IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE COPAXONE CONSOLIDATED CASES	Civil Action No. 14-1171-GMS **(CONSOLIDATED)**

MEMORANDUM

I. INTRODUCTION

In this consolidated Hatch-Waxman patent infringement action, Plaintiffs Teva Pharmaceuticals USA Inc. ("Teva"), Teva Pharmaceutical Industries Ltd. ("Teva Ltd."), Teva Neuroscience Inc., and Yeda Research and Development Co. Ltd. ("Yeda") (collectively "Teva") allege patent infringement by Defendants Sandoz Inc., Momenta Pharmaceuticals Inc., Dr. Reddy's Laboratories Inc. ("DRL"), Dr. Reddy's Laboratories Ltd. ("DRL Ltd."), Mylan Pharmaceuticals Inc., Synthon Pharmaceuticals Inc. ("Synthon"), Synthon B.V., Synthon s.r.o. Blansko ("Synthon s.r.o"), Amneal Pharmaceuticals LLC ("Amneal"), Amneal Pharmaceuticals Company GmbH ("Amneal GmbH"), and Pfizer Inc. Plaintiffs allege that, by filing Abbreviated New Drug Applications ("ANDAs") seeking approval to market generic versions of COPAXONE® 40mg, Defendants infringed U.S. Patent Nos. 8,399,413 ("the '413 patent"), 8,232,250 ("the '250 patent"), 8,969,302 ("the '302 patent"), and 9,155,776 ("the '776 patent"). The court held a seven-day bench trial in this matter beginning on September 26, 2016. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit and whether Defendants' generic pharmaceutical compositions infringe the patents-in-suit. (D.I. 272); (D.I. 273).

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that all asserted claims of the patents-in-suit are invalid as obvious. The findings of fact and conclusions of law relevant to the court's decision are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Teva is a Delaware Corporation with its principal place of business at 1090 Horsham Road, North Wales, PA 19454.

2. Plaintiff Teva Ltd. is an Israeli company with its principal place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva, 49131, Israel.

3. Plaintiff Teva Neuroscience is a Delaware corporation with its principal place of business at 901 E. 104th Street, Suite 900, Kansas City, Missouri 64131.

4. Plaintiff Yeda is an Israeli company with its principal place of business at P.O. Box 95, Rehovot, 76100, Israel.

5. Defendant Amneal is a limited liability company organized and existing under the laws of Delaware with a principal place of business at 400 Crossing Blvd., Third Floor, Bridgewater, NJ 08807-2863.

[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 254, Ex. A.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs, corrected some formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

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

6. Defendant Amneal GmbH is a limited liability company organized and existing under the laws of Switzerland with a principal place of business at Turnstrasse 30, 6312 Steinhausen, Switzerland.

7. Defendant DRL Ltd. is a corporation organized and existing under the laws of India with its principal place of business at 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Telangana 500 034, India.

8. Defendant DRL is a corporation organized and exiting under the laws of New Jersey with its principal place of business at 107 College Road East, Princeton, NJ 08540, and is a wholly-owned subsidiary of DRL Ltd.

9. Defendant Mylan is a corporation organized and existing under the laws of West Virginia with its principal place of business at 781 Chestnut Ridge Rd., Morgantown, WV 26505. Mylan is a wholly-owned subsidiary of Mylan Inc., which is a corporation organized and existing under the laws of Pennsylvania with its principal place of business at 1000 Mylan Blvd., Canonsburg, PA 15317.

10. Defendant Sandoz is a corporation organized and existing under the laws of Colorado with its principal place of business at 100 College Road West, Princeton, NJ 08540.

11. Defendant Momenta is a corporation organized and existing under the laws of Delaware with its principal place of business at 675 West Kendall Street, Cambridge, MA 02142.

12. Defendant Synthon is a corporation organized and existing under the laws of North Carolina with its principal place of business at 1007 Slater Road, Suite 150, Durham, NC 27703.

13. Defendant Synthon B.V. is a corporation organized and existing under the laws of the Netherlands with its principal place of business at Microweg 22, P.O. Box 7071, 6503 CM Nijmegen, The Netherlands.

14. Synthon s.r.o is a Czech entity having a principal place of business at Brnenska 32/cp.597, 678 17 Blansko, Czech Republic. Synthon and Synthon s.r.o are sister companies with Synthon B.V. as their ultimate parent company.

15. Defendant Pfizer is a corporation organized and existing under the laws of Delaware with its principal place of business at 235 East 42nd Street, New York, NY 10017.

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

B. Background

17. These consolidated actions arise out of Defendants' respective submissions of ANDAs under § 505(j) of the Federal Food, Drug and Cosmetic Act to the United States Food and Drug Administration ("FDA") with certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market and sell glatiramer acetate ("GA") for injection, in 40 mg/mL prefilled syringes.

18. The three-times-weekly 40 mg/mL dose of GA was approved by the FDA in January 2014.

19. Teva is the holder of New Drug Application ("NDA") number 20-622, which was supplemented by Teva in 2013 to receive approval by the FDA of the use of GA 40 mg/mL three times per week, marketed as COPAXONE® 40 mg/mL, for the treatment of patients with relapsing forms of multiple sclerosis such as relapse-remitting multiple sclerosis.

20. Teva, Teva Ltd. and Teva Neuroscience's (collectively, "Teva") COPAXONE® 40 mg/mL product is supplied as single-dose prefilled synringes that contain 40 mg/mL GA for injection, manufactured by Teva Ltd., and marketed and sold in the United States by Teva Neuroscience.

C. The Patents-in-Suit

i. The '250 Patent

21. The '250 patent, entitled "Low Frequency Glatiramer Acetate Therapy" was issued on July 31, 2012.

22. Ety Klinger is the named inventor of that patent.

23. The '250 patent was submitted by Teva to the FDA to be listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as "the Orange Book" with respect to the COPAXONE® 40 mg/mL product.

ii. The '413 Patent

24. The '413 patent, entitled "Low Frequency Glatiramer Acetate Therapy" was issued on March 19, 2013.

25. Ety Klinger is the named inventor of that patent.

26. The '413 patent was submitted by Teva to the FDA to be listed in the Orange Book with respect to the COPAXONE® 40mg/mL product.

iii. The '302 Patent

27. The '302 patent, entitled "Low Frequency Glatiramer Acetate Therapy" was issued on March 3, 2015.

28. Ety Klinger is the named inventor of the '302 patent.

29. The '302 patent was submitted by Teva to the FDA to be listed in the Orange Book with respect to the COPAXONE® 40 mg/mL product.

iv. The '776 Patent

30. The '776 patent, entitled "Low Frequency Glatiramer Acetate Therapy" was issued on October 13, 2015.

31. Ety Klinger is the named inventor of the '776 patent.

32. The'776 patent was submitted by Teva to the FDA to be listed in the Orange Book with respect to the COPAXONE® 40 mg/mL product.

D. The Asserted Claims

i. '250 patent, Claims 1, 5, 13–17

Claims 1, 5, 13–17 read:

1. A method of alleviating a symptom of relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis comprising administering to the human patient a therapeutically effective regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient to alleviate the symptom of the patient.

5. The method of claim 1, wherein alleviating a symptom comprises reducing brain atrophy in the patient.

13. The method of claim 1, wherein the patient has not received glatiramer acetate therapy prior to initiation of the regimen.

14. The method of claim 1, wherein the frequency of an immediate post injection reaction or the frequency of an injection site reaction is reduced relative to daily subcutaneous administration of 20 mg glatiramer acetate.

15. A method of increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis which comprises reducing frequency of subcutaneous injections from daily subcutaneous injections of a pharmaceutical composition comprising a 20 mg dose of glatiramer acetate to a regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate over a period of seven days with at least one day between every injection, wherein the regimen is therapeutically effective, so as to thereby increase the tolerability of GA treatment in the patient.

16. The method of claim 15, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an immediate post injection reaction.

17. The method of claim 15, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an injection site reaction.

ii. '413 patent, claims 1, 7, 15, and 20

1. A method of reducing the frequency of relapses in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and has MRI features consistent with multiple sclerosis comprising administering to the human patient a therapeutically effective dosage regimen of three subcutaneous injections of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient to reduce the frequency of relapses in the patient.

7. The method of claim 1, wherein the frequency of an immediate post injection reaction or the frequency of an injection site reaction is reduced relative to daily subcutaneous administration of 20 mg glatiramer acetate.

15. The method of claim 14, wherein, the lesion is a demyelinating white matter lesion visible on brain MRI and wherein the white matter lesion is at least 3 mm in diameter.

20. A method of reducing the frequency of relapses in a human patient who has experienced a first clinical episode and has MRI features consistent with multiple sclerosis comprising administering to the human patient a therapeutically effective dosage regimen of three subcutaneous injections of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient, wherein the pharmaceutical composition further comprises mannitol, and wherein the pharmaceutical composition has a pH in the range of 5.5 to 7.0, the regimen being sufficient to reduce the frequency of relapses in the patient.

ii. '302 patent, claims 1, 10, and 11

1. A method of treatment of a human patient suffering from a relapsing form of multiple sclerosis comprising administration to the human patient of three subcutaneous injections of a 40 mg/ml dose of glatiramer acetate per week so as to treat the human patient.

