

NOTE: This disposition is nonprecedential.

**United States Court of Appeals  
for the Federal Circuit**

---

**VANDA PHARMACEUTICALS INC.,**  
*Plaintiff-Appellant*

v.

**TEVA PHARMACEUTICALS USA, INC., APOTEX  
INC., APOTEX CORP.,**  
*Defendants-Appellees*

---

2023-1247

---

Appeal from the United States District Court for the District of Delaware in Nos. 1:18-cv-00651-CFC, 1:18-cv-00689-CFC, 1:19-cv-00560-CFC, 1:19-cv-00685-CFC, 1:19-cv-02202-CFC, 1:19-cv-02375-CFC, 1:20-cv-00083-CFC, 1:20-cv-00093-CFC, 1:20-cv-01104-CFC, 1:20-cv-01333-CFC, 1:21-cv-00121-CFC, 1:21-cv-00282-CFC, Chief Judge Colm F. Connolly.

---

Decided: May 10, 2023

---

NICHOLAS P. GROOMBRIDGE, Groombridge, Wu, Baughman & Stone LLP, New York, NY, argued for plaintiff-appellant. Also represented by ERIC ALAN STONE, JOSEPHINE YOUNG; JENNIFER REA DENEALD, DANIEL KLEIN, MICHAEL F. MILEA, Cold Spring, NY.

JOHN CHRISTOPHER ROZENDAAL, Sterne Kessler Goldstein & Fox, PLLC, Washington, DC, argued for defendant-appellee Teva Pharmaceuticals USA, Inc. Also represented by WILLIAM MILLIKEN, BYRON LEROY PICKARD, SASHA RAO, DEIRDRE M. WELLS.

AARON S. LUKAS, Cozen O'Connor P.C., Washington, DC, argued for defendants-appellees Apotex Inc., Apotex Corp. Also represented by WILLIAM BLAKE COBLENTZ; KERI SCHAUBERT, New York, NY.

---

Before DYK, BRYSON, and PROST, *Circuit Judges*.

DYK, *Circuit Judge*.

Vanda Pharmaceuticals Inc. sued Apotex Inc. and Apotex Corp. (collectively, “Apotex”) and Teva Pharmaceuticals USA, Inc. alleging that their abbreviated new drug applications (“ANDAs”) infringed claims in four patents owned by Vanda. Those claims relate to a method of treating Non-24-Hour Sleep-Wake Disorder (“Non-24”) with tasimelteon. The district court held that all of the asserted claims were invalid as obvious. *We affirm.*

#### BACKGROUND

Non-24 is a circadian rhythm disorder that occurs in individuals whose biological clocks are not synchronized, that is, entrained, to the 24-hour day. Non-24 causes too little nighttime sleep and too much daytime sleep. It can be treated by causing entrainment, i.e., synchronizing a person’s circadian rhythm to the 24-hour day. “Approximately 55 to 70 percent of totally blind individuals . . . suffer from Non-24.” J.A. 11.

Vanda sells a tasimelteon drug product (Hetlioz®) that is approved by the Food and Drug Administration (FDA)

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

3

and indicated for the treatment of Non-24. Vanda owns patents related to using tasimelteon to treat Non-24.

Appellees Teva and Apotex both filed ANDAs with the FDA “seeking approval for the commercial manufacture, use, and sale of tasimelteon.” J.A. 15. At issue in this case are four claims from four different unexpired Vanda-owned patents, U.S. Patent No. RE46,604 (the RE604 patent); U.S. Patent No. 10,149,829 (the ’829 patent); U.S. Patent No. 9,730,910 (the ’910 patent); and U.S. Patent No. 10,376,487 (the ’487 patent), all of which are listed in the FDA’s Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) for Hetlioz®. Teva’s and Apotex’s ANDAs both included certifications pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV) (“Paragraph IV Certifications”) alleging that the asserted claims are invalid and that all or most of the claims will not be infringed by the ANDA products.<sup>1</sup>

Vanda sued Teva and Apotex in the District of Delaware alleging that their ANDA submissions constituted infringement of claim 3 of the RE604 patent; claim 14 of the ’829 patent; claim 4 of the ’910 patent; and claim 5 of the ’487 patent. Teva and Apotex stipulated to infringement of claim 5 of the ’487 patent, denied infringement as to the other claims, and alleged that all asserted patent claims were invalid.

