United States Court of Appeals for the Federal Circuit

IN RE: COPAXONE CONSOLIDATED CASES

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Plaintiffs-Appellants

v.

SANDOZ INC., MOMENTA PHARMACEUTICALS INC., DR REDDY'S LABORATORIES LTD, DR REDDY'S LABORATORIES INC., MYLAN PHARMACEUTICALS INC., MYLAN INC., SYNTHON PHARMACEUTICALS, INC., SYNTHON B.V., SYNTHON S.R.O. BLANSKO, AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS COMPANY GMBH, PFIZER INC.,
Defendants-Appellees

2017-1575

Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-01171-GMS, 1:14-cv-01172-GMS, 1:14-cv-01278-GMS, 1:14-cv-01419-GMS, 1:15-cv-00124-GMS, 1:15-cv-00306-GMS, Judge Gregory M. Sleet.

Decided: October 12, 2018

JOHN C. O'QUINN, Kirkland & Ellis LLP, Washington, DC, argued for plaintiffs-appellants. Also represented by LESLIE M. SCHMIDT, New York, NY; ELIZABETH HOLLAND, Goodwin Procter LLP, New York, NY; WILLIAM G. JAMES, II, WILLIAM M. JAY, Washington, DC; DARYL L. WIESEN, Boston, MA.

DEANNE MAYNARD, Morrison & Foerster LLP, Washington, DC, argued for defendants-appellees. Defendants-appellees Sandoz Inc., Momenta Pharmaceuticals Inc. also represented by SETH W. LLOYD; WILLIAM A. RAKOCZY, MATTHEW V. ANDERSON, THOMAS EHRICH, ERIN FORBES, CHRISTOPHER PATRICK GALLIGAN, DEANNE M. MAZZOCHI, RACHEL WALDRON, Rakoczy Molino Mazzochi Siwik LLP, Chicago, IL.

SHANNON BLOODWORTH, Perkins Coie, LLP, Washington, DC, argued for defendants-appellees. Defendants-appellees Mylan Pharmaceuticals Inc., Mylan Inc. also represented by ROBERT SWANSON, BRANDON MICHAEL WHITE; DAVID LEE ANSTAETT, Madison, WI; DAN L. BAGATELL, Hanover, NH; CHRISTINA JORDAN MCCULLOUGH, Seattle, WA.

FRANK D. RODRIGUEZ, Budd Larner, P.C., Short Hills, NJ, for defendants-appellees Dr. Reddy's Laboratories Ltd, Dr. Reddy's Laboratories Inc. Also represented by ELLEN TCHORNI LOWENTHAL, LOUIS HARRY WEINSTEIN.

EDWARD ANTHONY FIGG, Rothwell, Figg, Ernst & Manbeck, PC, Washington, DC, for defendants-appellees Synthon Pharmaceuticals, Inc., Synthon B.V., Synthon S.r.o. Blansko. Also represented by SETH EDWARD

COCKRUM, SHARON DAVIS, JENNIFER NOCK, BRETT ALAN POSTAL.

ANTHONY JAMES FITZPATRICK, Duane Morris LLP, Boston, MA, for defendants-appellees Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals Company GmbH, Pfizer Inc. Also represented by VINCENT CAPUANO, CHRISTOPHER S. KROON; PATRICK GALLAGHER, Boca Raton, FL.

Before REYNA, BRYSON, and STOLL, *Circuit Judges*.

REYNA, *Circuit Judge*.

Plaintiffs-Appellants Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co., Ltd., appeal the decision of the United States District Court for the District of Delaware invalidating all asserted claims of patents directed to COPAXONE® 40mg/mL, a product marketed for treatment of patients with relapsing forms of multiple sclerosis. Because the district court correctly held the asserted claims invalid as obvious under 35 U.S.C. § 103, we affirm.[1]

---

[1] In a companion case decided today, *Yeda Research & Development Co., v. Mylan Pharmaceuticals Inc.*, Nos. 17-1594, 17-1595, 17-1596 (Fed. Cir. Oct. 12, 2018), Yeda Research and Development Co. appealed from the Patent Trial and Appeal Board's final written decisions finding all claims of U.S. Patent Nos. 8,232,250, 8,399,413, and 8,969,302 unpatentable as obvious in three related *inter partes* review proceedings.

BACKGROUND

I. Patents at Issue

Yeda Research & Development Co., Ltd. is the assignee of U.S. Patent Nos. 8,232,250, 8,399,413, 8,969,302, and 9,155,776 (the '250, '413, '302, and '776 patent, respectively), all entitled "Low Frequency Glatiramer Acetate Therapy." The patents, collectively referred to as the "Copaxone patents," share a common specification and claim priority to the same two provisional applications. J.A. 57–69. The earliest priority date of the Copaxone patents is August 20, 2009. J.A. 23.

The Copaxone patents describe and claim COPAXONE® 40mg/mL, a treatment for relapsing-remitting multiple sclerosis ("RRMS"). RRMS is a form of multiple sclerosis, an autoimmune disorder that causes the body's immune system to attack the central nervous system. RRMS is characterized by unpredictable relapses followed by periods of remission with no new signs of disease activity.

The active ingredient in COPAXONE® 40mg/mL is glatiramer acetate ("GA"), a synthetic mixture of polypeptides. GA is also known as "copolymer 1" or "Cop. 1." COPAXONE® 40mg/mL is supplied as a single-dose prefilled syringe. Broadly, the treatment consists of the injection of 40mg of GA three times a week, abbreviated "40mg GA 3x/week." Relevant to this appeal, side effects of GA injections include injection-site reactions ("ISRs") and immediate post-injection reactions ("IPIRs"). ISRs are physical symptoms at the injection site, such as swelling or itchiness. IPIRs are reactions immediately following an injection, such as flushes, sweating, or palpitations.