10. A method of treatment of a human patient suffering from a relapsing form of multiple sclerosis comprising subcutaneous injection by the human patient of a 40 mg/ml dose of glatiramer acetate three times per week with at least one day between every subcutaneous injection, wherein the glatiramer acetate is present in 1 ml of a pharmaceutical composition in a prefilled syringe for self injection by the human patient, and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range of 5.5 to 7.0.

11. The method of claim 10, wherein each subcutaneous injection is on day 1, day 3 and day 5; day 1, day 3 and day 6; day 1, day 4 and day 6; day 2, day 4 and day 6; day 2, day 4 and day 7; 2, day 5 and day 7; or day 3, day 5 and day 7 every week.

iii. '776 patent, claims 1, 2, 5, 6, 9, 12, 16, and 17

1. A method of treating a human patient suffering from a relapsing form of multiple sclerosis, while inducing reduced severity of injection site reactions in the human patient relative to administration of 20 mg of glatiramer acetate s.c. daily, the method consisting of one subcutaneous injection of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate on only each of three days during each week of treatment with at least one day without a subcutaneous injection of the pharmaceutical composition between each day on which there is a subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe, and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range 5.5 to 7.0,so as to thereby treat the human patient with reduced severity of injection site reactions relative to administration of 20 mg of glatiramer acetate s.c. daily.

2. The method of claim 1, which induces reduced frequency and severity of immediate post injection reactions and injection site reactions in the human patient relative to administration of 20 mg of glatiramer acetate s.c. daily.

5. A method for reducing the frequency of relapses by 30% or more as compared to placebo in a human population, for reducing brain atrophy, for reducing the cumulative number of enhancing lesions on T1-weighted images, or for reducing the level of disability as measured by EDSS Score of a human patient suffering from a relapsing form of multiple sclerosis, while inducing reduced severity of injection site reactions in the human patient relative to administration of 20 mg of glatiramer acetate s.c. daily, which method consists of one subcutaneous injection of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate on only each of three days during each week of treatment with at least one day without a subcutaneous injection of the pharmaceutical composition between each day on which there is a subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe, and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range 5.5 to 7.0,so as to thereby reduce the frequency of relapses by 30% or more as compared to placebo in a human population, reduce brain atrophy, reduce the cumulative number of enhancing lesions on T1- weighted images, or reduce the level of disability as measured by EDSS Score of the human patient with reduced severity of injection site reactions relative to administration of 20 mg of glatiramer acetate s.c. daily.

6. The method of claim 5, which reduces brain atrophy and for reducing the frequency of relapses by 30% or more as compared to placebo in a human population.

9. The method of claim 5, which induces reduced frequency and severity of immediate post injection reactions and injection site reactions in the human patient relative to administration of 20 mg of glatiramer acetate s.c. daily.

12. A method for improving the tolerability of glatiramer acetate treatment of a human patient suffering from a relapsing form of multiple sclerosis which is as effective as administration of 20 mg of glatiramer acetate s.c. daily, which method consists of one subcutaneous injection of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate on only each of three days during each week of treatment with at least one day without a subcutaneous injection of the

pharmaceutical composition between each day on which there is a subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe, and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range 5.5 to 7.0, so as to thereby treat the human patient as effectively as by administration of 20 mg of glatiramer acetate s.c. daily, and with reduced severity of injection site reactions relative to administration of 20 mg of glatiramer acetate s.c. daily.

16. A method for improving the tolerability of glatiramer acetate therapy reducing the frequency of relapses, reducing brain atrophy, reducing the cumulative number of enhancing lesions on T1- weighted images, or reducing the level of disability as measured by EDSS Score, of a human patient suffering from a relapsing form of multiple sclerosis as effectively as administration of 20 mg of glatiramer acetate s.c. daily, which method consists of one subcutaneous injection of 1 ml of a pharmaceutical composition comprising 40 mg of glatiramer acetate on only each of three days during each week of treatment with at least one day without a subcutaneous injection of the pharmaceutical composition between each day on which there is a subcutaneous injection, wherein the pharmaceutical composition I in a prefilled syringe, and wherein the pharmaceutical composition further comprises mannitol and has a pH in the range 5.5 to 7.0, so as to thereby reduce the frequency of relapses, reduce brain atrophy, reduce the cumulative number of enhancing lesions on T1 weighted images, or reduce the level of disability as measured by EDSS Score, of the human patient as effectively as by administration of 20 mg of glatiramer acetate s.c. daily, and with reduced severity of injection site reactions relative to administration of 20 mg of glatiramer acetate s.c. daily.

17. The method of claim 16, which reduces the frequency of relapses as effectively as administration of 20 mg of glatiramer acetate s.c. daily.

E. Defendants' ANDAs

i. <u>Amneal ANDA</u>

33. Amneal GmbH, through its U.S. agent Amneal LLC, filed an ANDA under 21 U.S.C. § 355(j) seeking FDA approval for GA injection, 40 mg/mL, which was assigned ANDA number 207553 ("Amneal's GA Product"), prior to the expiration of the '250 and '413 patents.

34. Amneal GmbH also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '250 and '413 patents are invalid, unenforceable, and/or would not be infringed by Amneal's GA Product.

35. By letter dated January 23, 2015, Amneal LLC sent notice to Teva that Amneal LLC had filed ANDA No. 207553 seeking approval to market Amneal's GA Product prior to the expiration of the '250 and '413 patents ("First Notice Letter").

36. Amneal also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '302 patent are invalid, unenforceable, and/or would not be infringed by Amneal's GA Product.

37. By letter dated March 18, 2015, Amneal LLC notified Teva that it had filed an amendment to ANDA No. 207553 with a Paragraph IV certification related thereto seeking approval to market Amneal's GA Product prior to the expiration of the '302 patent.

38. Amneal also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '776 patent are invalid, unenforceable, and/or would not be infringed by Amneal's GA Product.

39. By letter dated October 29, 2015, Amneal LLC notified Teva that it had filed an amendment to ANDA No. 207553 with a Paragraph IV certification related thereto seeking approval to market Amneal's GA Product prior to the expiration of the '776 patent.

ii. Amneal Procedural History

40. On February 3, 2015, Plaintiffs sued Amneal LLC in this court for patent infringement of the '250 and '413 patents, related to ANDA No. 207553. See Teva Pharms. USA, Inc., et al. v. Amneal Pharms. LLC, C.A. No. 15-124-GMS (D. Del.). Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Plaintiffs sued Amneal within 45 days of receipt of Amneal's First Notice Letter.

41. On March 9, 2015, this court consolidated the multiple pending actions regarding GA 40 mg/mL products into Civil Action No. 1:14-cv-01171-GMS.

42. On April 10, 2015, Plaintiffs also sued Amneal LLC in this court for patent infringement of the '302 patent, related to ANDA No. 206767. See Teva Pharms. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 1:15-0306-GMS (D. Del.). That action was consolidated with the current action.

43. On April 30, 2015, Plaintiffs filed a First Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The First Amended Complaint named both Amneal LLC and Amneal GmbH as defendants.

44. On November 10, 2015, Plaintiffs filed a Second Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The Second Amended Complaint alleged infringement of the '776 patent.

iii. Amneal Stipulations

45. Amneal has stipulated that, for purposes of this action, its ANDA product contains "GA" as recited in the claims of the patents-in-suit. (D.I. 195).

iv. DRL ANDA

46. DRL filed an ANDA under 21 U.S.C. § 355(j) seeking FDA approval for GA injection, 40 mg/mL, which was assigned ANDA number 206767 ("DRL's GA Product"), prior to the expiration of the '250 patent and the '413 patent.

47. DRL also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '250 and '413 patents are invalid, unenforceable, and/or would not be infringed by DRL's GA Product.

48. By letter dated August 1, 2014, DRL sent notice to Teva that DRL had filed ANDA No. 206767 seeking approval to market DRL's GA Product prior to the expiration of the '250 and '413 patents ("First Notice Letter").

49. Teva received DRL's First Notice Letter on or about August 6, 2014.

50. DRL also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '302 patent are invalid, unenforceable, and/or would not be infringed by DRL's GA Product.

51. By letter dated May 19, 2015, DRL sent notice to Teva that DRL had filed ANDA No. 206767 seeking approval to market DRL's GA Product prior to the expiration of the '302 patent.

52. DRL also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '776 patent are invalid, unenforceable, and/or would not be infringed by DRL's GA Product.

53. By letter dated January 14, 2016, DRL sent notice to Teva that DRL had filed ANDA No. 206767 seeking approval to market DRL's GA Product prior to the expiration of the '776 patent.

v. DRL Procedural History

53. On September 10, 2014, Plaintiffs sued DRL in this court for patent infringement of the '250 and '413 patents, related to ANDA No. 206767. See Teva Pharms. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 14-1172-GMS (D. Del.). Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Plaintiffs sued DRL within 45 days of receipt of DRL's First Notice Letter.

54. On March 9, 2015, this Court consolidated the multiple pending actions regarding GA 40 mg/mL products into Civil Action No. 1:14-cv-01171-GMS.

55. On April 10, 2015, Plaintiffs also sued DRL in this court for patent infringement of the '302 patent, related to ANDA No. 206767. See Teva Pharms. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 1:15-0306-GMS (D. Del.). That action was consolidated with the current action.

56. On November 10, 2015, Plaintiffs filed a Second Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The Second Amended Complaint alleged infringement of the'776 patent.

vi. DRL Stipulations

57. DRL has stipulated that, for purposes of this action, its ANDA product contains "GA" as recited in the claims of the patents-in-suit. (D.I. 195).

vii. Mylan ANDA

58. Mylan filed an ANDA under 21 U.S.C. § 355(j) seeking FDA approval for GA injection, 40 mg/mL, which was assigned ANDA number 206936 ("Mylan's GA Product") prior to the expiration of the '250 and '413 patents.