In a thorough opinion, the district court held that all four claims were invalid for obviousness. The court also held that Teva and Apotex did not infringe claim 3 of the RE604 patent, but did not make infringement findings for the asserted claims in the ’829 patent or ’910 patent.

---

<sup>1</sup> Teva’s certification alleged that no asserted claims would be infringed, and Apotex’s alleged that three of the four asserted claims would not be infringed.

Vanda appealed the district court's obviousness and infringement determinations.

We have jurisdiction under 28 U.S.C. § 1295(a)(1).

#### DISCUSSION

“[W]e review a district court's conclusions of law *de novo* and its findings of fact for clear error.” *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017). “Obviousness is a question of law, based on underlying factual findings . . .” *Id.*

#### I. RE604 Patent

Vanda alleged that Teva and Apotex infringed claim 3 of the RE604 patent, which depends from claims 1 and 2:

1. A method of entraining a patient suffering from Non-24 to a 24 hour sleep-wake cycle in which the patient awakens at or near a target wake time following a daily sleep period of approximately 7 to 9 hours, and maintaining said 24 hour sleep-wake cycle said method comprising: treating the patient by orally administering to the patient 20 mg of tasimelteon once daily before a target bedtime.
2. The method of claim 1 wherein the patient is totally blind.
3. The method of claim 2 wherein the tasimelteon is administered 0.5 to 1.5 hours before the target bedtime.

J.A. 117 (RE604 patent, col. 38, ll. 25–36). The district court held that claim 3 would have been obvious over two combinations of prior art references: Hack,<sup>2</sup> the

---

<sup>2</sup> Lisa M. Hack et al., *The Effects of Low-Dose 0.5-mg Melatonin on the Free-Running Circadian Rhythms of Blind Subjects*, 18 J. Biological Rhythms 420 (2003).

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

5

'244 Publication,<sup>3</sup> and Lankford;<sup>4</sup> and, alternatively, Hack, the '244 Publication, and Hardeland.<sup>5</sup>

Vanda claims that the district court made several errors in determining that claim 3 was obvious. Vanda first argues that the district court erred in stating that a skilled artisan would look to Hack, a prior art reference that explains that melatonin can be used to entrain blind patients with Non-24, when considering whether there would have been a reasonable expectation that tasimelteon would entrain. The district court did not err.

Of course, tasimelteon and melatonin are not identical. *See* J.A. 19,299–300 (Emens 858:21–859:9) (testimony that melatonin and tasimelteon have different binding affinities for melatonin receptors); J.A. 20,525–26 (Hardeland) (noting that melatonin and tasimelteon have some structural differences). However, as Lankford explains, “tasimelteon has high affinity for both the [melatonin] receptors, both in ranges similar to that of melatonin.” J.A. 20,539. The district court noted that prior art references concluded that tasimelteon and melatonin are similar, and, because of their similarities, “tasimelteon could . . . potentially entrain patients suffering from circadian rhythm sleep disorders.” J.A. 25 (citing J.A. 20,523 (Hardeland); J.A. 20,539 (Lankford)). There was no error in the district court’s choice to credit statements in the prior art explaining the similarities between tasimelteon and melatonin and why

---

<sup>3</sup> Int’l Pat. Application No. WO 2007/137244.

<sup>4</sup> D. Alan Lankford, *Tasimelteon for Insomnia*, 20 *Expert Op. Investigational Drugs* 987 (2011).

<sup>5</sup> Rüdiger Hardeland, *Tasimelteon, a Melatonin Agonist for the Treatment of Insomnia and Circadian Rhythm Sleep Disorders*, 10 *Current Op. Investigational Drugs* 691 (2009).

those similarities would have made data for melatonin relevant to tasimelteon.

Vanda's second argument is that, contrary to the district court's conclusion, none of the prior art references "would give a skilled artisan a reasonable expectation of success in using 20mg of tasimelteon . . . to entrain." Appellant's Br. 36. Vanda is incorrect.

The district court found that the claim element "orally administering to the patient 20 mg of tasimelteon" was disclosed in Hardeland, the '244 Publication, and Lankford.