Prior to COPAXONE® 40mg/mL, in 1996 the Food and Drug Administration ("FDA") approved COPAXONE® 20mg/mL, a regimen consisting of the daily injection of

20mg GA. Daily GA injections were known to subject patients to discomfort, including side effects in the form of ISRs and IPIRs. J.A. 20692.

For analyzing the obviousness of the Copaxone patents in this case, a key limitation of the asserted claims is the administration of a 40mg GA dose in three subcutaneous injections over seven days. Claim 1 of the '250 patent is representative:

> 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.

'250 patent col. 16 ll. 35–45.

Apart from claim 1 of the '302 patent,[2] all asserted independent claims require at least one day between doses. '250 patent col. 16 ll. 35–45, col. 17 l. 25–col. 18 l. 6; '413 patent col. 16 ll. 26–36, col. 18 ll. 14–28; '302 patent col. 17 ll. 4–12; '776 patent col. 16 ll. 35–50, col. 16 l. 61–col. 17 l. 19, col. 17 ll. 37–54, col. 17 l. 65–col. 18 l. 22.

---

[2] Claim 1 of the '302 patent does not specify any particular interval between doses. '302 patent col. 16 ll. 37–41. Independent claim 10 of the '302 patent requires that the injection be administered "three times per week with at least one day between every subcutaneous injection." *Id.* col. 17 ll. 4–12.

Certain dependent claims of the '250, '413, and '776 patents further require improved tolerability and/or reduced frequency of injection reactions in the claimed regimen as compared to a 20mg GA daily regimen. *See, e.g.*, '250 patent col. 17 ll. 21–24, col. 18 ll. 7–15; '413 patent col. 16 ll. 51–54; '776 patent col. 16 ll. 51–54, col 17 l. 65–col. 18 l. 25..

The '776 patent contains additional limitations, namely, the requirement that the 40mg GA 3x/week regimen "reduce[] severity of injection site reactions" compared to a 20mg daily regimen, as seen in claim 1:

> 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*.

'776 patent col. 16 ll. 35–50 (emphasis added).

II. Prior Art References

The first clinical trial for using GA to treat multiple sclerosis took place in 1987 by Dr. Bornstein et al. ("Bornstein"),[3] which was followed by a Teva Phase III clinical trial in 1995. Both Bornstein and the Phase III trial tested 20mg GA daily. J.A. 20378–84, 20464–20782. Since GA was developed in an expedited manner under orphan drug status in the United States at a time when no other disease modifying multiple sclerosis treatments were available, the 20mg/day dose was selected without performing conventional optimal-dose-finding studies. J.A. 24967.

The Bornstein study showed that GA administered subcutaneously for two years at a daily dose of 20mg "produced clinically important and statistically significant beneficial effects." J.A. 20383. Participants in both Bornstein and the Phase III trial reported ISRs and IPIRs as side effects. J.A. 20383, 20480. The Phase III trial noted "adverse experience" as the main reason contributing to patient dropout, and "[t]he most common adverse event associated with dropout was injection site reaction." J.A. 20480. A Phase III trial reviewer made recommendations for future researchers to explore dose-response and dose-ranging studies, asking "Is 20 mg the optimum dose? Are daily injections necessary?" J.A. 20502.

In 1996, following both Bornstein and the Phase III clinical trial, FDA approved Teva's New Drug Application ("NDA") for COPAXONE® 20mg, 20mg GA injected daily. In its 1996 Summary Basis of Approval ("SBOA"), FDA recommended that Teva "evaluate the necessity of daily [GA] injections as opposed to more infrequent intermit-

---

[3] Murray B. Bornstein et al., *A Pilot Trial of COP 1 in Exacerbating-Remitting Multiple Sclerosis*, 317 New Eng. J. Med. 408, 408–14 (1987).

tent administration of the drug" because the daily dosing regimen "seems like it would subject the patient to an excessive amount of discomfort if it is not necessary to maintain efficacy." J.A. 20692.

A 2002 study by Flechter et al.[4] ("Flechter") evaluated the treatment of RRMS with 20mg of GA administered every other day. J.A. 20436–40. Flechter concluded that "alternate-day treatment with Copolymer 1 is safe, well tolerated, and probably as effective as daily Copolymer 1 in reducing relapse rate and slowing neurologic deterioration." J.A. 20440. Flechter also noted that patient dropout rates decreased when GA was administered every other day as opposed to daily. J.A. 20440 ("It should be stressed that the dropout rate was lower in the alternate-day group than in the daily-injection regime (39.7% versus 60.3%, $p < 0.01$).").

Cohen,[5] published in 2007, was a "double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS." J.A. 20388–95. Cohen compared daily subcutaneous injections of 20mg and 40mg GA dosages, and concluded that the 40mg dose may be "more effective" than the 20mg dose "in reducing MRI activity and clinical relapses." J.A. 20389. Cohen also noted that the onset of action of the 40mg dose is more rapid compared to 20mg. J.A. 20394. ISRs were the most frequent adverse event for both doses, occurring at roughly equal rates. J.A. 20392–93. IPIRs occurred more frequently in the 40mg group than the 20mg group. *Id.* Cohen thus concluded

---

[4] Shlomo Flechter et al., *Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*, 25 Clinical Neuropharmacology 11, 11–15 (2002).

[5] J.A. Cohen et al., *Randomized, Double-Blind, Dose-Comparison Study of Glatiramer Acetate in Relapsing-Remitting MS*, 68 Neurology 939, 939–44 (2007).

that the overall safety and side effect profile of the 40mg dose was "similar" to the 20mg dose, but "was associated with a greater incidence of certain adverse effects." J.A. 20394.