59. Mylan also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '250 and '413 patents are invalid, unenforceable, and/or would not be infringed by Mylan's GA Product.

60. By letter dated August 28, 2014, Mylan sent notice to Teva that Mylan had filed ANDA No. 206936 seeking approval to market Mylan's GA Product prior to the expiration of the '250 and '413 patents ("First Notice Letter").

61. Mylan also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '302 patent are invalid, unenforceable, and/or would not be infringed by Mylan's GA Product.

62. By letter dated March 9, 2015, Mylan sent notice to Teva that Mylan had filed ANDA No. 206936 seeking approval to market Mylan's GA Product prior to the expiration of the '302 patent.

63. Mylan also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '776 patent are invalid, unenforceable, and/or would not be infringed by Mylan's GA Product.

64. Mylan also notified Teva that it had filed an amendment to ANDA No. 206936 with a Paragraph IV certification related thereto seeking approval to market Mylan's GA Product prior to the expiration of the '776 patent.

viii. Mylan Procedural History

65. On October 6, 2014, Plaintiffs sued Mylan in this court for patent infringement of the '250 and '413 patents, related to ANDA No. 206936. See Teva Pharms. USA, Inc., et al. v. Mylan Pharms Inc., et al., C.A. No. 14-1278-GMS (D. Del.). Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Plaintiffs sued Mylan within 45 days of receipt of Mylan's First Notice Letter.

66. On March 9, 2015, this court consolidated the multiple pending actions regarding GA 40 mg/mL products into Civil Action No. 1:14-cv-01171-GMS.

67. On April 10, 2015, Plaintiffs sued Mylan in this court for patent infringement of the '302 patent, related to ANDA No. 206936. See Teva Pharms. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 1:15-0306-GMS (D. Del.). That action was consolidated with the current action.

68. On November 10, 2015, Plaintiffs filed a Second Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The Second Amended Complaint alleged infringement of the'776 patent.

ix. Mylan Stipulations

69. Mylan has stipulated that, for purposes of this action, its ANDA product contains "GA" as recited in the claims of the patents-in-suit. (D.I. 195).

x. Sandoz Inc. ANDA

70. Sandoz Inc. filed an ANDA under 21 U.S.C. § 355(j) seeking FDA approval for GA injection, 40 mg/mL, purported to be generic to Teva's COPAXONE® 40 mg/mL product, which was assigned ANDA number 206921 ("Sandoz Inc.'s GA Product"), prior to the expiration of the '250 and '413 patents.

71. Sandoz Inc. also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '250 and '413 patents are invalid, unenforceable, and/or would not be infringed by Sandoz Inc.'s GA Product.

72. By letter dated August 27, 2014, Sandoz Inc. sent notice to Teva that Sandoz Inc. had filed ANDA No. 206921 seeking approval to market Sandoz Inc.'s GA Product prior to the expiration of the '250 and '413 patents ("First Notice Letter").

73. Teva received Sandoz Inc.'s First Notice Letter on or about August 28, 2014.

74. Sandoz Inc. also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '302 patent are invalid, unenforceable, and/or would not be infringed by Sandoz Inc.'s GA Product.

75. By letter dated March 6, 2015, Sandoz Inc. sent notice to Teva that Sandoz Inc. had filed ANDA No. 206921 seeking approval to market Sandoz Inc.'s GA Product prior to the expiration of the '302 patent.

76. Sandoz Inc. also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '776 patent are invalid, unenforceable, and/or would not be infringed by Sandoz Inc.'s GA Product.

77. Sandoz Inc. also notified Teva that it had filed an amendment to ANDA No. 206921 with a Paragraph IV certification related thereto seeking approval to market Sandoz Inc.'s GA Product prior to the expiration of the '776 patent.

xi. Sandoz Procedural History

78. On September 10, 2014, Plaintiffs sued Sandoz Inc. and Momenta Pharmaceuticals, Inc. in this court for patent infringement of the '250 and '413 patents, related to ANDA No. 206921. See Teva Pharm. USA, Inc., et al. v. Sandoz, Inc., et al., C.A. No. 1:14-cv-01171 GMS (D. Del.). Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Plaintiffs sued Sandoz Inc. and Momenta Pharmaceuticals, Inc. within 45 days of receipt of Sandoz Inc.'s First Notice Letter.

79. On March 9, 2015, this Court consolidated the multiple pending actions regarding GA 40 mg/mL products into Civil Action No. 1:14-cv-01171-GMS.

80. On April 10, 2015, Plaintiffs sued Sandoz Inc. and Momenta Pharmaceuticals, Inc. in this court for patent infringement of the '302 patent, related to ANDA No. 206921. See Teva Pharm. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 1:15-cv-00306-GMS (D. Del.). That action was consolidated with the current action.

81. On November 10, 2015, Plaintiffs filed a Second Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The Second Amended Complaint alleged infringement of the'776 patent.

xii. Synthon Pharmaceuticals, Inc.'s ANDA

82. Synthon Pharmaceuticals, Inc. filed an ANDA under 21 U.S.C. § 355(j) seeking FDA approval for GA injection, 40 mg/mL, purported to be generic to Teva's COPAXONE® 40 mg/mL product, which was assigned ANDA number 206873 ("Synthon Pharmaceuticals' GA Product"), prior to the expiration of the '250 and '413 patents.

83. Synthon Pharmaceutical Inc. also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '250 and '413 patents are invalid, unenforceable, and/or would not be infringed by Synthon Pharmaceuticals' GA Product.

84. By letter dated October 8, 2014, Synthon Pharmaceutical Inc. sent notice to Teva that Synthon Pharmaceutical Inc. had filed ANDA No. 206873 seeking approval to market Synthon Pharmaceuticals' GA Product prior to the expiration of the '250 and '413 patents ("First Notice Letter").

85. Teva received Synthon Pharmaceuticals Inc.'s First Notice Letter on or about October 9, 2014.

86. Synthon Pharmaceutical Inc. also filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '302 patent are invalid, unenforceable, and/or would not be infringed by Synthon Pharmaceuticals' GA Product.

87. By letter dated March 27, 2015, Synthon Pharmaceutical Inc. sent notice to Teva that Synthon had filed ANDA No. 206873 seeking approval to market Synthon Pharmaceuticals' GA Product prior to the expiration of the '302 patent.

88. Synthon Pharmaceutical Inc. filed with the FDA a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the claims of the '776 patent are invalid, unenforceable, and/or would not be infringed by Synthon Pharmaceuticals' GA Product.

89. Synthon Pharmaceutical Inc. notified Teva that it had filed an amendment to ANDA No. 206873 with a Paragraph IV certification related thereto seeking approval to market Synthon Pharmaceuticals' GA Product prior to the expiration of the '776 patent.

xiii. Synthon Procedural History

90. On November 18, 2014, Plaintiffs sued Synthon Pharmaceuticals, Inc., Synthon s.r.o., and Synthon B.V. in this Court for patent infringement of the '250 and '413 patents, related to ANDA No. 206873. See Teva Pharms. USA, Inc., et al. v. Synthon Pharms. Inc., et al., C.A. No. 14-1419-GMS (D. Del.). Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), Plaintiffs sued Synthon Pharmaceuticals, Inc., Synthon s.r.o., and Synthon B.V. within 45 days of receipt of Synthon Pharmaceuticals, Inc.'s First Notice Letter.

91. On March 9, 2015, this court consolidated the multiple pending actions regarding GA 40 mg/mL products into Civil Action No. 1:14-cv-01171-GMS.

92. On April 10, 2015, Plaintiffs sued Synthon Pharmaceuticals, Inc., Synthon s.r.o., and Synthon B.V. in this court for patent infringement of the '302 patent, related to ANDA No. 206873. See Teva Pharms. USA, Inc., et al. v. Dr. Reddy's Labs., Ltd., et al., C.A. No. 1:15- 0306-GMS (D. Del.). That action was consolidated with the current action.

93. On November 10, 2015, Plaintiffs filed a Second Amended Complaint in In re Copaxone 40 mg Consolidated Cases, C.A. No. 1:14-cv-01171-GMS (D. Del.). The Second Amended Complaint alleged infringement of the'776 patent.

xiv. Synthon Stipulations

94. Synthon Pharmaceuticals, Inc., Synthon s.r.o., Synthon B.V., and Pfizer, Inc. have stipulated that, for purposes of this action, Synthon Pharmaceuticals, Inc.'s ANDA product contains "GA" as recited in the claims of the patents-in-suit. (D.I. 195).

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b), (c), and (d), and 1400 (b). After

having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that all asserted claims of the patents-in-suit are invalid. The court's reasoning follows.

A. Obviousness[2]

i. The Legal Standard

Under 35 U.S.C. § 103(a), a patent may not be obtained "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282(a). A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[3] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*,

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[2] The court acknowledges that Defendants asserted affirmative defenses of non-infringement, obviousness, non-enablement, and indefiniteness. Because the court found all asserted claims of the patents-in-suit invalid as obvious, it declined to address Defendants other affirmative defenses.