Hardeland summarizes a phase II clinical trial by Rajaratnam et al.<sup>6</sup> that looked at the effect of tasimelteon on phase shifting, which is necessary for and related to entrainment. In that study, trial participants were given either a placebo or 10mg, 20mg, 50mg, or 100mg of tasimelteon after having their bedtimes shifted by five hours. Only the 100mg dose produced a statistically significant phase shift compared to the placebo. However, the 20mg dose produced a phase shift of over one hour, which was greater than the shift of about thirty minutes observed with the placebo (although the difference was not statistically significant). Based on this and other data, Hardeland concluded that the prior art showed that tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders, such as . . . entrainment difficulties" and stated that "[t]he most effective doses of

---

<sup>6</sup> Shantha M. W. Rajaratnam et al., *Melatonin Agonist Tasimelteon (VEC-162) for Transient Insomnia After Sleep-Time Shift: Two Randomised Controlled Multicentre Trials*, *Lancet* (Dec. 2, 2008).

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

7

tasimelteon were in the range of 20 to 50 mg/day.”<sup>7</sup>  
J.A. 20,529.

Relying on the Rajaratnam study, Dr. Jonathan Emens, one of Teva and Apotex’s expert witnesses, testified: “You would never really need a shift of more than an hour, and so [a phase shift of over an hour caused by a 20mg dose of tasimelteon] would be a sufficient shift to treat any individual with Non-24. ” J.A. 19,267 (Emens 729:16–18). While Dr. Emens recognized that a 20mg dose of tasimelteon did not have a statistically significant effect on phase shifting, J.A. 19,302–03 (Emens 870:4–871:23); J.A. 19,304 (Emens 877:11–16); J.A. 19,306 (Emens 884:17–21), he still concluded that Rajaratnam suggested that 20mg of tasimelteon can cause entrainment, *see* J.A. 19,267 (Emens 729:9–18). The district court found Dr. Emens to be “very credible” and “found his testimony to be compelling.” J.A. 10 (citation omitted).

The ’244 Publication, an international patent application filed by Vanda, also summarized the Rajaratnam study. Based largely on that study, the ’244 Publication stated that “[a]n oral dose of about 20 to about 50 mg is effective in treating sleep disorders when administered about 1/2 hour before sleep time.” J.A. 20,629. The ’244 Publication also claimed using 20mg of tasimelteon to treat

---

<sup>7</sup> Vanda is incorrect in saying that “Hardeland was flat-out wrong” in its interpretation of Rajaratnam. Appellant’s Reply Br. 10. Vanda argues that “Hardeland wrote that Rajaratnam had *not tested* doses below 100mg.” Appellant’s Reply Br. 10. While the sentence in Hardeland that Vanda relies on for that assertion is admittedly poorly worded, *see* J.A. 20,529, Vanda has not shown that “Hardeland was flat-out wrong” in its interpretation of Rajaratnam. It is clear reading Hardeland that Rajaratnam tested a 20mg dose of tasimelteon. *See* J.A. 20,527–28.

a circadian rhythm disorder. J.A. 20,630. Dr. Emens stated that the '244 Publication “says [tasimelteon] . . . can . . . cause entrainment . . . specifically at doses of about . . . 20 to 50 milligrams.” J.A. 19,267 (Emens 727:17–21). Thus, Vanda’s own patent application found significance in the 20mg result from the Rajaratnam study.

Lankford, another prior art reference, stated that a then-ongoing phase III trial of tasimelteon in blind people with Non-24 was “designed to assess the effectiveness of 20 mg of tasimelteon, compared with placebo, in improving nighttime sleep.” J.A. 20,539. Vanda argues that “the court erred in finding that Vanda’s ongoing clinical trial [mentioned in Lankford] would give an ordinary artisan an expectation of success.” Appellant’s Br. 40 (capitalization changed). Contrary to Vanda’s characterization, the district court did not find that Vanda’s ongoing clinical trial would have given a POSA an expectation of success in using tasimelteon to treat Non-24 in and of itself. Instead, the district court found “Lankford’s disclosure of Vanda’s Phase III trial would also have contributed to a skilled artisan’s expectation of success.” J.A. 43. There is no error in the district court’s use of the then-ongoing clinical trial as one piece of evidence, combined with other prior art references, to support an obviousness determination.

Taken together, the evidence is sufficient to support the district court’s finding that the tasimelteon prior art would have given a skilled artisan a reasonable expectation of success of entrainment with 20mg.<sup>8</sup>

---

<sup>8</sup> Vanda also argued that the district court erred in concluding, as part of its analysis of objective indicia of non-obviousness, that success in entrainment with 20mg of tasimelteon would not have been unexpected. For the reasons explained above, we find no error.



VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

9

Vanda's final argument is that the district court erred in its assessment of the objective indicia of non-obviousness. First, Vanda argues that the district court "disregarded the contrary evidence" of long-felt need, Appellant's Reply Br. 14, namely "the Reexamination Specialists' finding [in reexamination] that Vanda had 'provided evidence that the invention satisfies a long felt need,'" Appellant's Br. 43 (quoting J.A. 22,842). Vanda argues that the district court was required to weigh such evidence as part of secondary considerations concerning obviousness. However, "[t]he fact that the district court did not in its opinion recite every piece of evidence does not mean that the evidence was not considered." *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1343 (Fed. Cir. 2003) (citation omitted).

Vanda also argues that the district court disregarded evidence from Non-24 sufferers that "until tasimelteon nothing worked for them." Appellant's Reply Br. 14; *see also* Appellant's Br. 43. The district court did not disregard this evidence. It explained that Vanda cited one article that "recounts the successful treatment of one adolescent Non-24 patient who had previously been treated unsuccessfully with melatonin" and that the remaining evidence cited by Vanda was "cursory at best." J.A. 57. We find no error in the district court's determination that evidence of the successful treatment of one person does not constitute evidence of long-felt need and that the remaining evidence was cursory. The district court correctly found that long-felt need was not established.

Vanda finally argues that the district court erred by "dismiss[ing] the praise that Vanda has received because it was not 'praise specifically directed at the treatment method claimed in the RE604 patent.'" Appellant's Br. 43 (quoting J.A. 57). This was not an error. "[O]bjective evidence of non-obviousness fails [when] it is not 'commensurate in scope with the claims which the evidence is offered

to support.” *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) (quoting *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983)).

In sum, we find no error in the district court’s determination that claim 3 of the RE604 patent is invalid for obviousness.

## II. ’487 Patent

Vanda alleged that Teva and Apotex infringed claim 5 of the ’487 patent, which depends from claims 1 and 4:

1. A method of treating a human patient suffering from a circadian rhythm disorder or a sleep disorder that comprises orally administering to the patient an effective dose of tasimelteon without food, wherein the effective dose is 20 mg/d.

...

4. The method of claim 1, wherein the patient is suffering from a circadian rhythm disorder.

5. The method of claim 4, wherein the circadian rhythm disorder is Non-24 Disorder.

J.A. 198 (’487 patent, col. 4, ll. 2–16).

The district court held that claim 5 would have been obvious. At issue is the claim element that tasimelteon is administered “without food.” We agree with the district court because it would have been obvious to try administering tasimelteon without food.

“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.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). “If one of these predictable solutions leads to the anticipated success, the combination was obvious to

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

11

try.” *Valeant Pharms. Int’l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020).

In this case, there was market pressure (regulatory advice) to determine if food would have an effect on the efficacy of a drug, such as tasimelteon. At the time Vanda’s tasimelteon product was being developed, the FDA recognized that “[f]ood can change the [bioavailability] of a drug . . . [and f]ood effects on [bioavailability] can have clinically significant consequences.” U.S. Food & Drug Admin., Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies 2 (2002).<sup>9</sup> Therefore, a POSA would have understood that administering a drug with or without food could make it more or less effective. The guidance document also states that “[f]ood effect [bioavailability] studies are usually conducted for new drugs,” *id.* at 1, and that “[f]ood-effect [bioavailability] information should be available to design clinical safety and efficacy studies and to provide information for the CLINICAL PHARMACOLOGY and/or DOSAGE AND ADMINISTRATION sections of product labels.” *Id.* at 3.<sup>10</sup> Based on this language, it is clear that food-effect studies were expected to be performed on new drugs, meaning clinicians and others who purchased or prescribed the drug would have expected food effect information about the drug to have been developed.

---

<sup>9</sup> Vanda cited this guidance document in its clinical study report on tasimelteon. J.A. 23,145.

<sup>10</sup> In a later publication, the FDA clarified its position. See U.S. Food & Drug Admin., Bioavailability Studies Submitted in NDAs or INDs – General Considerations: Guidance for Industry 8 (2022) (noting that “[t]he effect of food on the [bioavailability] of the test product should also be assessed” when describing study design considerations for bioavailability studies for new drug applications).

