Trials@uspto.gov
571.272.7822

Paper 15
Date: December 20, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TWI PHARMACEUTICALS, INC.,
Petitioner,

v.

MERCK SERONO SA,
Patent Owner.

IPR2023-00049
Patent 7,713,947 B2

Before ULRIKE W. JENKS, ZHENYU YANG, and TINA E. HULSE, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION
Granting Petitioner's Request for Rehearing
37 C.F.R. § 42.71(d)
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

TWi Pharmaceuticals, Inc. ("Petitioner") requests rehearing of our Institution Decision ("Decision") denying *inter partes* review of claims 36, 38, 39, and 41–48 of U.S. Patent No. 7,713,947 B2 (Ex. 1001, "the '947 patent") entered on March 28, 2023 (Paper 10, "Dec."). Paper 11 ("Req. Reh'g"). Petitioner requested institution of *inter partes* review on the basis of anticipation by Bodor[1] under 35 U.S.C. § 102(e), obviousness under 35 U.S.C. § 103(a) over Bodor and the knowledge of a person of ordinary skill in the art, and obviousness under 35 U.S.C. § 103(a) over Bodor and Rice.[2] Paper 1 ("Pet.").

In its Request for Rehearing, Petitioner contends that the Board overlooked or misapprehended that the inventors of the '947 patent did not invent weight-based dosing, overlooked or misapprehended the scope of the prior art references and materials incorporated by reference therein, and misinterpreted the claims. *See generally* Req. Reh'g.

For the following reasons, Petitioner's Request for Rehearing is granted, and we institute trial on all challenged claims on all grounds raised in the Petition. *See* Pet. 27–55.

II. STANDARD OF REVIEW

A party requesting rehearing has the burden to show a decision should be modified by specifically identifying all matters the party believes were misapprehended or overlooked, and the place where each matter was

[1] US 7,888,328 B2, issued Feb. 15, 2011 (Ex. 1029, "Bodor").
[2] Rice et al., *Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial*, NEUROLOGY, 54(5):1145–1155 (2000) (Ex. 1008, "Rice").

addressed previously in a motion, opposition, or a reply. 37 C.F.R. § 42.71(d). When rehearing a decision on institution, we review the decision for an abuse of discretion. 37 C.F.R. § 42.71(c). An abuse of discretion may arise if a decision is based on an erroneous interpretation of law, if a factual finding is not supported by substantial evidence, or if the decision represents an unreasonable judgment in weighing relevant factors. *Star Fruits S.N.C. v. United States*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004); *In re Gartside*, 203 F.3d 1305, 1315–16 (Fed. Cir. 2000).

III. ANALYSIS

Independent claim 36 recites, "[a] method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine" following the sequential steps of administrating cladribine during an induction period, followed by a cladribine-free period, followed by a cladribine maintenance period, followed by a cladribine-free period. Ex. 1001, 19:14–30. The total amount of cladribine administered during the induction period is in a range from 1.7–3.5 mg/kg, while the total amount of cladribine administered during the maintenance period is about 1.7 mg/kg. *Id.*

In the Decision, we found that Petitioner has not shown that the dosage of cladribine administered in Bodor's maintenance period "would necessarily be" the same dosage administered in the first round because Bodor instructs that its methods are to be used with continuous clinical evaluations for beneficial effect to determine any need for adjusting a particular treatment dose, instead of remaining silent on the dosage for subsequent rounds. Dec. 13–14. Specifically, we found that Bodor's teaching

to adjust the dosage of cladribine does not involve considerations based on patient weight, but instead focuses on "the particular exigencies specific to a given mammal" and "concurrent evaluation of beneficial effect." Ex. 1029, 13:31–40; Dec. 12, *see also id.* at 16.

In its Request for Rehearing, Petitioner argues that we overlooked or misapprehended the scope of Patent Owner's claims because "the Challenged Claims do not require the maintenance period to be at the same dosage—the issue is that they allow the maintenance period to be at the same dosage." Req. Reh'g 13 (emphasis omitted). Petitioner argues that we overlooked or misapprehended its evidence because the claims do not exclude "flat dosing," or dosing with the same amount of cladribine every day during the induction and maintenance period cycles. Req. Reh'g 14 (citing Pet. 42–48). Petitioner contends that instead, the claims require that the total dosage of cladribine reaches the claimed amounts, and Bodor discloses those amounts when the drug is administered to a patient of average weight. *Id.*

Having reconsidered the record before us, we are persuaded that Petitioner has met its burden under 37 C.F.R. §§ 42.71(c) and (d) and presented sufficient evidence to support a reasonable likelihood that Bodor either alone or in combination with Rice renders obvious the method of treating multiple sclerosis by administering cladribine to a patient in the same claimed total amount for both the induction period and maintenance period to support Petitioner's challenge to claim 36.

