No. 23-768

In the Supreme Court of the United States

VANDA PHARMACEUTICALS INC.,

Petitioner,

v.

TEVA PHARMACEUTICALS USA, INC.; APOTEX INC.; APOTEX CORP.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR RESPONDENTS IN OPPOSITION

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QUESTION PRESENTED

When Teva and Apotex sought FDA approval to market generic versions of Vanda's drug Hetlioz, Vanda sued for patent infringement. After trial, the district court held the asserted claims of Vanda's four asserted patents to be obvious in view of public information that predates Vanda's patents. In so doing, the district court applied the well-settled standard for assessing obviousness set forth by this Court in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), and *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). The Federal Circuit affirmed. At no time in the proceedings before the district court or the Federal Circuit did Vanda challenge the obviousness standard applied by either court.

Under the circumstances, the question presented is:

Whether the district court and the court of appeals erred in holding the asserted patent claims invalid as obvious based on evidence that all of the elements of the asserted claims were known in the prior art and that a person having ordinary skill in the art not only would have been motivated to combine those previously known elements to arrive at the claimed inventions but also would have reasonably expected to succeed in doing so.

CORPORATE DISCLOSURE STATEMENT

Teva Pharmaceuticals USA, Inc. is an indirect wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., which is publicly traded.

Teva Pharmaceutical Industries Ltd. is the only publicly traded company that owns 10% or more of Teva Pharmaceuticals USA, Inc.

Apotex Corporation and Apotex Inc. are indirect wholly owned subsidiaries of SK Capital Management, LLC. No publicly held corporation owns 10% or more of the stock of Apotex Corporation or Apotex Inc.

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INTRODUCTION

This case concerns the validity of four Vanda patent claims related to Vanda's sleep drug Hetlioz, whose active ingredient is tasimelteon. The district court—in a comprehensive and thorough opinion applying a legal standard that both parties agreed governs—found those claims invalid as obvious. The Federal Circuit affirmed in a nonprecedential opinion.

Those decisions were enormously consequential for Vanda, because they mean that Vanda's decade-long monopoly on tasimelteon has come to an end. But the decisions are decidedly inconsequential for the law. This case involves nothing more than the routine, fact-bound application of settled obviousness law in an unreported, nonprecedential decision that will have no appreciable impact on future cases.

The fact-bound and nonprecedential nature of the Federal Circuit's decision is reason enough for this Court to decline review. But there is more. Vanda's petition largely abandons the arguments it made below and instead asks this Court to establish a *new* legal standard—one under which only an advance that is completely "predictable" (rather than expected) may be deemed obvious—that (i) Vanda never advocated in the courts below; (ii) contradicts longstanding precedent from this Court, the Federal Circuit, and the regional circuits; and (iii) would have no impact on the outcome of this case because Vanda's patents are invalid even under Vanda's brand-new standard. In short: the sole argument in Vanda's petition is forfeited, meritless, and non-dispositive. It is hard to imagine a poorer candidate for certiorari.

STATEMENT OF THE CASE

A. Vanda unsuccessfully attempted to prolong its monopoly on tasimelteon.

The story of tasimelteon begins with the naturally occurring hormone melatonin. Melatonin is produced by the human body and is involved in regulating an individual's sleep-wake cycle or circadian rhythm. Dosing patients with additional melatonin has been a treatment for circadian-rhythm disorders since the 1980s. By the year 2000, researchers had shown that administration of melatonin could "entrain" (or synchronize to the Earth's daytime-nighttime cycles) the circadian rhythm in patients suffering from one such disorder: Non-24-Hour Sleep-Wake disorder (Non-24). Non-24 is a condition in which an individual's sleep-wake cycle becomes unsynchronized from the Earth's cycle of daytime and nighttime. It affects mainly the blind, who cannot process signals from sunlight about the time of day.

Because melatonin is a naturally occurring molecule that has been known for decades, there was little prospect of meaningful patent protection for melatonin. That created an incentive for researchers to find other drugs that were patentable and would bind to the same receptors in the body as melatonin and so would have similar effects. Drugs that target melatonin receptors in this way are called melatonin-receptor agonists. Tasimelteon is one such drug. Ramelteon (about which more will be said below) is another.

Tasimelteon is the active ingredient in Vanda's Hetlioz product. In 2014 the U.S. Food and Drug

Administration (FDA) approved Hetlioz to treat Non-24.

Vanda did not invent tasimelteon; pharmaceutical giant Bristol Myers Squibb (BMS) did that. More than 25 years ago—in January 1999—BMS obtained a patent that covered not only tasimelteon itself but also the use of tasimelteon to treat circadian-rhythm-related sleep disorders (like Non-24). *See* U.S. Patent No. 5,856,529. BMS granted an exclusive license to Vanda, which enjoyed a monopoly on U.S. sales of tasimelteon until BMS's '529 patent expired in December 2022.

Vanda did not want to relinquish its tasimelteon monopoly, however. So Vanda obtained additional patents concerning uses of tasimelteon. Vanda asserted this new crop of patents against companies, including respondents Teva and Apotex, that sought FDA approval to market generic versions of Hetlioz after BMS's '529 patent expired.

Vanda waited until 2012—more than 13 years after BMS's tasimelteon patent had issued—before it began filing applications for its follow-on tasimelteon patents. That decade-plus delay turned out to be fatal. The district court held that Vanda's four patents at issue are invalid as obvious in view of the pre-2012 prior art related to circadian-rhythm disorders—a crowded field that includes a vast body of patents and scientific publications concerning melatonin, tasimelteon, and other melatonin-receptor agonists.

The district court's ruling was a commercial disaster for Vanda. Hetlioz is one of only two products that Vanda sells, and it brings in hundreds of millions of dollars in annual revenue—in part because of the

high price that Vanda charges. The list price for Hetlioz is more than $793 per tablet, so a year's supply costs more than $285,000. And, because Non-24 is a chronic condition, patients need to take Hetlioz day after day, year after year.

