IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS, INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., *et al.*, Defendants.	Civil Action No. 18-651-CFC

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OPINION

December 13, 2022
Wilmington, Delaware

COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of separate filings of Abbreviated New Drug Applications (ANDAs) by Defendant Teva Pharmaceuticals USA, Inc. and by Defendants Apotex Inc. and Apotex Corp. (collectively, Apotex) with the U.S. Food and Drug Administration (FDA) for approval to market generic versions of Plaintiff Vanda Pharmaceuticals Inc.'s Hetlioz® drug product.

Hetlioz® is the only FDA-approved drug indicated for the treatment of Non-24-hour sleep-wake disorder, a circadian rhythm sleep disorder suffered by individuals whose biological clocks do not synchronize to a 24-hour day. Vanda sells Hetlioz® in 20 milligram tasimelteon capsules.

Vanda has asserted four patents. It alleges that, pursuant to 35 U.S.C. § 271(e)(2)(A), Defendants' ANDA submissions to the FDA constitute infringement of claim 3 of U.S. Patent No. RE46,604 (the RE604 patent), claim 14 of U.S. Patent No 10,149,829 (the #829 patent), claim 4 of U.S. Patent No. 9,730,910 (the #910 patent), and claim 5 of U.S. Patent No. 10,376,487 (the #487 patent).

Defendants have stipulated to infringement of claim 5 of the #487 patent. They otherwise deny infringement and assert in their defense that the asserted patent claims are invalid.

I held a four-day bench trial, and, as required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arises were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., and specifically by the so-called Hatch-Waxman Amendments to the FDCA. Justice Kagan provided in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the uses for which the drug may be marketed. The FDA may approve a brand-name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.
>
> Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch-Waxman Amendments.

Those amendments allow a generic competitor to file an abbreviated new drug application (ANDA) piggy-backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method-of-use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).

> After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.
>
> * * * *
>
> [One of those ways] is to file a so-called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue [under 35 U.S.C. § 271(e)(2)(A)]. Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (irrelevant citations and internal quotation marks omitted).

II. FINDINGS OF FACT

A. The Parties

1) Vanda is a Delaware corporation with its principal place of business in Washington, District of Columbia. D.I. 287 ¶ 3. Vanda owns the asserted patents. D.I. 287 ¶ 1.

2) Teva is a Delaware corporation with its principal place of business in New Jersey. D.I. 287 ¶ 7.

3) Apotex Inc. is a Canadian corporation with its principal place of business in Ontario, Canada. D.I. 287 ¶ 36.

4) Apotex Corp. is a Delaware corporation with its principal place of business in Florida. D.I. 287 ¶ 36. Apotex Corp. is a wholly owned subsidiary of Apotex Inc. D.I. 287 ¶ 36.

B. The Parties' Witnesses

1. Vanda's Witnesses

a. Fact Witnesses

5) Dr. Mihael Polymeropoulos is Vanda's Chief Executive Officer and an inventor of the asserted patents. Tr. of March 28 to March 31, 2022 Trial at 98:4–5 (Polymeropoulos). Polymeropoulos owns four percent of Vanda's shares. Tr. at 160:19–21 (Polymeropoulos).

6) Ravi Pandrapragada is Vanda's Associate Director of Chemistry, Manufacturing, and Controls. Tr. at 255:21–24 (Pandrapragada).

b. Expert Witnesses

7) Dr. Daniel Combs is a sleep medicine physician at the Banner University Medical Group and an Assistant Professor of Medicine at the University of Arizona College of Medicine. PTX 823 at 1.

8) Dr. Stephen C. Bergmeier is the Chair of the Department of Chemistry and Professor of Chemistry at Ohio University and the co-founder of Promiliad Biopharma. PTX 822 at 1–2.

9) Dr. Steven W. Lockley is an Associate Professor of Medicine at Harvard Medical School, a Professor of Sleep and Chronobiology at the University of Surrey, and a neuroscientist at Brigham and Women's Hospital. Tr. at 896:2–7 (Lockley).

10) Dr. Andrew Parkinson is the Chief Executive Officer of XPD Consulting and an Adjunct Professor of Pharmacology and Toxicology at Kansas University Medical Center. PTX 827 at 1.

11) Dr. Charles A. Czeisler is the Director of the Division of Sleep Medicine at Harvard Medical School, Chief of the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital, and a Professor of Medicine at Harvard Medical School. PTX 824 at 2, 4. Dr. Czeisler is the chair of Vanda's scientific advisory board and has been a consultant for Vanda since 2004. Tr. at 1212:22–1213:5 (Czeisler). He currently receives $8,500 each month from Vanda

for his consulting services and owns shares of Vanda's stock that are collectively worth somewhere between $1.5 and $2 million. Tr. at 1213:7–1214:4 (Czeisler).

2. Defendants' Witnesses

a. Fact Witnesses

12) David DeCicco is Teva's Director of Regulatory Affairs. He has held his position at Teva for approximately three years. Tr. at 303:15–21 (DeCicco). His responsibilities include reviewing and approving FDA submissions from Teva's research and development and commercial facilities. Tr. at 303:34–304:1 (DeCicco).

13) Bisht Bhupesh Perni Singh is an Apotex employee. Tr. at 306:10–14 (Singh). He is responsible for managing Apotex's communications with the FDA. Tr. at 306:17–22 (Singh).

b. Expert Witnesses

14) Deborah Jaskot is a pharmaceutical consultant who provides regulatory advice to generic and brand pharmaceutical companies. Tr. at 397:2–8 (Jaskot). Jaskot is an expert in the field of FDA regulations and the FDA drug approval process. D.I. 299 ¶ 1; Tr. at 396:7–12 (Jaskot). Jaskot previously worked for Teva as Vice President of U.S. Generic Regulatory Affairs and North American Policy. Tr. at 397:16–20 (Jaskot); DTX 399 at 1. While at Teva, Jaskot was the primary liaison with the FDA's Office of Generic Drugs and the Office of Pharmaceutical Science. Tr. at 398:16–20 (Jaskot); DTX 399 at 1–2.

15) Dr. John Winkelman is the founder and Chief of the Sleep Disorders Clinical Research Program at Massachusetts General Hospital and a Professor at Harvard Medical School. Tr. at 493:15–17 (Winkelman).

16) Dr. Robert Perni is a Vice President of Research & Development at IM Therapeutics and a Principal at JMD Pharma Creativity, LLC. DTX 401 at 1.

17) Dr. Jonathan Emens is an Associate Professor of Psychiatry and an Assistant Professor of Medicine at Oregon Health & Science University and a Deputy Director of Mental Health at the VA Portland Healthcare System. DTX 397 at 1–2. I found at trial and confirm here that Dr. Emens was very credible. As I stated at the conclusion of the trial:

> [H]is mannerism while testifying, his directness and lack of hesitation. He does not appear to have any source of bias. And so, I found his testimony to be compelling. And . . . that's a factual finding that I'm making. And I'm making it today because I have had many days watching these witnesses, all of whom are very, very impressive, but his testimony in particular stuck out to me.

Tr. at 1258:2–10.

18) Dr. David Greenblatt is a Professor in the Department of Immunology at the Tufts University School of Medicine. DTX 398 at 1.

C. Non-24-Hour Sleep-Wake Disorder (Non-24)

19) Circadian rhythms are internal physiological and behavioral patterns that are regulated by an endogenous pacemaker located in the suprachiasmatic

nuclei (SCN) of the human brain. Tr. at 705:23–706:9 (Emens); PTX 815 at 17; PTX 002 at 1–2.

20) In most people, including most blind people, the period generated by the SCN is slightly longer than 24 hours. Tr. at 1182:25–1183:8 (Czeisler); JTX 145 at 2.

21) Non-24-hour sleep-wake disorder (Non-24), also called free-running disorder, is a circadian rhythm disorder occurring in individuals whose 24-hour biological clock is no longer synchronized (i.e., entrained) to the 24-hour day. PTX 005; Tr. at 115:17–116:5 (Polymeropoulos); PTX 002 at 1; PTX 815 at 17; JTX 084 at 3.

22) Doctors and other experts who study sleep disorders, refer to this lack of synchronization as a lack of entrainment, and they use "entrainment" and "synchronization" (and "entrain" and "synchronize") interchangeably when discussing Non-24. *See, e.g.*, PTX 005 at 1.

23) Approximately 55 to 70 percent of totally blind individuals (i.e., those lacking conscious light perception) suffer from Non-24.

24) The symptoms of Non-24 are sleep disturbance—i.e., decreased and poor nighttime sleep and increased daytime sleep—and lack of daytime alertness. PTX 005 at 1; Tr. at 496:18–25, 528:20–529:7 (Winkelman); Tr. at 214:12–215:11 (Combs).

25) Sleep disturbance is the main reason why patients suffering from Non-24 seek treatment from a doctor. Tr. at 496:18–25 (Winkelman); *see also* PTX 815 at 17 (tasimelteon clinical report noting that "[p]oor quality or quantity of sleep and excessive daytime sleepiness resulting from Non-24 are common complaints" of patients).

26) Lack of entrainment is the only known cause of Non-24. Tr. at 212:4–10 (Combs); Tr. at 524:15–17 (Winkelman); PTX 005.

D. The Goals of Non-24 Treatment

27) When treating a patient, doctors can choose to address the patient's symptoms, the cause of the patient's illness, or both the symptoms and the cause. Tr. at 496:14–498:5 (Winkelman). As Dr. Winkelman credibly testified:

> [Y]ou can treat the underlying cause or you can treat the symptoms. In medicine, we understand this distinction with patients every day . . . ."