Teva's own prior art patent application, International Patent Application No. WO 2007/081975, *Method of Treating Multiple Sclerosis* ("Pinchasi"), was published shortly after the Cohen study. J.A. 20925–56. Pinchasi discloses a 40mg GA, every other day dosing regimen for the treatment of RRMS. Pinchasi cites to the data from Cohen 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 RRMS patients. The improvement in efficacy, however, is not accompanied by a corresponding increase of adverse reactions which would be expected upon a doubling of the administered dose." J.A. 20944.

The FORTE study,[6] published in 2008, evaluated the safety, tolerability, and efficacy of 40mg GA compared to 20mg GA. J.A. 20411, 20414–22. FORTE concluded that both the 40mg and 20mg doses "were equally effective in reducing clinical relapses and MRI activity," and that the 40mg dose has a "safety profile similar to that observed in previous studies of 20mg GA." J.A. 20411. FORTE also confirmed Cohen's finding that the 40mg dose provided an earlier onset of action. J.A. 20422 (noting a "[t]rend for an earlier effect of high [40mg] dose on MRI activity").

---

[6] Giancarlo Comi, Jeffrey A. Cohen, Massimo Filippi for the FORTE Study Group, *Results from a Phase III, One-Year, Randomized, Double-Blind, Parallel-Group, Dose-Comparison Study with Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis*, 14 Multiple Sclerosis S299, S299–S301 (2008).

A 2008 study by Omar Khan and others[7] ("Khan 2008") compared the effect of daily versus every other day administration of 20mg GA subcutaneous injections for the treatment of RRMS. J.A. 20883. The study abstract noted that although the recommended dose for treating RRMS is daily 20mg GA injections, "the optimal dose remains unknown" and that there is "considerable interest in alternate dosing regimens of GA" because daily injections "can be challenging for long-term patient compliance." J.A. 20883. Thirty patients were randomly assigned to receive 20mg GA dosed daily or every other day. After two years, there were "no differences" between the two groups in relapse rate or disease progression. J.A. 20883. Additionally, after the first two years elapsed, patients in each group were given the option to continue or switch groups, and were monitored for an additional two years. Every patient in the daily group opted to switch to every other day administration. After four years, there was no difference between the crossover group and the group that was always dosed every other day. The Caon reference,[8] published in 2009, reports the same data from the Khan 2008 study, but further noted that "[i]njection related lipoatrophy was significantly less" in the every other day group. J.A. 20386.

---

[7] Omar Khan et al., *Randomized, Prospective, Rater-Blinded, Four-Year, Pilot Study to Compare the Effect of Daily Versus Every-Other-Day Glatiramer Acetate 20 Mg Subcutaneous Injections in Relapsing-Remitting Multiple Sclerosis*, 14 Multiple Sclerosis S296, S296 (2008).

[8] Christina Caon et al., *Randomized, Prospective, Rater-Blinded, Four Year Pilot Study to Compare the Effect of Daily Versus Every Other Day Glatiramer Acetate 20 mg Subcutaneous Injections in RRMS*, 72 Neurology (Suppl. 3) A317 (2009).

III. State of the Art References

There are two additional references relevant to this appeal, a 2009 study by Omar Khan[9] ("Khan 2009") and Teva's own Glatiramer Acetate Low-frequency Administration ("GALA") Phase III trial of 40mg GA administered three times per week. J.A. 23904–05, J.A. 8246–8417. Khan 2009 and GALA were both published after August 20, 2009, the priority date of the asserted patents, and thus do not qualify as statutory prior art.

The district court admitted the Khan 2009 reference for the limited purpose of showing the state of the art at the time of the invention. *In re Copaxone Consolidated Cases*, No. 14-1171-GMS, 2017 WL 401943, at *14 (D. Del. Jan. 30, 2017). Khan 2009 was published three weeks after August 20, 2009, the priority date of the Copaxone patents, but the study began two years earlier. J.A. 23904–05. The study abstract noted that "[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." J.A. 23904. Following the results of Khan 2008, which showed that alternate day administration of GA appears to be as effective as daily administration, Khan 2009 compared 20mg GA administered twice a week to 20mg GA administered daily in a pilot, prospective, randomized, and rater-blinded two-year study. J.A. 23904.

Concerning GALA, the district court recognized that the GALA trial protocol does not qualify as prior art. *In re Copaxone*, 2017 WL 401943, at *20. Instead, the dis-

---

[9] O. Khan et al., *Glatiramer Acetate 20mg Subcutaneous Twice-Weekly Versus Daily Injections: Results of a Pilot, Prospective, Randomised, and Rater-Blinded Clinical and MRI 2-Year Study in Relapsing-Remitting Multiple Sclerosis*, 15 Multiple Sclerosis S249, S249–50 (2009).

trict court admitted GALA as an admission by Teva to inform on the motivations of those having ordinary skill in the art at the time of the invention. In its submission to FDA, Teva explained that, after the FORTE study demonstrated that the 40mg dose was equally 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." J.A. 8266. Citing the small-scale studies with 20mg GA in the prior art, such as Khan 2008, GALA noted that results "demonstrated effects in relapse rate reduction which were comparable to daily injections of GA 20mg, suggesting a lower injection frequency can be considered." J.A. 8266, 8352. The GALA protocol selected a dosing regimen of 40mg GA 3x/week, in part because "the subjects will receive approximately the same weekly dose, given by 3 subcutaneous injections instead of with a daily injection frequency of 7 injections." J.A. 8266.