To summarize, Bodor teaches two treatment regimens for treating multiple sclerosis with a cladribine-cyclodextrin complex.

> 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex . . . would be administered [orally] once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment.

Ex. 1029, 13:20–30. Petitioner acknowledges that Bodor does not explicitly suggest applying the same regimen again after a cladribine-free period but finds that repeating the treatment protocol is reasonably inferred. Pet. 33 (citing Ex. 1005 ¶¶ 109, 111–113), *see id.* at 48 (citing Ex. 1005 ¶¶ 168–170); Ex. 1029, 18:45–19:3, 20:1–20 (Examples 4 and 5 each describing that treatment days are separated by cladribine-free days); Ex. 1003 at 389; Ex. 1004 at 141. Bodor also teaches that the dosing regimen can be tailored to suit the needs of the patient. Specifically, Bodor teaches that "one of skill will appreciate that the therapeutically effective amount of cladribine administered . . . may be lowered or increased by fine tuning and/or by administering cladribine . . . with another active ingredient." Ex. 1029, 13:31–35, *see also id.* 13:37–40 ("Therapeutically effective amounts may be easily determined . . . empirically by starting at relatively low amounts and by step-wise increasing with concurrent evaluation of beneficial effect."). Based on these disclosures, we agree with Petitioner that it would be reasonable to infer from Bodor's teachings in conjunction with the knowledge of the ordinary artisan that the cladribine dosing protocol in Bodor is repeated. Pet. 33; *see also* Ex. 1005 ¶¶ 109–123, 119 ("common practice in the industry when prescribing a second round of an

immunosuppressant was to utilize the same dosing regimen as in the induction phase").

In its Request for Rehearing, Petitioner argues that we misinterpreted the claims. "All that is required is that the total dose reach a stated level in each period, and Bodor discloses a total dose within that range for what a person of ordinary skill in the art would understand to be an average patient." Req. Reh'g 14 (emphasis omitted) (citing Pet. 42–48).
Dr. Greenberg testifies that Bodor's total dosage of cladribine ranges from 100–140 mg in the two-month treatment period. Ex. 1005 ¶ 104. The issue, as presented by Petitioner, is that the '947 patent claims simply use a different way of reciting a total dose of cladribine administered during the treatment phase when compared to the methods and dosage taught by Bodor. We agree with Petitioner that the method and cladribine dosage in the '947 patent claims overlap with the method and dosage taught by Bodor.

To determine the total amount of cladribine administered as claimed in the '947 patent requires knowledge of the weight of the patient. In the Petition, Petitioner relied on a patient weighing 70 kilograms (≈ 154 pounds) to be an acceptable average human weight as understood in the medical community. Pet. 31 (citing Ex. 1005 ¶ 105). Patients, however, come in all shapes and sizes as recognized in the '947 patent disclosure and further supported by Dr. Greenberg's testimony and referenced exhibit. *See* Ex. 1001, 3:8 ("patients of about 52 and about 75 kilos); *see also* Ex. 1005 ¶ 106 ("the average weight of individuals in the United States is higher than the global average, with an overall average weight (men and women combined) of roughly 177 lbs in 2002."); Ex. 1030 ("the average weight for men aged 20-74 years rose dramatically from 166.3 pounds in 1960 to 191

pounds in 2002, while the average weight for women the same age increased from 140.2 pounds in 1960 to 164.3 pounds in 2002."). To arrive at the average weight of 177 pounds means that there are patients in the population that are above and below that average. *See generally* Ex. 1030.

