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

REPLY BRIEF FOR PETITIONER

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Cases—continued

Statutes

REPLY BRIEF FOR PETITIONER

The petition raises a critical question—the legal standard governing obviousness. The Federal Circuit's reasonable-expectation-of-success standard departs materially from the approach this Court has employed for more than a century (see Pet. 13-17; Professor Amicus Br. 3)—and it conflicts with case law from sister circuits both before and after creation of the Federal Circuit (Pet. 20-25).

Review is urgent, as the Federal Circuit's wayward standard is now enabling patent challengers to use the "mere commencement of a clinical trial [to] show[] that skilled artisans would have reasonably expected the tested methods to succeed"—undermining incentives necessary for "high-risk, high-investment pharmaceutical research." Salix Amicus Br. 1, 3.

The Federal Circuit's improper standard is outcome determinative here. This is an especially attractive vehicle because it presents four different patents across which the correct standard may be assessed. And the prior art does not remotely suggest that the results claimed by Vanda's patents were "predictable." Rather, as the Federal Circuit self-consciously understood, its invalidation of Vanda's patents relied entirely on the reasonable-expectation-of-success framework. Using that standard, the court invalidated Vanda's claims based in material part on evidence describing clinical *trials*, where no results were yet available. It is self-evident that a skilled artisan will often have a "reasonable expectation" that the next experiment will achieve "success" well before one could conclude that success is "predictable."

In claiming (at 17-19) that Vanda waived its argument, respondents misunderstand the rules governing review. Because it was passed on below—indeed,

it was integral to the decision—the question presented is ripe for review.

If left unchecked, the Federal Circuit's improper standard "will inevitably lead to fewer treatments being developed for small and underserved patient populations across the United States." Patients' Amicus Br. 4. Review is warranted.

A. The question presented—which is undeniably important—warrants review.

1. The Federal Circuit's reasonable-expectation standard conflicts with this Court's precedents.

Both before and after *Graham*, the Court has employed a "predictability" standard for obviousness, a standard more protective of innovation than the Federal Circuit's reasonable-expectation-of-success approach. Pet. 13-17. Far from "novel" (Opp. 29), the Court has for more than 150 years "consistently said that obviousness turns on whether an invention would be plainly indicated or plainly foreshadowed by the prior art, be the predictable result of the prior art, or fall within the ability of all skilled artisans in the field." Professor Amicus Br. 13. See also Pet. 14-15.

In attempting to recast the Federal Circuit's standard as consistent with this Court's precedents, respondents are notably unable to cite any precedent from this Court endorsing the Federal Circuit's capacious test. See Opp. 20-23. Understandably so because "none of this Court's cases before [Section] 103's enactment in 1952, nor after, has used 'reasonable expectation of success' as the basis for assessing obviousness." Professor Amicus Br. 12.

All respondents can muster is a passing use of the word "expect" in *KSR*'s summary of *Sakraida*'s holding. Opp. 23 (quoting *KSR Int'l Co.* v. *Teleflex, Inc.*,

550 U.S. 398, 417 (2007)). In the same breath, however, the Court explained that "*Sakraida* and *Anderson's–Black Rock* are illustrative—a court must ask whether the improvement is more than the *predictable use* of prior art elements according to their established functions." 550 U.S. at 417 (emphasis added). This is no endorsement of the Federal Circuit's standard; it is a reiteration that predictable results—like the "[e]xploitation of the principle of gravity" in *Sakraida* v. *Ag Pro, Inc.* (425 U.S. 273, 282 (1976))—have long been a feature of this Court's jurisprudence.