IV. Proceeding Below

This appeal arises out of five consolidated district court cases. The Defendants-Appellees in this case are generic drug manufacturers who (prior to the expiration of the Copaxone patents) submitted Abbreviated New Drug Applications ("ANDAs") to FDA for approval to engage in the manufacture and sale of generic versions of COPAXONE® 40mg administered 3 times per week. *In re Copaxone*, 2017 WL 401943, at *1–10. Appellants Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co., Ltd. (collectively, "Teva") sued Appellees in the United States District Court for the District of Delaware, alleging that their respective ANDA filings infringed claims 1, 5, 13–17 of the '250 patent, claims 1, 7, 15, and 20 of the '413 patent, claims 1, 10, and

11 of the '302 patent, and claims 1, 2, 5, 6, 9, 12, 16, and 17 of the '776 patent. *Id.*

Following a *Markman* hearing, the district court entered a claim construction order. *In re Copaxone 40 Mg*, No. 14-1171-GMS, 2016 WL 873062, at *1–2 (Mar. 7, 2016) ("*Claim Construction Order*"). Relevant to this appeal, the district court construed the '250 and '413 patents' "sufficiency"[10] terms and the '776 patent's "reduced frequency of relapses"[11] and "effectiveness"[12] terms as non-limiting statements of intended effect. *Id.* at *1 & nn.1–2.

The district court held a seven-day bench trial during which it considered the invalidity of the asserted claims of the Copaxone patents. The district court found that a 40mg GA dose was explicitly disclosed in references that predate the Copaxone patents, specifically Cohen, Pinchasi, and FORTE. *In re Copaxone*, 2017 WL 401943, at *14. The court rejected Teva's arguments that Cohen and FORTE taught away from a 40mg dose, and that a person of ordinary skill in the art ("POSITA") would have thought that 20mg was the optimal dose. *Id.* at *14–15. The district court also found that, as of the priority date, POSITAs knew that daily injections were difficult to tolerate based on the 1996 FDA SBOA, Flechter, and

---

[10] *E.g.*, '250 patent col. 16 ll. 44–45 ("the regimen being sufficient to alleviate the symptom of the patient"); '413 patent col. 16 ll. 35–36 ("the regimen being sufficient to reduce the frequency of relapses in the patient").

[11] *E.g.*, '776 patent col. 17 ll. 20–22 ("which reduces brain atrophy and for reducing the frequency of relapses by 30% or more as compared to placebo in a human population").

[12] *E.g.*, '776 patent col. 17 ll. 39–40 ("which is as effective as administration of 20 mg of glatiramer acetate s.c. daily").

Khan 2008. *Id.* at *15–16. Relying in part on trial testimony, the district court found that POSITAs were familiar with the adverse reactions, pain, and treatment adherence problems associated with daily injections, and would have been motivated to pursue less frequent dosing with a reasonable probability of success. *Id.* at *16. The district court found that Pinchasi is the closest prior art because it discloses a dosing regimen that differs from the claimed regimen by only one dose every two weeks. *Id.* at *17.

In light of these factual findings, the district court concluded that a 40mg GA 3x/week dosage would be obvious to try, noting that there were only two tested dosage amounts in the prior art—20mg and 40mg—and that researchers were pursuing less frequent dosing regimens while recognizing there are a limited number of days in a week on which to test frequency. *See id.* at *19. The court recognized that obvious-to-try logic is not always appropriate, but found that "[h]ere, 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." *Id.* The district court cited to Khan 2009, Teva's GALA study, and trial testimony as evidence of the motivations of POSITAs at the time of the invention, and noted evidence and testimony supporting the proposition that a dosing schedule based on three predetermined days each week is preferable for patients over an every other day schedule. *Id.* at *20. The district court highlighted testimony from Dr. Green that a regimen of injections on three pre-determined days of each week is more convenient for patients and has better patient adherence than an every other day regimen, in which the days on which patients inject differ depending on the week. *Id.* The district court also noted a study showing that Rebif®, an injectable MS treatment dosed three times a week, has

increased patient adherence compared to the daily 20mg GA regimen. *Id.*

In light of additional testimony that a POSITA would expect the number of ISRs to decrease as the number of injections per week decreased, as well as disclosures in Flechter, Khan 2008, and Caon, the district court held obvious the dependent claims of the '250 and '413 patents requiring that the 40mg GA 3x/week regimen reduce the frequency of ISRs and IPIRs as compared to a 20mg/day regimen. *Id.* at *17–18. The district court also found obvious claim 15 of the '250 patent, which requires the claimed method improve tolerability as compared to a 20mg/day regimen. *Id.* at *17. The court further determined the claims of the '776 patent to be obvious in light of Caon and expert evidence presented at trial. *Id.* at *22–23. Finally, the court considered objective indicia of nonobviousness, and concluded that none of them warranted a finding of nonobviousness of the Copaxone patents. *Id.* at *25.

Following its analysis, the district court held all asserted claims of the Copaxone patents invalid as obvious under § 103. Teva appeals the district court's claim construction and obviousness decisions. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Claim Construction

Claim construction seeks to ascribe the "ordinary and customary meaning" to claim terms as a person of ordinary skill in the art would have understood them at the time of invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–14 (Fed. Cir. 2005) (en banc) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Where the district court's claim construction relies only on intrinsic evidence, as is the case here, the construction is a legal determination reviewed de novo. *Poly-Am., L.P. v.*

API Indus., Inc., 839 F.3d 1131, 1135–36 (Fed. Cir. 2016) (citing *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015)).