Tr. at 496:14–17 (Winkelman).

28) Entrainment can be a goal of Non-24 treatment. Tr. at 116:6–117:1 (Polymeropoulos); Tr. at 212:4–10 (Combs); Tr. at 529:15–20 (Winkelman); PTX 815 at 17.

29) Limiting sleep disturbances so as to increase nighttime sleep and decrease daytime sleep can also be a goal of Non-24 treatment. Tr. at 496:18–25, 498:9–16, 499:8–10 (Winkelman); JTX 084 at 3, 9.

30) Vanda argues, but it did not establish by a preponderance of the evidence, that "[*t*]*he* goal in treating individuals with Non-24 is to synchronize their circadian clock with the external light-dark cycle." D.I. 312 ¶ 38 (emphasis added). Vanda cites in support of this argument the testimony of three witnesses (Drs. Combs, Winkelman, and Polymeropoulos) and a sentence from a clinical study report for tasimelteon (PTX 815). But that record evidence does not establish by a preponderance of the evidence that entrainment is necessarily the only goal of Non-24 treatment.

31) Dr. Combs, for example, testified only that entrainment can be *a* goal in treating individuals with Non-24, *see* Tr. at 212:9–10 (Combs) ("to treat Non-24, a goal would be to entraining the patient"), and when pressed on cross-examination he acknowledged that tasimelteon can also be used to increase nighttime sleep and reduce daytime sleep:

> Q. . . . [D]o you agree that in addition to entraining a Non-24 patient, that tasimelteon can also increase total sleep time per day and reduce total naptime per day?
>
> A. When patients are most symptomatic, I absolutely agree.

Tr. at 242:10–15 (Combs).

32) Dr. Winkelman similarly testified that entrainment can be *a* goal of Non-24 treatment but that treating sleep disturbances is also a goal. *See* Tr. at 496:18–25, 498:9–16, 499:8–10 (Winkelman).

33) Dr. Polymeropoulos testified that "we knew that a goal, the goal, of a successful treatment Non-24-hour sleep-wake disorder that would be accepted by experts would have been the demonstration of entrainment of the 24-hour circadian rhythm." Tr. at 212:4–10 (Polymeropoulos). I find it telling that he first stated, "a goal," before he corrected himself and said, "the goal." And I also discount Dr. Polymeropoulos's testimony because of what I observed to be a self-serving demeanor on the stand and because he is a named inventor with a financial interest in the outcome of this litigation.

34) The sentence in the clinical study Vanda relies on reads: "The ultimate goal in treating individuals with Non-24 is to synchronize their circadian clock with the 24-hour day so that all of their physiology and behavior is aligned appropriately with the 24-hour social day." PTX 815 at 17. But as Dr. Winkelman credibly testified, the *ultimate* goal in a treatment is not necessarily or always *the* goal of the treatment regimen. Indeed, the word "ultimate" makes clear that there are *other* goals, as "ultimate" is a relative term that describes "the best or most extreme of its kind." *See Ultimate*, MERRIAM-WEBSTER.COM, https://www.merriam-webster.com/dictionary/ultimate (last visited Dec. 12, 2022).

35) Finally, the cited clinical study itself undermines Vanda's argument that the sole goal of Non-24 treatment is entrainment. The study identifies "secondary objectives" of Non-24 treatment that include increased nighttime sleep

in the lower quartile of nights (LQ-nTST) and decreased daytime sleep in the upper quartile of days (UQ-dTSD). PTX 815 at 9; Tr. at 508:3–13, 508:19–509:3 (Winkelman).

E. Defendants' ANDAs and Drug Labels

36) Tasimelteon is the active pharmaceutical ingredient in Vanda's Hetlioz® drug product and in each of Defendants' ANDA products. D.I. 287, Ex. 1 ¶ 106.

37) Teva filed ANDA No. 211601 with the FDA seeking approval for the commercial manufacture, use, and sale of tasimelteon prior to the expiration of the asserted patents. D.I. 287 at 44–45.

38) Teva's ANDA contains a certification pursuant to 21 U.S.C. § 355(j)(2)(a)(vii)(IV) alleging that each of the asserted claims is invalid and will not be infringed by Teva's ANDA Product. D.I. 287 at 44.

39) Teva delivered letters to Vanda notifying Vanda of Teva's Paragraph IV certifications. D.I. 287 at 44–46.

40) Apotex filed ANDA No. 211607 with the FDA seeking approval for the commercial manufacture, use, and sale of tasimelteon prior to the expiration of the asserted patents. D.I. 287 at 46–47.

41) Apotex's ANDA contains a Paragraph IV Certification alleging that each of the asserted claims is invalid, and that, except for claim 5 of the #487

patent, Apotex's ANDA Product will not infringe the asserted patents. D.I. 287 at 47.

42) Apotex delivered letters to Vanda notifying Vanda of Apotex's Paragraph IV certifications. D.I. 287 at 46–49.

43) A drug label contains instructions for prescribers about how to use a medication. Tr. at 211:18–21 (Combs). The intended audience for a drug label is whoever is prescribing the medication, which in the case of tasimelteon would be primarily sleep medicine physicians. Tr. at 211:22–24 (Combs).

44) The language in Defendants' proposed labeling for each of their respective proposed ANDA products is essentially the same in all relevant respects to Vanda's FDA-approved Hetlioz® drug labeling. D.I. 287, Ex. 1 ¶ 97.

45) Defendants' proposed labels for tasimelteon are, in all relevant ways, the same as the parts of Vanda's Hetlioz® label directed to the treatment of Non-24, pharmacokinetics, and drug-drug interactions. D.I. 287, Ex. 1 ¶ 97.

46) Each of Defendants' ANDA products contains 20 milligrams of tasimelteon. D.I. 287, Ex. 1 ¶ 99.

47) Each of Defendants' labels recommends that 20 milligrams of tasimelteon be administered one hour before bedtime, at the same time every night. D.I. 287, Ex. 1 ¶ 100; JTX 030 at 2; JTX 033 at 3.

48) The intended audience for Teva's proposed label is prescribers such as physicians. Tr. at 304:7–16 (DeCicco). Teva expects prescribers of its generic tasimelteon product to "follow what's in the labeling." Tr. at 304:17–21 (DeCicco).

49) The intended audience for Apotex's proposed label is prescribers. Tr. at 307:11–14 (Singh). The purpose of Apotex's proposed label "is to guide the physicians and to know more about the product and the molecule." Tr. at 307:11–14 (Singh). Apotex expects prescribers to follow the information in Apotex's label when prescribing tasimelteon and understands that "the dosage regime is as per the labeling that is approved for the brand and that is what we have to follow." Tr. at 307:15–19, 308:1–8 (Singh).

50) Defendants' labels for each of their proposed drugs state that they are "indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in adults." JTX 030 at 2; JTX 033 at 3.

51) Defendants' labels do not use the words "entrain," "entrainment," "synchronize," "synchronization," or "synchronizing."

52) I find credible Dr. Winkelman's testimony that defendants' labels "do not encourage, recommend, require or promote the use of defendants' products as a method specifically here for entraining a patient." Tr. at 495:21–24 (Winkelman).

53) Vanda argues that section 1 of Defendants' labels promotes and encourages treating Non-24 by entraining because that section "states that tasimelteon is indicated for the treatment of Non-24." D.I. 311 at 21. But as noted above, although entrainment can be a goal—and indeed the ultimate goal—of Non-24 treatment, it is not necessarily the only goal of such treatment.

54) Vanda also argues that sections 2.2 and 2.4 encourage and promote the treatment of Non-24 by entrainment. D.I. 311 at 22. Section 2.2 instructs prescribers to administer 20mg of tasimelteon one hour before bedtime at the same time every night. JTX 030 at 2; JTX 033 at 3. Section 2.4 instructs that a patient who cannot take tasimelteon at the same time on a given night should skip that day's dose rather than take it too early or too late. JTX 030 at 2; JTX 033 at 3. A prescriber, however, would understand that tasimelteon induces sleepiness and for that reason might want the patient to take tasimelteon near bedtime every night for its soporific effect and not for entrainment. Tr. at 1210:24–1211:6 (Czeisler). Thus, I find that sections 2.2 and 2.4 do not necessarily imply that a prescriber should use tasimelteon to entrain the patient.

55) Vanda also argues that section 14.1 and Table 3 of Defendants' labels teach and promote the use of tasimelteon to treat Non-24 through entrainment because they "describe[] the results seen in patients in Vanda's SET and RESET clinical trials." D.I. 311 at 23. The description of those results, however, makes

no mention of entrainment endpoints; instead it reports two sleep-measure "efficacy endpoints" for "duration and timing of nighttime sleep and daytime naps . . . based on [1] the 25% of nights with the least nighttime sleep, and [2] the 25% of days with the most daytime nap time." JTX 030 at 8–9; JTX 033 at 10–11; Tr. at 500:11–501:1 (Winkelman). These endpoints measure the drug's effect on symptoms of Non-24—i.e., insufficient nighttime sleep and increased daytime sleep. Tr. at 499:3–22, 500:11–501:1, 501:9–14, 503:3–504:25 (Winkelman).

56) I found credible Dr. Winkelman's testimony that if the intent of Defendants' labels were to induce the treatment of Non-24 by entrainment, one would expect the clinical studies reported in Defendants' labels to include entrainment endpoints such as biomarkers for "melatonin . . . or cortisol or some hormone that could represent entrainment." Tr. at 501:18–22 (Winkelman).