Dr. Greenberg provides calculations for the total cladribine dose administered based on the method disclosed in the '947 patent claims. Dr. Greenberg's calculations are based on a patient weighing either 70 kilograms or 80.28 kilograms. Ex. 1005 ¶¶ 105–106. Applying the lowest claimed dosage of 1.7 mg/kg as recited in the '947 patent claims, the 70-kilogram patient would receive a total dose of 119 mg while the 80.28-kilogram patient would receive 136 mg cladribine. Ex. 1001, 19:17-28; Ex. 1005 ¶¶ 104 ("10 mg oral tablet may be administered to a patient (10 –14 days), and the resulting range of total dosages (100 mg–140 mg in 10 mg increments)"), 107 ("the dosing regimen of Bodor would recognize that it disclosed oral administration of 10 mg doses of cladribine over a two-month period, with the total dose achieved at the end of that period being about 1.7 mg/kg for a sizeable amount of the patient population, which is within the claimed range of about 1.7 mg/kg to about 3.5 mg/kg.").

In our Decision, we found that "Petitioner's examples involve a strategic selection of patient weights and treatment durations that support calculations resulting in a 1.7 mg/kg total dosage for the treatment period . . . [however, this] demonstrates only the total dose that is possible for some patients." Dec. 13, *see also* 18 ("It is only by employing a strategy that exemplifies treatment of patients having specifically selected weights and specifically selected treatment durations that Petitioner is able to show that

Bodor's method of treating MS with 10 mg of the cladribine complex daily arrives at about a total dosage of 1.7 mg/kg at the end of a treatment period."). Upon review of Petitioner's arguments, our focus in the Decision on that single 70 kg patient as being insufficient was in error. Here, Bodor's treatment method of administering 100–140 mg of cladribine to a patient population ranging anywhere in size from 70–80.28 kilograms would reasonably overlap with the dosage as recited in the '947 patent. *See* Pet. 45 ("These teachings arrive at 1.7 mg/kg for numerous patients and a large section of the patient population."); Ex. 1005 ¶ 107 (a person of ordinary skill in the art "reading the dosing regimen of Bodor would recognize that it disclosed oral administration of 10 mg doses of cladribine over a two-month period, with the total dose achieved at the end of that period being about 1.7 mg/kg for a sizeable amount of the patient population."), *see also id.* at ¶¶ 105-106. "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

As for the remaining arguments in the Request regarding Bodor either alone or in the combination with Rice, we will revisit those issues after the record has been fully developed. Req. Reh'g 9–15.

IV. 35 U.S.C. § 325(d)

Section 325(d) provides that the Director[3] may "reject the petition" if "the same or substantially the same prior art or arguments previously were

[3] The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

presented to the Office." The Board analyzes this issue under a two-part framework:

> (1) [determining] whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, [determining] whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, Paper 6 at 8.

The first prong of the *Advanced Bionics* framework requires us to determine whether the Petition advances the same or substantially the same art or arguments that were previously presented to the Office. *Advanced Bionics*, 8.

Patent Owner argues that we should exercise our discretion under § 325(d) and deny institution. Prelim. Resp. 8–21. Specifically, Patent Owner argues that the same or substantially the same prior art and arguments that Petitioner relies on for its grounds of unpatentability—namely, "Bodor's counterpart—Bodor '101 (Ex. 1007), which Petitioner states has the same disclosure as Bodor (Pet., 24–25, n.4)—and Rice were considered by the Examiner during prosecution." *Id.* at 9.

Petitioner acknowledges that "Bodor was present during prosecution." Pet. 12; *see also id.* at 25 n.4 ("Bodor was also published as WO 2004/087101 A2, which was published on October 14, 2004, and therefore prior art under § 102(a). Ex. 1007. Both references have the same disclosure."). Petitioner also acknowledges that Rice was considered during prosecution. Pet. 18 ("The Examiner considered Rice (submitted via an IDS)").

Here, both Petitioner and Patent Owner agree that Bodor and Rice were before the Office, therefore, the first part of the framework is satisfied. *See* Pet. 12, 18; Prelim Resp. 9.

Next, we consider "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics*, 8. Patent Owner argues that "Petitioner fails to identify any error by the Examiner." Prelim. Resp. 15 (citing *Advanced Bionics*, 8–9, n.9). Patent Owner contends that "[t]he Examiner made the same argument that Petitioner currently makes in alleging that Bodor discloses a specific dose within the claimed dose range, thus reading on the claimed range." Prelim. Resp. 16 (emphasis removed). Patent Owner contends that they "repeatedly argued that Bodor did not teach a maintenance dosage as claimed—neither the same as nor lower than the total induction dosage." *Id.* at 19 (emphasis removed).