Teva contends that the district court erroneously construed certain claim terms as non-limiting and disregarded them for nonobviousness purposes. Teva points to the "sufficiency" terms of the '250 and '413 patents as being limiting. Claim 1 of the '250 patent recites "A method of alleviating a symptom of relapsing-remitting multiple sclerosis . . . comprising administering to the human patient a therapeutically effective regimen . . . , *the regimen being sufficient to alleviate the symptom of the patient*." '250 patent col. 16 ll. 35–45 (emphasis added). Similarly, claims 1 and 20 of the '413 patent both recite "[a] method . . . comprising administering to the human patient a therapeutically effective dosage regimen . . . , *the regimen being sufficient to reduce the frequency of relapses in the patient*." '413 patent col. 16 ll. 26–36, col. 18 ll. 14–27 (emphasis added). Teva also contests the district court's construction of the "reduced frequency of relapse" terms and "effectiveness" terms in the '776 patent as non-limiting. For example, claim 5 of the '776 patent describes "a method for reducing the frequency of relapses"; claims 6, 16, and 17 contain similar limitations. '776 patent col. 16 ll. 61–65, col. 17 ll. 20–22, 65–66, col. 18 ll. 23–25. Claim 12 describes "[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," and claims 16 and 17 contain similar limitations. *Id.* col. 17 ll. 36–40 (emphasis added), col. 17 l. 65–col. 18 l. 5, col. 18 ll. 23–25.

The district court construed these terms to be non-limiting statements of intended effect, holding that those terms are "strikingly similar to those in the patents in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*,

246 F.3d 1368 (Fed. Cir. 2001)." *Claim Construction Order*, 2016 WL 873062, at *2 n.2. In *Bristol-Myers*, the court held that certain terms were non-limiting because they "merely express[ed] a purpose" and "only state[d] an intended result of the claimed method." 246 F.3d at 1374–75. The court stated that express dosage amounts are material claim limitations, but statements of intended results from their administration, such as "an antineoplastically effective amount," "does not change those amounts or otherwise limit the claim." *Id.* at 1375. Claim language without any bearing on the claimed methods should be deemed non-limiting when it does not result in "a manipulative difference in the steps of the claim." *Id.* at 1376.

We see no meaningful difference between the claims in *Bristol-Myers* and those at issue here. The phrase "the regimen being sufficient to reduce the frequency of relapses in the patient" does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims. The claims are clear that the dosing has to be "therapeutically effective regimen"; the addition of "the regimen being sufficient to" be therapeutically effective is superfluous, does not change the claimed method or require any additional required structure or condition for the claims, and is therefore non-limiting.

Teva argues that the "'sufficiency' terms were added during prosecution to overcome rejections." Appellants' Opening Br. 74. Teva overstates the intrinsic record. Claim 1 of the '250 patent was amended to overcome a § 112 rejection based on the examiner's read of the claims prior to amendment as permitting only a single seven-day period of administration, rather than an ongoing treatment regimen. *See* J.A. 26417–18, 26464–65 (same, for the '413 patent). The claim was amended to replace the ambiguous "therapeutically effective dose" with "therapeutically effective regimen of," as follows:

> 1. (Currently Amended) 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 ~~therapeutically effective~~ 40mg dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient ~~so as~~ to ~~thereby~~ alleviate the symptom of the patient.

J.A. 26430.

"As amended the claims cannot be reasonably construed to read on only a single seven day period of administration, at least because the claims as amended require a 'regimen.'" J.A. 26436; *see also* J.A. 26483 (same, for the '413 patent). Given this evidence, the addition of "a therapeutically effective regimen" would have alone been sufficient to overcome the rejection, and thus we are unpersuaded by Teva's contention that addition of the "regimen being sufficient . . ." term was necessary or relevant to the examiner's approval. Accordingly, we find no error in the district court's construction.

II. Obviousness under 35 U.S.C. § 103

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

skill in the art." 35 U.S.C. § 103(a) (2006).[13] Obviousness is a question of law with underlying factual findings relating to the scope and content of the prior art; the differences between the claims and the prior art; the level of ordinary skill in the pertinent art; and any secondary considerations of non-obviousness. *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018) (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966)). The inherent teaching of a prior art reference is a question of fact. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014).

After a bench trial, we review a district court's conclusions of law de novo and its findings of fact for clear error. *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1341 (Fed. Cir. 2015). A factual finding is clearly erroneous if the Court is left with "the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

On appeal, Teva disputes that the 40mg GA 3x/week dosing regimen disclosed in the Copaxone patents would have been obvious to a person of skill in the art. Teva also appeals the invalidation of claim limitations in the '250 and '413 patents relating to improved tolerability and reduced frequency of adverse effects, and the invalidation of the '776 patent's claims relating to reduced severity of

---

[13] Congress amended § 103 when it passed the Leahy-Smith America Invents Act (AIA). Pub. L. No. 112–29, § 3(c), 125 Stat. 284, 287 (2011). Because the applications that led to the patents at issue have never contained a claim having an effective filing date on or after March 16, 2013 (the effective date of the statutory changes enacted in 2011), or a reference under 35 U.S.C. §§ 120, 121, or 365(c) to any patent or application that ever contained such a claim, the pre-AIA § 103 applies. *Id.* § 3(n)(1), 125 Stat. at 293.

injection site reactions. Teva does not appeal on the objective indicia of nonobviousness. We address each argument in turn.

A. 40mg GA 3x/week Dosing Regimen

Teva contends that the district court erred in finding the claimed 40mg GA 3x/week dosing regimen obvious. Specifically, Teva argues that the district court impermissibly relied on hindsight and an improper "obvious to try" analysis, and analyzed the obviousness of individual claim elements, rather than the invention as a whole. Teva further maintains that the district court's decision is at odds with this court's decision in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012).