57) Accordingly, I find that Vanda failed to prove by a preponderance of the evidence that Defendants' ANDA labels instruct, recommend, encourage, teach, or promote the use of Defendants' tasimelteon drug products to treat Non-24 by entraining a patient to a 24-hours sleep-wake cycle.

F. The Asserted Patents

1. The RE604 Patent

58) The RE604 patent, titled "Treatment of Circadian Rhythm Disorders," has a priority date of January 26, 2012, the filing date of U.S. Provisional Patent Application No. 61/590,974. D.I. 287 at 50.

59) Vanda asserts claim 3 of the RE604 patent, which depends from claims 1 and 2.

60) Claims 1, 2, and 3 read as follows:

> 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.

JTX 001 at 41.

2. The #829 Patent

61) The #829 patent, titled "Treatment of Circadian Rhythm Disorders," has a priority date of October 15, 2012, the filing date of U.S. Provisional Patent Application No. 61/714,149. D.I. 287 at 51.

62) Vanda asserts claim 14 of the #829 patent, which depends from claim 13.

63) Claims 13 and 14 read as follows:

> 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.

JTX 003 at 35.

3. The #910 Patent

64) The #910 patent, titled "Treatment of Circadian Rhythm Disorders," has a priority date of November 12, 2013, the filing date of U.S. Provisional Patent Application No. 61/903,354. D.I. 287 at 52.

65) Vanda asserts claim 4 of the patent, which depends from claims 1, 2, and 3.

66) Claims 1, 2, 3, and 4 read as follows:

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

JTX 004 at 41.

4. The #487 Patent

67) The #487 patent, titled "Method of Treatment," has a priority date of November 12, 2013, the filing date of U.S. Provisional Patent Application No. 61/903,354. D.I. 287 at 53

68) Vanda asserts claim 5 of the #487 patent, with depends from claims 1 and 4.

69) Claims 1, 4, and 5 read as follows:

> 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.

JTX 005 at 4.

G. The Artisan of Ordinary Skill

70) Initially, the parties offered competing but similar definitions of the artisan of ordinary skill to whom the asserted patents are directed. Defendants' artisan called for a higher level of education and more experience in conducting clinical trials than Vanda's artisan. *Compare* D.I. 287 at 601–02 (Vanda's definition) *with* D.I. 287 at 612 (Defendants' definition).

71) Before trial, however, the parties stipulated that "[e]ach Party's expert is qualified as an expert in the relevant field" and that "[f]or the purposes of the infringement and invalidity analysis" of the patents asserted at trial "each expert's opinion would be the same using either definition of a person of ordinary skill in the art." D.I. 298 ¶¶ 1, 4. Accordingly, I make no finding of fact with respect to the artisan of ordinary skill.

H. Knowledge of an Artisan of Ordinary Skill as of January 26, 2012

1. Exogenous Melatonin Could Effectively Entrain Blind People with Non-24

72) As early as 2000, it was well known among artisans of ordinary skill that exogenous melatonin was a drug that could entrain blind patients with Non-24 to a normal 24-hour sleep-wake cycle. Tr. at 709:18–22 (Emens).

73) Skilled artisans, moreover, knew the mechanism by which exogenous melatonin achieved entrainment. Tr. at 709:23–25 (Emens).

74) Exogenous melatonin is a melatonin agonist that binds to the melatonin 1 and melatonin 2 receptors, often referred to as the MT1 and MT2 receptors. Tr. at 710:1–3 (Emens).

75) Skilled artisans knew that exogenous melatonin's binding affinities for these receptors were what gave the drug its ability to reset or "phase shift" a person's circadian rhythm and thereby entrain them to a normal 24-hour cycle. Tr. at 710:1–3 (Emens).

76) By 2007, the use of melatonin to treat Non-24 was formally recommended by the American Academy of Sleep Medicine. DTX 037 at 11; *see* Tr. at 722:20–723:22 (Emens).

77) Prior art described the "[d]aily administration of exogenous melatonin [a]s the current treatment of choice for this so-called 'non-24 h sleep/wake disorder.'" DTX 039 at 1.

2. Tasimelteon is a Melatonin Agonist with Similar Properties to Exogenous Melatonin

78) As of January 26, 2012, skilled artisans knew that tasimelteon is a melatonin agonist with similar properties to exogenous melatonin.

79) Early animal studies of tasimelteon concluded that tasimelteon was "a novel melatonin receptor agonist that may be a useful treatment for sleep disorders

that result from disruption of circadian rhythms" in humans. JTX 091 at 1; Tr. at 725:5–726:11 (Emens).

80) By 2007, Vanda filed an international patent application (the #244 Publication) directed to administering tasimelteon to treat circadian rhythm disorders and sleep disorders. DTX 041.

81) The #244 Publication describes tasimelteon as a "specific and potent agonist of the MT1[] and MT2[] melatonin receptors" in the human brain and as a compound that "demonstrates potent chronobiotic activity" in the human body. DTX 041 at 2; *see* Tr. at 727:15–19 (Emens).

82) Other prior-art references concluded that (1) tasimelteon was like exogenous melatonin in that both had similar binding affinities for the MT1 and MT2 receptors and could phase-shift a person's circadian rhythm and (2) tasimelteon could therefore potentially entrain patients suffering from circadian rhythm sleep disorders. *See* DTX 016 at 1 ("Tasimelteon . . . is a melatonin receptor agonist. Because of the high density of melatonin receptors in the circadian pacemaker, the suprachiasmatic nucleus, melatonergic actions can phase-shift circadian rhythms and promote sleep."); DTX 020 at 6 ("[T]asimelteon has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin. Therefore, tasimelteon should be especially well suited for treatment of

CRSDs [circadian rhythm sleep disorders]. . . . Tasimelteon has already demonstrated its circadian phase-resetting effects.").

83) Vanda's CEO wrote in a 2009 article that "a phase-shifting drug, such as tasimelteon, has therapeutic potential for circadian rhythm sleep disorders." Tr. at 175:7–10 (Polymeropoulos).

3. 20 mg Dosage of Tasimelteon

84) A skilled artisan would have known in January 2012 that Vanda sought international patent protection in 2007 for orally administering 20 milligrams of tasimelteon, once a day, 0.5 to 1.5 hours before bedtime. DTX 041 at 25–26; Tr. at 726:12–728:6 (Emens).

85) As of 2010, a person of ordinary skill in the art would also have known from the prior art that Vanda had initiated a phase III clinical trial for tasimelteon in which totally blind subjects with Non-24 were being administered the drug in 20 milligram doses. DTX 020 at 6; Tr. at 797:3–12, 799:8–15 (Emens).

4. Potential Drug-Drug Interactions

86) Cytochrome P450 (CYP) enzymes play an important role in a person's metabolism of drugs. Tr. at 1041:1–25 (Greenblatt). A skilled artisan would have known as of January 2012 that six to eight CYP enzymes are responsible for the metabolism of nearly 90 percent of all drugs. Tr. at 1031:18–25

(Greenblatt); Tr. at 1147:7–13, 1147:25–1148:5 (Parkinson); *see also* JTX 095 at 1; DTX 009 at 2.

87) "Drug-drug interaction" refers to the situation where two drugs are given together and one of them alters the metabolism of the other." Tr. at 1041:4–5 (Greenblatt).

88) A skilled artisan would have been aware in January 2012 of the FDA's requirements for *in vitro* testing of all new drugs to identify enzymes, including CYP1A2 and CYP3A4, that contribute to a drug's metabolism. Tr. at 1032:23–1033:3, 1033:14–22 (Greenblatt); Tr. at 1148:6–11 (Parkinson).

89) Drugs that reduce another drug's metabolism and increase that drug's plasma concentrations are known as "CYP inhibitors." Tr. at 1041:3–15 (Greenblatt).

90) It was common knowledge as of January 2012 that fluvoxamine was an inhibitor, if not the strongest inhibitor, of CYP1A2. Tr. at 1043:3–9 (Greenblatt); Tr. at 1149:3–7 (Parkinson).

91) Drugs that induce the expression of CYP enzymes and cause increased metabolism and decreased plasma concentrations of another drug are called "CYP inducers." Tr. at 1041:3–22, 1042:9–23 (Greenblatt); *see also* DTX 024 at 3; DTX 009 at 4–5; JTX 095 at 3.

92) It was common knowledge as of January 2012 that rifampicin (i.e., rifampin) was the strongest inducer of CYP3A4. Tr. at 1043:10–17 (Greenblatt); Tr. at 1148:18–22 (Parkinson). Rifampin and rifampicin are synonyms. *See* Tr. at 39:25–40:1; Tr. at 158:6–10 (Polymeropoulos).

93) A skilled artisan would have been aware in January 2012 that one can predict possible drug-drug interactions for any new drug, even before the drug reaches the clinical phase of development. Tr. at 1149:8–1150:14 (Parkinson); *see also* DTX 009 at 7.

94) A skilled artisan would have been aware in January 2012 of the prior FDA approval of ramelteon and that tasimelteon and ramelteon bind to the same melatonin receptors (MT1 and MT2) and have similar half lives in the body. Tr. at 1035:7–18, 1037:5–18, 1040:6–19 (Greenblatt); *see also* DTX 016 at 3; JTX 035 at 1, 3.

