes such as . . . endogenous nitric oxide release, and expression of inducible nitric oxide synthase." (DTX 1340 at 6) However, the FDA rejected this language, requiring instead that the label read, "The mechanism of action of Oracea® in the treatment of inflammatory lesions of rosacea is unknown." (PTX 426 at 5) These points, too, confirm the Court's finding that Galderma failed to prove by a preponderance of the evidence that rosacea is caused by an increase in NO and overexpression of iNOS.

iii. Conclusion: No infringement

Galderma has not proven by a preponderance of the evidence that rosacea is marked by

the upregulation of NO or iNOS or that NO or iNOS cause the papules and pustules of rosacea. The failure of proof on this point renders the conclusion of Galderma's syllogism – that Mylan's Generic Product inhibits NO and iNOS – also unproven. Accordingly, the Court finds that Galderma has not met its burden of demonstrating that Mylan's Generic Product infringes the asserted claims of the Amin patents.

2. Indirect Infringement

Given the above analysis, by which the Court concludes that use of Mylan's Generic Product in a manner consistent with its Label would not directly infringe the Amin Patents, it follows that Galderma has also failed to prove indirect infringement, under theories of either induced or contributory infringement. *See Dynacore*, 363 F.3d at 1272.

B. Invalidity

Mylan seeks to invalidate the Amin Patents on the following grounds: (i) the asserted claims of the '395 patent and the '775 patent are invalid as anticipated under 35 U.S.C. § 102; and (ii) claims 2 and 14 of the '395 patent and claim 2 of the '775 patent are invalid for lack of enablement under 35 U.S.C. § 112, ¶ 1. The Court concludes that Mylan has met its burden of proof – clear and convincing evidence of invalidity – with respect to anticipation.

1. Inherent anticipation

Mylan contends that all of the asserted claims of the Amin Patents are inherently anticipated because they merely recognize an inherent property of a tetracycline to decrease NO production and inhibit iNOS expression. "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*,

190 F.3d 1342, 1347 (Fed. Cir. 1999). To prove inherent anticipation, Mylan must demonstrate, by clear and convincing evidence, that the missing element not explicitly described in the prior art is necessarily present. *See Cont'l Can Co. v. Monsanto*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Put differently, "anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002).

Mylan contends that the prior art disclosed low dosages of doxycycline, including 20 mg twice-daily, to treat chronic inflammatory conditions. In particular, Mylan relies on eight prior art references which, it argues, disclose the mechanism of action of the Amin Patents. Four of these prior art references describe treatment of periodontitis or rheumatoid arthritis – both of which are chronic inflammatory conditions characterized by excess endogenous production of NO and an abnormally high level of activity of iNOS – with 40 mg of doxycycline daily. (DTX 2183 ("Golub 1990"); DTX 2181 ("Bouwsma"); DTX 2182 ("Schroeder"); DTX 2184 ("Greenwald 1994")) The other four prior art references disclose the use of higher doses of tetracyclines – between 60 and 200 mg – to treat periodontitis or rheumatoid arthritis. (DTX 2188 ("Golub 1983"); DTX 2186 ("Greenwald 1987"); DTX 1603 ("Golub 1992"), DTX 2187 ("Tilley")) In Mylan's view, these eight prior art references inherently anticipate the Amin Patents.

The Court is persuaded that at least the larger dose prior art references inherently anticipate the Amin Patents. The record shows that at these dosages (between 60 and 200 mg of a tetracycline) NO production or iNOS expression will be inhibited. (Tr. 718) Hence, the inventors of the Amin Patents were not free to patent this inherent property. *See King Pharms.,*

Inc. v. Eon Labs, Inc., 616 F.3d 1267, 1275 (Fed. Cir. 2010) ("[M]erely discovering and claiming a new benefit of an old process cannot render the process again patentable.") (internal quotation marks omitted).

2. Lack of Enablement

Because the Court will invalidate the Amin Patents due to inherent anticipation, it is not necessary to determine if claims 2 and 14 of the '395 patent and claim 2 of the '775 patent are also invalid due to lack of enablement.

