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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DO KYU PYUN and KYOUNG JIN OO[1]

Appeal 2024-002219
Application 17/859,603
Technology Center 1600

Before JOHN G. NEW, JOHN E. SCHNEIDER, and
RACHEL H. TOWNSEND *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42(a) (2021). Appellant identifies JW Pharmaceutical Corporation of The Republic of Korea as the real party-in-interest. App. Br. 4.

I. SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 18–20, which stand rejected as unpatentable under 35 U.S.C. ¶ 103 as being obvious over the combination of Ahn et al. (US 2011/0028467, February 3, 2011) ("Ahn '467"), S.O. Ahn et al., *Stronger Uricosuric Effects of the Novel Selective URAT1 Inhibitor UR-1102 Lowered Plasma Urate in Tufted Capuchin Monkeys to a Greater Extent than Benzbromarone*, 357 J. PHARMACOL. EXP. THER. 157–166 (2016) ("Ahn 2016"), A.B. Nair et al., *A Simple Practice Guide for Dose Conversion between Animals and Human*, 7 J. BASIC CLIN. PHARMACY 27–31 (2016) ("Nair"), and A.B. de Souza et al., *Standard Electrocardiographic Data from Capuchin Monkeys (Cebus apella, Linnaeus, 1758)*, 57(1) J. AM. ASSOC. LAB. ANIMAL SCI. 13–17 (2018) ("de Souza").

Claims 18–20 also stand rejected as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Ahn '467, Ahn 2016, and U.S. Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*, 1–27 (2005) ("FDA Guidance").

We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

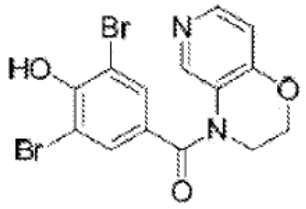
II. NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to a composition for treatment or prevention of hyperuricacidemia, gout, nephritis, chronic renal insufficiency, nephrolith, uremia, urolithiasis, or a uric acid-related disease. Spec. 47.

III. REPRESENTATIVE CLAIM

Independent claim 18 is representative of the claims on appeal and recites:

> 18. A method for treating hyperuricemia, gout disease, nephritis, chronic renal failure, nephrolithiasis, uremia, urolithiasis, or a disease associated with uric acid, comprising:
>
> orally administering once daily a pharmaceutical composition which comprises as an active ingredient a compound of the following Formula I, or a pharmaceutically acceptable salt thereof or a hydrate thereof at a human dose of greater than 2 mg to 10 mg or less based on the free base of the compound of Formula I to a human subject in need thereof:



I

App. Br. 22.

IV. ISSUES AND ANALYSES

We review appealed rejections for reversible error based on the arguments and evidence Appellant provides for each issue Appellant identifies. 37 C.F.R. § 41.37(c)(1)(iv); *Ex parte Frye*, 94 USPQ2d 1072, 1075 (BPAI 2010) (precedential) (*cited with approval in In re Jung*, 637 F.3d 1356, 1365 (Fed. Cir. 2011) (holding that "it has long been the Board's practice to require an applicant to identify the alleged error in the examiner's rejections")). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a

preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

We decline to adopt the Examiner's findings and conclusions that the claims are obvious over the cited prior art. We explain our reasoning below.

A. Ground 1: Rejection of claims 18–20 over Ahn '467, Ahn 2016, Nair, and de Souza

1. The Examiner's findings and conclusions

The Examiner finds that Ahn '467 teaches the claimed compound as its Compound 4 and its HCl salt as Compound 33, as well as methods of synthesis. Final Act. 10 (citing Ahn '467 ¶¶ 664, 218, 397). The Examiner finds that Ahn '467 also teaches oral administration of this family of compounds and dosages of 1–200 mg/day. *Id.* (citing Ahn '467 ¶¶ 184, 185).

The Examiner points to Example 4 of Ahn '467, in which the claimed compound (Ahn '467's Compound 4) is administered to Cebus monkeys at a dosage of 3.75 mg/kg to test for uricosuric effectiveness. Final Act. 10 (citing Ahn '467 ¶¶ 722–730).

The Examiner finds that Ahn 2016 teaches the claimed compound, which it designates as UR-1102. Final Act. 10 (citing Ahn 2016, 158, Fig. 1). The Examiner finds that Ahn 2016 discloses a study in which, *inter alia*, 3mg/kg was administered to Cebus monkeys by oral gavage once daily to determine its effectiveness against benzbromarone in lowering blood urate levels. *Id.* at 11 (citing Ahn 2016, Abstr., 159, 162, Table 2). The Examiner finds that Ahn 2016 teaches that UR-1102 administered at 3mg/kg/day demonstrated both better systemic exposure and significantly greater plasma urate-lowering effectiveness than benzbromarone at equivalent or higher

doses. *Id.* (citing Ahn 2016, 164). The Examiner notes that Ahn 2016 explains that there are significant differences between species in terms of urate metabolism and that inhibition of renal urate transporter 1 (URAT1, a urate reabsorption transporter) by UR-1102 would be expected to cause significant urate-lowering in hyperuricemia patients. *Id.* The Examiner finds that Ahn 2016 further teaches that UR-1102 would be expected to show a much more significant effect in human patients than the decreases in plasma urate level achieved in Cebus monkeys. *Id.*