95) Further, a skilled artisan would have looked to ramelteon as relevant to understanding possible drug-drug interactions for tasimelteon because ramelteon and tasimelteon are structurally similar, as both drugs have a dihydrobenzofuran structure and a propanamide residue. Tr. at 1040:6–22 (Greenblatt); DTX 016 at 4–5.

96) A skilled artisan would have known that ramelteon is metabolized by CYP1A2 and CYP3A4. Tr. at 1038:25–1039:13, 1040:6–24 (Greenblatt); Tr. at 1156:6–10 (Parkinson); *see also* JTX 093 at 4; JTX 035 at 2, 10.

97) A skilled artisan also would have known that ramelteon's *in vivo* metabolism resulted in large drug-drug interactions with fluvoxamine (CYP1A2 inhibitor) and rifampin (CYP3A4 inducer).

98) A skilled artisan would have known in January 2012 that ramelteon underwent a 100-fold increase in blood plasma levels when it was co-administered with the CYP1A2 inhibitor fluvoxamine. Tr. at 1043:18–1045:12, 1116:24–1117:13 (Greenblatt); *see also* DTX 028 at 9; JTX 093 at 4. 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. Tr. at 1045:15–23 (Greenblatt).

99) A skilled artisan also would have known in January 2012 that ramelteon undergoes an 80 percent decrease in blood plasma levels when it is co-administered with the CYP3A4 inducer rifampin. Tr. at 1046:5–21 (Greenblatt); *see also* JTX 035 at 10.

100) Further, a skilled artisan would have been aware in January 2012 that these well-known drug-drug interactions for ramelteon are reflected in its FDA-approved label, which discloses that ramelteon and fluvoxamine should not be co-administered. Tr. at 1045:24–1046:3, 1116:24–1117:13 (Greenblatt); JTX 035 at 8, 10; JTX 093 at 4. A skilled artisan would also have known at the time that co-administration of ramelteon with rifampin decreases ramelteon's exposure and thus its efficacy. Tr. at 1046:5–1047:5, 1116:24–1117:13 (Greenblatt); *see also* JTX 035 at 10; JTX 093 at 4.

I. Prior Art

1. Hack

101) Hack is a scientific article titled "The Effects of Low-Dose 0.5-mg Melatonin on the Free-Running Circadian Rhythms of Blind Subjects." JTX 146.

102) Hack was published in 2003 and therefore qualifies as prior art to the asserted patents. JTX 146; Tr. at 718:24–719:15 (Emens).

103) Hack discloses a study in which low dosages of exogenous melatonin administered to blind patients with Non-24 resulted in successful entrainment to 24-hour sleep-wake cycles. JTX 146 at 1; Tr. at 719:16–20, 804:8–20 (Emens).

104) Hack further discloses that these patients slept an average of 6.6 hours per night, with a standard deviation of 1.1 hours. JTX 146 at 6; Tr. at 804:21–

805:5 (Emens). Thus, Hack teaches that some of these patients slept between 7 and 9 hours.

105) Hack explains that "[t]he aim of developing melatonin treatment regimens to entrain the underlying circadian oscillator is to optimally treat the clinical 'non-24-h sleep-wake disorder' condition that develops as a result of misalignment of the circadian system with the social 24-h day." JTX 146 at 8.

106) Hack states that "several recent studies have reexamined the ability of melatonin to entrain free-running rhythms in totally blind people and found that entrainment could be achieved following daily oral melatonin treatment" with doses including 5, 10, and 0.5 milligrams of melatonin. JTX 146 at 2.

107) Hack also states that "[p]revious studies have shown that chronic usage of melatonin is necessary for free-running blind people to remain entrained to the 24-h day." JTX 146 at 2.

108) Hack concludes "that a daily dose of 0.5 mg melatonin is effective at entraining the free-running circadian systems in most of the blind subjects studied" and that "[o]ptimal treatment with melatonin for this non-24-h sleep disorder should correct the underlying circadian disorder (to entrain the sleep-wake cycle)." JTX 146 at 1.

109) An artisan of ordinary skill would have understood from Hack in January 2012 that exogenous melatonin can be administered to entrain a patient

with Non-24 to a 24-hour sleep-wake cycle where the patient sleeps for approximately seven to nine hours. Tr. at 803:8–16 (Emens).

2. Lankford

110) Lankford, titled "Tasimelteon for Insomnia," is a prior art scientific article published in 2011. DTX 020.[1] As its title suggests, Lankford discloses the use of tasimelteon to treat insomnia. Tr. at 798:24–799:2 (Emens).

111) Lankford discloses that tasimelteon "has high affinity for both the MT1 and MT2 receptors, both in ranges similar to that of melatonin" with "already demonstrated . . . circadian phase-resetting effects" in the clinical trial setting. DTX 020 at 6.

112) Lankford concludes that tasimelteon should therefore "be especially well suited for treatment of" circadian rhythm sleep disorders (CRDs). DTX 020 at 6.

[1] Vanda argued for the first time, and only in cursory fashion, in its post-trial brief that Lankford "is not even prior art" "because it represents Vanda's own work and was published in May of 2011, less than a year before the priority date of the RE604 Patent." D.I. 317 at 16. Vanda cited no facts to support this assertion and it did not object at trial or before trial to the introduction of Lankford into evidence or to Dr. Emens's reliance on Lankford as prior art. Vanda forfeited its right to argue that Lankford does not constitute prior art by not raising it in timely fashion, by failing to object to Lankford's admission at trial, and by the passing manner in which it raised the argument in its post-trial brief.

113) Lankford discloses several clinical studies in which 20 and 50 milligram doses of tasimelteon were administered to healthy volunteers and patients with insomnia 30 minutes before bedtime. DTX 020 at 5.

114) Lankford also disclosed the existence of Vanda's clinical trial for Hetlioz®, which it described as "an ongoing Phase III trial of tasimelteon in blind people with no light perception and with non-24 h[our] sleep-wake disorder" that is "designed to assess the effectiveness of 20 mg [of] tasimelteon." DTX 020 at 6; Tr. at 799:8–15 (Emens).

115) Because a person of ordinary skill in the art would understand that Non-24 was a type of circadian rhythm disorder and that one way of "treating" a circadian rhythm disorder was entraining the patient with a melatonin agonist to phase shift, a person of ordinary skill in the art would understand Lankford as teaching or suggesting that tasimelteon could likely entrain blind patients with Non-24. Tr. at 803:17–804:7 (Emens).

3. Hardeland

116) Hardeland is a 2009 prior art reference titled "Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders." DTX 016; Tr. at 729:21–730:2 (Emens).

117) Hardeland discloses that "[t]he chronobiotic effects of melatonin are predominantly exerted through its binding to the G-protein-coupled melatonin

receptors," MT1 and MT2, which Hardeland says are "located in the suprachiasmatic nucleus (SCN), which acts as the circadian pacemaker." DTX 016 at 1.

118) Hardeland further discloses that "[m]elatonin has been used to treat various circadian and sleep disorders" and that "[s]uch treatments are particularly successful if the primary objective is to readjust the circadian phase." DTX 016 at 2.

119) Hardeland describes tasimelteon as "a melatonin receptor agonist" and "an investigational melatonergic drug" that is "being developed for the treatment of insomnia, circadian rhythm sleep disorders and depression." DTX 016 at 1–2.

120) Hardeland states that "current knowledge indicates that tasimelteon is suitable for phase-shifting the circadian clock." DTX 016 at 8.

121) Hardeland states that tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders" or "other types of entrainment difficulties" and observes that "[t]hese properties are expected from a melatonergic drug" and have "also [been] observed with melatonin." DTX 016 at 7.

122) Hardeland discloses Vanda's Phase III clinical trial in which tasimelteon was administered 30 minutes before bedtime in dosages of 20, 50, and 100 milligrams. DTX 016 at 6.

123) Hardeland further discloses that tasimelteon and ramelteon have "structural similarity . . . as [both] compounds share the dihydrobenzofuran structure and the propanamide residue" DTX 016 at 3–4.

124) Hardeland states that "[a] study using microsomes that overexpress specific CYP isoenzymes suggested that tasimelteon was primarily metabolized by the CYP1A2 . . . isoenzyme[] . . . ." DTX 016 at 4.

125) Hardeland also discloses that "tasimelteon is metabolized by the CYP isoenzyme[] 1A2" and that because of that phenomenon "coadministration of any drug that inhibits [this] isoenzyme[] should be regarded with caution." DTX 016 at 6.

126) An artisan of ordinary skill would have understood from Hardeland as of January 2012 that tasimelteon acts as a melatonin agonist receptor that can phase shift the circadian clock and, through that mechanism, can treat by entrainment circadian rhythm sleep disorders. Tr. at 730:17–19, 811:24–812:9 (Emens).

127) A skilled artisan would also have understood from Hardeland in January 2012 that "[e]ffective doses of tasimelteon were in th[e] 20- to 50-milligram range" 30 minutes before bedtime. Tr. at 812:18–813:9 (Emens).

4. Pandi-Perumal

128) Pandi-Perumal is a 2011 prior art reference titled "Pharmacotherapy of Insomnia with Ramelteon: Safety, Efficacy and Clinical Applications." JTX 093.

129) Pandi-Perumal discloses the use of ramelteon, a melatonin receptor agonist, for the treatment of insomnia. JTX 093 at 1–2.

130) Pandi-Perumal discloses that potential off-label uses of ramelteon include treating circadian rhythm sleep disorders. JTX 093 at 1.

131) Pandi-Perumal teaches that ramelteon is a melatonin receptor agonist that specifically acts through the MT1 and MT2 melatonin receptors. JTX 093 at 1–2.