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

566 F.3d 989, 993–94 (Fed. Cir. 2009). Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" *KSR Int'l Co.*, 550 U.S. at 421, "might support an inference of obviousness." *Ortho–McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

ii. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to all the patents-in-suit would have: (1) several years' experience in the pharmaceutical industry or in practicing medicine; (2) experience with drug development in the pharmaceutical industry or in medical practice; (3) a Ph.D. in

pharmacology or an M.D. with experience in clinical pharmacology; and (4) experience with MS and GA. (D.I. 273 at 13–14); (D.I. 272 at 6).

iii. Obviousness of the '250, '413 and '302 Patents

Defendants challenge the validity of the asserted claims of the '250, '413, '302, and '776 patents. Because the '776 patent includes limiting language not found in the other three patents, the obviousness of the '776 patent will be addressed separately. (D.I. 273 at 13); *see infra* § III(A)(iv).

Plaintiffs assert claims 1, 5 and 13–17 of the '250 patent, claims 1, 7, 15 and 20 of the '413 patent, and claims 1, 10 and 11 of the '302 patent. (D.I. 273 at 14). The obviousness analysis for the '250, '413, and '302 patents hinges on the core elements of the asserted claims: (1) a 40mg dose of GA that is (2) administered in three subcutaneous injections over seven days with at least one day between injections. *Id.* Although claim 1 of the '302 patent does not include the limitation that the injections be at least one day apart, claims 4 and 5 provide that the three injections be administered on three days of each week selected from a group of various combinations of days of the week, all with at least one day between injections. '302 patent, col. 16 ll. 47–58. Independent claim 10 of the '302 patent further discloses administering 40mg of GA "three times per week with at least one day between every subcutaneous injection." '302 patent, col. 17 ll. 7–8.

Defendants contend that the '250, '413 and '302 patents are obvious because the prior art provided motivation to create a 40mg, thrice-weekly injection regimen, as well as a reasonable expectation of success with that regimen. It is well-established that "when there is a design need or market pressure to solve a problem and there are a finite number of identified, and predictable solutions, a person of ordinary skill has good reason to pursue the known options." KSR Int'l Co., 550 U.S. at 421. When the solution does in fact yield the anticipated success, that result cannot be

deemed a product of innovation. *Id.* Defendants argue that there was clear market pressure to create a less frequent dosage form of GA to improve patient tolerability, and, due to prior art disclosures of positive results with less frequent dosing, there was a reasonable expectation that such a dosage form would be successful. Prior to addressing expert testimony on motivations to combine prior art references, the court will conduct a detailed analysis of the statutory prior art published before the earliest priority date of the patents-in-suit: August 20, 2009.

1. Scope and Content of the Prior Art

As early as 1996, an FDA reviewer suggested to Teva that they explore less frequent dosing of GA. JTX7079 at 252. That suggestion was part of the FDA's Summary Basis of Approval (SBOA) for 20mg daily COPAXONE®. The reviewer included a section in the summary entitled, "[a]re daily injections really necessary?" *Id.* In that section, the toxicology reviewer explained that the daily injection dosing regimen seemed "like it would subject the patient to an excessive amount of discomfort if it is not necessary to maintain efficacy." *Id.* The toxicology reviewer recommended that Teva "evaluate the necessity of daily s.c. injections as opposed to more infrequent intermittent administration of the drug." *Id.*

The Flechter reference was a 2002 open, multicenter two-year study on patients suffering from a relapsing form of MS. The study evaluated the "long-term neurologic course of the disease and the long-term safety of [GA] in patients" receiving 20 mg on an alternate-day basis. JTX7078 at 1. The study performed analyses on "two efficacy parameters: frequency of exacerbations and score on the Expanded Disability Status Scale (EDSS)." *Id.* at 1–2 (internal citations omitted). Flechter discloses, at the least, that daily injections may be unnecessary. (D.I. 271 at 20). Though Flechter notes that the results of the preliminary open-label study "should be confirmed by randomized double-blind examinations," the study's results nonetheless suggest that alternate-day

therapy is well tolerated and "compar[es] favorably with the effects of daily injections of [GA] in patients with relapsing MS." JTX7078 at 1.

The Cohen reference, a "Randomized, Double-Blind, Dose-Comparison Study of Glatiramer Acetate in Relapsing-remitting MS," was published in 2007. The study compared the 20mg and 40mg GA dosage forms. The nine-month study, which started enrolling participants as early as 2003, concluded that "onset of action of the 40-mg dose is more rapid compared with 20 mg." The study noted, however, that "[a] larger, longer study will be necessary to confirm the sustainability of the efficacy advantage of the higher dose." The study also went on to explain that "[t]he overall safety and side effect profile of the 40-mg dose in this trial [was] similar [to the 20-mg dose], although it was associated with a greater incidence of certain adverse effects." JTX7060 at 7.

Plaintiffs' own prior art patent application ("Pinchasi") was published only a few months after the Cohen study, though it claimed a January 11, 2006, priority date. The Pinchasi reference discloses a 40mg GA, every other day, dosing regimen to treat MS. Pinchasi cites to the data from the 2007 Cohen study to conclude that "[t]he increased efficacy observed with 40 mg/day GA in reducing MRI-measured disease activity and relapse rate indicates that it is well tolerated and can improve the treatment of [relapsing-remitting multiple sclerosis patients]." JTX7101 at 19. The Pinchasi reference also cites to the Cohen study data for the conclusion that there was an "accelerated rate at which the 40mg/day dose became effective." *Id.* at 20. The Pinchasi reference further notes that the improvement in efficacy was not accompanied by an increase in adverse reactions. *Id.* at 19.

The FORTE study, published in 2008, reported the results of a phase III, one-year, randomized, double-blind parallel-group, dose-comparison study with GA in relapsing-remitting

MS. JTX7063 at 1. The study sought to expand upon the phase II Cohen study, which found the 40mg daily dosing of GA may be more effective than 20mg daily dosing. *Id.* The study compared the safety, tolerability and efficacy of the 20mg/daily dosage regimen to the 40mg/daily regimen. *Id.* The primary endpoint of the study was the rate of confirmed relapses observed during the study. *Id.* The conclusions from the FORTE study were that both dosage forms were safe, well-tolerated and "equally effective in reducing clinical relapses and MRI activity." *Id.* Though seventy-seven percent of patients in both treatment groups remained relapse-free and both groups showed a reduction in new T2 lesions over time, the study still reported a trend for a faster reduction in the first trimester in the 40mg dose group. *Id.*

In 2008, Omar Khan, along with others from the Wayne State University School of Medicine, published the results of a randomized, prospective, rater-blinded, four-year pilot study to compare the effect of daily versus every-other-day dosing of 20mg GA in relapsing-remitting multiple sclerosis patients. JTX7089 at 4. The background section of the abstract for that study stated that "[t]he recommended dose of GA in RRMS is 20 mg subcutaneous (SC) daily (QD) although the optimal dose remain unknown. There is considerable interest in alternate dosing regimens of GA in RRMS. Daily SC injectable therapy can be challenging for long-term patient compliance." *Id.* Thirty patients were randomly assigned to receive 20mg of GA dosed every-day or every-other-day (QOD). *Id.* "After 2 years, there were no differences in the relapse rate, disease progression, T2W lesion volume or Gd enhancing lesions between the two groups." *Id.* After 2 years, all patients in the everyday group opted to switch to the every-other-day group. *Id.* When the researchers followed-up after four years there was no difference between the group that decided to cross-over from every-day to every-other-day and the group that was always dosed every-other-

day. *Id.* The researchers did note that large, multi-center studies were still necessary to confirm their findings.

The Caon reference, published in 2009, reports the same data from the Khan 2008 study. Trial Tr. 1320:14–18. As such, the study objective indicates that the researchers "conducted a pilot trial to compare the effect of GA 20 mg SC daily to every other day (QOD) in clinical, MRI, and immunologic outcomes in RRMS." JTX7058 at 2. Caon, like Khan 2008, reported that after two years there was no difference in relapse rate, MRI outcome, or disease progression between the QOD and QD groups. *Id.* Caon additionally noted that "[i]njection related lipoatrophy was significantly less in the QOD group." *Id.*

Omar Khan conducted another study that was published in 2009, although it began two years earlier. The study is not statutory prior-art because it was published three-weeks after the priority date of the patents-in-suit. 35 U.S.C. § 102(a). The court ruled, however, that because the study began before the priority date, it could be used to show the state of the art at or around the time of the invention. Tr. 721:6–724:17; *see Thomas & Betts Corp. v. Litton Systems, Inc.*, 720 F.2d 1572, 1581 (Fed. Cir. 1983) ("Thus, the M & E criteria, though not technically prior art, were, in effect, properly used as indicators of the level of ordinary skill in the art to which the invention pertained."). The pilot, prospective, randomized, and rater-blinded two-year study examined GA 20mg SC twice-weekly injections versus daily injections in relapsing-remitting MS patients. Though the court cannot consider the results of the study, the objective section of the abstract evidences the state of the art in 2007 when the study began: "[t]here is considerable interest in studying a more patient friendly dosing regimen of GA that may be as efficacious and better tolerated than daily GA." DTX1154 at 1.

2. Selecting the 40mg Dose

As is clear after a recitation of the prior art, a 40mg dosage form of GA was explicitly disclosed in references that pre-date the patents-in-suit. The Cohen study reported that the overall safety and side-effect profile of the 40mg dose was similar to the 20mg dose. JTX7060 at 7. Plaintiffs' own prior art patent application claimed a 40mg dosage form. JTX7107 at 22. The FORTE study also disclosed that the 40mg dosage form was safe, well-tolerated and "equally effective in reducing clinical relapses and MRI activity." JTX7063 at 1.