III. THE CHANG PATENT

A. Infringement

1. Galderma Proved Infringement of Claims 4 and 18 of the Chang '532 Patent

Mylan has conceded infringement of claims 1-3, 5, 7-9, 13-17, and 19-21 of the Chang '532 patent. (C.A. No. 10-892 D.I. 103) Mylan denies infringement of dependent claims 4 and 18. Claims 4 and 18 require a steady state blood concentration of doxycycline of between 0.3 µg/ml to 0.8 µg/ml achieved by a once-daily dosage of 40 mg doxycycline. (PTX 5 col. 12 lines 11-13; *id.* at col. 13 lines 14-16)

According to Galderma, the maximum plasma concentration (C_{max}) at steady state reached after administration of Mylan's Generic Product is 0.6 µg/ml. Mylan does not seriously dispute that the C_{max} value of its Generic Product will be below the 0.8 µg/ml value recited in claims 4 and 18. The real dispute is whether Mylan's Generic Product will achieve the 0.3 µg/ml C_{min} value recited in the claims. Mylan's expert, Dr. Chambers, testified that the mean trough concentration of Mylan's Generic Product is 0.3 µg/ml. (Tr. 640) It follows, in Galderma's view, that the steady state blood levels achieved with Mylan's Generic Product are between 0.3

µg/ml and 0.6 µg/ml.

Mylan disagrees. First, Mylan points out that Galderma has submitted no empirical study or data demonstrating that Mylan's Generic Product meets the C_{min} level recited in the claims. Mylan also faults Galderma for relying on individual patient data, as opposed to mean values, the latter being – in Mylan's view – standard practice for the FDA and the scientific community generally. (Tr. 815-16) Moreover, Mylan contends that rounding is inappropriate.

Mylan's arguments are unavailing.[26] Because Mylan's Generic Product is bioequivalent to Oracea® (SUF ¶ 69), Galderma may rely on the pivotal pK study of Oracea®. (Tr. 181-82, 249-51; *see also* Tr. 814 (Dr. Friend relying on pK study of Oracea®)) Hence, Galderma does not need to submit an empirical study of Mylan's Generic Product. Moreover, Mylan relies on data from the pivotal pK study of Oracea® in its own proposed Label. (DTX 1305) Even if Dr. Friend is correct that the fact that Mylan's Generic Product involves a minitablet disbursed throughout powder could affect C_{min} results, the record does not provide a basis to conclude that the effect would serve to alter the serum concentrations to keep them ***outside*** the 0.3 µg/ml-0.8 µg/ml range as opposed to keeping the serum concentrations ***inside*** the range recited in the claims. (Tr. 817 (Dr. Friend testifying minitablet "means that you're not automatically going to get the exact same pharmacokinetic parameters as the Oracea formulation"))

In a further attempt to minimize the import of the Oracea® pK study, Mylan emphasizes

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[26]Galderma relies on Mylan's purported admission in the Pre-Trial Order that the trough plasma concentration of its ANDA Product is 0.3 µg/ml. (D.I. 258 Ex. 3, ¶ 39) Galderma further cites *White v. Arco/Polymers, Inc.*, 720 F.2d 1391, 1396 (5th Cir. 1983), for the proposition that "factual assertions in pleadings and pretrial orders are considered to be judicial admissions conclusively binding on the party who made them." (*See also* D.I. 267 at 15 n.1) As Mylan points out, however, the Pre-Trial Order also contains a statement that the average C_{min} for the pivotal pK study is 0.164 µg/ml, so the Pre-Trial Order contains an inconsistency. (Tr. 856-57)