The Examiner next points to Nair, finding that it teaches a method for calculating an initial human equivalent dosage ("HED") based upon the no observed adverse effect level ("NOAEL") of a drug, as derived from preclinical, animal-based, toxicological studies. Final Act. 11 (citing Nair, 27–28, Fig. 1). The Examiner finds that Nair teaches the following equation (Eq. 1) for determining an HED from a dosage administered to an animal:

> HED mg/kg = Animal NOAEL (mg/kg) x (Weight $_{animal}$ [kg]/ Weight $_{human}$ [kg])$^{(1-0.67)}$

Id. at 12 (citing Nair, 28[2]). The Examiner also finds that Nair teaches dividing the calculated HED by 10 as a safety factor, based upon minimum risk of toxicity, rather than minimum pharmacological activity in humans. *Id.* at 11 (citing Nair, 27).

Using Nair's formula, the Examiner calculates the HED when the average mass of a Cebus monkey is 1.5 kg (*see* de Souza, 15), the average mass of an adult human is 60 kg (*see* Nair, Table 1), and based on a dosage

[2] The exponential term applied to the animal/human weight ratio incorporates the allometric exponent *b*, which is the mg/m^2 normalization ratio, accounting for differences in body surface area. *See* Nair 28; FDA Guidance, App'x A.

in a Cebus monkey of 3.75 mg/kg (*see* Ahn '467 ¶ 725). Final Act 12. Using these variables, the Examiner calculates an HED for a human of 1.11 mg/kg or, for a 60 kg human, 66 mg. *Id.* at 13. Dividing by the safety factor of 10 (*see* Nair, 27), the Examiner calculates a final dosage of 6.6 mg which is within the claimed range of 2mg to 10mg. *Id.*

The Examiner reasons that the difference between the teachings of Ahn '467 and Ahn 2016 and Appellant's claims is that the claims require a "human dose of greater than 2mg to 10mg or less" administered "to a human," whereas Ahn '467 and Ahn 2016 provide dosage data for the claimed composition when administered to a Cebus monkey. Final Act. 13. However, the Examiner explains, the conversion to an HED, by the method of Nair, based on the Cebus monkey trial dosages of Ahn '467 and Ahn 2016, results in a dosage that falls within the claimed range of 2mg to 10mg. *Id.*

The Examiner concludes that a person of ordinary skill in the art would have been motivated to administer 2 to 10 mg to a human, because one would expect there to be a more significant effect of the drug in human patients, as described by Ahn 2016. Final Act. 14 (*see* Ahn 2016, 164). The Examiner notes a prima facie case of obviousness can be established in a case in which the claimed range lies inside ranges disclosed by the prior art. *Id.* (citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); MPEP § 2144.05).

2. Appellant's arguments

Appellant argues that: (a) the cited prior art does not disclose all elements of the method of Claim 18; (b) the Examiner has misinterpreted the

art; and (c) the cited art would not have guided a skilled artisan to a human dose of greater than 2 mg to 10 mg or less of Formula I. App. Br. 7–15. Because we find argument (b) to be dispositive of the appeal, we address only that argument.

Appellant argues that the cited combination of Ahn '467, Ahn 2016, Nair, and de Souza would not have provided any motivation to a person of ordinary skill in the art to supplement the allegedly missing features discussed in the previous section. App. Br. 11.

Appellant argues that the Examiner relies on Equation 1 of Nair, and further includes an adjustment with an arbitrary safety factor to arrive at an HED of 2 to 10 mg. App. Br. 11 (citing Final Act. 11–12). According to Appellant, the Examiner's calculation of the HED based upon the lowest dose for Cebus monkeys of 3.75 mg/kg in Ahn '467 is foundationally incorrect, because the HED should be evaluated based on the highest dose tolerated in the animals. *Id.* Appellant argues, therefore, that Ahn '467 teaches that the dose for calculating the appropriate HED is 15 mg/kg. *Id.*

However, Appellant argues, even were one to use the lowest dose provided to the Cebus monkeys, the Examiner still does not arrive at the correct HED. Appellant argues, based upon Nair Equation 1, that the Examiner calculates an HED of 1.11 mg/kg, which equates to a total dose of 66.0 mg for a 60 kg average human. App. Br. 11. Appellant notes that the Examiner then divides the 66 mg dose by 10, resulting in a dose of 6.6 mg. *Id.* Appellant asserts that this is incorrect, because the 66 mg is the HED, according to Nair. *Id.* Appellant argues that this safety factor is irrelevant to the claimed invention, because it is not used for finding an effective dosage in humans but, rather, for determining a safe initial dose in clinical trials. *Id.*

Appellant notes that Nair does not apply this safety factor in its conversions. *Id.* (citing Nair, Eq. 1–3). According to Appellant, Nair teaches that the calculated dose where the HED adjusted by the safety factor is a dose with "minimum risk of toxicity," instead of one with "minimum pharmacologic activity in humans." *Id.* (citing Nair, 27). Appellant contends that this initial safe dose would not necessarily have a therapeutic effect. *Id.* Summarizing, Appellant argues that the Examiner's calculations are either irrelevant to the claimed method or inconsistent with the teachings of Nair. *Id.* at 13.