The invalidity ruling meant that Hetlioz for the first time faced competition from generic tasimelteon products. That competition brought patients and payors the benefits of lower cost and greater availability. Vanda has since filed multiple additional lawsuits against Teva, Apotex, and FDA aimed at thwarting this budding generic competition. The present petition is just one more of Vanda's frantic legal maneuvers.[1]

There is no dispute that the asserted patent claims are all combinations of elements that were publicly known before Vanda applied for its patents in 2012. The courts below found, after careful analysis, that

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[1] Vanda's dubious legal gambits since facing generic competition include suing the FDA to force the agency to withdraw approval for the generic products because the generics' packaging does not include the word "tasimelteon" in Braille. *Vanda Pharmaceuticals, Inc. v. Food and Drug Administration et al.*, No. 1:23-cv-00280 (D.D.C.). Vanda also sued respondent Teva under the Lanham Act alleging, among other things, that the statement on Teva's Web site that its generic product is "brand equivalent" to Hetlioz falsely communicates that Teva's product is FDA-approved to treat conditions other than Non-24. *Vanda Pharmaceuticals Inc. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 1:24-cv-00018 (D.Del.). Vanda has also sued both Teva and Apotex asserting that they infringe yet another follow-on patent. *Vanda Pharmaceuticals Inc. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 1:23-cv-00152 (D.Del.); *Vanda Pharmaceuticals Inc. v. Apotex Inc. et al*, No. 1:23-cv-00153 (D.Del.).

persons having ordinary skill in the art would have had a motivation to combine these previously known elements to arrive at the claimed inventions and would have reasonably expected to succeed in doing so. The thrust of Vanda's petition is that the courts below should have required that the success be "predictable" rather than expected. It is far from clear exactly how Vanda thinks a prediction differs from an expectation. But it is apparent from context that Vanda wants this Court to make it much tougher to invalidate patents as obvious than it has ever been before.

Notably, Vanda never raised any question about the legal standard for obviousness before now. It also appears that *no one else* has ever asked a lower court to consider this question. None of the cases Vanda cites in its petition has done so, even though a "reasonable expectation of success" has been part of the legal standard for obviousness for decades.

This Court, too, has endorsed consideration of the expectations of skilled artisans as part of the obviousness inquiry. In *KSR*, for example, the Court reiterated that "when a patent 'simply arranges old elements with each performing the same function it had been known to perform,' and yields *no more than one would expect* from such an arrangement, the combination is obvious." 550 U.S. at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)) (emphasis added). This is precisely the analysis—and conclusion—of the lower courts here.

B. The district and appellate courts carefully applied well-settled legal principles to the complicated facts of this case in holding Vanda's patent claims invalid as obvious.

The evidentiary basis for the district court's obviousness conclusions and the pertinent portions of the Federal Circuit's opinion are described briefly below.

1. Asserted claim 3 of the RE '604 patent was held invalid.

Asserted claim 3 of U.S. Patent RE46,604 (the "RE '604 patent"), reproduced at App. 4a,[2] requires entraining a blind Non-24 patient to a 24-hour sleep/wake cycle by orally administering 20 milligrams of tasimelteon sometime from one-and-a-half hours to one half-hour before bedtime. Teva and Apotex demonstrated that a person having ordinary skill in the relevant art at the time of the invention would have found this dosing regime and result obvious based on publicly available information that predates Vanda's 2012 patent application—namely, either the Lankford or Hardeland reference combined with the Hack reference and the '244 Publication.

Hack. Hack is a 2003 journal article entitled *The Effects of Low-Dose 0.5-mg Melatonin on the Free-Running Circadian Rhythms of Blind Subjects*. It summarizes prior work done on melatonin, explaining that melatonin's ability to shift human circadian

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[2] "App." citations refer to the Appendices attached to the Petition.

rhythms had been documented as early as 1985; that melatonin has the ability to entrain circadian rhythms in blind people suffering from Non-24; and that melatonin should be given close to bedtime for the treatment of Non-24. *See* App. 41a.

Lankford. Lankford is a 2011 journal article entitled *Tasimelteon for Insomnia*. As noted by the appellate court, Lankford describes clinical trials in which a 20-milligram dose of tasimelteon was administered 30 minutes before bedtime to blind patients suffering from Non-24. App. 7a. The article identifies tasimelteon as a melatonin receptor agonist and says: "Therefore, tasimelteon should be especially well-suited for treatment of [circadian rhythm sleep disorders]." C.A. App. 20539; *see* App. 51a.

Hardeland. Hardeland is a 2009 review article entitled *Tasimelteon, a Melatonin Agonist for the Treatment of Insomnia and Circadian Rhythm Sleep Disorders*. As noted by the appellate court, Hardeland summarizes a clinical trial that looked at the effect of tasimelteon on phase shifting (i.e., shifting the time when certain hormones are released indicating to the body that it should sleep), which is necessary for and related to entrainment. App. 6a. In the study, participants given 20mg of tasimelteon had a phase shift of over one hour, which was greater than the shift of about thirty minutes observed with the placebo (although the difference was not statistically significant). *Ibid.* Based on this and other data, Hardeland concludes that tasimelteon "may be useful in the treatment of sleep disturbances related to circadian rhythm sleep disorders, such as … entrainment difficulties" and states that "[t]he most

effective doses of tasimelteon were in the range of 20 to 50 mg/day." *Ibid.*

'244 Publication. International Patent Application No. WO 2007/137244 (the '244 Publication) is a patent application filed by Vanda that was published in 2007. It explains that tasimelteon "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." App. 46a. It also states that "[e]ngagement of these receptors by melatonin is believed to regulate circadian rhythms, including the sleep/wake cycle" and that, "[c]onsistent with its receptor binding profile, [tasimelteon] demonstrates potent chronobiotic activity in preclinical models of acute phase-shifting and chronic re-entrainment." *Ibid.* The publication describes clinical trials involving tasimelteon and states that "[a]n oral dose of about 20 to about 50 mg is effective in treating sleep disorders when administered about 1/2 hour before sleep time." App. 7a. The '244 Publication also claims using 20mg of tasimelteon to treat circadian rhythm disorders. *Ibid.*

Teva and Apotex presented expert testimony on the obviousness of the RE '604 patent from Dr. Jonathan Emens, a professor in both the Medicine and Psychiatry departments at Oregon Health and Science University and a board-certified sleep physician with more than 25 years of experience researching sleep medicine and circadian physiology. The district court found Dr. Emens "very credible" and "found his testimony to be compelling." App. 25a.