that the mean C_{min} value of the 31 subjects was 0.164 μg/ml, well below 0.3 μg/ml. (PTX 464 at GAL 0004375) But claims 4 and 18 are not directed to mean values across a large population; neither claim mentions "mean" values whatsoever. (PTX 5 col. 12 lines 11-13; *id.* at col. 13 lines 13-15) Instead, these claims are directed to administration of a single pill (claim 4) or treating a single patient (claim 18). Hence, in the context of the Chang Patent, even if only 1 of 31 subjects in the pivotal pK study had a C_{min} of 0.3 to 0.6 μg/ml, this is a sufficient basis from which to find infringement. The pivotal pK study demonstrates that one patient – without rounding – had measured concentrations of between 0.3 and 0.8 μg/ml during the entire 24-hour period. (DTX 1305; Tr. 253) Additionally, after rounding, three of the 31 patients in the pivotal PK study had measured concentrations of between 0.3 and 0.8 μg/ml at all measured times. (PTX 464 at GAL 0004365-66; *see also* Tr. 183; Tr. 251-52)[27]

One final argument against infringement must be addressed: two of the named inventors of the '532 patent – Drs. Chang and Raoufinia – testified that a 75:25 formulation of 40 mg once-daily administration of doxycycline does not yield blood plasma levels of 0.3 μg/ml to 0.8 μg/ml. (Tr. 920-21 (discussing Chang Figure 5), 937-38) This testimony, however, was based solely on

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[27]The ***extent*** of infringement – be it 1 patient or (with rounding) 3 patients, or 1 out of every 31 patients who use Mylan's Generic Product (or 3 out of every 31 patients, with rounding) may be relevant to the proper remedy to be accorded to Galderma. *See generally Mars, Inc. v. Coin Acceptors, Inc.*, 527 F.3d 1359, 1366 (Fed. Cir. 2008) ("The correct measure of damages is a highly case-specific and fact-specific analysis."); *see also* 7-20 *Chisum on Patents* § 20.01 ("The means of achieving this goal of full compensation necessarily varies with the circumstances of the case, such as the type of invention covered by the patent, the manner in which the patent owner sought to exploit it, and the nature and extent of the infringer's illicit acts."); *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006) (explaining that injunctive relief is not automatic in patent cases). As explained later in this Opinion, the Court is requiring additional briefing on the issue of remedies.

data and figures contained in the Chang Patent itself. It was not based on the data provided in the Oracea® pivotal pK study. Hence, the co-inventors' testimony does not defeat Galderma's evidence of infringement.

Accordingly, the Court concludes that Galderma has proven by a preponderance of the evidence that Mylan's Generic Product infringes claims 4 and 18 of the Chang Patent.

2. Indirect infringement

Mylan's Vice-President of Regulatory Affairs, S. Wayne Talton, testified that Mylan does not have any expectation that its Generic Product will be used in the marketplace for any other purposes other than those uses enumerated on its Label, which includes treating the papules and pustules of rosacea. (Tr. 324) In order to find induced infringement, "[t]he pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). There is no serious dispute that Mylan intends to have its prospective customers use its Generic Product to treat rosacea, and accordingly, Mylan will induce and contribute to infringement of the asserted claims of the Chang Patent. *See generally* 35 U.S.C. § 271(b) (2006) ("Whoever actively induces infringement of a patent shall be liable as an infringer.").

B. Invalidity

Mylan seeks to invalidate the Chang Patent on the following grounds: (i) the asserted claims of the '532 patent are invalid as anticipated under 35 U.S.C. § 102; (ii) the asserted claims of the '532 patent are invalid as obvious under 35 U.S.C. § 103; (iii) claims 4 and 18 are invalid for failure to meet the written description requirement under 35 U.S.C. § 112, ¶ 1; and (iv) all

claims of the '532 patent are invalid because the named inventors did not themselves invent the subject matter sought to be patented under 35 U.S.C. § 102(f).