Plaintiffs highlight that the Cohen study was small, found "no statistically significant difference between the 20mg and the 40mg daily dosages" and showed "that 40 mg was more painful, not as well tolerated, and resulted in increased adverse events as compared to 20mg." (D.I. 272 at 18). Plaintiffs additionally argue that the Pinchasi reference, claiming a 40mg dosage form of GA, would not render the patents-in-suit obvious because the FORTE study caused the MS community to "abandon[] the 40mg dose." (D.I. 272 at 17). FORTE post-dates Pinchasi, and Plaintiffs contend that the FORTE study failed in that the 40mg/daily dose of GA did not demonstrate increased efficacy over the 20mg/daily dose. (D.I. 272 at 19). After the FORTE study, Teva announced in a July 7, 2008 press release that "COPAXONE® 20mg, the leading multiple sclerosis therapy, remains the optimal treatment dose." JTX7035 at 1. Plaintiffs' expert, Dr. Ziemssen, concluded that the 40mg dose was "dead" after the FORTE results were release. Trial Tr. 1340:9–15. After analysis of the FORTE and Cohen studies, however, the court disagrees with Dr. Ziemssen.

First, the court finds that persons having ordinary skill in the art would not agree with Teva's statement that 20mg is the optimal treatment dose. JTX7035 at 1. Though not a study investigating the efficacy of the 40mg dosage form of GA, Khan 2008 states that "the optimal treatment dose

remains unknown." JTX7089 at 4. Khan 2009, admitted for the limited purpose of showing the state of the art at the time of invention, also indicates that "[t]he optimal dose of glatiramer acetate (GA) in RRMS remains unknown." DTX1154 at 1. Khan 2009 demonstrates that, even after FORTE, persons having ordinary skill in the art would not consider 20mg/day to be the optimal dose.

Second, the court finds that Cohen and FORTE do not teach away from a 40mg dose. Despite the fact that the Cohen study reported higher incidences of certain adverse effects in patients given the 40mg GA dose, Dr. Cohen still concluded that overall efficacy results suggested that 40mg of GA may be more effective than the 20mg dose in reducing clinical relapse. JTX7060 at 2. Further, Teva decided to conduct the FORTE study, a large Phase III clinical trial of 40mg/daily versus 20mg/daily, after the Cohen results were published. *See* JTX7063 at 1. The court finds that Teva would not have invested in a large Phase III clinical trial were it not intrigued by the prospects of the 40mg dosage form and the Cohen study results. The court also finds that the results of the FORTE study—a 40mg dosage form was as effective as 20mg, yet did not cause an increase in adverse effects—completely undermines Plaintiffs argument. *See See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (finding that a later prior art study demonstrating that intermittent dosing was as effective as continuous treatment undermined any argument that earlier study taught away from monthly dosing); *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.").

Dr. Ziemssen contends that because the FORTE study failed, persons having ordinary skill in the art would have abandoned efforts to create a 40mg dosage form of GA. Trial Tr. 1246:19–

23. Dr. Ziemssen agreed with Defendants, however, when they asked "[w]e can agree that the FORTE study was powered to try to find a 30-percent improvement in the 40-milligram product versus the 20-milligram product for the efficacy end point. Right?" Trial Tr. 1401:12–22. While the FORTE study "failed" in the sense that it did not meet its primary endpoint—establishing that 40mg/day GA reduced annual relapse rates by thirty-percent compared to GA 20mg/day—it did not fail in the sense that it declared the 40mg dose ineffective. Trial Tr. 1401:23–1402:13. *See Hoffman La-Roche*, 748 F.3d at 1331 (stating that, while a study failed to demonstrate that intermittent dosing reduced vertebral fractures by a statistically significant amount, it did not teach that infrequent dosing is ineffective in treating osteoporosis).

The FORTE study reported that the 40 mg and 20 mg GA formulations "were safe and well-tolerated, and were equally effective in reducing clinical relapses and MRI activity." JTX7063 at 1. The study also reported a trend for faster reduction of gadolinium-enhancing and new T2 lesions in the first trimester of treatment with 40mg GA. *Id.* When Dr. Comi, the principal investigator for the FORTE study, presented the results of the FORTE study at the preeminent MS seminar, he stated that the 40mg dose was equally effective to 20mg with "no unexpected adverse effect with high dose." JTX7064 at 9. The court, therefore, is not persuaded that it would have been nonobvious to a person having ordinary skill in the art to use a 40mg dosage form, or that success with that dosage form would have been unexpected. *See Hoffmann-La* Roche, 748 F.3d at 1332 ("Even though the 5mg dose did not demonstrate greater efficacy than the 2.5mg dose, it was still deemed an equivalently effective dose so that someone scaling it to a single monthly dose of 150mg . . . would have anticipated equivalent success . . . .").

3. TIW Dosing Regimen

By the priority date, persons having ordinary skill in the art knew that daily injections were difficult to tolerate. Trial Tr. 894:16–896:17. Specifically, they knew that injection-site reactions ("ISRs") and immediate post-injection reactions ("IPIRs") were reasons for nonadherence to the 20mg/daily COPAXONE® treatment regimen. *Id.*

In 1996, the SBOA posed the question, "[a]re daily injections really necessary." JTX7079 at 252. Plaintiffs suggest that the reviewer asked that question out of concern that too much GA would accumulate in the system with daily dosing. (D.I. 272 at 20). The paragraph that follows the heading, "[a]re daily injections really necessary," however, makes clear that the examiner was concerned with "subject[ing] the patient to an excessive amount of discomfort" with a daily dosing regimen. JTX7079 at 252. Only after first voicing a concern about the discomfort of daily injections does the reviewer then state "[f]urthermore, if there should be a problem in humans with saturation of the clearance mechanism . . . this problem might be lessened with intermittent rather than daily administration." *Id.* Use of the word "furthermore" indicates that the reviewer's concern about patient discomfort with daily injections was distinct from his concern about GA accumulation in the system over time. The court thus finds that the reviewer's question and his recommendation "that the Sponsor evaluate the necessity of daily s.c. injections as opposed to more infrequent intermittent administration of the drug," *id.*, would have motivated those having ordinary skill in the art to pursue less frequent GA dosing schedules.

The 2002 Flechter study only provided further motivation to pursue less frequent GA dosing schedules. The main conclusion from the Flechter study was that "alternate-day treatment with [GA] [was] safe, well tolerated, and probably as effective as daily [GA]." JTX7078 at 5. Plaintiffs contend that the study's size and methodological flaws preclude a person having

ordinary skill in the art from drawing conclusions about the efficacy of less frequent GA dosing. (D.I. 272 at 25). Flechter does acknowledge that because the study was uncontrolled, "all conclusions cannot be used to prove efficacy." JTX7078 at 5. Regardless of Flechter's methodological flaws, the court is not persuaded by Plaintiff's argument. The court finds that the preliminary observations made in the Flechter study combined with the statement that preliminary observations would "have to be examined in larger studies, preferably comparing daily with alternate-day administration of Copolymer 1 in a blinded manner," JTX7078 at 5, would provide those in the art with motivation to conduct further studies on less frequent GA dosing.

Just like Flechter, the Khan 2008 study demonstrated that 20mg administered every other day may be as effective as 20mg of GA administered every day. The court finds that the study added further support to Defendants' proposition that there was considerable interest in alternate dosing regimens of GA for relapsing-remitting MS patients. Aside from explicitly noting such an interest existed as part of the background section of the study's abstract, the study also reported that when the patients in the 20 mg every day dose group were given the option to switch to receiving 20 mg every other day, all of them opted to switch to less frequent dosing. JTX7089 at 4.

Plaintiffs seek to discredit the Khan reference by pointing out that, like Flechter, Khan was an open label, small study that reported no data and was not designed to demonstrate the efficacy of an every-other-day GA regimen. (D.I. 272 at 25). Plaintiffs further explain that those in the art would not conclude that patients chose to switch from every day injections to every-other-day injections because of improved tolerability. Plaintiffs make a good point considering that the patients in the Khan "had not previously taken GA, and therefore, would not have experienced both regimens, and could not be comparing their tolerabilities, in making the

decision to switch." (D.I. 272 at 25). The court finds, however, that those in the art would, in fact, conclude that patients decided to switch to reduce the discomfort associated with daily injections. Trial testimony clearly showed that those in the art were familiar with the adverse reactions, pain, and treatment adherence problems associated with daily injections. Trial Tr. 89:5–16, 733:18–734:9, 926:3–14. Testimony additionally demonstrated that those in the art would opine that reducing the number of injections would reduce the pain and adverse reactions they cause. Trial Tr. 914:5–13 ("If you reduce the frequency of injections, well, it's clearly obvious that you would reduce the frequency of those injection site reactions or immediate post-injection reactions.").

Even if Khan were a small study with ill-defined endpoints, as Plaintiffs claim, it nonetheless demonstrated that "[a]fter 2 years, there were no differences in the relapse rate, disease progression, change in T2W lesion volume, or Gd enhancing lesions between the two groups." JTX7089 at 4. As Caon reported, the study also showed that "[i]njection related lipoatrophy was significantly less in the [every other day] group." JTX7058 at 2. Plaintiffs maintain that those in the art would not draw conclusions about tolerability based on Khan/Caon because the reference provides "no information regarding the tolerability of the 40mg dose, no description of what is meant by significantly less lipoatrophy, and no information about how the two regimens compared with respect to the other adverse events." (D.I. 272 at 26). Regardless of the purported shortcomings of the Khan 2008 study, the court finds that even the preliminary findings would have motivated a person having ordinary skill in the art to pursue less frequent dosing and given them a reasonable probability of success. The court also finds it unlikely that Khan and his associates would invest in another study, Khan 2009, investigating even less frequent GA dosing, had they not been encouraged by the results of Khan 2008. DTX1154 1–2.