132) Pandi-Perumal reports that ramelteon was developed in part to have a melatonin receptor agonist with a longer half-life than melatonin, which has an approximately 30-minute half-life. JTX 093 at 3.

133) Pandi-Perumal discloses that the half-life of circulating ramelteon is one to two hours, depending on the dose. JTX 093 at 3.

134) Pandi-Perumal teaches that ramelteon is metabolized by CYP1A2, CYP2C19, and CYP3A4. JTX 093 at 4; Tr. at 1038:25–1039:13 (Greenblatt). According to Pandi-Perumal, "[i]n view of the fact that ramelteon is mainly

metabolized by CYP1A2 and CYP2C19, drugs that inhibit these enzymes can considerably increase the levels of the agonist." JTX 093 at 4.

135) Pandi-Perumal expressly warns that "ramelteon should not be used in combination with fluvoxamine [or] ciprofloxacin." JTX 093 at 4.

136) Pandi-Perumal further states that the "CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II" and that "[t]o avoid losses in efficacy, this and other strong upregulators of relevant CYP enzymes should be avoided." JTX 093 at 4; Tr. at 1051:6–11 (Greenblatt).

5. The #244 Publication

137) Vanda filed the #244 Publication (International Patent Application Number WO 2007/137244) on May 22, 2006. DTX 041.

138) The #244 Publication is a prior art reference because it was published on November 29, 2007. DTX 041; Tr. at 726:12–727:8 (Emens).

139) The #244 Publication is directed to "a method of administering MA-1 to a human subject in need thereof which comprises orally administering MA-1 to the subject in an amount of about 10 mg to about 100 mg per day." DTX 041 at 3.

140) The #244 Publication describes its inventive subject matter as pertaining to the "use of the melatonin agonist herein referred to as MA-1, to treat sleep disorders and circadian rhythm disorders." DTX 041 at 3.

141) MA-1 is tasimelteon. Tr. at 727:13–14 (Emens).

142) The #244 Publication discloses that "MA-1 is a specific and potent agonist of the MT1R and MT2R melatonin receptors in the Suprachiasmatic nucleus (SCN), the region of the brain associated with the biological clock. Engagement of these receptors by melatonin is believed to regulate circadian rhythms, including the sleep/wake cycle. Consistent with its receptor binding profile, MA-1 demonstrates potent chronobiotic activity in preclinical models of acute phase-shifting and chronic re-entrainment." DTX 041 at 2.

143) The #244 Publication describes several clinical studies assessing the safety and efficacy of tasimelteon and concludes from these studies that tasimelteon "was well-tolerated at doses of 10, 20, 50, and 100 mg." DTX 041 at 23.

144) The #244 Publication concludes that "[a]n oral dose of about 20 to about 50 mg [of tasimelteon] is effective in treating sleep disorders when administered about 1/2 hour before sleep time." DTX 041 at 24.

145) The #244 Publication explains that treatment with tasimelteon "is continued until the patient's circadian rhythm is restored to normal, i.e., until the patient's normal daily function is not inhibited by the underlying circadian rhythm disorder." DTX 041 at 5–6. It goes on to state that treatment with tasimelteon

"can continue for some time after these end points are achieved so as to lessen the likelihood of relapse." DTX 041 at 6.

146) Claim 5 of the #244 Publication claims administering tasimelteon "to treat or prevent a circadian rhythm disorder or a sleep disorder." DTX 041 at 25. Claim 8 of the #244 Publication depends from claim 7 and specifies that the tasimelteon is "administered at about 0.5 hours prior to bedtime." DTX 041 at 25.

147) Claim 9 of the #244 Publication depends from claim 8 and specifies that the tasimelteon "is orally administered at a dose of about 20 mg/day or about 50 mg/day." DTX 041 at 26.

148) An artisan of ordinary skill would have understood from the #244 Publication as of January 2012 that tasimelteon administered in doses of 20 to 50 milligrams about a half hour before bedtime can reset a patient's circadian clock and cause entrainment. Tr. at 727:15–22 (Emens).

J. The Relevant Teachings and Suggestions of the Prior Art Combinations Asserted by Defendants to Invalidate Claim 3 of the RE604 Patent

149) Defendants argue that claim 3 of the RE604 patent is invalid as obvious in light of the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, Hardeland, and the #244 Publication.

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"

150) The combinations of Hack, Lankford, and the #244 Publication and of Hack, Hardeland, and the #244 Publication each teach or suggest that "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 seven to nine hours." Tr. at 803:8–16; 811:24–812:1 (Emens).

151) As noted above, an artisan of ordinary skill would have understood in January 2012 that Hack disclosed administering exogenous melatonin to entrain a patient with Non-24 to a 24-hour sleep-wake cycle where the patient sleeps for approximately seven to nine hours. Tr. at 803:8–16 (Emens). A skilled artisan would have understood that Lankford taught or suggested at that time that tasimelteon could likely entrain blind patients with Non-24. Tr. at 803:17–804:7 (Emens). An artisan would have understood from Hardeland as of January 2012 that tasimelteon acts as a melatonin agonist receptor that can phase shift the circadian clock and, through that mechanism, can treat by entrainment circadian rhythm sleep disorders. And a skilled artisan would have known from the #244 Publication that tasimelteon administered in doses of 20 to 50 milligrams about a half hour before bedtime can reset a patient's circadian clock and cause entrainment. Tr. at 727:15–22 (Emens).

2. "and maintaining said 24-hour sleep-wake cycle"

152) Both Hack and the #244 Publication teach maintaining a 24-hour sleep-wake cycle. As noted above, Hack teaches that chronic usage of melatonin is necessary for free-running blind people to remain entrained to the 24-hour day, and the #244 Publication teaches that treatment with tasimelteon should be continued until normal circadian rhythm is restored and that this treatment can continue for some time to reduce the likelihood of relapse. *See also* Tr. at 805:18–806:11 (Emens).

3. "orally administering to the patient 20 mg of tasimelteon"

153) As noted above, the oral administration of 20 milligrams of tasimelteon is disclosed in Lankford, Hardeland, and the #244 Publication.

4. "0.5 to 1.5 hours before the target bedtime"

154) As noted above, Lankford, Hardeland, and the #244 Publication all teach the administration of tasimelteon 0.5 to 1.5 hours before the target bedtime.

5. "wherein the patient is totally blind"

155) As noted above, Hack and Lankford disclose treatment of blind people. *See also* Tr. at 808:22–809:13 (Emens).

K. Findings Relating to A Skilled Artisan's Motivation to Combine Defendants' Asserted Prior Art References for Claim 3 of the RE604 Patent and Expectation of Success

156) I find that a skilled artisan would have been motivated to combine the Hack and #244 Publication references with the Lankford reference, Hardeland reference, or both references.

157) With respect to the Hack, Lankford, and #244 Publication combination, I base this finding on the disclosures of the references discussed above and the following testimony of Dr. Emens, whom I found to be very credible:

> . . . [T]he Hack publication that tells me that melatonin can entrain individuals with Non-24. So I know melatonin can achieve the desired treatment effect.
>
> Then I have Lankford and the [#]244 Publication telling me that I have a drug, tasimelteon, that's acting on the same types of receptors, melatonin receptors. They point out that it has the exact same mechanism and the action; namely, it can reset the timing of the biological clock. It can cause these phase shifts. And furthermore that it can cause entrainment.
>
> And, finally, that it would probably be an effective treatment for, as they point out there, numerous circadian rhythm sleep disorders, such as Non-24. So I think they have a really clear motivation to want to combine them.

Tr. at 810:4–19 (Emens).

158) With respect to the combination of the Hack, Hardeland, and the #244 Publication, I base this finding on the disclosures of the references noted above and the following testimony from Dr. Emens:

> [W]e know from Hack that melatonin can entrain blind individuals with Non-24. [The] [#]244 Publication and Hardeland tell me I have a drug, tasimelteon, that binds in a way similar to melatonin, can cause those same phase shifts as melatonin, and can be useful for entrainment, which, again, is what Hack had shown with melatonin. And so, clearly, there would have been motivation to combine these references.

Tr. at 813:19–814:7 (Emens).

159) I similarly find, based on the disclosures of the references discussed above and Dr. Emens's testimony, that an artisan of ordinary skill would have had as of the priority date of the RE604 patent a reasonable expectation of success in entraining a totally blind patient with Non-24 by combining the teachings of the Hack, Lankford, and the #244 Publication. As Dr. Emens explained, "Lankford kind of really spells it out for us" as "Lankford talks about how tasimelteon should be especially well[-]suited for the treatment of circadian rhythm disorders. And, again, the [#]244 Publication similarly says it should be effective in treating sleep disorders." Tr. at 810:25–811:1–5 (Emens). Lankford's disclosure of Vanda's Phase III trial would also have contributed to a skilled artisan's expectation of success. As Dr. Emens explained:

> [I]f someone is going to be spending the time and money to do a big Phase 3 trial, all that effort, as well as money, then that would say to me, and to a person of ordinary skill in the art, that clearly there was a reasonable expectation that they are going to succeed. Otherwise, I don't think they would have invested the time and money in the Phase 3 trial.

Tr. at 811:10–16 (Emens).