We first address Teva's contention that the district court engaged in an impermissible "obvious to try" analysis. In *KSR*, the Supreme Court endorsed the use of an "obvious to try" analysis in certain cases:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

We have previously identified two categories of impermissible "obvious to try" analyses that run afoul of *KSR* and § 103: when what was "obvious to try" was (a) to vary all parameters or try every available option until one succeeds, where the prior art gave no indication of critical parameters and no direction as to which of many possibil-

ities is likely to be successful; or (b) to explore a new technology or general approach in a seemingly promising field of experimentation, where the prior art gave only general guidance as to the particular form or method of achieving the claimed invention. *See In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

This case falls into neither of the two impermissible categories. Here, the prior art focused on two critical variables, dose size and injection frequency, and provided clear direction as to choices likely to be successful in reducing adverse side effects and increasing patient adherence. As of the priority date, only two GA dose sizes had been shown to be effective, safe, and well-tolerated: 20mg and 40mg. Concerning frequency, the 1996 FDA SBOA, Flechter, and Khan 2008 all encouraged POSITAs to pursue a less frequent than daily dosing regimen; these references indicated that less frequent injections of GA were just as effective as daily injections, and less frequent injections improved patient adherence and reduced adverse reactions. The district court also properly relied on Khan 2009 not as statutory prior art, but for the fact that POSITAs were interested in pursuing less frequent dosing regimens. *In re Copaxone*, 2017 WL 401943, at *14.

Given this motivation, a POSITA had only a limited number of permutations of dose and frequency to explore that were not already disclosed in the prior art. Because a thrice-weekly 40mg injection would result in a total weekly dose very close to that in the already-approved daily 20mg injection—120mg/week versus 140mg/week—the district court found a POSITA would have had a reasonable expectation of success in pursuing the thrice-weekly dose frequency in terms of effectiveness, patient adherence, and FDA approval. *Id.* at *19 (quoting *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.")). The district court gave appropriate weight to the testimony of Dr. Green regarding patient compliance with thrice-weekly administrations and the Rebif® regimen, noting that "[e]ven though Rebif® is a different MS drug with a different mechanism of action, . . . 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." *Id.* at *20.

Teva faults the district court for "narrowing the universe" of possible GA regimens and using hindsight and the GALA protocol to reach its obviousness conclusion. Appellants' Opening Br. 42 (arguing the district court limited a POSITA to "two dosing options (40mg and 20mg), two regimens (1x/week and 3x/week), and one form (injections)"). We disagree; the district court had ample evidence besides hindsight and the disclosures in GALA on which to find a thrice-weekly dosing regimen of 40mg GA obvious to try. *See In re Copaxone*, 2017 WL 401943, at *17–22. Although the universe of potential GA doses is theoretically unlimited, the universe of dosages in the prior art that had clinical support for being effective and safe consisted of only two doses: 20mg and 40mg. Even if there were multiple injection frequencies not yet tested in the prior art—1x, 2x, 3x a week etc.—these still represent a limited number of discrete permutations.

This is not a situation where the prior art gave no direction in how to reach a successful result; the prior art clearly indicated that less frequent doses should be explored (i.e., moving away from the daily, "7x/week" dose towards less frequent doses) and that higher doses, while maintaining the same weekly dose (i.e., moving from 20mg daily to 40mg every other day), could increase efficacy while not affecting adverse reactions. Furthermore, the district court made factual findings specifically

in support of thrice-weekly injections. *E.g.*, *id.* at *19 (total weekly dose of 40mg GA 3x/week is very close to the total weekly dose for the approved daily 20mg GA regimen); *id.* at *20 ("[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."); *id.* (finding motivation to pursue a 3x/week regimen based on patient adherence rates in the Rebif® therapy). And contrary to Teva's argument that the court assumed without support that GA must be injected, the district court did not err in not considering other forms of GA. Evidence considered by the district court reveals that an oral version of Copaxone was proven to be ineffective by 2005. *Id.* at *23; J.A. 4016. We recognize that the prior art did not conclusively teach that a regimen of 40mg GA 3x/week would be effective. However, "[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329, 1331 (Fed. Cir. 2014); *see also In re O'Farrell*, 853 F.2d at 903 ("Obviousness does not require absolute predictability of success.").

Nor do we find merit in Teva's argument that the district court separately analyzed the 40mg dose limitation and the 3x/week limitation, without considering them together "except to conclude that the mash-up would be obvious to try." Appellants' Opening Br. 55. We note that the district court spent considerable time discussing why the combination of a 40mg dose administered 3x/week would be obvious to try. *See In re Copaxone*, 2017 WL 401943, at *19. And while "[t]he determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim," *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008), this court has previously employed the same frequency-and-dosage-amount approach to obviousness used by the district court here. In *Hoffmann-La Roche*, 748

F.3d at 1329, the court considered whether it would have been obvious at the time of invention to select a once a month oral dosing regimen of 150mg of ibandronate to treat osteoporosis. The court first discussed how the prior art taught that infrequent dosing, such as monthly dosing, was preferred. *Id.* at 1329–31. The court then separately discussed why a POSITA would have selected a 150mg dose, before considering the limitations together and concluding that "[a]t the very least, the 150mg dose was obvious to try." *Id.* at 1331–33. Teva makes no convincing argument why a similar approach is inappropriate here.

Teva makes numerous challenges to factual findings by the district court, none of which we find persuasive. For instance, Teva argues that Cohen and FORTE teach away from using 40mg GA. The district court, however, found that the decision to include 40mg in the later FORTE study indicates that Cohen did not teach away from trying 40mg. *In re Copaxone*, 2017 WL 401943, at *15. The district court further noted although the FORTE study ostensibly "failed" at meeting its stated goal of establishing that 40mg/day was 30% more effective than 20mg/day, FORTE still found that 40mg was equally effective with "no unexpected adverse effect," and thus did not teach away. *Id.* We see no clear error in these findings. *See 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."). Nor are we swayed by Teva's arguments that the district court misread Khan 2008 and Caon in suggesting that patients in the 20mg/day group switched to 20mg every other day to reduce discomfort associated with daily injections. The district court cited extensive testimony clearly showing that POSITAs "were familiar with the adverse reactions, pain, and treatment adher-

ence problems associated with daily injections."[14] *In re Copaxone*, 2017 WL 401943, at *16. Given the evidence presented, the district court's finding that patients wanted to switch to the every other day regimen to reduce discomfort associated with daily injections is a reasonable conclusion and not clearly erroneous.