3. Analysis

We are not persuaded that the Examiner has established that a person of ordinary skill in the art would have had a reasonable expectation of success in treating a person having a disease associated with uric acid with a dosage in the claimed range of Appellant's Formula I.

We begin by agreeing with the Examiner that the calculation of the HED as 66 mg/kg, based upon the 3.75 mg/kg dose taught by Ahn '467 and the mean body mass of a Cebus monkey of 1.5 kg is mathematically correct. Furthermore, we agree with the Examiner that Nair teaches dividing the HED by a factor of 10 as a safety measure. Specifically, Nair teaches that:

> In step 4, the HED is divided by a factor value of 10, to increase safety of [the] first human dose. This safety factor is accountable for differences in physiological and biological processes between human and animal species. In the final step, the value obtained is converted to pharmacologically active dose in humans.

Nair, 28. Furthermore, Nair teaches that this selection of a dose "is based on minimum risk of toxicity, instead of choosing one with minimum pharmacologic activity in humans." *Id.* at 27. In short, Nair teaches a

method for calculating a safe dose, rather than an efficacious one, consistent with the emphasis on patient safety, and minimizing adverse drug effects, that is the primary criterion of Phase I clinical trials in humans. *See, e.g.*, University of Cincinnati College of Medicine, *Clinical Trials Phases Defined*, *available at*: https://med.uc.edu/depart/psychiatry/research/clinical-research/crm/trial-phases-1-2-3-defined (last visited July 18, 2025).

The Examiner's selection of Ahn '467's monkey trial dosage of 3.75 mg/kg is also appropriate. Ahn 2016 teaches, relative to its more extensive study, that:

> These results suggested that a dose of UR-1102 one-third that of benzbromarone would have the same URAT1 inhibitory activity in monkeys; in fact, *both the uricosuric and urate-lowering effects of UR-1102 at 3 mg/kg, the lowest dose, were comparable to those of benzbromarone at 100 mg/kg, the highest dose, with maximum efficacy*. Moreover, the maximum efficacy of UR-1102 at 30 mg/kg was significantly higher than that of benzbromarone at 100 mg/kg.

Ahn 2016, 162–163 (emphasis added). Anh 2016 thus teaches that a dose of 3 mg/kg (the lowest dose employed in the study) is efficacious in Cebus monkeys, and we find that the Examiner's selection of the 3.75 mg/kg, as disclosed by Example 4 of Ahn '467, is not an inappropriate choice for calculating the HED.

Furthermore, we acknowledge that Ahn 2016 teaches that, because human and Cebus monkey physiologies differ somewhat, it would have been reasonable to expect that the claimed compound (i.e., UR-1102 in Ahn 2016) would be more efficacious in humans than in Cebus monkeys. Ahn 2016 teaches that:

> In humans, as mentioned earlier, URAT1 mutations cause severe hypouricemia, and most gout patients are classified as under-

> excretors; therefore, URAT1 inhibition would be expected to cause significant urate-lowering in gout patients. On the other hand, Cebus monkeys have a certain level of uricase, and additionally their rate of urate synthesis is 7–8 times that in humans.… UR-1102 would be expected to show a much more significant effect in patients with gout than the greater decrease in plasma urate level it achieved in these monkeys.

Ahn 2016, 164.

Nevertheless, Nair teaches that the HED is meant to be a dose in humans equivalent to that used in animal studies at which there were no observable adverse effects ("NOAEL"). Nair, 27. With the Examiner's calculated HED of 66 mg, per Nair, the claimed compound would therefore have to be at least six to ten times as effective in humans than in Cebus monkeys to be as efficacious in treating uric-acid related diseases at the claimed doses. We conclude, based upon the evidence of record, and despite the speculative predictions of Ahn 2016, that a person of ordinary skill in the art could not have reasonably expected a ten-fold increase in the efficacy of the claimed compound in humans compared to Cebus monkeys.

We therefore conclude that Appellant's claims 18–20 are not obvious over the cited prior art because a person of ordinary skill in the art would not have had a reasonable expectation of success in administering the claimed compound in a human to treat uric acid-related diseases. Furthermore, because we find this analysis to be dispositive of the appeal, we do not address Appellant's other arguments.[3]

[3] We note however, that our conclusions with respect to Ground 1 would apply equally to Ground 2, because the Examiner's findings and conclusions and Appellant's arguments are essentially the same.

V. CONCLUSION

The rejection of claims 18–20 as unpatentable under 35 U.S.C. § 103 is reversed.

REVERSED

DECISION SUMMARY

Claim(s) Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed
18–20	103	Ahn '467, Ahn 2016, Nair, de Souza		18–20
18–20	103	Ahn '467, Ahn 2016, FDA Guidance,		18–20
Overall Outcome				18–20