160) I similarly find, based on the disclosures discussed above and the following testimony from Dr. Emens, that a skilled artisan would have had a reasonable expectation of success in combining the teachings of Hack, Hardeland, and the #244 Publication to successfully entrain a totally blind patient who suffers from Non-24:

> . . . Hardeland points out quite explicitly that tasimelteon should be useful for treating circadian rhythm sleep disorders explicitly. As well as, and, again, this is important, other types of entrainment difficulties.
>
> So Hardeland calls out that it would be useful for entrainment specifically. And what's interesting is that Hardeland says you would expect this based on the fact that it's a melatonin (inaudible), meaning it's a melatonin agonist. So Hardeland is clearly not surprised here by that.
>
> And also . . . Hardeland concludes that, again, tasimelteon should be appropriate for phase shifting the circadian clock and resetting the time after the 24-hour biological clock. And, therefore, should be useful in the treatment of circadian rhythm sleep disorders. And then as I stated before, the [#]244 culls out that it should be effective in treating sleep disorders.

Tr. at 814:11–815:3 (Emens).

L. Findings Relevant to the Prior Art Combinations Asserted by Defendants to Invalidate Claim 14 of the #829 Patent

161) Defendants argue that claim 14 of the #829 patent is invalid as obvious in light of the combinations of (1) Hack, Lankford, the #244 Publication, and Hardeland and (2) Hack, the #244 Publication, and Hardeland.

1. "A method of treating a patient for [Non-24-Hour Sleep-Wake] disorder . . . with 20 mg of tasimelteon once daily"

162) I have already found that the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, the #244 Publication, and Hardeland each teach the treatment of patients with 20 milligrams of tasimelteon once daily; that a skilled artisan would have been motivated to combine respectively these references; and that a skilled artisan would reasonably have expected that such treatment would succeed.

2. "wherein the patient is being treated with a strong CYP1A2 inhibitor selected from a group consisting of fluvoxamine, ciprofloxacin, and verapamil, the method comprising . . . discontinuing treatment with the strong CYP1A2 inhibitor"

163) I have already found that Hardeland discloses that tasimelteon is primarily metabolized by CYP1A2 and that Hardeland expressly cautions against the administration of any drug with tasimelteon that inhibits CYP1A2.

164) An artisan of ordinary skill who intended to administer tasimelteon to a patient who was already taking a CYP1A2 inhibitor would have expected that

tasimelteon should not be co-administered with a CYP1A2 inhibitor and would have heeded Hardeland's warning against co-administering tasimelteon and CYP1A2 inhibitors, especially in light of the well-known drug-drug interaction between ramelteon and fluvoxamine. Tr. at 1043:18–1046:4, 1116:24–1117:13 (Greenblatt); *see also* DTX 028 at 9; JTX 093 at 4; JTX 035 at 10. Thus, a skilled artisan would have found it obvious to discontinue treatment of a patient with a strong CYP1A2 inhibitor such as fluvoxamine before treating that patient with tasimelteon. Tr. at 1049:3–1050:19 (Greenblatt).

M. Findings Relevant to the Prior Art Combinations Asserted by Defendants to Invalidate Claim 4 of the #910 Patent

165) Defendants argue that claim 4 of the #910 patent is invalid as obvious in light of the combinations of (1) Hack, Lankford, the #244 Publication, and Pandi-Perumal and (2) Hack, the #244 Publication, Hardeland, and Pandi-Perumal.

1. "A method of treating a [light perception impaired] patient for [Non-24] disorder . . . with . . . 20 mg of tasimelteon once daily before a target bedtime"

166) I have already found that the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, the #244 Publication, and Hardeland each teach the treatment of light perception impaired (i.e., blind) patients suffering from Non-24 with 20 milligrams of tasimelteon once daily before a target bedtime; that a skilled artisan would have been motivated to combine respectively these

references; and that a skilled artisan would reasonably have expected that such treatment would succeed.

2. "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"

167) I have already found that Pandi-Perumal teaches that (1) ramelteon is a melatonin receptor agonist that specifically acts through the MT1 and MT2 melatonin receptors; (2) ramelteon is metabolized by CYP3A4; (3) ramelteon should not be used in combination with fluvoxamine or ciprofloxacin; (4) the CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II; and (5) to avoid losses in efficacy, relevant CYP enzymes should be avoided when administering ramelteon.

168) I have already found that an artisan of ordinary skill would have understood in January 2012 that drug-drug interactions are predictable, and the artisan would have looked to ramelteon to predict tasimelteon drug-drug interactions because of the many known similarities between ramelteon and tasimelteon, including the fact that ramelteon and tasimelteon have similar structures, half-life durations, and affinities for melatonin receptors (MT1 and MT2).

169) I have already found that an artisan of ordinary skill would have known that ramelteon is metabolized by CYP1A2 and CYP3A4, that ramelteon's *in vivo* metabolism resulted in large drug-drug interactions with fluvoxamine (a CYP1A2 inhibitor) and rifampin (a CYP3A4 inducer), that ramelteon undergoes an 80 percent decrease in blood plasma levels when it is co-administered with the CYP3A4 inducer rifampin, and that co-administration of ramelteon with rifampin results in decreased exposure and thus efficacy.

170) In light of Pandi-Perumal and the well-known similarities between ramelteon and tasimelteon, if, as of January 2012, a skilled artisan wanted to administer tasimelteon to a patient who was already taking the CYP3A4 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. *See* Tr. at 1035:7–18, 1037:5–18, 1040:6–24, 1046:5–1047:5 1047:23–1048:19, 1050:20–1052:2 (Greenblatt); *see also* DTX 016 at 3–5; JTX 035 at 1, 3, 10; JTX 093 at 4.

N. Findings Relevant to the Prior Art Combinations Asserted by Defendants to Invalidate Claim 5 of the #487 Patent

171) Defendants argue that claim 5 of the #487 patent is invalid as obvious in light of the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, Hardeland, and the #244 Publication.

1. "A method of treating a human patient suffering from [Non-24] disorder . . . that comprises orally administering to the patient an effective dose of tasimelteon . . . wherein the effective dose is 20 mg/d.

172) I have already found that the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, Hardeland, and the #244 Publication each teach the treatment of Non-24 patients with 20 milligrams of tasimelteon once daily; that a skilled artisan would have been motivated to combine respectively these references; and that a skilled artisan would reasonably have expected that such treatment would succeed.

2. "without food"

173) The parties stipulated that for purposes of the #487 patent, "without food" means "the patient has not consumed food within 30 minutes prior to administration of tasimelteon and does not consume food with the administration of tasimelteon." D.I. 183 at 3.

174) The #244 Publication, Hardeland, and Lankford each disclose administration of tasimelteon 30 minutes before bedtime. *See* DTX 016 at 6; DTX 041 at 24; DTX 020 at 5.

175) Dr. Emens testified credibly that "it's more likely than not" that an artisan of ordinary skill who was administering tasimelteon within 30 minutes of the patient's bedtime would do so "without food" and that it would have been obvious to an artisan of ordinary skill to administer tasimelteon without food 30

minutes before bedtime. Tr. at 803:5–23 (Emens).

O. Alleged Objective Indicia of Nonobviousness

176) Vanda argues that the nonobviousness of the asserted claims is demonstrated by four "objective indicia"—unexpected results, long-felt need, industry praise, and failure of others.

1. Alleged Unexpected Results of the RE604 Patent

a. Half-Life

177) Vanda argues that "[t]asimelteon's relatively long half-life would have led one of skill not to expect that tasimelteon would work for treating Non-24 by entrainment." D.I. 311 at 38. It cites Lankford in support of this assertion.

178) Lankford discloses that melatonin had a "short half-life" that is "typically in the range 20 - 30 min, though sometimes less, with a maximum period of 45 min" and that, because of its half-life, "it is unsurprising that while melatonin has shown some effectiveness, though inconsistently, in treating sleep onset insomnia, it has not demonstrated similar effectiveness in the treatment of sleep maintenance type insomnia." DTX 020 at 4.

179) But Lankford further disclosed that "[i]n rats and monkeys, the half-life of tasimelteon was approximately 2 h[,] which is longer than the half-life of melatonin," and that "there has been considerable interest in developing, for the treatment of both sleep onset and maintenance type insomnia either sustained release forms of melatonin or melatonergic agonists with longer half-lives than

exogenous melatonin." DTX 020 at 4.

180) Lankford concludes that

> the half-life of melatonin is a relatively short (20-30 min) while the half-life of tasimelteon is apparently longer, at least based on animal studies. The longer half-life could make tasimelteon more suitable for treating insomnias other than just the sleep onset type.

DTX 020 at 7.

181) Accordingly, I find that Lankford does not demonstrate that a skilled artisan would not have expected that tasimelteon would work for Non-24 treatment by entrainment.

182) On the contrary, as I found above and based on the credible testimony of Dr. Emens, a skilled artisan as of January 2012 would have understood Lankford as teaching or suggesting that tasimelteon could likely entrain blind patients with Non-24.

183) Vanda cites the testimony of Dr. Emens and Dr. Czeisler for the proposition that "[a] longer half-life increases the risk that tasimelteon's effects will 'spill over' into the period when stimulation actually delays the patient's circadian phase, thus counteracting any benefit obtained from advancing the patient's circadian phase when the medicine is first administered." D.I. 311 at 38. The cited testimony of Dr. Emens, however, established only that at some undefined point a dosage of melatonin can be high enough to create "both kind of

helpful phase advances and unhelpful phase delays" that would "counteract each other" and accordingly fail to achieve the phase shift necessary for entrainment. Tr. at 840:22–843:19 (Emens). Neither that testimony nor Dr. Czeisler's testimony cause me to question my finding—based on Dr. Emens's testimony and the disclosures in the prior art discussed above—that a skilled artisan would have reasonably expected in January 2012 that tasimelteon would work for treating Non-24 by entrainment. (I did not find Dr. Czeisler, especially given his substantial financial ties to Vanda that were not disclosed until cross-examination, to be as credible as Dr. Emens.)

b. Dosage

184) Vanda argues "[t]hat 20mg of tasimelteon proved efficacious was unexpected." D.I. 311 at 38.