Dr. Emens explained in detail why a person having ordinary skill in the art would regard the asserted claim of the RE '604 patent as obvious, when considering the information about tasimelteon from either Lankford or Hardeland together with the information on melatonin from Hack, in view of the statements in the '244 Publication explaining why tasimelteon would be expected to have effects on the body similar to melatonin. The district court credited this testimony and held claim 3 invalid. App. 48a–52a.

Vanda did not argue in either the district court or the appellate court that either court applied an erroneous legal standard when assessing obviousness. Instead, Vanda argued that the district court got the facts wrong. *See* App. 5a (quoting Vanda's appeal brief 36). Contrary to the district court's conclusion, Vanda contended, none of the prior-art references "would give a skilled artisan a reasonable expectation of success in using 20 mg of tasimelteon … to entrain." *Ibid.* The Federal Circuit explained why Vanda was incorrect.

To give just the highlights: the Federal Circuit noted that Hardeland summarizes the results of a phase II clinical trial studying the effect of tasimelteon on phase shifting the circadian clock. App. 6a. The court noted that the 20 mg dose of tasimelteon produced a phase shift of over one hour. *Ibid.* The Federal Circuit highlighted Dr. Emens's testimony that "You would never really need a shift of more than an hour, and so [a phase shift of over an hour caused by a 20mg dose of tasimelteon] would be a sufficient shift to treat any individual with Non-24." *Ibid.* The appellate court also pointed out that

Vanda's own '244 Publication "found significance in the 20mg result" and emphasized Dr. Emens's testimony that the '244 Publication would tell persons of ordinary skill in the art that tasimelteon "can … cause entrainment … specifically at doses of about … 20 to 50 milligrams." App. 7a.

Vanda had contended—among other things—that the district court erred in its treatment of the Lankford reference, which describes a phase III clinical trial "designed to assess the effectiveness of 20mg of tasimelteon, compared to placebo, in improving nighttime sleep" in blind Non-24 patients. *Ibid.* (citing Lankford at 991). Vanda argued that the district court "erred in finding that Vanda's ongoing clinical trial [mentioned in Lankford] would give an ordinary artisan an expectation of success." *Ibid.* (citing Vanda's appeal brief 40). The Federal Circuit rejected that argument as relying on a mischaracterization of the district court's opinion:

> Contrary to Vanda's characterization, the district court did not find that Vanda's ongoing clinical trial would have given a [person having ordinary skill in the art] an expectation of success in using tasimelteon to treat Non-24 in and of itself. Instead, the district court found "Lankford's disclosure of Vanda's Phase III trial would also have contributed to a skilled artisan's expectation of success." J.A. 43. There is no error in the district court's use of the then-ongoing clinical trial as one piece of evidence, combined with other prior art references, to support an obviousness determination.

App. 7a–8a. After carefully reviewing the trial evidence, the Federal Circuit affirmed that claim 3 was invalid as obvious. App. 9a.

2. Asserted claim 4 of the '910 patent and asserted claim 14 of the '829 patent were held invalid.

U.S. Patent Nos. 9,730,910 (the '910 patent) and 10,149,829 (the '829 patent) both deal with avoiding harmful interactions between tasimelteon and other drugs. To understand these patents, it is helpful to understand something about how the body metabolizes drugs.

To explain this background at trial, Teva and Apotex presented testimony from Dr. David Greenblatt, a Professor in the Department of Immunology at Tufts University School of Medicine with more than 40 years of experience in molecular and clinical pharmacology. Dr. Greenblatt—one of the nation's foremost experts on drug-drug interactions—explained that there is a group of enzymes found predominantly in the liver that plays an important role in breaking down drugs. They are known as the cytochrome P450 enzymes (or CYP enzymes). Two prominent CYP enzymes are CYP1A2 and CYP3A4.

A drug or other molecule that is acted on by an enzyme is known as a *substrate* of that enzyme. A drug that decreases the activity of an enzyme is known as an *inhibitor*. And a drug that increases the activity of an enzyme is known as an *inducer*.

The evidence showed that, by general rule, doctors avoid prescribing a drug that is a substrate

for a given enzyme together with another drug that is a strong inhibitor or strong inducer of that same enzyme. A strong inhibitor will reduce the enzyme's action in metabolizing the substrate, leading to a *higher* blood concentration of the substrate drug than would otherwise be the case. The effect is as if one had administered a higher dose of the substrate drug, which can entail dangerous side effects. Conversely, a strong inducer will increase the enzyme's action in metabolizing the substrate drug, leading to a *lower* blood concentration of the substrate drug than would otherwise be the case. The effect is as if one had administered a lower dose of the substrate drug, which could prevent the drug from being effective.

With that background in place, one can consider the asserted claims.

The '910 patent. Asserted claim 4 of the '910 patent, reproduced at App. 11a–12a, claims a simple method: A doctor starts with a Non-24 patient being treated with rifampicin (a strong CYP3A4 inducer). Then she discontinues the rifampicin treatment before treating the patient with tasimelteon.