Teva further contends that the district court erred in relying on Flechter for its finding that a POSITA would have been motivated to pursue a less than daily dosing regimen. We do not reach this argument given that the district court correctly found similar motivations in other references, such as the SBOA and Khan 2008. Teva also takes issue with the district court's use of the Pinchasi reference. Although the court noted that "Pinchasi is the closest prior art," *id.* at *17, this observation is not improper; courts are required to determine "the scope and content of prior art" and the "*differences* between prior art and claims." *PAR Pharm.*, 773 F.3d at 1193 (emphasis added). Contrary to Teva's assertion that the district court gave no reason why a person of ordinary skill would have started with Pinchasi, the district court in fact

---

[14] *See, e.g.*, J.A. 4676–77 (Kolodny deposition, describing needle fatigue associated with Copaxone 20mg/day); J.A. 4869 (Dr. Green, describing Khan 2008: "It reveals clear and obvious patient preference for an every-other-day dosing regimen when compared to a daily dosing regimen given the option."); J.A. 4857 (Dr. Green: "As we discussed, most of the adverse events associated with the use of glatiramer acetate, and in fact the most troubling set of adverse events had to do with injection site reactions or immediate post-injection reactions. Both of those are tied to injections. So 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.").

addressed Pinchasi fourth in its discussion on the thrice weekly dosing limitation, after the SBOA, Flechter, and Khan 2008/Caon references. *See In re Copaxone*, 2017 WL 401943, at *15–17. Teva raises additional arguments regarding factual findings made by the district court, none of which we find persuasive.

Finally, this court's decision in *In re Cyclobenzaprine*, 676 F.3d at 1063, does not warrant a different outcome. Teva argues that prior to the invention, higher doses of GA were not necessarily known to be more effective, GA's pharmacokinetic and pharmacodynamic ("pk/pd") profile was and remains unknown, GA's mechanism of action is still unknown, and the cause of patient's reactions to injections of GA is unknown. Teva contends that the unpredictable nature of GA categorically precludes the obvious-to-try analysis employed by the district court. Appellants' Opening Br. 50.

In *Cyclobenzaprine*, we held that bioequivalence alone could not establish obviousness because "skilled artisans could not predict whether any particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation." 676 F.3d at 1070. The court applied traditional motivation and reasonable-expectation-of-success analysis, reasoning that "[w]hile it may have been obvious to experiment with the use of the same PK profile [from an immediate-release formulation] when contemplating an extended-release formulation, there [wa]s nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Id.* In *Cyclobenzaprine*, there were no prior art clinical studies to suggest what would be a therapeutically effective formulation.

We do not read *Cyclobenzaprine* as establishing a rigid rule categorically precluding obviousness findings without pk/pd data. Further, *Cyclobenzaprine* is distin-

guishable in that, there, the obviousness proof relied entirely on the bioequivalence of certain pharmacokinetic profiles. Bioequivalence is not argued here; instead, obviousness is proven through human clinical studies establishing the safety, efficacy, and tolerability of GA at doses and dose frequencies similar to the claimed regimen. In this case, the evidence shows that pk/pd data was largely irrelevant to the invention. Numerous clinical studies in the prior art describe GA and its effects on the human body. Although the precise mechanism of GA is not known, it is known to be immunomodulating—i.e., it changes the immune system—and is not necessarily measurable in the bloodstream and its levels are not indicative of efficacy. *See In re Copaxone*, 2017 WL 401943, at *21–22; J.A. 3998–99, 4886–87. Testimony was given at trial that pharmacokinetic studies for drugs like GA are less appropriate than for small molecule drugs, such as those at issue in *Cyclobenzaprine*. J.A. 4886–87. GA was also known to be "forgiving," in that occasional missed doses would not reduce efficacy, and that fact gave POSITAs further confidence in eliminating one dose every two weeks. J.A. 4848–49; 4884–85; 4732. Higher doses were clinically shown to be at least as effective as lower doses; Cohen shows, at the very least, that 40mg is as effective and well-tolerated as 20mg, but with a more rapid onset of action. Finally, Teva itself, in its 1996 application to FDA, indicated that pharmacokinetic studies "would be of limited value." J.A. 20689.

In light of the foregoing, we hold that the 40mg GA 3x/week regimen is obvious in light of the prior art, and find no clear error in the conclusion that a POSITA would be motivated to combine the 40mg GA dose, which had proven efficacy, with a 3x/week frequency, which was desirable because the prior art indicated that less frequent administration increased patient adherence while maintaining efficacy.

B. Improved Tolerability and Reduced Frequency Limitations

Claims 14, 16, and 17 of the '250 patent and claim 7 of the '413 patent require that the 40mg GA 3x/week regimen reduce the frequency of ISRs and IPIRs relative to the daily 20mg GA regimen. Claim 15 of the '250 patent, on which claims 16 and 17 depend, requires that the claimed regimen improve tolerability as compared to the daily 20mg regimen.

Teva argues that the prior art did not lead POSITAs to expect improved tolerability and reduced frequency of injection reactions from the claimed regimen compared to 20mg GA daily. We disagree, and find no clear error in the district court's findings regarding Khan 2008, Caon, and Flechter, all of which demonstrate that improved tolerability and less frequent injection reactions were expected from the claimed less frequent regimen, as compared to 20mg daily. *See In re Copaxone*, 2017 WL 401943, at *17–18. Caon, for example, disclosed that the frequency of a severe injection-site reaction, lipoatrophy, was "significantly less" for the every-other-day patient group than for the daily group. J.A. 20386. Pinchasi recognized that a 40mg GA dose resulted in increased efficacy "not accompanied by a corresponding increase of adverse reactions." J.A. 20944. The court also relied upon testimony from Dr. Green that reducing the frequency of injections was expected to reduce the number of injection-related reactions.