The Pinchasi patent application claims a 40mg GA dose, administered every other day. The court agrees with Defendants that Pinchasi is the closest prior art because Pinchasi differs from the claimed regimen by only one dose every two weeks. (D.I. 272 at 17). Plaintiffs argue that a person having ordinary skill in the art would not have used the 40 mg every-other-day regimen as the starting point for development because the MS community abandoned the 40mg dose after the FORTE study. Trial Tr. 1340:9–15. For the reasons previously stated, the court does not find Plaintiffs argument persuasive.

Plaintiffs further argue that Pinchasi would not provide those in the art with the motivation to pursue less frequent dosing because "it provides no data (or even a clinical trial protocol) on EOD administration." (D.I. 272 at 18). Again, the court does not find that argument persuasive. Dr. Klinger, the inventor of the 40mg, thrice-weekly GA dosage form, admitted that the patents-in-suit provided no clinical or pre-clinical data to support a 40mg dose of GA administered three times a week. Trial Tr. 198:14–20. While the lack of clinical data in the Pinchasi patent might have caused the MS community to be skeptical of the efficacy of every-other-day administration, the patents-in-suit disclose no additional data beyond the teaching of Pinchasi or the other prior art references. It would constitute clear error for the court to discredit the Pinchasi reference for the same lack of dosing frequency clinical data from which the patents-in-suit suffer. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (finding clear error where the district court held an invention nonobvious because prior art failed to explain how a higher once-weekly dose would avoid adverse effects, but the patent-in-suit also did not provide any clinical data showing the tolerability of the higher once-weekly dose).

4. Improved Tolerability and Reduced Frequency Limitations

Claims 7, 14, 16, and 17 of the '250 patent and claim 7 of the '413 patent require that the 40mg, three-times-a-week regimen reduce the frequency of injection site reactions and immediate post-injection reactions as compared to a 20mg daily regimen. Claim 15 of the '250 patent requires that the claimed regimen improve tolerability as compared to a 20mg daily regimen. The court finds these claim limitations obvious as well.

Plaintiffs take issue with the fact that Defendants' expert, Dr. Green, provided no support for his "conclusory" assertion that those in the art would expect that the number of injection site reactions decrease as the number of injections per week decreased. (D.I. 272 at 31). The court disagrees with Plaintiff's characterization of Dr. Green's testimony as conclusory. Instead, it is simply common sense that if a patient experiences adverse reactions from an injection, reducing the number of injections they receive would reduce the number of times they have a reaction. It is unclear to the court why Dr. Green would need to support that statement with evidence. There is, however, evidence on the record that does provide the support Plaintiffs seek.

Dr. Wolinksy, a person having ordinary skill in the art, realized the association between injection site reactions and the number of injections per week. On some occasions, he would prescribe COPAXONE® 20mg for use every other day, and off-label use, for his patients who were "doing extremely well on the drug but [were] having trouble with injection site problems." Trial Tr. 762:11–763:10. Even more persuasive evidence that the improved tolerability and reduced frequency limitations are obvious can be found in the Khan/Caon and Flechter studies.

That Khan/Caon study, researching the effects of administering 20mg of GA every other day, found that the frequency of one type of injection-related adverse event—lipoatrophy—was "significantly less" in the every-other-day group as opposed to the group receiving daily

injections. JTX7058 at 2. The Flechter study also supports Defendants' assertion that those in the art would expect a smaller number of injections per week to lead to a reduced frequency in injection-site reactions. Flechter reported that the patient drop-out rate was lower in the group that received 20mg every other day, than in the group that received 20mg daily—"(39.7% versus 60.3%, $p<0.01$)." JTX7078 at 5. The prior art, analyzed as a whole, supports Defendants' contention that the improved tolerability and reduced frequency of injection site reactions claim limitations are obvious.

Plaintiffs argue that the prior art actually suggests that a 40mg dose of GA would increase the frequency of adverse events. Accordingly, there could be no reasonable expectation that a 40mg dose, administered thrice-weekly would reduce the frequency of injection-site reactions as compared to a 20mg daily regimen. (D.I. 272 at 25). The court disagrees.

The Pinchasi application explicitly states that the 2007 Cohen study demonstrated an improvement in efficacy associated with the 40mg dose, "not accompanied by a corresponding increase of adverse reactions which would be expected upon a doubling of the administered dose." JTX7107 at 19. The FORTE study also disclosed that injection site reactions were reported with similar incidence for both the 20mg and 40 mg doses. JTX7063 at 1; JTX7035 at 1 ("The 40mg dose did not demonstrate increased efficacy in reducing the relapse rate; however, the higher dose maintained the favorable safety and tolerability profile of COPAXONE® 20mg."). Plaintiffs' even stated to the FDA that the FORTE study showed "local reactions at the injection sites and immediate transient reactions following injection were reported with a similar incidence for both doses" and "one may certainly expect a reduction in the frequency of such reactions with this new dose regimen, further enhancing subject adherence to treatment." JTX7033 at 22. The court therefore disagrees with Plaintiffs that a 40mg, thrice-weekly dosing

regimen would not be expected to reduce the frequency of injection-site reactions and improve tolerability.

5. Obvious to Try

A 40mg dosage form was explicitly mentioned in the prior art, and there was a motivation in the MS community to explore a less frequent dosing regimen to alleviate the well-known adverse side effects associated with daily injections. As Plaintiffs point out however, there exists no prior art reference explicitly disclosing a three-times-a-week injection regimen. This is a case where evidence adduced at trial renders a less frequent dosage form obvious to try. *See Hoffmann-La Roche*, 748 F.3d at 1331 (holding the "150 mg dose was obvious to try" because "[t]here was a need to solve the problem of patient compliance by looking to less-frequent dosing regimens").

The court wishes to make clear that it is not applying what amounts to an impermissible "obvious-to-try" standard. The Federal Circuit has cautioned time and again that the obvious-to-try standard commonly leads to two types of errors:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentations, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In re O'Farrell, 853 F.2d at 903. This case does not fall into either of the scenarios outlined in *O'Farrell*. Here, there was market pressure to solve a known problem—the fact that many MS patients could not tolerate daily injections—and there were a finite number of predictable solutions that a person of ordinary skill in the art would have good reason to pursue. *See KSR Int'l Co.*, 550 U.S. at 421. Once it became clear that researchers could

maintain the efficacy of GA treatments while decreasing the total amount of the drug patients received or the frequency with which they received it, there were only so many combinations of dosage and frequency that they could study.

The 40mg dose was obvious to try because it was one of two doses studied extensively. The prior art demonstrates that a number of studies looked at the safety, efficacy, and tolerability of a 20mg dose and a 40mg dose. The 40mg dose was shown to be as safe, effective, and tolerable as the 20mg dose. JTX7063 at 1. It was therefore obvious for Plaintiffs to experiment with and have a reasonable probability of success with that dose. *See Hoffmann-La Roche*, 748 F.3d at 1331 (holding that "a person skilled in the art looking to scale to a monthly dose . . . was faced with a very limited set of possibilities" because "even though the 5 mg dose did not demonstrate greater efficacy than the 2.5 mg dose, it was still deemed an equivalently effective dose so that someone scaling it to a single monthly dose . . . would have anticipated equivalent success").

There were also a finite number of days on which to administer injections considering there are only seven days in a week. The prior art disclosed that administering GA every other day was as effective as administering it every day, while decreasing the adverse side effects associated with daily injections. JTX7078 at 4–5; JTX7089 at 4. At the time of the priority date, those having ordinary skill in the art, including Teva, would have known that researchers were pursuing even less frequent dosing. *See* DTX1154 at 1–2 (investigating bi-weekly injections). This really left Teva with only two options that were not already disclosed in the prior art and that allowed at least one day between injections: (1) once-weekly injections; or (2) thrice-weekly injections.

The studies already completed by those in the art provided more support for a thrice-weekly injection regimen. It is well known that the FDA considers the safety and efficacy of a proposed drug or clinical trial protocol before granting a pharmaceutical manufacturer the ability to run those trials on human subjects. 21 C.F.R. § 312.56 (2016). It is therefore not farfetched to assume a person of ordinary skill in the art would have been motivated to pursue a regimen close to the ones already known to be safe and effective. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) ("The potential for FDA approval also may properly be considered, as it was here, in determining whether one of ordinary skill would be motivated to develop a drug product and whether there was skepticism regarding the efficacy of such a product."). Further, the decision to use a 40mg GA dose with a thrice-weekly injection regimen was obvious to try because, again, it increased the chances of FDA approval. The total weekly dose the patients would receive under the new regimen was very close to the total weekly dose for the approved 20mg, everyday regimen—120mg/week versus 140mg/week. Trial Tr. 940:17–941:13. Such actions by Teva are actually supported by their disclosures to the FDA in the GALA protocol.

