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Paper 84
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC. and AMNEAL PHARMACEUTICALS LLC,
Petitioners,

v.

YEDA RESEARCH AND DEVELOPMENT CO. LTD.,
Patent Owner.

Case IPR2015-00830
Patent 8,969,302 B2[1]

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and TINA E. HULSE, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION
Granting-in-Part Patent Owner's Request for Rehearing
37 C.F.R. § 42.71

[1] Case IPR2015-01981 has been joined with Case IPR2015-00830.

I. INTRODUCTION

Yeda Research & Development Co. Ltd. ("Patent Owner") filed a Request for Rehearing (Paper 81, "Reh'g Req.") of our Final Written Decision (Paper 80, "Dec.") holding that claims 1–12 of U.S. Patent No. 8,969,302 B2 (Ex. 1001, "the '302 patent") are unpatentable.

Patent Owner requests a rehearing of our decision, arguing that we misapprehended and overlooked the prior art teachings that (1) less-frequent-than-daily administration, and (2) a 40 mg dose of glatiramer acetate would have been expected to decrease tolerability of glatiramer acetate ("GA") treatment. Reh'q Req. 4–11.

For the reasons stated below, Patent Owner's request is *granted-in-part*.

II. STANDARD OF REVIEW

The party requesting rehearing has the burden to show that the decision should be modified. Under 37 C.F.R. § 42.71(d), the request for rehearing must identify, specifically, all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply.

III. ANALYSIS

A. Evidence Relating to the Combination of Flechter and Pinchasi

Patent Owner first asserts that we "misconstrued data in Flechter[2] illustrating that alternate day dosing was as effective as daily dosing and

[2] S. Flechter et al., *Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration*, 25 CLINICAL NEUROPHARM. 11–15 (2002) (Ex. 1008).

found instead that the data taught that less-frequent-than-daily administration would have been more tolerable than daily administration." Reh'g Req. 6 (citing Dec. 29). Upon review of the Decision, we agree that the analysis in the cited portion of our Decision does not conflate efficacy with tolerability. See Final Dec. 32–33. Accordingly, we grant this portion of Patent Owner's Request for Reconsideration and retract our reliance on the efficacy data of Flechter in Section II.C.5 of the Decision as the basis for rejecting Patent Owner's argument regarding the lack of motivation to combine Pinchasi and Flechter. We concurrently issue a modified Final Written Decision (Paper 90) to reflect this change.

We, nonetheless, are not persuaded by Patent Owner's argument that Flechter suggests that less frequent injections were less tolerable than daily injections reported in Meiner.[3] In particular, Patent Owner points us to the Patent Owner Response, which compares the alternate-day data in Flechter with the daily administration data of Meiner. Reh'g Req. 7–8 (citing PO Resp. 35–36). Although Flechter itself did not compare the data, Patent Owner and its declarant, Dr. Tjalf Ziemssen, M.D., Ph.D., compare Flechter's data reporting adverse events in its patients with Meiner's data reporting adverse events in a different cohort of patients. PO Resp. 35–36; Ex. 2135 ¶ 89. From that comparison, Patent Owner argues that Flechter's data allegedly teaches that alternate-day administration is less tolerable than daily administration. Reh'g Req. 8.

[3] Meiner et al., *Copolymer 1 in Relapsing-Remitting Multiple Sclerosis: a Multi-Centre Trial, in Frontiers in Multiple Sclerosis: Clinical Research and Therapy* (Abramsky et al. eds., 1997) (Ex. 1009).

We note—and agree with—Dr. Ziemssen's testimony that a person of ordinary skill in the art "generally would not view this type of cross-study comparison between different study populations as a basis for drawing any comparative conclusions." Ex. 2135 ¶ 87. We are therefore unpersuaded by his ad hoc comparison of Flechter's data with that of Meiner. *Id.* ¶ 89. Instead, we find more credible Flechter's conclusion that alternate-day administration of glatiramer acetate was "well tolerated, comparing favorably with the effects of daily injections of Copolymer 1 in patients with relapsing MS." Ex. 1008, 1; *see also id.* at 5 ("The results of this trial suggest 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.").

Accordingly, we are not persuaded that a person of ordinary skill in the art considering combining a higher dose of GA with Flechter's alternate-day dosing schedule would conclude that such a regimen would likely exacerbate the frequency of injection site reactions, as Patent Owner asserts. *See* PO Resp. 36.

B. Evidence of Decreased Tolerability of 40 mg GA

Patent Owner further argues that we overlooked evidence that a 40 mg dose of GA would have been expected to result in decreased tolerability when compared to 20 mg GA. Reh'g Req. 8–11. Patent Owner cites Cohen, which compares the occurrence of different categories of adverse events when administering 40 mg GA daily versus 20 mg GA daily, and complains that we did not discuss Cohen in our Final Written Decision. *Id.* (citing Ex. 1006, Table 3).