The claim is rendered obvious by the prior-art combinations discussed above with the addition of the Pandi-Perumal reference. Pandi-Perumal is a 2011 review article entitled *Pharmacotherapy of Insomnia with Ramelteon: Safety, Efficacy and Clinical Applications.* Pandi-Perumal deals with ramelteon, a melatonin-receptor agonist with a similar chemical structure to tasimelteon. *See* App. 45a. Pandi-Perumal reports that ramelteon is metabolized by the CYP1A2 and CYP3A4 enzymes. *Ibid.* Pandi-Perumal specifically warns that co-

administration of rifampicin (also known as rifampin) has been shown to considerably decrease blood levels of ramelteon, resulting in losses of efficacy. App. 45a–46a. And Pandi-Perumal warns that coadministration of ramelteon with rifampin and other strong inducers of CYP3A4 should be avoided. *Ibid.*

The district court credited Dr. Greenblatt's testimony and held claim 4 to be invalid because the drastic effect of rifampicin on ramelteon reported in Pandi-Perumal would lead a skilled artisan to expect a similarly drastic effect of rifampicin on tasimelteon. App. 54a–56a; 60a–61a.

Vanda did not argue in the district court or the appellate court that either court applied an erroneous legal standard when assessing obviousness. Instead, Vanda argued that, as a matter of fact, a skilled artisan would not have expected CYP3A4 to be a problem for tasimelteon because (1) a skilled artisan would not have looked to the ramelteon art when considering drug interactions with tasimelteon and (2) one study by Vachharajani that looked at metabolism of tasimelteon by CYP3A4 in the *absence* of a strong CYP3A4 inducer did not identify metabolism of tasimelteon by CYP3A4. App. 13a.

The Federal Circuit considered and rejected both arguments on the facts. App. 13a–14a. First, the court saw "no error in the district court's finding that a skilled artisan would have looked to the ramelteon art because ramelteon and tasimelteon bind to the same receptors, have similar half lives in the body, and are structurally similar." App. 13a. Next, the court noted that Vachharajani "does not refute the

conclusion that a skilled artisan would recognize that tasimelteon and ramelteon have similar properties, nor does it suggest that the metabolism of tasimelteon by CYP3A4 in its induced and uninduced (natural) states would be the same." *Ibid.* The court noted that "it is possible for CYP3A4 to metabolize a drug after being induced even if CYP3A4 does not metabolize that drug in its uninduced state." *Ibid.* Specifically, the court cited the testimony of Dr. Greenblatt, which the district court had credited: "induction causes a massive increase in the amount of enzymes, and you cannot exclude a major role of CYP3A4 [in metabolizing tasimelteon] in the induced state even if you can't detect it in the uninduced state." App. 14a. Accordingly, the Federal Circuit found "no error in the district court's finding that it was obvious to avoid coadministration of rifampicin and tasimelteon, and that claim 4 [of the '910 patent] would have been obvious." *Ibid.*

The '829 patent. Asserted claim 14 of the '829 patent, reproduced at App. 14a, requires starting with a Non-24 patient being treated with fluvoxamine, ciprofloxacin, or verapamil—all strong CYP1A2 inhibitors—and then discontinuing treatment with that drug before treating the patient with 20 milligrams of tasimelteon daily.

This claim is rendered obvious by the same combination of prior-art references discussed above: Hardeland, Hack, and the '244 Publication, either with or without Lankford. Hardeland has the key information: it states that "tasimelteon [is] primarily metabolized by CYP1A2" and thus "coadministration of any drug that inhibits [this enzyme] should be regarded with caution." App. 44a.

The district court also considered the Vachharajani study of ramelteon, which showed "that ramelteon underwent a 100-fold increase in blood plasma levels when it was co-administered with the CYP1A2 inhibitor fluvoxamine." App. 40a. The district court observed, based on Dr. Greenblatt's testimony, 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." *Ibid.* Because tasimelteon was known to be a CYP1A2 substrate and because strong CYP1A2 inhibitors had a dramatic impact on the blood plasma levels of ramelteon, which has many structural and functional similarities to tasimelteon, the district court held claim 14 of the '829 patent invalid as obvious. App. 52a–53a; 73a.

Again, Vanda did not argue in the district court or the appellate court that either court applied an erroneous legal standard when assessing obviousness. Instead, Vanda argued that a skilled artisan would not think it obvious to avoid coadministering tasimelteon with a strong CYP1A2 inhibitor because the prior art did not explicitly tell skilled artisans *not* to prescribe the two together. App. 15a. The Federal Circuit rejected this argument, noting that, "[t]aken together, Hardeland's warning and the ramelteon study supported the district court's finding that a skilled artisan would have expected that taking a CYP1A2 inhibitor with tasimelteon would have negatively

impacted the efficacy of tasimelteon and so the two should not be given together." *Ibid.*

3. Asserted claim 5 of the '487 patent was held invalid.

To practice asserted claim 5 of U.S. Patent No. 10,376,487 (the '487 patent), reproduced at App. 9a, a doctor needs only to administer 20 milligrams per day of tasimelteon to a Non-24 patient without food. Notably, the claim does *not* require that the administration without food have any particular effect as compared to administration with food. The parties stipulated at the district court that "without food" means that the patient has no food within 30 minutes before the drug is administered. App. 56a.

Teva and Apotex argued that this claim is rendered obvious by the same combinations of prior-art references discussed in connection with the RE'604 patent. The prior art describes various instances in which Non-24 patients received 20 mg of tasimelteon half an hour before bedtime. *Ibid.* The evidence showed that most people do not eat right before they go to bed, so the instruction to take the drug shortly before bedtime would result in many people taking the drug without food. App. 56a–57a. The evidence also showed that published FDA guidance instructs drug companies to conduct studies to determine whether food would affect the efficacy of a drug such as tasimelteon. App. 10a–11a. This regulatory advice created a motivation to determine whether food would have an effect on drug efficacy.