The court recognizes that the GALA protocol is not prior art. The court agreed with Defendants at trial, however, that the GALA protocol can properly be considered as an admission of a party opponent. *See* Fed. R. Evid. 801(d)(2). Similar to how the court treated the Khan 2009 reference, the court will use Teva's admissions in the GALA protocol to inform its analysis of the motivations of those having ordinary skill in the art at the time of the invention. The statements that Teva made to the FDA in the GALA protocol

confirm the court's analysis and the art's inherent motivations to pursue a 40mg three-times-a-week GA regimen.

Plaintiffs explained to the FDA that after the FORTE study demonstrated that a higher dose is just as effective as the 20mg dose, "the natural next step [was] to reduce the dosing regimen of GA and find the optimal regimen that [would] improve the convenience of treatment and reduce the burden and adverse events associated with daily subcutaneous injections." JTX7022 at 21. The use of the 40mg dose and the characterization of the FORTE study to the FDA as "show[ing] [a] similar quality, safety and efficacy profile compared to that of the GA 20mg dose" undermines Plaintiffs argument that the 40mg dose was "dead" after FORTE. *Id.*

Plaintiffs also cited to the Flechter and Khan 2008 studies to support their proposed regimen because patients that participated in those studies "found the reduced frequency regimens preferable and associated with a lower of [sic] injection related adverse events. *Id.* Plaintiffs state that because the prior art studies were not large or well controlled, they decided on a "conservative" regimen where the patients "[would] receive approximately the same weekly dose, given by 3 subcutaneous injections instead of with a daily injection frequency of 7 injections" and the "reduction in injection frequency would be offset by the use of a higher dose already shown to be effective and safe in daily use." *Id.* This comports with the court's finding that a skilled artisan would be motivated to try regimens close in total milligrams per week to the regimens already approved by the FDA and known to be effective.

As part of the rationale for the three-injections-per-week dose regimen, Plaintiffs explained to the FDA that such a schedule would be more convenient for patients,

enhancing long-term adherence. The court finds that Plaintiff's statement to the FDA accurately reflects the motivations of those in the art. Defendants' expert, Dr. Green, testified that those having ordinary skill in the art would have been motivated to pursue a set dosing regimen where patients inject GA on three pre-determined days each week. Trial Tr. 90017–901, 933:21–24, 972:9–13. Such a regimen would be more convenient for patients than every-other-day dosing where the number of times and the days on which you inject will differ depending on the week. This point is underscored by the fact that Rebif®, another injectable MS treatment, was dosed three times a week. *Id.* Plaintiffs claim that those in the art would not have been motivated to pursue three injections per week based on Rebif® because it was a completely different type of MS therapy. (D.I. 272 at 20). The court disagrees, however, considering a study showed that patient adherence to the Rebif® regimen was better than it was for the 20mg daily GA regimen. JTX7069 at 3 (Global Adherence Study). Even though Rebif® is a different MS drug with a different mechanism of action, the court finds that those in the art would still be motivated to try dosing GA three times a week based on the higher rates of patient adherence to the Rebif® therapy.

Plaintiffs argue that their admissions to the FDA could not provide support for the obviousness of the patents-in-suit because Defendants' admitted in emails and PowerPoint presentations that it was unlikely Plaintiffs' would secure FDA approval with such little evidence of efficacy. (D.I. 272 at 30). Defendants explain that their internal records only show that they were "uncertain the FDA would grant approval to run trials comparing TIW [three injections per week] to placebo (no treatment), instead of 20mg daily GA—not whether GA TIW would itself show efficacy." (D.I. 273 at 26). Because the GALA protocol proposed comparing 40mg, three-times-a-week to placebo and not 20mg GA

daily, it would not be possible to definitively show that the new regimen was worse, equivalent, or better than 20mg every day. *Id.* The court agrees with Defendants characterization of their statements in the PowerPoint presentation, and, accordingly, does not find Plaintiffs arguments persuasive on this point.

Plaintiffs offer Momenta's Senior Vice President of Development and Chief Medical Officer's deposition testimony as proof of nonobviousness. At his deposition, Dr. Roach testified that he was personally not convinced by "an every-other-day dosing schedule and wouldn't be surprised if other AEs show up with this higher dose." Trial Tr. 1506:2–6. The court, however, gives little weight to that statement. First, it appears that Dr. Roach was talking about the GALA protocol, but the GALA protocol did not even disclose an every-other-day dosing schedule. More important, Dr. Roach admitted that most of Momenta's work with GA had nothing to do with his group or his responsibilities. Trial Tr. 1493:14–18. Dr. Roach also stated in his deposition that he was not familiar with the pharmacokinectics of GA in any significant detail. *Id.* at 19–21. It therefore does not appear to the court that Dr. Roach could offer a credible opinion on the efficacy of every-other-day dosing or the adverse effects that may occur with a higher dose.

Plaintiffs maintain that a person having ordinary skill in the art would not have been motivated to try dosing GA three times a week because those in the art believed that daily injections of GA were necessary to maintain efficacy. (D.I. 272 at 22). Though the mechanism of action for GA remains unknown, one of the proposed theories necessitates constant activation of the GA T cells to enable them to cross the blood brain barrier and overcome the constant pro-inflammatory effects of MS. JTX7120 at 3–4. Plaintiff's expert argued that the only way to achieve that constant activation of the GA T cells was with

daily injections. Trial Tr. 1268:2–8. The court does not give much weight to this argument because the prior art clearly establishes that many researchers were experimenting with less frequent dosing of GA. *See* JTX7089 at 4; JTX7058; JTX7078; DTX1154. Flechter, Khan 2008, Khan 2009, and Plaintiffs' own patent application all disclosed less frequent dosing schedules. Flechter and Khan 2008 showed that administering GA every other day did not affect efficacy. JTX7089 at 4; JTX7078 at 4–5. Teva's expert, Dr. Ziemssen, also admitted that there is no paper suggesting that the activated GA T cells that cross the blood-brain barrier die within 24 hours of activation. Trial Tr. 1435:17–21. The court thus does not find that GA's mechanism of action teaches away from three-times-a-week dosing.

Plaintiffs insist that because "GA is not a typical small molecule drug and has no known [pharmacokinetic/pharmacodynamic] relationship . . . the effect of any changes to its regimen cannot be predicted." Therefore, even though the prior art discloses an every-other-day regimen with a 48-hour gap between doses, that would not have provided those in the art with a reasonable expectation that a thrice-weekly regimen with a 72-hour gap would be effective. Plaintiffs cite *In re Cyclobenzaprine*, 676 F.3d 1063 (Fed. Cir. 2012), for the general proposition that when the pharmacokinetic/pharmacodynamic ("PK/PD") profile of a drug is unknown, it is hard for skilled artisans to predict how changes to the drug dosage form will change the effect that the drug renders on the body. *See* 676 F.3d at 1070.

The PK/PD profile represents the relationship between how a person's body metabolizes a drug (PK) and how the drug effects the patient's body (PD). *Id.* at 1067. In *Cyclobenzaprine*, the Federal Circuit overturned the district court's obviousness

conclusion. *Id.* at 1070. The district court concluded that the PK/PD relationship was irrelevant to the obviousness inquiry because a skilled artisan would expect the extended release formulation to have the same PD effect on the body if it mirrors the immediate release formulation's PK profile. *See id.* The Federal Circuit found, to the contrary, that though "it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Id.* *Cyclobenzaprine* is inapposite to the issues currently before the court.

In *Cyclobenzaprine*, the Federal Circuit explained that the district court "could not find obviousness without finding that the prior art would have taught or suggested a therapeutically effective formulation to one of ordinary skill in the art." *Id.* The record was devoid of such evidence. *Id.* Here, the prior art suggests a number of therapeutically effective dosing regimens for GA. *See* JTX7063 at 1 (demonstrating that a 40mg daily formulation was safe and effective); JTX7078 at 4–5 (demonstrating that a 20mg every-other-day formulation was safe and effective).

Additionally, the fact that the PK/PD profile was unknown is irrelevant here. GA is an immunomodulating drug that is not necessarily measurable in the bloodstream, and, even if it is, measuring the levels in the blood does not indicate anything about the effect of the drug on the patient. Trial Tr. 86:20–87:16. In fact, because the mechanism of action for GA was unknown, there was absolutely no reason to believe that a gap of 72 hours between injections would be detrimental, whereas a gap of 48 hours between injections would be tolerable and effective. The contention that those in the art would have been

dissuaded from pursuing any gaps between dosing over 48 hours is further undermined by the Khan 2009 study started two years before the priority date, studying a twice-weekly GA dosing schedule. As a result, the court does not find *Cyclobenzaprine* instructive.

iv. Obviousness of the '776 Patent

Teva asserts claims 1, 2, 5, 6, 9, 12, 16 and 17 of the '776 patent. The '776 patent claims a 40 mg, thrice-weekly GA dosing regimen that reduces severity, not just frequency, of injection site reactions and/or immediate post-injection reactions relative to the 20mg GA daily regimen. The specification of the '776 patent defines tolerability as "associated with the frequency and severity of post injection reactions and injection site reactions." JTX7003 at col.7, ll.38–42. The court has already addressed why the claims directed to reducing the frequency of injection site reactions are obvious. *See supra* § III(A)(3)(iv). The court finds that the claims directed to reducing the severity of injection site reactions are also obvious.