Teva finds fault with the district court's reference to "common sense" in its reliance on Dr. Green's testimony. During trial, Appellees' expert Dr. Green testified that a POSITA would expect reducing the frequency of injections to be associated with enhanced overall tolerability of the regimen. J.A. 4911. In its post-trial briefing, Teva argued that Dr. Green's testimony was conclusory and unsupported by the prior art. The district court rejected

this characterization, noting that "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." *In re Copaxone*, 2017 WL 401943, at *17. The district court went on to identify additional evidence in the record to support Dr. Green's statement, including evidence in the Khan 2008/Caon and Flechter studies, and testimony from Dr. Wolinksy, Teva's own expert, who testified that he had prescribed COPAXONE® 20mg for use every other day, off-label use, for his patients who were "doing extremely well on the drug but [were] having trouble with injection site problems." *Id.* We see no error in what is essentially a credibility determination, where the district court credited Dr. Green's expert testimony, supported by other evidence in the record, that a reduction in the number of injections would result in less frequent reactions. *See* J.A. 4857.

Teva also argues that the district court erred by relying on Teva's GALA protocol. The district court did not use GALA as invalidating prior art, but instead as evidence of a POSITA's motivations and expectations when reading the prior art at the time of the invention. *In re Copaxone*, 2017 WL 401943, at *20. With respect to the sufficiency limitations, the district court used GALA only for that limited purpose, noting Teva's statement to FDA that "*one may certainly expect* a reduction in the frequency of such reactions with this new dose regimen, further enhancing subject adherence to treatment." *Id.* at *18 (emphasis added) (quoting J.A. 8267). The district court's reliance on GALA merely as confirmation of how a POSITA would understand FORTE, which is prior art, is not erroneous.

C. Reduced Severity Claims of the '776 Patent

The asserted claims of the '776 patent contain additional limitations requiring that the 40mg GA 3x/week

regimen "reduce[s] severity of injection site reactions" compared to a 20mg daily regimen. *See, e.g.*, '776 patent col. 17 ll. 37–54; col. 17 l. 65–col. 18 l. 22. The parties stipulated that "severity" means "the intensity of a patient's ISRs and/or IPIRs." J.A. 1994. "Severity" appears in the specification of the '776 patent only once in connection with injection site reactions, in the definition of "tolerability," which means "associated with the frequency and *severity* of post injection reactions and injection site reactions." '776 patent col. 7, ll. 37–42 (emphasis added). "Tolerability influences the period that a patient can follow GA treatment." *Id.*

After reviewing the prior art, the district court concluded that the '776 patent's claims directed to reducing the severity of injection site reactions would have been obvious. *In re Copaxone*, 2017 WL 401943, at *22. The district court broadly relied on two different types of evidence in reaching this conclusion: evidence and testimony relating to lipoatrophy and evidence relating to tolerability.

Concerning the evidence relating to lipoatrophy, the district court pointed to trial testimony establishing that lipoatrophy, the loss of subcutaneous fat at the injection site, is a severe ISR, and Caon's disclosure that "[i]njection related lipoatrophy was significantly less" on the 20mg every other day regimen than on the daily 20mg regimen. *Id.* The court also relied on Teva's expert Dr. Fox, who testified 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.* We agree with the district court that this evidence "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." *Id.*

In addition to the evidence regarding lipoatrophy, the district court also pointed to a press release issued by

Teva summarizing FORTE, which admitted that the 40mg dose "maintained the favorable safety and tolerability profile of COPAXONE® 20mg," and testimony from the named inventor, Dr. Klinger, 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." *Id.* at *23. Citing Dr. Klinger's testimony, the district court correctly concluded that "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." *Id.*

Teva contends that the district court erroneously conflated frequency with severity, and that evidence of reduced frequency of ISRs cannot prove reduced severity of ISRs. While we agree that the two concepts are distinct, we conclude that the district court did not err. Frequency and severity of ISRs are not interchangeable, but Dr. Fox's testimony established that, in certain instances, they are related:

> Q. Doctor, is severity the same thing as frequency?
>
> A. No, they're related, but they are separate topics.
>
> Q. How do they relate to one another?
>
> A. There, as I mentioned before . . . , there are some events like lipoatrophy that would be considered to be more severe. So 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.
>
> Q. So do you consider these two concepts to be mutually exclusive?
>
> A. No, they are not. They are related.

J.A. 5523.

Caon showed that reducing the frequency of injections from daily to every other day resulted in "significantly less lipoatrophy," a severe ISR. This statement in Caon can be read as indicating either that lipoatrophy occurred less frequently with less frequent injections—which, according to Dr. Fox's testimony, "by definition" means reduced severity—or the expression of the lipoatrophy itself was less severe. It was not unreasonable for the district court to conclude from this evidence that a POSITA would think it obvious that the 40mg GA 3x/week regimen, with its less frequent injections, would result in reduced severity of at least one ISR, lipoatrophy, particularly given Dr. Fox's testimony endorsing the same. *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 also disputes the district court's reliance on the FORTE press release. However, given that the findings made by the district court in reaching its obviousness conclusion, based on the other evidence relied on by the court, were not clearly erroneous, we do not reach this argument.

CONCLUSION

In light of the foregoing, we conclude that the district court did not err in invalidating all asserted claims of the Copaxone patents as obvious.

AFFIRMED

COSTS

No costs.