The Federal Circuit noted that, "as the [patent] specification appears to recognize, there were only

two permutations for the food variable: tasimelteon could have been administered with food [i.e., eating within 30 minutes of administration] or without food [i.e., not eating within 30 minutes of administration]." App. 11a (citing '487 patent, col. 2, ll. 18–19 (describing a study in which "each subject received 100 mg tasimelteon either with or without food.")). The appellate court echoed the district court's observation that "[w]hether to administer tasimelteon with food is a binary choice." *Ibid.* The appellate court concluded that, "[u]nder these circumstances, given the FDA guidance, it would have been obvious to try administering tasimelteon without food." *Ibid.* Because the claim requires nothing more, the Federal Circuit affirmed the district court's ruling that the claim is invalid for obviousness. *Ibid.*

REASONS FOR DENYING THE PETITION

I. VANDA FAILED TO PRESERVE ITS QUESTION PRESENTED FOR APPELLATE REVIEW.

Vanda forfeited the sole argument made in its petition. At no time in the whole course of this case before its petition for a writ of certiorari did Vanda suggest that there was any problem with the well-settled standard for evaluating obviousness that both the district court and the appellate court applied. On the contrary, Vanda consistently framed its arguments in terms of whether a person having ordinary skill in the art would have been motivated to combine the prior-art references and would have reasonably expected success in doing so. Even as late as its petition to the Federal Circuit for rehearing en

banc, Vanda made no suggestion that anything other than a reasonable expectation of success should be required for obviousness. Instead, Vanda argued that—as a factual matter—Teva and Apotex failed to make the required showing. *See, e.g.*, Vanda Petition for Rehearing 11–12 (Fed. Cir. Dkt. No. 57) (arguing that a clinical trial "will rarely be enough to provide a [skilled artisan] with a reasonable expectation of success").

The courts below can hardly be faulted for failing to apply an obviousness standard that Vanda never asked them to apply. Vanda thus forfeited the issue, and in the process deprived this Court of the benefit of any analysis by the lower courts of Vanda's proposed new legal standard.

As is apparent from the detailed and carefully reasoned opinions of both courts below, the invalidation of Vanda's patents resulted from the fact-bound application of settled law. Indeed, Vanda does not even try to argue that its claims should survive under the longstanding test for obviousness that both courts below applied. It is only by advocating a brand-new legal standard that Vanda can urge error.

Vanda's eleventh-hour pivot, however, comes at a cost: This Court routinely denies certiorari when, as here, the petitioner has failed to preserve an issue for review. *See Clingman v. Beaver*, 544 U.S. 581, 598 (2005) ("We ordinarily do not consider claims neither raised nor decided below."); *Lytle v. Household Mfg., Inc.*, 494 U.S. 545, 551, n.3 (1990) ("Applying our analysis … to the facts of a particular case without the benefit of a full record or lower court determinations is not a sensible exercise of this

Court's discretion."); *United States v. Mendenhall*, 446 U.S. 544, 551 n.5 (1980) (matters "neither raised before nor decided by the courts below" are considered only "in exceptional circumstances"). And denial is the appropriate course here. No exceptional circumstances exist that would justify granting certiorari to impose a new legal test for obviousness that neither court below was asked to consider and that, as far as Respondents can glean, no court has yet been asked to apply.

II. THE APPELLATE COURT APPLIED THE CORRECT LEGAL STANDARD FOR OBVIOUSNESS, AND THERE IS NO DISAGREEMENT AMONG THE FEDERAL COURTS ON THE LEGAL STANDARD THAT WOULD WARRANT THIS COURT'S REVIEW.

This Court is not "a court of simple error correction." *Overton v. Ohio*, 534 U.S. 982, 985 (2001) (Mem.) (Breyer, J., respecting the denial of certiorari). At bottom, however, error correction is all Vanda seeks. There is no significant question of law here—only a patent owner who thinks the district court got the facts wrong. The decisions below, moreover, "lack[] significant value as precedent," *id.*, both because they are unpublished and because they apply well-settled law on which there is no split of authority. It is Vanda's belated proposal that obviousness requires *more* than an expectation of success—not anything that happened in the courts below—that would break new ground and contradict this Court's precedent. Certiorari should be denied.

A. The nonprecedential decision of the appellate court is fully consistent with this Court's precedents.

This Court articulated the general framework for evaluating obviousness under 35 U.S.C. § 103 in its 1966 *Graham v. John Deere* decision:

> 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.

383 U.S. at 17. The Court explained that this framework was a codification of judicial precedents on patentability going back to this Court's 1850 decision in *Hotchkiss v. Greenwood*, 52 U.S. (11 How.) 248 (1850). There, this Court emphasized that, to obtain a patent, an inventor must do more than what an artisan of ordinary skill would be expected to do:

> "[U]nless more ingenuity and skill … were required … than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention. In other words, the improvement is the work of

> the skillful mechanic, not that of the inventor."

Graham, 383 U.S. 11 (quoting *Hotchkiss,* 52 U.S. at 267).

This Court renewed its emphasis on the ingenuity and skill of the ordinary artisan in its 2007 *KSR* decision. *KSR* held that the Federal Circuit had been too reluctant to hold patents obvious. Specifically, this Court rejected the rigid "teaching, suggestion, or motivation" (or TSM) test that the Federal Circuit had developed, "under which a patent claim is only proved obvious if 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art." 550 U.S. at 407.

In place of the rigid TSM test, this Court read the statute and its own precedents as requiring an "expansive and flexible approach." *Id.* at 415. Often, the Court explained,

> it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.

Id. at 418. But "the analysis need not seek out precise teachings directed to the specific subject matter of the

challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418. The Court emphasized that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 421.

The problem with the TSM test was that, by placing off-limits much of the information and reasoning that an artisan of ordinary skill would be expected to consider, the test allowed too many dubious patents to survive—a problem that was particularly acute when all the elements of a claimed invention were known in the prior art. This Court has long emphasized the need for "caution in granting a patent based on the combination of elements found in the prior art," because a "'patent for a combination which only unites old elements with no change in their respective functions … obviously withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men.'" *Id.* at 415–16 (quoting *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152–53 (1950)). That concern "is a principal reason for declining to allow patents for what is obvious." *Id.* at 416.