Galderma responds that Mylan has failed to prove by clear and convincing evidence that any claim of the Chang Patent is invalid. Specifically, (i) no prior art discloses every limitation of any claim of the Chang Patent, so there is no invalidity due to anticipation; (ii) the invention of the Chang Patent would not be obvious to one having ordinary skill in the art, a conclusion that is bolstered by the presence of secondary considerations of non-obviousness; (iii) Mylan has not proven that the inventors were not in possession of the inventions claimed in claims 4 and 18, rendering the challenge under § 112, ¶ 1 non-meritorious; and (iv) no claim of the Chang Patent was fully conceived by someone other than the named inventors before it was conceived by the named inventors, so the presumption that the named inventors are, indeed, the inventors is not overcome.

The Court concludes, for the reasons set forth below, that Mylan has failed to prove any of its invalidity defenses by the necessary clear and convincing evidence.

1. Anticipation: Ashley '932 and '854 patent applications

Mylan contends that all asserted claims of the Chang Patent are anticipated by the Ashley '932 application. The Court disagrees.

A patent is invalid for anticipation only "if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *see also Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 995 (Fed. Cir. 2000) ("This court requires that a party seeking to invalidate a patent under § 102 show that the allegedly invalidating prior art contains 'each and every element of [the] claimed

invention.'"). All of the asserted claims of the '532 patent require a composition of doxycycline consisting of 30 mg immediate release ("IR") and 10 mg delayed release ("DR"). (PTX 5) Neither the Ashley '932 application – nor the '854 application, which is incorporated in its entirety in the '932 application – discloses this IR/DR combination. (DTX 2111 at MYL - DJ002074; *see also* DTX 1008)

Mylan contends that the '854 application teaches methods of tetracycline delivery, including various controlled release formulations. Specifically, Mylan contends that the '854 application discloses the ratio of 30:10 IR/DR beads. The portion of the '854 application on which Mylan relies, however, states only the following:

> In a preferred embodiment, the controlled-release composition is entrapped in the upper portion of the gastrointestinal tract, for example, the stomach or duodenum. Such compositions are typically manufactured by utilizing controlled-release agents of a larger particle size, as is known in the art. It is preferred that at least 50%, more preferably 80% of the tetracycline in the composition be released in the upper GI tract.

(DTX 1008 at MYL DJ 002239) Nothing in this passage mentions IR beads, DR beads, or any specific IR/DR ratio.

Mylan's expert, Dr. Friend, testified that the '932 application was the closest prior art to the Chang patent. (Tr. 832) Dr. Friend, however, admitted that the Ashley '932 application does not disclose the "secret sauce" of a 30:10 IR/DR ratio or even a formulation containing both IR and DR beads. (Tr. 829-30) Dr. Friend further conceded that the '932 application does not contain any example of a controlled release formulation, or any formulation, that will give steady state blood levels of 0.1-1.0 ug/ml. (Tr. 831-32) Additionally, Dr. Friend admitted that his opinion on anticipation requires him to "piece together" disclosures from various portions of two

different prior art references. (Tr. 855) By definition, this is not anticipation by a single piece of prior art.

In sum, Mylan failed to prove by clear and convincing evidence that the Chang Patent is anticipated by the '932 and '854 applications.

2. Obviousness

Section 103(a) forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *KSR Int'l*, 550 U.S. at 406. Obviousness is a question of law based on underlying findings of fact. *See In re Kubin,* 561 F.3d 1351, 1358 (Fed. Cir. 2009). The analysis is a "functional," "flexible," and "expansive" approach that focuses on the content of the prior art, and the critical inquiry is whether "[t]he combination of familiar elements according to known methods" is likely to do nothing more than "yield predictable results." *Id.* at 416. When determining obviousness, courts use a four-part test that requires the Court to examine: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) the objective evidence of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *see also In re Kubin*, 561 F.3d at 1358; *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1320 (Fed. Cir. 2004).

As there is no significant dispute in the parties' positions on the level of ordinary skill in the art, the Court turns to Mylan's prior art references, paying particular attention to the differences between the Chang Patent and the prior art. The Court also considers the objective

indicia of nonobviousness.

a. Ashley '932 application

Mylan's central argument that the Chang Patent is obvious in light of the '932 application comes from a statement in Dr. Chang's deposition. When Dr. Chang was questioned about why CollaGenex chose the 40 mg 75:25 combination, Dr. Chang responded: "You keep asking – keep asking 40 milligram, 45 milligram, and different ratio. That's – I tell you it is not much difference, just the trade-off here and there. . . . So you give to anybody who know the business, they can combination of all this to pick out one they think is suitable for the product." (Tr. 908-09) From this, Mylan contends that Dr. Chang admitted that the Chang Patent is obvious.