Petitioner contends that under the second prong of the *Advanced Bionics* framework the Office erred in allowing the broader claim 36.

> [C]laim 36 recites a total dosage range for the induction period (about 1.7 mg/kg to about 3.5 mg/kg) and a total dosage range[] for the maintenance period (about 1.7 mg/kg). Ex. 1001 at 12, col. 19, ℓℓ. 14–30. While most of the claimed dosage range for the induction period is higher than the claimed total dosage during the maintenance period, the claimed dosage range includes a value that is equivalent to the claimed total dosage during the maintenance period (1.7 mg/kg). As such, the literal language of claim 36 is not limited to a treatment regime where the total dose of cladribine during the maintenance period is lower than the total dose of cladribine during the induction period, and in fact, claim 36 covers an embodiment where the

> total dose of cladribine during the maintenance period ***is equal to*** the total dose of cladribine during the induction period.

Pet. 12–13. Petitioner contends that "the equal dosages embodiment [of claim 36] was never properly examined during prosecution" and urges us to institute. Pet. 17. Petitioner contends that "Examiner either misapprehended the scope of claim 36 or overlooked it." Pet. 14.

Petitioner contends that both "Examiner and Patent Owner understood Bodor to teach the equivalent dosages embodiment." Pet. 14 (citing Ex. 1003, 389 (Office Action mailed Aug. 3, 2009) ("Bodor teaches that for the treatment of multiple sclerosis, 10 mg of cladribine in solid dosage form is to be administered orally once per day for a period of five to seven days in the first month, repeated for a period of five to seven days in the second month, followed by 10 months of no treatment."); Ex. 1004, 141); *see also* Ex. 1004, 156 (Office Action Response in child '173 application) ("Rather, the teaching of the reference [Bodor] would suggest that the same dosing regime be applied to the patient. . . . This would have resulted in the same total dose of cladribine being administered to the patient in both the induction phase and the maintenance phase."). Petitioner contends that because Examiner understood Bodor to teach administering the same dose of cladribine during the induction and maintenance phase, the only reasonable explanation for allowing claim 36 is that Examiner understood "claim 36 to mean that the total cladribine dosage in the induction phase must be one of the numbers higher than 1.7 mg/kg (misconstruing the claim term in a way that impacts patentability)." Pet. 15.

Having considered the record, we agree with Petitioner that the Office erred in its evaluation of the cited art (now asserted) as required by

Advanced Bionics. *Advanced Bionics* cautions that "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." Paper 6, 9. Here, both Examiner and Patent Owner interpret Bodor to disclose administering the *same dose* of cladribine in both the induction and maintenance phase. Claim 36 encompasses administering the same dose of cladribine – 1.7 mg/kg – in *both* the induction and maintenance phase. By interpreting claim 36 as requiring a maintenance dose that is lower than the induction dose, we agree with Petitioner that Examiner misapprehended the scope of claim 36.

We, therefore, decline to exercise our discretion to deny institution under § 325(d).

V. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one of the challenged claims of the '947 patent is unpatentable. Patent Owner has not persuaded us to exercise our discretion to deny institution of trial. We, therefore, institute trial on all challenged claims and on all grounds raised in the Petition.

At this stage of the proceeding, we have not made a final determination as to the patentability of any challenged claim or as to the construction of any claim term. Any final determination will be based on the record developed during trial. We place Patent Owner on express notice that any argument not asserted in a timely-filed Response to the Petition, or in another manner permitted during trial, shall be deemed waived, even if that argument was presented in the Preliminary Response.

VI. ORDER

ORDERED that Petitioner's Request for Rehearing is granted;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 36, 38, 39, and 41–48 of the '947 patent is instituted with respect to the grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '947 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

FOR PETITIONER:
Philip Segrest
Nathan Sportel
Stephen Howe
HUSCH BLACKWELL, LLP
philip.segrest@huschblackwell.com
nathan.sportel@huschblackwell.com
steve.howe@huschblackwell.com

FOR PATENT OWNER:

Emily Whelan
Deric Geng
Cindy Kan
WILMER CUTLER PICKERING HALE AND DORR LLP
emily.whelan@wilmerhale.com
deric.geng@wilmerhale.com
cindy.kan@wilmerhale.com