185) As made clear from my finding above, Hardeland, Lankford, and Vanda itself in the #244 Publication, contradict this contention.

c. Timing of Administration

186) Citing only Dr. Czeisler's trial testimony, Vanda contends that "[i]t was unexpected that success could be obtained administering tasimelteon before bedtime, rather than several hours earlier." D.I. 311 at 39.

187) As discussed above, substantial record evidence contradicts this contention. Vanda itself stated in the #244 Publication that tasimelteon should be

administered "about 1/2 hour before sleep time," DTX 041 at 24; *see also* DTX 041 at 25–26, and Vanda's prior-art clinical trial protocol instructed that tasimelteon should be administered one hour before bedtime. *See* DTX 042 at 9–10; *see also* DTX 020 at 5; DTX 041 at 10; DTX 016 at 5–6; Tr. at 807:13–808:20, 812:24–813:9 (Emens).

d. Phase-Response Curve

188) Vanda argues that the absence in January 2012 (and still today) of a phase-response curve for any dose of tasimelteon means that "it . . . cannot be determined *a priori* whether a given dose of tasimelteon at a given time can shift *or* entrain the circadian rhythm" and thus the results claimed in the RE604 patent were unexpected. D.I. 311 at 39. Vanda argues that this lack of phase-response curve data is important because that data "are an important first step in determining when and how much medicine to give." D.I. 311 at 39. This assertion is irrelevant, as the prior art discussed above uniformly described administering tasimelteon shortly before bedtime and also discussed the appropriate dose.

2. Alleged Unexpected Results of the #487 Patent

189) Vanda argues that as of the priority date of the #487 patent, "it would have been unexpected that administration of tasimelteon with food would decrease its efficacy in treating Non-24." D.I. 311 at 40. But Vanda cites no evidence adduced at trial that shows or suggests in any way what a skilled artisan

in January 2012 would have expected when tasimelteon is administered with and without food. Accordingly, Vanda's contention about alleged unexpected results of administering tasimelteon without food necessarily fails. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (holding that "by definition, any superior property must be unexpected to be considered as evidence of non-obviousness" and that unexpected results "evidence must fail [if] the record is devoid of *any* evidence of what the skilled artisan would have expected") (emphasis in the original).

3. Alleged Unexpected Results of the #910 Patent

190) Vanda argues that it "would have been an unexpected result as of the priority date of the [#]910 Patent that tasimelteon should not be co-administered with rifampicin, a strong CYP3A3 inducer." D.I. 311 at 41. According to Vanda, "[t]he only source of original data regarding tasimelteon's metabolism concluded '[n]o metabolism of BMS-214778 was observed following incubation with . . . [CYP]3A4.'" D.I. 311 at 41. But, as Dr. Greenblatt credibly explained at trial, a skilled artisan aware of this source of data would not have "exclude[d] a major role of CYP3A4 in the induced state" because "induction causes a massive increase in the amount of enzymes," meaning "you can't exclude a major role of CYP3A4 in the induced state even if you can't detect it in the uninduced state." Tr. at 1116:13–20 (Greenblatt). A skilled artisan would have

been particularly likely to suspect a potential interaction between tasimelteon and strong CYP3A4 inducers given the knowledge in the art that (i) the structurally analogous compound ramelteon exhibited a "large" drug-drug interaction with strong CYP3A4 inhibitors, Tr. at 1116:21–1117:13 (Greenblatt), and (ii) CYP3A4 resides in the gastrointestinal tract, is the "most abundant" enzyme in the liver, and metabolizes a large percentage of drugs. *See* Tr. at 1050:20–1052:2 (Greenblatt); Tr. at 1146:19–25 (Parkinson).

191) In addition, for the reasons discussed above, I find that a skilled artisan would have expected that tasimelteon should not be co-administered with rifampin.

4. Alleged Unexpected Results of the #829 Patent

192) Vanda argues:

> While here the sole piece of prior art taught that CYP1A2 was one of the four enzymes 'primarily' responsible for tasimelteon in an *in vitro* laboratory test, the undisputed record evidence from both parties' experts is that a skilled artisan could not determine from that lone fact whether to avoid administering tasimelteon and a strong CYP1A2 inhibitor, or whether to increase or decrease the dose of one or the other, or whether no adjustment is needed. FDA draft guidelines for that decision require at least one more type of *in vitro* assay and *in vivo* data.

D.I. 311 at 41–42 (citations omitted).

193) I understand Vanda's argument to be that without *in vivo* tests, a skilled artisan could not have known with certainty whether the co-administration

of tasimelteon and strong CYP1A2 inhibitors should be avoided. That may be true, but I will make no finding of fact to that effect because it has no bearing on the issues before me. *See Pfizer*, 480 F.3d at 1364 (holding that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success" and that "the expectation of success need only be reasonable, not absolute").

194) For the reasons discussed above, I have already found that an artisan of ordinary skill would have expected that tasimelteon should not be co-administered with a CYP1A2 inhibitor and would have heeded Hardeland's warning against co-administering tasimelteon and CYP1A2 inhibitors, especially in light of the well-known drug-drug interaction between ramelteon and fluvoxamine.

5. Alleged Long-Felt Need of the Claimed Non-24 Treatment

195) Vanda argues that "[b]efore [it] invented the method of claim 3 of the Non-24-Treatment Patent, there was a long-felt, unmet need for a safe and effective treatment for Non-24, particularly in patients in whom melatonin was not effective." D.I. 311 at 42.

196) The record evidence Vanda cites in support of this assertion does not demonstrate a long-felt need for the treatment method claimed in claim 3 of the RE604 patent.

197) Vanda first cites Dr. Combs's testimony about an article he authored in 2019—i.e., the year after this case was filed and seven years after the priority date of the RE604 patent. *See* D.I. 311 at 42 (citing Tr. at 203:2–203:16 (Combs)). The article recounts the successful treatment of one adolescent Non-24 patient who had previously been treated unsuccessfully with melatonin. Given the date of the article and the fact that it discusses only one patient's experience, the article fails to show a long-felt need for the claimed treatment.

198) The remaining record evidence cited by Vanda, *see* D.I. 311 at 43, is cursory at best and suggests at most that there was some need among Non-24 patients for whom melatonin had not worked for another drug; it does not suggest that there was a need for a specific method of using that drug. Moreover, as Dr. Emens credibly testified, by 2003 melatonin was viewed in the field as effective treatment for Non-24. *See* Tr. at 716:2–721:4 (Emens); Tr. at 1217:14–23 (Emens); *see also* JTX 146 at 1 (stating that Hack's "findings demonstrate that a daily dose of 0.5 mg melatonin is effective at entraining the free-running circadian systems in most of the blind subjects studied").

6. Alleged Industry Praise for the Claimed Non-24 Treatment

199) Vanda points to various examples of praise it has received from industry groups and organizations that support the blind. But it does not cite any praise specifically directed at the treatment method claimed in the RE604 patent.

Accordingly, I find that whatever industry praise Vanda received is of minimal probative value with respect to the obviousness of the claimed method.

7. Alleged Failure of Others to Develop the Claimed Non-24 Treatment

200) Vanda argues that "melatonin researchers" had failed to demonstrate in a large-scale study that melatonin can effectively entrain Non-24 patients and that "no one has ever entrained a patient using 20mg of melatonin[.]" D.I. 311 at 45. But, as I have already found above, it was well-known in the field as of 2000 that melatonin could entrain Non-24 blind patients to a normal 24-hour sleep-wake cycle. The absence of a large-scale study does not refute that finding. And the fact that the effective dose of *tasimelteon* turned out to be different than the effective dose of *melatonin* is of no moment.

201) Vanda also argues that "BMS [Bristol Myers Squibb] failed to develop any successful treatment using tasimelteon." D.I. 311 at 45. But Vanda cites nothing in the record that shows that BMS ever tried to develop tasimelteon to treat Non-24.

8. Alleged Failure to Recognize CYP3A4 Metabolism

202) Vanda argues that "BMS also failed to recognize that tasimelteon is metabolized by CYP3A4." D.I. 311 at 46. But here again, Vanda cites no record evidence that BMS ever tried to develop the claimed method of the #910 patent.

III. LEGAL STANDARDS

A. Direct Infringement

Analyzing infringement involves two steps. The first step is to construe disputed patent terms consistent with how they would be understood by an artisan of ordinary skill. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The second step is to determine whether the accused products or methods infringe the patent by comparing those products or methods to the construed claims. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The first step in the infringement analysis is a question of law; the second is a question of fact. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). A patentee bears the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984).