Indeed, this Court has been unsparing in its criticism of would-be patent monopolists like Vanda who try to forestall competition with patents that combine known prior-art elements in conventional ways without achieving any surprising or unexpected result. In *Atlantic Works v. Brady*, 107 U.S. 192 (1883), the Court warned that "[t]o grant a single party a monopoly of every slight advance made" without requiring more than "ordinary mechanical or

engineering skill" is "unjust in principle and injurious in its consequences" because

> [i]t creates a class of speculative schemers who make it their business to watch the advancing wave of improvement, and gather its foam in the form of patented monopolies, which enable them to lay a heavy tax upon the industry of the country, without contributing anything to the real advancement of the art.

Id. at 200. In *KSR* this Court struck a similar chord: "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." 550 U.S. at 419.

Notwithstanding Vanda's protestations to the contrary, this Court has considered the expectations of persons of skill in the art as part of the obviousness inquiry. In *KSR*, for example, the Court cited with approval its own prior conclusion that "when a patent 'simply arranges old elements with each performing the same function it had been known to perform,' and yields *no more than one would expect* from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida*, 425 U.S. at 282) (emphasis added). *KSR*'s statement that, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious *unless its actual application is beyond his or her skill*," *ibid.* (emphasis added), likewise implicates the expectations of a skilled artisan: using the technique is obvious unless a skilled artisan

would not reasonably expect to be able to apply the technique successfully. The Federal Circuit's formulation of the legal test for obviousness is fully consistent with this Court's emphasis on the knowledge and ingenuity of a skilled artisan.

Notably, the effect of the Federal Circuit's "reasonable expectation of success" formulation of the legal test for obviousness is to *raise* the bar for finding a patent claim obvious. Not every combination of prior-art elements is obvious; there must be both a motivation to combine them and a reason to expect that the combination would succeed. *See Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017) (Federal Circuit will not find obviousness if the evidence shows that "one would no more have expected failure than success"). Vanda thus has things backwards: the "reasonable expectation of success" inquiry operates as a bulwark against too readily finding obviousness—not a means for courts to invalidate truly innovative patents.

Furthermore, even where a combination would be expected to succeed, the Federal Circuit considers "unexpected results" among the objective indicia of nonobviousness that this Court noted could prove "instructive." *KSR*, 550 U.S. at 415; *see Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 963–64 (Fed. Cir. 2023) (invention's 20-fold difference in potency, "when an otherwise two-fold difference would have been expected by the skilled artisan" was an unexpected result precluding a finding of obviousness). That principle further ensures genuinely unexpected advances receive patent protection.

Here, all of the elements of the asserted claims are found in the prior art, and the evidence showed that persons having ordinary skill in the art not only would have been motivated to combine them, but that the resulting combination yielded no more than those skilled artisans would reasonably have expected. The courts below correctly invalidated the asserted patent claims as obvious, consistent with this Court's decisions in *Graham, Sakraida,* and *KSR.*

B. Vanda's proposed new legal standard for obviousness is illogical and inconsistent with this Court's cases.

Vanda's new proposed legal test for obviousness rests on a fundamental logical fallacy. Vanda takes snippets of text from this Court's prior opinions indicating that a patent was invalid because some element of the claim at issue would have been "perfectly plain" or "immediately recognized" by a skilled artisan or "plainly indicated" in the prior art and then concludes that a patent can be invalid *only* under those circumstances. But the conclusion plainly does not follow from the premise. This Court has neither stated nor implied, as Vanda would have it, that an invention is obvious *only* when it would have been perfectly plain, immediately recognized, or plainly indicated. *Contra* Pet. 14. On the contrary, the inquiry has always been about whether an artisan of ordinary skill, in view of the prior art and the artisan's level of skill, would have had "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418.

That approach makes good sense, as this case illustrates. There is no reason to suppose that

artisans of ordinary skill would ignore ongoing clinical trials or find it obvious to try only modifications for which success is completely guaranteed, as would be the case under Vanda's new legal test. Where, as here, numerous prior-art references, including Vanda's own prior-art patent application, suggest to the skilled artisan that a particular dosing regimen for a drug is likely to be effective, the mere fact that the clinical trial testing the regimen has not yet been completed does not make the claimed regimen any less obvious. And this Court has never said otherwise. Indeed, Vanda's suggestion that patents cannot be invalidated as obvious absent knowing the combination will work is precisely the sort of overly rigid and formalistic analysis that this Court rejected in *KSR* in favor of a more "expansive and flexible approach" that recognizes the skilled artisan to be "a person of ordinary creativity, not an automaton." 550 U.S. at 415, 421.

Requiring predictable knowledge in outcomes before a patent can be held invalid as obvious would put on the obviousness inquiry a straight-jacket of precisely the type that *KSR* rejected. It would also render patentable a whole swath of very obvious innovations, particularly in the chemical and biological arts. Nothing in this Court's cases requires such an illogical result.

C. There is no split among the circuits concerning Vanda's question presented.

Vanda's assertion that "[t]he standard for obviousness has divided the circuits" (Pet. at 20) is

wrong. There is no circuit split. The Federal Circuit's precedent is uniform on this point, as Vanda implicitly concedes. With one exception, all of the cases Vanda cites for its purported split predate both this Court's decision in *KSR* as well as the creation of the Federal Circuit as the court with nationwide jurisdiction over patent cases. *See* Pet. 20–25. Some of the cases also predate the Court's 1966 decision in *Graham*, and one even predates the Patent Act of 1952. *See id.* And, most fundamentally, none of the cited cases addresses the question presented: none considers the difference, if any, between a predictable result and a reasonably expected result.