The Court does not agree. In other portions of his testimony, Dr. Chang makes clear that his team conducted various *in silico* modeling tests to obtain results for several different release profiles that could have potentially satisfied the desired pharmacokinetic parameters sought by CollaGenex. (Tr. 907) From these results, CollaGenex determined which profile it desired. But the fact remains that skill was involved in picking the precise formulation to achieve CollaGenex's parameters, and the precise formulation ultimately settled upon was novel. In other words, when Dr. Chang testified that "anybody who knows the business" could have picked the 75:25 IR:DR ratio (Tr. 906-09), he meant anybody who knew the range already determined by Dr. Chang and his colleagues.

b. Ashley '932 application in combination with either '304 or '819 patents

Mylan contends that the '932 application in combination with the '304 patent or the '819 patent renders the Chang Patent obvious. The '304 patent describes a once-daily formulation of minocycline that contains IR and DR beads. (DTX 2119 at col. 1 lines 12-15) As Mylan

observes, "the '304 patent teaches a range of mixtures of IR and DR particles, in ratios between about 20:80 to about 80:20, which range encompasses the ratio of 75:25 claimed in the Chang patent." (D.I. 265 at 26) Ordinarily, "where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Tyco Healthcare Group LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1373 (Fed. Cir. 2011); *see also Iron Grip Barbell*, 392 F.3d at 1322 (same). However, a party may rebut this presumption "by a showing that the prior art taught away from the invention or by a showing of new and unexpected results relative to the prior art." *Id.* at 1322.

As Mylan's Dr. Friend admitted, the possible range of combinations taught by the '304 patent is huge. (Tr. 845) Dr. Friend also acknowledged that the "point" of the '304 patent is to keep blood plasma levels above the therapeutic minimum, such that the drug will act as an antibiotic. (Tr. 846-47) Thus, the '304 application teaches away from the Chang patent, which expressly limits the C_{max} to a steady state so as to ***avoid*** antibiotic effect. Therefore, Galderma has rebutted the presumption that the range recited in the '304 patent – from 20:80 to 80:20 IR:DR ratio – renders the Chang Patent formulation (75:25 IR:DR ratio) obvious.

Mylan next contends that the '932 application in combination with the '819 patent renders the asserted claims obvious. Again, the Court disagrees. The '819 patent is directed to oral pulsed dosed delivery of amphetamines, including the use of Shire Laboratories' Microtrol technology.[28] (DTX 2116 at col. 3 lines 16-19) In support of its position, Mylan points out that when Shire was first considering the development of Oracea®, Shire touted its Microtrol

[28]Shire Laboratories is the predecessor to the Supernus Pharmaceuticals, the current assignee of the '532 patent. (Tr. 788; SUF ¶ 31)

technology, and specifically referenced the '819 patent. (DTX 1090 at 3) Mylan also relies on Dr. Chang's description of the incorporation of Microtrol technology into the product requested by CollaGenex as "a straightforward program." (DTX 1094 at 1)

Mylan's expert, Dr. Friend, testified that there was no reason why one of skill in the art would have looked to the '819 patent, which covers amphetamine salts, to develop a once-daily formulation of doxycycline. (Tr. 848-49) Indeed, Dr. Friend described "[t]he use of amphetamines" as "very far from the Chang patent." (Tr. 849) Also, the purpose of the '819 invention was to provide steadily increasing blood plasma concentrations of amphetamines, while in the Chang Patent the intent is to keep serum concentrations below a ceiling. (Tr. 850)