Here, as the specification appears to recognize, *see* J.A. 197 ('487 patent, col. 2, ll. 18–19), there were only two permutations for the food variable: tasimelteon could have been administered with food or without food. In other words, there were two identifiable and predictable options. As the district court recognized, “[w]hether to administer tasimelteon with food is a binary choice.” J.A. 72. Under these circumstances, given the FDA guidance, it would have been obvious to try administering tasimelteon without food. Therefore, we agree with the district court that claim 5 of the '487 patent is invalid for obviousness.

### III. '910 Patent

Vanda alleged that Teva and Apotex infringed claim 4 of the '910 patent, which depends from claims 1, 2, and 3:

1. A method of treating a patient for a circadian rhythm disorder wherein the patient is being treated with rifampicin, the method comprising:
  - (A) discontinuing the rifampicin treatment and then
  - (B) treating the patient with tasimelteon, thereby avoiding the use of tasimelteon in combination with rifampicin and also thereby avoiding reduced exposure to tasimelteon caused by induction of CYP3A4 by rifampicin.
2. The method of claim 1 that comprises treating the patient for Non-24-Hour Sleep-Wake Disorder.
3. The method of claim 2 wherein the patient is light perception impaired (LPI).
4. The method of claim 3 wherein treating the patient with tasimelteon comprises orally

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

13

administering to the patient 20 mg of tasimelteon once daily before a target bedtime.

J.A. 159 ('910 patent, col. 40, ll. 7–22).

The district court found claim 4 would have been obvious. With respect to obviousness, the only additional limitation at issue here with respect to claim 4 is the limitation in claim 1 of: “(A) discontinuing the rifampicin treatment and then (B) treating the patient with tasimelteon.” J.A. 159 ('910 patent, col 40, ll. 10–11). The focus of claim 1 is avoiding the coadministration of rifampicin (an antibiotic drug) and tasimelteon. Rifampicin, also known as rifampin, is a strong inducer of CYP3A4. CYP3A4 is an enzyme that is often involved in drug metabolism. A CYP3A4 inducer induces the expression of CYP3A4, which causes CYP3A4 to increase its drug metabolism thereby decreasing the amount of the metabolized drug in blood plasma.

As of January 2012, the priority date of the patent, it was known that ramelteon (a drug similar to tasimelteon) “undergoes an 80 percent decrease in blood plasma levels when it is co-administered with the CYP3A4 inducer rifampin” because it is metabolized by CYP3A4. J.A. 29.

The district court found that a POSA “would have looked to ramelteon to predict tasimelteon drug-drug interactions because of the many known similarities between ramelteon and tasimelteon.” J.A. 47. Based on the ramelteon studies, the district court held that if “a skilled artisan wanted to administer tasimelteon to a patient who was already taking . . . rifampin, then the artisan would have expected that tasimelteon should not be co-administered with rifampin and would have thought it necessary and obvious to stop treating the patient with rifampin before treating the patient with tasimelteon.” J.A. 48 (citations omitted).

We see no error in the district court’s finding that a skilled artisan would have looked to the ramelteon art because ramelteon and tasimelteon bind to the same receptors, have similar half lives in the body, and are structurally similar. The district court’s finding that a POSA “would have looked to ramelteon” is not clearly erroneous.

Vanda also argues that the prior art taught away from there being any problems with administering tasimelteon with a CYP3A4 inducer. It is true that the only cited prior art that studied the metabolism of tasimelteon by CYP3A4, the Vachharajani reference,<sup>11</sup> found that “[n]o metabolism of [tasimelteon] was observed following incubation with [CYP3A4].” J.A. 23,857. This conclusion was echoed in Hardeland, which did not include CYP3A4 in its list of enzymes that metabolize tasimelteon. However, these studies did not look into CYP3A4’s metabolism of tasimelteon after CYP3A4 had been induced by rifampicin, a requirement of the claims.

The evidence in Vachharajani and Hardeland does not refute the conclusion that a skilled artisan would recognize that tasimelteon and ramelteon have similar properties, nor does it suggest that the metabolism of tasimelteon by CYP3A4 in its induced and uninduced (natural) states would be the same. Induction of CYP3A4 by rifampicin causes a large increase in CYP3A4 activity. So, it is possible for CYP3A4 to metabolize a drug after being induced even if CYP3A4 does not metabolize that drug in its uninduced state. See J.A. 19,412 (Greenblatt 1,116:17–20). A credible Teva/Apotex expert testified that, for this reason, a skilled artisan who knew about the Vachharajani

---

<sup>11</sup> Nimish N. Vachharajani et al., *Preclinical Pharmacokinetics and Metabolism of BMS-214778, a Novel Melatonin Receptor Agonist*, 92 J. Pharm. Scis. 760 (2003).

VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

15

reference could not have ruled out an interaction between tasimelteon and a CYP3A4 inducer, like rifampicin—i.e., could not have ruled out that coadministration of tasimelteon and a CYP3A4 inducer such as rifampin would cause tasimelteon to be metabolized too quickly. J.A. 54; *see also* J.A. 19,412 (Greenblatt 1,116:17–20) (“[I]nduction causes a massive increase in the amount of enzymes, and you cannot exclude a major role of CYP3A4 [in metabolizing tasimelteon] in the induced state even if you can’t detect it in the uninduced state.”). We therefore find no error in the district court’s finding that it was obvious to avoid coadministration of rifampicin and tasimelteon, and that claim 4 would have been obvious.

#### IV. ’829 Patent

Vanda alleged that Teva and Apotex infringed claim 14 of the ’829 patent, which depends from claim 13:

13. A method of treating a patient for a circadian rhythm disorder or for a sleep disorder wherein the patient is being treated with a strong CYP1A2 inhibitor selected from a group consisting of fluvoxamine, ciprofloxacin, and verapamil, the method comprising:

(A) discontinuing treatment with the strong CYP1A2 inhibitor and then

(B) treating the patient with 20 mg of tasimelteon once daily.

14. The method of claim 13, that comprises treating the patient for Non-24-Hour Sleep-Wake Disorder.

J.A. 194 (’829 patent, col. 38, ll. 52–62). The claim elements at issue here are “(A) discontinuing treatment with the strong CYP1A2 inhibitor and then (B) treating the

patient with . . . tasimelton.” J.A. 194 (’829 patent, col. 38, ll. 57–59).

The district court relied on Hardeland and, as with claim 4 of the ’910 patent, a ramelteon study in finding that claim 14 of the ’829 patent would have been obvious. CYP1A2 is another enzyme that is often involved in drug metabolism. A CYP1A2 inhibitor decreases CYP1A2’s ability to metabolize drugs, leading to a higher concentration of drugs metabolized by CYP1A2 in blood plasma. The Hardeland reference states that “[a]s tasimelton is metabolized by [CYP1A2] . . . , coadministration of any drug that inhibits [this enzyme] should be regarded with caution.” J.A. 20,528. The ramelteon study showed that “ramelteon underwent a 100-fold increase in blood plasma levels when it was co-administered with the CYP1A2 inhibitor fluvoxamine.” J.A. 29 (citations omitted). The district court explained that, as with claim 4 of the ’910 patent, the ramelteon study is relevant to tasimelton and “[a] skilled artisan would have known that any drug-drug interaction resulting in a five-fold change in blood plasma levels is considered ‘large’ by FDA standards, and therefore a skilled artisan would have viewed the ramelteon-fluvoxamine drug-drug interaction as a ‘huge interaction’ and clearly significant.” J.A. 29 (citation omitted).

Vanda argues that the prior art does not tell a skilled artisan not to prescribe tasimelton with a CYP1A2 inhibitor and notes that the testing that explicitly showed that coadministration of tasimelton and a CYP1A2 inhibitor renders tasimelton ineffective was done after the priority date. This argument misunderstands the standard for obviousness.

Obviousness does not require certainty—it requires a reasonable expectation of success. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Taken together, Hardeland’s warning and the ramelteon study supported



VANDA PHARMACEUTICALS INC. v.  
TEVA PHARMACEUTICALS USA, INC.

17

the district court's finding that a skilled artisan would have expected that taking a CYP1A2 inhibitor with tasimelteon would have negatively impacted the efficacy of tasimelteon and so the two should not be given together. Appellees did not need to show that coadministration would have negatively impacted tasimelteon's efficacy, just that it would have been reasonable to expect it to do so. The district court did not err in finding that claim 14 would have been obvious.

#### CONCLUSION

The district court did not err in finding all of the challenged claims obvious. In light of our invalidity conclusion, we do not reach the question of infringement.

**AFFIRMED**