The sole post-Federal-Circuit case Vanda cites for the alleged circuit split does not take issue with the Federal Circuit's obviousness standard. On the contrary, that case relies for its legal framework on the Federal Circuit's decision in *Pfizer v. Apotex*—the very case that Vanda points to (at Pet. 7, 13–15, 34) as its prime example of the Federal Circuit's supposedly wrong obviousness inquiry. *See ABS Global, Inc. v. Inguran, LLC*, 914 F.3d 1054, 1066 (7th Cir. 2019) (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007), for the proposition that the "motivation to combine is always a factual question that is '[s]ubsumed within the *Graham* factors'"). The Seventh Circuit then went on to state that, to the extent the appellant raised disputes about whether there was factual support for the motivation to combine, the jury's verdict indicated that the jury resolved those factual questions in favor of the patentee. *Ibid.* This Court can look skeptically on fanciful claims of a split between the Federal Circuit and a regional circuit over substantive patent law.

Vanda's putative circuit split is illusory. Certainly, there is no live disagreement about the standard for obviousness that would justify a grant of certiorari.

III. THIS CASE IS A POOR VEHICLE FOR REACHING VANDA'S QUESTION PRESENTED, WHICH IS OF NO PARTICULAR IMPORTANCE.

Although obviousness is an issue frequently litigated in patent cases, Vanda has failed to show that the appellate court applied an erroneous standard or that there is any confusion or conflict among the federal courts about the proper test for obviousness. No one before Vanda seems to have raised the question whether reasonably expecting success is insufficient to render a claim obvious (as noted above, even Vanda did not think to raise the issue before filing its petition for certiorari). That no court has been called on to analyze the issue suggests it is not one of importance—let alone the extraordinary importance required to justify certiorari. Furthermore, this case is a poor vehicle to address Vanda's reformulation of the legal standard because changing the standard would be unlikely to change the outcome of this case.

A. This case is a poor vehicle for reaching Vanda's question presented.

Vanda argues that this case is a suitable vehicle to address its proposed question presented because "[o]bviousness was the sole basis for the decision below." Pet. 30. That highly general statement is accurate so far as it goes, but Vanda's conclusion does not follow. While obviousness—in general—is the

reason Vanda lost on each of its patents, Vanda would likely have still lost even under its own novel standard proposed for the first time in this Court.

The nub of Vanda's argument for a new legal standard for obviousness is that the outcome of clinical trials cannot be predicted with certainty. True enough. But Vanda grossly mischaracterizes the Federal Circuit's holding when it says that the Federal Circuit "effectively treats any 'viable' experiment as one that necessarily gives a skilled artisan a reason to expect a successful result from the experiment, making that result obvious and unpatentable," Pet. 16. Indeed, in its appeal to the Federal Circuit, Vanda wrongly accused the district court of doing the same thing, and the Federal Circuit called Vanda out on the mischaracterization: "Contrary to Vanda's characterization, the district court did not find that Vanda's ongoing clinical trial would have given a [person having ordinary skill in the art] an expectation of success in using tasimelteon to treat Non-24 in and of itself." App. 7a. Nor did the Federal Circuit embrace any such rule.

As a result, this unpublished decision is a poor vehicle for addressing the extent to which an incomplete clinical trial for a drug, on its own, could result in an obviousness finding. Here, the ongoing trial was one of many pieces of evidence related to certain claim elements (and was completely irrelevant to other elements). As explained above, the prior art indicated that tasimelteon binds to the brain's melatonin receptors and so was understood to be useful in treating circadian rhythm disorders such as Non-24. Previous experiments with tasimelteon indicated that a dose of 20 mg half an hour before

bedtime produces a phase-shift of the circadian rhythm suitable for entraining Non-24 patients to a regular 24-hour sleep-wake cycle. All this was known outside of the context of the clinical trial. Therefore—irrespective of the ongoing clinical trial—a person having ordinary skill in the art would have had a motivation to administer a 20 mg dose of tasimelteon half an hour before bedtime to entrain the circadian rhythms of blind people with Non-24 and would have expected to succeed in treating Non-24 by doing so.

That Vanda itself was known in the prior art to be testing just that dose at just that time for just that purpose is relevant to the obviousness inquiry because it confirms the prevailing wisdom in the field. If the rest of the prior art had indicated that 20 mg was the right dose but (contrary to what actually happened) Vanda were testing 80 mg or 4 mg, that fact would likewise have been relevant, as it might have raised a question in the mind of a skilled artisan about whether 20 mg was the appropriate dose. Either way, the existence of the clinical trial and the dosing regimen being used in it would inform a skilled artisan considering possible drugs for entraining the circadian rhythms of Non-24 patients. But, for the reasons given in detail by the courts below, the rest of the prior art already pointed strongly to obviousness; hence, the patents would be invalid even if the clinical trial protocol had not been available.

Vanda's criticisms of the Federal Circuit's decision are thinly veiled attempts to reargue factual issues on which Vanda lost at trial. With regard to the RE'604 patent, as discussed, the dosing regime was in the prior art.

With regard to the drug-drug interaction patents, the evidence established that persons of ordinary skill in the art would have expected tasimelteon to be metabolized by CYP1A2 and CYP3A4. It was thus entirely predictable that co-administration of tasimelteon with drugs that were strong inhibitors or inducers of those enzymes should be avoided because it would result in either dramatically higher or dramatically lower blood concentrations of tasimelteon. Vanda's proposed rewording of the legal standard to focus on whether the result was "predictable" rather than "expected" would not change that result. The "possibility" language Vanda quotes (Pet. 32) comes from the section of the Federal Circuit's opinion rejecting Vanda's separate argument that the prior art "taught away" from the invention because one reference (Vachharajani) found no metabolism of tasimelteon by CYP3A4. *See* App. 13a–14a. Vanda's attempt to twist that rejection of its teaching-away argument into a misstatement of the obviousness standard thus fails.