Nor does the use of Microtrol in the formulation of Oracea® render the Chang Patent obvious. Microtrol is the concept of "beads in a capsule," a title used for business development purposes. (Tr. 891-92) Co-inventor Bhatt explained that Microtrol "doesn't refer to a technology" but is, instead, "a very generic term that does not really focus on one idea." (Tr. 942) Simply because Microtrol may be used with a variety of drugs does not mean that Microtrol may be used in the formulation of ***any*** drug, or that it is obvious how to integrate Microtrol into any specific formulation to achieve a precise plasma range (like the one disclosed in the Chang Patent). Additionally, there is evidence of the existence of at least three types of controlled release agents: immediate release, sustained release, and delayed release. (Tr. 836; *see also* 1067 at SUP 001070) It was a further innovation to determine which type of release agent to use and in which precise formulation. All of the testing that went into devising and testing formulations, and the details of the Shire-CollaGenex agreement, further show that the Chang Patent invention was not predictable and therefore not obvious. (Tr. 907-14)

c. Objective indicia of non-obviousness

Given the Court's findings with respect to Mylan's invalidity evidence, it is not necessary to address Galderma's evidence of secondary considerations of non-obviousness.

3. Invalidity due to failure to name all inventors

Mylan contends that the Chang Patent is invalid for the additional reason that it was invented by someone other than the named inventors. Pursuant to 35 U.S.C. § 102(f), a court may invalidate a patent if it fails to list all of the inventors. In asserting this defense, Mylan must overcome, by clear and convincing evidence, the presumption that the inventors named on the patent are correct. *See University of Colorado Found., Inc. v. Am. Cyanamid Co.*, 342 F.3d 1298, 1308-09 (Fed. Cir. 2003).

The named inventors on the '532 patent are Dr. Richard Chang, Niraj Shah, and Dr. Arash Raoufinia. (PTX 5) Although CollaGenex provided Dr. Chang and his team at Shire with a target blood level for a once-daily doxycycline product, CollaGenex had no meaningful idea how to reach that target or even if it was possible to achieve. (Tr. 869-70) It was Chang and his co-inventors who created the novel formulation of 30 mg IR/10 mg DR beads that met the target blood levels. (Tr. 914-15)

Mylan makes much of the fact that Dr. Chang testified that CollaGenex picked the 3:1 ratio, but this omits another critical fact: that CollaGenex picked the ratio based on simulation data provided to CollaGenex by Dr. Chang and his team at Shire. (Tr. 917) As Dr. Chang explained, without the simulation data provided by Shire, "no one can make up the ratio." (Tr. 911) Thus, while Mylan cites to a portion of testimony in which Dr. Chang states that "[t]he ratio is picked by the – by CollaGenex" (Tr. 917), in the very next sentence Dr. Chang adds that

CollaGenex's decision was "based on our data" (*id.*).

Mylan references internal CollaGenex emails to further suggest that CollaGenex selected the specific formulation. (DTX 1095; DTX 1298) Each of Mylan's references clearly indicates that Shire's ultimate decision about the ratio was based completely on *in silico* modeling and other testing conducted under the supervision of Dr. Chang and his team. Dr. Ashley confirmed that "CollaGenex didn't define any formulation. Shire would have defined any formulation. . . . CollaGenex didn't define anything." (Tr. 964)

Additionally, Dr. Chang considers himself to be a joint inventor of the Chang Patent. (Tr. 915) Dr. Chang explained that he and his team were able to "put some meaning" to the general research goals that CollaGenex provided to Shire. (Tr. 916) Dr. Chang added that the numbers provided by CollaGenex were meaningless: "The number by itself is meaningless. But we have data. We have formula, can achieve that – that – that plasma profile. That mean a lot." (Tr. 913)[29] It is also notable that Mylan has not identified anyone who is a missing inventor. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1381-82 (Fed. Cir. 2000) (holding that defendant failed to show derivation as it did not introduce clear and convincing evidence that unnamed individual was true inventor).