Defendants' expert, Dr. Fox, testified at trial that those in the art consider lipoatrophy—"the destruction of subcutaneous fat at the injection site," Trial Tr. 681 at 16–17—to be an inherently severe injection site reaction. Trial Tr. 1580:12–19. Dr. Fox stated that "if there is a decrease in the frequency of lipoatrophy, there would, by definition, then also be a decrease in the severity of the adverse events." *Id.* As previously stated, the Caon prior art reference disclosed that "[i]njection related lipoatrophy was significantly less" on the 20mg every-other-day regimen than it was on the 20mg daily regimen. JTX7058 at 1. Though the court recognizes the shortcomings of this testimony and the fact that it conflates frequency and severity, it nonetheless provides a reasonable expectation to those skilled in the art that reducing the number of injections per week may also reduce the severity of injection site reactions. *See Hoffman-La Roche*, 748

F.3d at 1331 (holding that prior art references need only demonstrate "a reasonable expectation of success," not "conclusive proof of efficacy").

Teva stated in its press release summarizing the FORTE trial that the 40mg dose "maintained the favorable safety and tolerability profile of COPAXONE® 20mg." JTX7035 at 1. Dr. Klinger testified that if a 40 mg three-times-a-week regimen improves patient tolerability, then it inherently has to reduce the frequency and severity of injection site reactions. Trial Tr. 230:3–6. Applying Dr. Klinger's testimony to Teva's statement in the press release, it follows that the FORTE study showed that administering 40mg of GA daily to patients did not increase the frequency or severity of injection site reactions. That understanding, combined with previously mentioned prior art regarding the effects of less frequent injections, would lead a skilled artisan to expect a reduction in the frequency of injections to lead to a reduction in the severity of injection site reactions.

v. Secondary Considerations of Nonobviousness

1. Long-felt Need and the Failure of Others

There existed a long-felt need in the art for a GA regimen not requiring everyday injections. Evidence of a long-felt need is only probative of nonobviousness, however, when both "a demand existed for the patented invention, and others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1083 (Fed. Cir. 2012). Here, those having ordinary skill in the art did not try, but fail to find a solution to the known issues with daily injections.

It is true that the court heard testimony on Teva's failed endeavors to find an alternate dosage form. Trial Tr. 100:25–110:25. Among those failures were a higher molecular weight version of COPAXONE® and an oral formulation that would eliminate the need for injections all

together. Trial Tr. 109:11–25. By the priority date, however, there were solutions in the prior art. The Flechter and Khan 2008 studies demonstrated that less frequent injections could possibly lead to increased tolerability. JTX7089 at 4; JTX7078 at 4–5. Teva even filed the Pinchasi application, directed at solving the very problem they claim to solve with the patents-in-suit. JTX7107 at 20, 22. It is not clear to the court why solutions to the known problem of patient tolerability were not commercialized sooner, but the court does not think that this fact weighs in Plaintiff's favor.

Defendants' expert, Dr. Hay, testified that Teva had several molecule patents that would prevent another entity from commercializing a less frequently dosed GA product. Trial Tr. 1696 at 9–11. Plaintiffs tried to undermine Dr. Hay's testimony on blocking patents by noting that Sandoz had filed an ANDA for GA in 2008 and Momenta had filed a patent application for GA at that time as well. Trial Tr. 1724:17–21. It is not clear to the court exactly how those facts undermine Dr. Hay's testimony. The court thus finds it plausible that the existence of Teva's GA patents could have deterred other large pharmaceutical companies from investing in research for a less frequently dosed form of GA. *See Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d at 740 (holding that any inference of non-obviousness gleaned from evidence of commercial success is undermined when blocking patent preclude others from entering the market). The court does not find that there was a long-felt, but unresolved need, probative of nonobviousness. Instead, the court finds that the prior art disclosed solutions to the long-felt need, and Teva simply won the race to the patent office.

2. Unexpected Results

A prima facie showing of obviousness can be rebutted by a demonstration of "unexpected results"—"the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). The court finds that the though the claimed invention exhibits an advantage over the 20mg daily form of COPAXONE, that advantage was not surprising or unexpected given the prior art studies.

The FORTE study showed that a 40mg dose of GA, administered daily, was as safe and effective as a 20mg dose, and was not associated with more injection site reactions. JTX7063 at 1. Flechter and Khan 2008 showed that less frequent dosing was as effective as every day injections, and less frequent dosing could reduce the number of injection site reactions patients experienced as a result of the injections. JTX7089 at 4; JTX7078 at 4–5. Accordingly, the fact that the 40mg dose, administered three times a week, was effective in reducing the number of relapses, lesions, and injection site reactions was expected.

According to the Plaintiffs, a person of skill in the art would not have expected the 40mg, three-times-a-week regimen to be as effective as 20mg daily, while also improving tolerability. (D.I. 272 at 33). Plaintiffs maintain that an improvement in tolerability associated with a 40mg, thrice-weekly dosing regimen for GA was not confirmed until the results of the GLACIER study were published in 2015. *Id.* The court previously articulated why it was expected that a 40mg, three-times-a-week dose would improve tolerability. *See supra* § III(A)(3)(iv), (A)(4). The court therefore finds that there were no unexpected results to support a finding of nonobviousness.

At trial, Dr. Klinger testified that Teva's admissions to the FDA in the GALA protocol were incorrect. To support a 40mg, three-times-a-week regimen, Teva cited to the FORTE,

Flechter, and Khan 2008 studies. JTX7022. Dr. Klinger agreed that the FORTE study provided motivation to investigate the safety and efficacy of a reduced frequency injection. Trial Tr. 193:25–194:8. She disagreed, however, with the GALA protocol's use of Flechter and Khan 2008 to support the three-times-a-week injection regimen. Trial Tr. 195:7–15; 198:6–13. The court does not give much weight to Dr. Klinger's testimony. It appears to the court that Dr. Klinger's testimony was offered as convenient support for a finding of unexpected results. Dr. Klinger claims there was no preclinical or clinical data by the priority date to support the efficacy and tolerability of the 40mg, three-times-a-week regimen. Trial Tr. 199:15–19. If the court were to find Dr. Klinger's testimony credible, Teva would have administered a drug to hundreds of chronically ill patients with no reasonable expectation that the drug would be effective, safe or tolerable.

Dr. Klinger states that it was actually the TV-5010 clinical trial conducted by Teva that convinced her that a 40mg, three-times-a-week dosage regimen could be effective and more tolerable. Trial Tr. 226:24–227:7. TV-5010 was a mixture of peptides, very similar to COPAXONE®, except, on average, it contained peptides with higher molecular weights. Trial Tr. 106:10–18. Teva's admissions in the GALA protocol undermine the veracity of Dr. Klinger's testimony because the protocol completely fails to mention the TV-5010 studies as a rationale for the proposed dosage regimen. JTX7022 at 21. The inconsistencies between Dr. Klinger's testimony and Teva's Gala protocol admissions serve to only further support the court's belief that both Teva and Dr. Klinger were well aware of the race to patent a more tolerable form of COPAXONE® 20mg daily. The court sees the '250, '413, '302, and '776 patents as nothing more than "life-cycle management"—an attempt to continue to monopolize a multi-billion dollar market for a blockbuster drug. *See* DTX1339 at 3 (recognizing that Teva was "playing against

the clock," so the short term objective for GA life-cycle management was to use current GA in a "high dose (>20 mg) 2-3 times a week," which wouldn't require preclinical studies, to "fight generics").

3. Commercial Success

The court gives little probative weight to the fact that COPAXONE® 40mg was commercially successful. The commercial success of an invention may be relevant to nonobviousness if a nexus exists between the commercial success and the claimed invention. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011). If, however, "commercial success is due to an element in the prior art, no nexus exists." *Id.*

No evidence was adduced at trial supporting a nexus between COPAXONE® 40mg, three-times-a-week's success and features not already found in the prior art. No one disputes that COPAXONE® 40 is a successful drug. The court, however, finds Defendants' arguments persuasive that COPAXONE® 40's success was due to "aggressive pricing, promotion, and COPAXONE® brand loyalty." *See* Trial Tr. 1456:9–16; 1677:17–19 ("COPAXONE® 40 has,. since the first month of launch, also been priced substantially lower than COPAXONE® 20, roughly four to five hundred dollars lower on average."); DTX1491 at 1 ("Slide 10 in the pricing assumptions you can see that we are planning a 10% increase on the 20mg in July of 2015 to increase the spread between 20mg and 40mg to help drive 40mg conversions."). The commercial success of COPAXONE® 40mg, three-times-a-week thus does not undermine the court's obviousness finding.

None of the secondary considerations warrant a finding of nonobviousness of the patents-in-suit.

III. CONCLUSION

In sum, the court finds that all asserted claims of the patents-in-suit are invalid as obvious.[4]

Dated: January 30, 2017

UNITED STATES DISTRICT JUDGE

[4] The court wishes to note that in IPR proceedings, the PTAB also found all claims of the '250, '413, and '302 patents unpatentable. *See Mylan Pharms. Inc. v. Yeda Research and Dev. Co.*, No. IPR2015–00643 (PTAB Aug. 24, 2016); *Mylan Pharms. Inc. v. Yeda Research and Dev. Co.*, No. IPR2015–00644 (PTAB Aug. 24, 2016); *Mylan Pharms. Inc. v. Yeda Research and Dev. Co.*, No. IPR2015–00830 (PTAB Sept. 1, 2016). The patentees may appeal the PTAB decisions to the Federal Circuit, potentially presenting an interesting procedural issue. If the Federal Circuit chooses to hear the appeal from the PTAB and the Plaintiffs in this case decide to appeal to the Federal Circuit, two essentially identical cases, albeit with different standards of proof, will be before the Federal Circuit.