With regard to the take-without-food patent, Vanda's asserted claim is invalid as obvious because it claims administering tasimelteon without food, full stop—something that was indisputably found in the prior art. The asserted claim does not require that taking the drug without food have any effect whatsoever. This lack of a claimed food effect distinguishes Vanda's patent from other patents in which a non-obvious food effect was described and claimed. *See, e.g.*, *Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*, 731 F. App'x 962, 965, 970 (Fed. Cir. 2018) (affirming nonobviousness of patent that claimed a particular "blood concentration

level of oxymorphone … upon dosing of controlled release oxymorphone in fed versus fasting conditions"). Vanda's assertion that, "while the general idea that food may affect a drug's bioavailability was well known, the specific effect of food on tasimelteon was not known until tested," Pet. 33—even if it were true—is thus irrelevant. The asserted claim *does not claim any food effect*, unpredictable or otherwise.

Vanda argued below that its patents had achieved unexpected results—because Vanda recognized that the Federal Circuit has long treated such results as indicia of nonobviousness. The district court found that that set of arguments failed on the facts, not the law, App. 58a–62a, and the Federal Circuit affirmed. App. 8a n.8. "Where an intermediate court reviews, and affirms, a trial court's factual findings, this Court will not 'lightly overturn' the concurrent findings of the two lower courts." *Easley v. Cromartie*, 532 U.S. 234, 242 (2001). But that is just what Vanda's petition—which contends Vanda has patented something unpredictable or unexpected—asks this Court to do.

In short, this case is not a suitable vehicle for considering Vanda's proposed new phrasing for the legal standard for obviousness. The new standard would not have any impact on the outcome of the case; Vanda would still lose on the facts. Furthermore, both the district court's and the appellate court's opinions were unpublished, so they will not have any precedential impact on future cases.

There may someday be a case in which Vanda's question presented is preserved for review and would

impact the result of the suit and create perturbations in the law for future cases. Perhaps then certiorari will be warranted. But this is not such a case.

B. Even if Vanda had preserved its proposed question presented for review, that question is not important enough to warrant resolution by this Court.

Apart from bland generalities about the importance of patents to creating incentives for innovation, Vanda provides no concrete reason why its question presented is important enough to justify review by this Court. Indeed, Vanda's inability to cite any case actually addressing the question presented speaks volumes. If there was genuine concern that the Federal Circuit had been applying the wrong standard for obviousness for decades, one would expect the issue to have come up by now.

It is also noteworthy that Congress, when it overhauled the patent laws in 2011 in the Leahy-Smith America Invents Act, Pub. L. 112-29, made no change to the standard for obviousness. That strongly suggests Congress intended to leave in place the well-settled legal standard. "Congress is understood to legislate against a background of common-law principles, and when a statute covers an issue previously governed by the common law, we interpret the statue with the presumption that Congress intended to retain the substance of the common law." *Samantar v. Yousuf*, 560 U.S. 305, 320 n.13 (2010); *see Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 139 S. Ct. 628, 634 (2019) (presumption that the AIA codified "settled pre-AIA precedent").

Moreover, if there was a genuine problem with the Federal Circuit's articulation of the standard for obviousness, then there would presumably be many opportunities to raise that issue in future obviousness cases, with a view to fleshing out the competing views and obtaining the considered analysis of the lower courts before this Court takes up the question. Allowing the question to percolate in this way would be appropriate even if the Court were inclined to revisit the obviousness standard.

Vanda's general policy arguments boil down to a naked plea for this Court to make it dramatically more difficult to invalidate patents as obvious than has ever before been the case. That would be bad policy for the reasons that this Court has already articulated, as described above, *see supra* Section II.A: allowing a patent on obvious, minor improvements to the prior art "withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men"; enables "speculative schemers" to "lay a heavy tax upon the industry of the country, without contributing anything to the real advancement of the art"; and may "deprive prior inventions of their value or utility." And, in the context of Hatch-Waxman Act cases like this one, Vanda's proposed new obviousness standard would reduce the availability of generic drugs, resulting in higher prices for payors and lower drug accessibility for patients.

Vanda asserts that this case is important because drug developers are "required to disclose ongoing clinical trials on clinicaltrials.gov" and that this Court should intervene to prevent the public disclosure of such clinical trials from being considered as part of

the obviousness inquiry. Pet 27–28. But Vanda's problem is not that it had to publish the protocol for its ongoing clinical trial. Vanda's problem is that it waited until 2012—after not only the protocol but also a wealth of other prior art rendering its purported inventions obvious had accumulated—to apply for the patents at issue. Vanda's own '244 Publication demonstrates that the dilemma Vanda now complains of is illusory: years before publishing its Phase III clinical trial protocol, Vanda applied for patent claims closely mirroring the ones it asserted in this case.

Vanda also argues that this Court's recent decision in *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023), somehow makes resolution of Vanda's question presented more urgent. Pet. 29–30. But *Amgen* was a case about enablement (§112 of the Patent Act); it had nothing to do with obviousness (§ 103). Method-of-treatment patents like those at issue here need not include clinical trial results to satisfy § 112. *See In re Montgomery*, 677 F.3d 1375, 1382 (Fed. Cir. 2012) ("It is well established that a patent may be secured, and typically is secured, before the conclusion of clinical trials."). This Court's decision in *Amgen* did not hold otherwise. *Amgen* did not involve questions about clinical trials at all; the question there was whether functionally defined claims to a genus of antibodies potentially spanning millions of species were supported by a specification that disclosed 26 example antibodies and invited artisans of ordinary skill to find others though "random trial-and-error." *Amgen*, 598 U.S. at 615. *Amgen* is irrelevant to this case, and Vanda's odd detour into enablement law under 35 U.S.C. § 112 provides no reason for this Court to review the decision of the appellate court.

CONCLUSION

This Court should deny Vanda's petition for a writ of certiorari.

Respectfully submitted,

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