In sum, Mylan has failed to rebut the presumption that the named inventors are, in fact, the inventors of the Chang Patent. Mylan has not proven by clear and convincing evidence that the named inventors are ***not*** the actual inventors. Accordingly, the claims of the '532 patent are

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[29]As Mylan argues (albeit in the context of the Ashley Patents), "'a research goal is not conception of the invention.'" (D.I. 275 at 7) (quoting Galderma's closing argument at Tr. 1004); *see also Purdue v. Faulding*, 48 F. Supp.2d at 435 (stating that general goal is not an invention).

not invalid under § 102(f).

4. Invalidity due to lack of written description

Finally, Mylan contends that claims 4 and 18 of the Chang Patent are invalid for failure to meet the written description requirement of 35 U.S.C. § 112, ¶ 1. In support of this argument, Mylan relies on what it portrays as "Dr. Friend's unrebutted testimony." (D.I. 265 at 30) Mylan's Dr. Friend opined that the example in Figure 5 of the Chang Patent does not meet the claimed blood levels because it shows some participants had values below 0.3 μg/ml at some points during a 24-hour period. (Tr. 812-13) However, the Court agrees with Galderma that Dr. Friend's opinion is based on reading into the Chang patent a limitation – i.e., that the blood levels be above 0.3 μg/ml in all patients at all times – that is not present in claims 4 and 18 of the patent.

Moreover, to satisfy the written description requirement, the patent, taken as a whole, must demonstrate that the inventors had possession of the claimed subject matter: "only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (internal citations omitted). The Court is persuaded by Dr. Rudnic's testimony that a person of ordinary skill in the art would understand that the Chang Patent inventors were in possession of their claimed invention. (Tr. 188) This conclusion is supported – albeit after the fact – by the results of the pivotal pK study.

Mylan has failed to demonstrate by the required clear and convincing evidence that claims 4 and 18 are invalid under 35 U.S.C. § 112 ¶ 1 for failure to satisfy the written description

requirement.

IV. REMEDY

Galderma asks that the Court convert its preliminary injunction into a permanent injunction and change the effective date of FDA approval of Mylan's ANDA to a date no earlier than the expiration of the last-to-expire of the patents-in-suit, including any regulatory exclusivity and patent term extensions. (D.I. 267 at 30) Galderma further asks the Court to convert Mylan's FDA approval to tentative approval and enjoin Mylan from infringing. (D.I. 274 at 20) Mylan, on the other hand, asks the Court to vacate its preliminary injunction. (D.I. 264 at 30)

Given the Court's conclusion that at least one valid patent claim is infringed (i.e., Chang Patent claims 1-5, 7-9, 13-21), Galderma is entitled to some relief. However, given that neither party prevailed in the entirety of its positions, and given that the Court's conclusion with respect to the sole basis on which the preliminary injunction was entered (i.e., infringement of the Ashley Patents) is different than its preliminary determination, the Court needs additional assistance from the parties in order to determine the proper remedy. It is also noteable that the only asserted patent that is infringed is a patent that issued well after Mylan filed its ANDA.

By separate Order, the Court will enter a schedule by which the parties will be required to submit briefs addressing the appropriate remedy. The preliminary injunction will remain in place until further Order of the Court.

CONCLUSION

For the reasons stated above, the Court finds that Galderma has failed to prove infringement of the asserted claims of the Ashley Patents and the Amin Patents. Galderma has

proved by a preponderance of the evidence that each of the asserted claims of the Chang Patent are infringed. The Court further finds that Mylan has failed to prove by clear and convincing evidence that any of the claims of the Ashley Patents or the Chang Patent are invalid but did succeed in proving that the Amin Patents are invalid.[30]

An Order will be entered following the Court's eventual decision on an appropriate remedy.

[30]Both parties moved for judgment as a matter of law during trial, pursuant to Federal Rule of Civil Procedure 52(c). The Court deferred ruling on these motions until after trial. (Tr. 329-31, 955) Having now made findings of fact and reached conclusions of law on a full post-trial record, the Court DENIES all motions for judgment as a matter of law.