As noted above, § 271(e)(2)(A) of the Patent Act defines the filing of an ANDA with a paragraph IV certification as an act of infringement. That definition "create[s] case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity" of patents listed in the Orange Book. *Glaxo*, 110 F.3d at 1569. "Notwithstanding this defined act of infringement, a district court's inquiry in a suit brought under § 271(e)(2) is the same as it is in any other infringement suit, *viz.*, whether the patent in question is 'invalid or *will not be*

infringed by the manufacture, use, or sale of the drug for which the [ANDA] is submitted.'" *Id.* (italics and alteration in original) (underline added) (quoting 21 U.S.C. § 355(j)(2)(A)(vii)(IV)). Thus, "the ultimate infringement question is determined by traditional patent law principles and, if a product that an ANDA applicant is asking the FDA to approve for sale falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). By the same token, if the product that an ANDA applicant is asking the FDA to approve falls outside the scope of an asserted patent, a judgment of noninfringement must follow. In short, "[w]hat [the ANDA applicant] has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Id.*

The infringement analysis in an ANDA case is most straightforward when the ANDA's specification directly addresses the elements of the asserted claims that are at issue. "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

As the Federal Circuit explained in *Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241 (Fed. Cir. 2000):

> If any of the statements in [the ANDA's] specification are false, [the ANDA filer] is subject to civil penalties and the withdrawal of the approval of its drug. Additionally, if [the ANDA filer] introduces a drug into interstate commerce without complying with the approval requirements of 21 U.S.C. § 355, it is subject to various additional penalties, including an injunction, criminal sanctions, seizure of the unapproved drug, and debarment of its corporation and individual officials from submitting or assisting in the submission of an ANDA in the future. [The ANDA filer] also would be subject to criminal prosecution for making false statements to the FDA under 18 U.S.C. § 1001, conspiring to defraud the United States under 18 U.S.C. § 371, and obstructing proceedings before a federal agency under 18 U.S.C. § 1501. If [the ANDA filer] changes its ANDA, it must file the changes with the FDA, and if the changes are to the drug's specification, [the ANDA filer] must obtain approval for the changes before they can be made.

Id. at 1249–50 (citations omitted). Because of these statutory and regulatory requirements and the consequences that flow from failing to abide by them, courts "cannot assume that [an ANDA filer] will not act in full compliance with its representations to the FDA." *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011).

This principle that an ANDA filer is bound by the representations and specifications in its ANDA is central to the infringement inquiry. And if an ANDA specification describes a product that either necessarily infringes an

asserted patent or necessarily does not infringe the patent, the specification dictates the outcome of the infringement analysis. *See Ferring B.V. v. Watson Lab'ys, Inc-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014) ("In some cases, the ANDA specification directly resolves the infringement question because it defines a proposed generic product in a manner that either meets the limitations of an asserted patent claim or is outside the scope of such a claim."); *Elan*, 212 F.3d at 1249 (finding that an ANDA specification that clearly defined a noninfringing product "mandate[d] a finding of no literal infringement").

When the ANDA specification does not answer the question of infringement, "[t]he relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Glaxo*, 110 F.3d at 1570. In such cases, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Id.*

B. Induced Infringement

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). A finding of inducement requires establishing an underlying act of direct infringement, the defendant's knowledge of or willful blindness with respect to the direct infringement, and that the defendant's specific intent was to encourage the acts that constituted direct infringement. *See DSU*

Med. Corp. v. JMS Co., 471 F.3d 1293, 1303, 1306 (Fed. Cir. 2006) (en banc in relevant part).

C. Obviousness

Under § 103 of the Patent Act, 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 to which said subject matter pertains." 35 U.S.C. § 103 (2006).

As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends

> itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts,

where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . . sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations." *Id.* at 1078.

True, less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial success, long felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge is to treat *Graham*'s invitation to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a

reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more

than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

IV. CONCLUSIONS OF LAW

A. Claim 3 of the RE604 Patent

1. Infringement

Vanda contends that Defendants' ANDA products will induce infringement of claim 3 of the RE604 patent. Defendants dispute only that they infringe claim 3's "entraining" and "daily sleep period of approximately 7 to 9 hours" limitations.

I have already found as a factual matter that Vanda did not prove by a preponderance of the evidence that Defendants' ANDA labels instruct, recommend, encourage, teach, or promote the use of Defendants' tasimelteon drug products to treat Non-24 by entraining a patient to a 24-hours sleep-wake cycle. Accordingly, Vanda has failed to establish that Defendants' ANDAs will induce the infringement of claim 3 of the RE604 patent. *See Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 572 U.S. 915 (2014) (holding that a method

patent "is not infringed unless all the steps are carried out" and that "inducement liability may arise if, but only if, there is direct infringement") (cleaned up). I therefore need not and do not address whether Defendants' ANDA products would induce infringement of the "daily sleep period" limitation.

2. Invalidity

I also agree with Defendants that they have proved by clear and convincing evidence that claim 3 is invalid for obviousness. As I found above as a factual matter, each element of the claimed method was taught or suggested by two different combinations of prior art references and an artisan of ordinary skill would have been motivated to combine the teachings and suggestions of those references to entrain a blind Non-24 patient with the claimed method and would have had a reasonable expectation of success in doing so. Accordingly, I conclude as a matter of law that claim 3 of the RE604 patent is invalid for obviousness.

B. Claim 14 of the #829 Patent

I agree with Defendants that they have proved by clear and convincing evidence that claim 14 of the #829 patent is invalid for obviousness in light of the combinations of (1) Hack, Lankford, the #244 Publication, and Hardeland and (2) Hack, the #244 Publication, and Hardeland. As I found above as a factual matter, both of these combinations teach the treatment of patients with 20 milligrams of tasimelteon once daily, that tasimelteon is primarily metabolized by CYP1A2, and

that tasimelteon should not be co-administered with any drug that inhibits CYP1A2. An artisan of ordinary skill who intended to administer tasimelteon to a patient who was already taking a CYP1A2 inhibitor would have expected that tasimelteon should not be co-administered with a CYP1A2 inhibitor and would have heeded Hardeland's warning against co-administering tasimelteon and CYP1A2 inhibitors, especially in light of the well-known drug-drug interaction between ramelteon and fluvoxamine. Thus, a skilled artisan would have found it obvious to discontinue treatment of a patient with a strong CYP1A2 inhibitor such as fluvoxamine before treating that patient with tasimelteon. Accordingly, I conclude as a matter of law that claim 14 of the #829 patent is invalid for obviousness.

Having decided that claim 14 is invalid, I need not and do not address whether Defendants' ANDA would infringe claim 14. *See Prima Tek II, L.L.C. v. Polypap, S.A.R.L.*, 412 F.3d 1284, 1291 (Fed. Cir. 2005) ("[T]here can be no . . . induced infringement of invalid patent claims.")

C. Claim 4 of the #910 Patent

I agree with Defendants that they have proved by clear and convincing evidence that claim 4 of the #910 patent is invalid for obviousness in light of the combinations of (1) Hack, Lankford, the #244 Publication, and Pandi-Perumal and (2) Hack, the #244 Publication, Hardeland, and Pandi-Perumal. As I found above

as a factual matter, both of these combinations teach the treatment of light perception impaired (i.e., blind) Non-24 patients with 20 milligrams of tasimelteon once daily before a target bedtime; that ramelteon is metabolized by CYP3A4 and should not be used in combination with fluvoxamine or ciprofloxacin; that the CYP inducer rifampin has been shown to considerably decrease levels of both ramelteon and its metabolite M-II; and that to avoid losses in efficacy, relevant CYP enzymes should be avoided when administering ramelteon. An artisan of ordinary skill in January 2012 would have looked to ramelteon to predict tasimelteon's drug-drug interactions because of the many known similarities between ramelteon and tasimelteon, including the fact that ramelteon and tasimelteon have similar structures, half-life durations, and affinities for melatonin receptors (MT1 and MT2). And in light of Pandi-Perumal and the well-known similarities between ramelteon and tasimelteon, if, as of January 2012, a skilled artisan had intended to administer tasimelteon to a patient who was already taking the CYP3A4 inducer 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. Accordingly, I conclude as a matter of law that claim 4 of the #910 patent is invalid for obviousness.

Having decided that claim 4 is invalid, I need not and do not address whether Defendants' ANDA would infringe claim 4. *See Prima Tek II,* 412 F.3d at 1291.

D. Claim 5 of the #487 Patent

I agree with Defendants that they have proved by clear and convincing evidence that claim 5 of the #487 patent is invalid as obvious in light of the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, Hardeland, and the #244 Publication.

As I found above as a factual matter, the combinations of (1) Hack, Lankford, and the #244 Publication and (2) Hack, Hardeland, and the #244 Publication each teach the treatment of Non-24 patients with 20 milligrams of tasimelteon once daily 30 minutes before bedtime. I also found that it is more likely than not that an artisan of ordinary skill who was administering tasimelteon within 30 minutes of the patient's bedtime would do so without food. And I found that it therefore would have been obvious to an artisan of ordinary skill to administer tasimelteon without food 30 minutes before bedtime.

Whether to administer tasimelteon with food is a binary choice. A drug is administered with or without food. "When two equally viable options are available, as here, then, without more, either one would seem to have been obvious." *C.R. Bard, Inc. v. Medline Indus., Inc.*, 2021 WL 3574043, at *4 (Fed.

Cir. Aug. 13, 2021); *see also Gen. Elec. Co. v. Raytheon Techs. Corp.*, 983 F.3d 1334, 1350 (Fed. Cir. 2020).

Accordingly, I conclude as a matter of law that claim 5 of the #487 patent is invalid for obviousness.

V. CONCLUSION

For the reasons discussed above, I find that Defendants' ANDA products do not infringe claim 3 of the RE604 patent and that claim 3 of the RE604 patent, claim 4 of the #829 patent, claim 14 of the #910 patent, and claim 5 of the #487 patent are invalid.

The Court will issue an Order directing the parties to submit a proposed order by which the Court may enter final judgments consistent with this Opinion.