As an initial matter, we considered all admissible evidence presented by both parties, but we acknowledge that we did not address every piece in our Decision, particularly if it was cumulative of other evidence. Accordingly, we did not expressly discuss Cohen because it is cumulative of the FORTE trial, which, according to Patent Owner, "was a large Phase III study that followed up on the Phase II study reported by Cohen." PO Resp. 17. Thus, Cohen does not add to our discussion of FORTE (Dec. 14), because both concluded that the 40 mg dose was safe and well tolerated, despite some incidents of injection site reactions. Ex. 1006 (Cohen), 1 (concluding the 40 mg dose was "safe and well tolerated"); Ex. 2001 (FORTE), 1 (finding that the 40 mg dose "maintained the favorable safety and tolerability profile of COPAXONE® 20 mg"). Thus, we were not persuaded by Patent Owner's argument that a person of ordinary skill in the art would not have used 40 mg GA because it was associated with more frequent adverse events.

Patent Owner also cites the FORTE study as showing a "statistically significant increase in treatment discontinuation due to injection site reactions" for the 40 mg dose compared with the 20 mg dose. Reh'g Req. 10–11 (citing PO Resp. 18; Ex. 2028, 5; Ex. 2135 ¶ 100). Patent Owner claims that it is the "only statistically significant finding from the study reported in the prior art." *Id.* We did not overlook or misapprehend this argument regarding the FORTE study. We simply found Patent Owner's argument unpersuasive. Although the Comi slides,[4] which reflect the results

[4] Giancarlo Comi, *FORTE: Results from a Phase III, 1-Year Randomized, Double-Blind, Parallel-Group, Dose-Comparison Study with Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis* (Ex. 2028) ("Comi

of the FORTE study, state that the difference in adverse events between 20 mg GA and 40 mg GA was statistically significant and "mainly due to Injection Site Reactions," that statistically significant difference is only among the patients who terminated the study early. Ex. 2028, 5 (Slide 14). The slides are silent as to any statistical significance for the injection site reactions across the entire patient population for the entire study. *Id.* at 9 (Slide 25). Slide 25 shows the percentage of patients who reported injection site reactions was 55.6% for 20 mg GA and 58% for 40 mg GA. *Id.* Patent Owner's declarant, Edward J. Fox, M.D., testified that he was "not certain of the statistical significance of those two numbers as reported on Slide 25." Ex. 2146, 141:4–142:19. Moreover, Slide 25 states "both doses were well-tolerated," and Slide 26 concluded "[g]ood safety and tolerability profile; no unexpected adverse effect with the high dose." Ex. 2028, 9. Thus, given the art as a whole repeatedly states 40 mg GA is well tolerated, we remain unpersuaded that the art suggested a 40 mg dose of GA was less tolerable than 20 mg GA, as Patent Owner asserts.

C. Prior Art as a Whole

Patent Owner argues that, when considered as a whole, "the prior art taught that decreased frequency of injection and increased dosage amount per injection were expected to decrease the tolerability of GA treatment." Reh'g Req. 11–12. Patent Owner further argues that a person of ordinary skill in the art "thus would not have been motivated to develop the claimed treatment regimen in an effort to increase tolerability of GA treatment." *Id.*

slides").

at 13. Patent Owner also criticizes our reliance on the Khan 2008[5] and Caon 2008[6] abstracts because neither reference contains any data nor did they administer a 40 mg dose. Reh'g Req. 12. Patent Owner continues, stating that the "reported data found in the prior art as a whole clearly suggested that decreased tolerability would result from a 40 mg, three times per week regimen and the Board's decision erred in finding otherwise." *Id.*

As explained above, we were not persuaded that the prior art suggested decreased tolerability. Indeed, in light of the prior art references each stating that the dosage regimens were well tolerated, we were persuaded that a person of ordinary skill in the art would have had a reason to combine the cited references to reach the claimed dosing regimen with a reasonable expectation of success.

D. Evidence Related to Secondary Considerations

Finally, Patent Owner asserts that the Board overlooked evidence regarding the expected decrease in tolerability in our discussion of secondary considerations. Reh'g Req. 12–13. Patent Owner also states that our "finding that Patent Owner failed to provide any evidence of improved tolerability over the Pinchasi reference (FWD at 24) is also incorrect." *Id.* at 14. First, we did not state that Patent Owner failed to provide *any* evidence

[5] 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 (2008) (Ex. 1010) ("Khan 2008").

[6] 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 A317 (Mar. 17, 2009) (Ex. 1011) ("Caon 2009").

of improved tolerability—we stated that Patent Owner provided "*insufficient* evidence of record showing any unexpected results between the claimed requirement of three doses per week compared to dosing every other day." Dec. 24 (emphasis added). As explained above, we did not find Patent Owner's characterizations of the prior art, including Cohen, persuasive.

IV. CONCLUSION

For the foregoing reasons, we conclude that Patent Owner has demonstrated that we misapprehended the evidence and argument regarding the combination of Pinchasi and Flechter and grant Patent Owner's request for rehearing as to this issue. We, therefore, modify Section II.C.5 of the Final Written Decision to include our analysis above in Section III.A. We further conclude, however, that Patent Owner has not demonstrated that we misapprehended any other evidence and argument and, therefore, deny Patent Owner's Request for Rehearing as to the remaining issues.

V. ORDER

Accordingly, it is ORDERED that Patent Owner's Request for Rehearing is GRANTED-IN-PART;

FURTHER ORDERED that a modified Final Written Decision is entered concurrently with this Order; and

FURTHER ORDERED that the original Final Written Decision (Paper 80) is vacated.

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