The Federal Circuit's deviation from this Court's precedent has substantial consequences. Respondents fail entirely to engage with the petition's explanation (at 16-17, 28-29) of how the Federal Circuit's reasonable-expectation standard repeatedly invalidates patents where the result cannot be fairly called "predictable." See, *e.g.*, *Bayer Schering Pharma AG* v. *Barr Lab'ys, Inc.*, 575 F.3d 1341, 1351 (Fed. Cir. 2009) (Newman, J. dissenting) (criticizing the Federal Circuit's invalidation of a patent as obvious by concluding the experiment was merely a "viable option"); *Merck & Cie* v. *Gnosis S.P.A.*, F.3d 829, 833-834 (Fed. Cir. 2015). This case is yet further illustration. See Pet. 30-34; pages 7-10, *infra*. Respondents' unsupported suggestion that the Federal Circuit's reasonable-expectation test *raises* the bar for obviousness is irreconcilable with the Federal Circuit's history of invalidating patents via weak obviousness evidence. Pet. 28-29.

The Federal Circuit's standard also conflicts with Section 103's text regarding the "manner" of invention. As the petition explained (at 18), Congress expressly jettisoned the requirement of a "flash of creative genius" and directed that "[p]atentability shall not be negatived by the manner in which the invention was made" (35 U.S.C. § 103 (1964)). Because

pharmaceutical innovation "necessarily builds upon past discoveries" and requires "long toil and experimentation" to achieve results (Pet. 18), the Federal Circuit's standard based on whether a skilled artisan might reasonably expect to succeed in an experiment effectively "negates" pharmaceutical patents based on "the manner in which the invention was made." 35 U.S.C. § 103. Respondents do not respond.

2. The divergent results among the lower courts further counsels in favor of review.

Respondents are wrong to contend (at 27) that the Seventh Circuit "relie[d] on" the Federal Circuit's reasonable-expectation standard in *ABS Global, Inc.* v. *Inguran, LLC*, 914 F.3d 1054 (7th Cir. 2019). *ABS Global* cited precedents only from this Court in articulating the obviousness standard. See *id.* at 1064-1066. The court referenced *Pfizer, Inc.* v. *Apotex, Inc.* once in discussing the defendant's argument that "the existence of factual disputes" regarding motivation to combine would render "judgment as a matter of law inappropriate." *Id.* at 1066. Yet the Seventh Circuit rejected that argument because this Court has held that obviousness is a legal question. *Id.* at 1066-1067. The Seventh Circuit never once relied on Federal Circuit law in its analysis of obviousness (*id.* at 1067-1069), a striking omission. Far from a "fanciful" claim of a conflict (Opp. 27), the only way to read the Seventh Circuit's decision is as rejecting the Federal Circuit's obviousness standard by overt refusal to employ it. 914 F.3d at 1067-1069.

Respondents are further incorrect (at 26-27) to disregard all the conflicting cases that predate the Federal Circuit. In considering whether to review a Federal Circuit doctrine—where traditional circuit conflicts generally do not develop—the Court

regularly considers whether that court has diverged from pre-1982 regional circuit law. That animated review in *KSR*. Pet. at 20-24, *KSR*, *supra* (No. 04-1350). So too in *Pfaff* v. *Wells Electronics, Inc.*, where the Court specifically noted the conflicting pre-1982 cases as one factor justifying review. 525 U.S. 55, 60 (1998).

The regional circuits consistently focused on "predictable results." Each regional circuit to address the standard before the creation of the Federal Circuit held a result that "could not have been *predicted beforehand*" is not obvious. *Penn Int'l Indus.* v. *Pennington Corp.*, 583 F.2d 1078, 1082 (9th Cir. 1978) (emphasis added). See *Eli Lilly & Co.* v. *Premo Pharm. Lab'ys, Inc.*, 630 F.2d 120, 130 (3d Cir. 1980) (results that "were not predictable to chemists or other persons skilled in the prior art" are nonobvious); *Ling-Temco-Vought, Inc.* v. *Kollsman Instrument Corp.*, 372 F.2d 263, 267 (2d Cir. 1967) (material that performs in "a readily predictable manner" is obvious); *Eli Lilly & Co.* v. *Generix Drug Sales, Inc.*, 460 F.2d 1096, 1103 (5th Cir. 1972) (similar). Tellingly, respondents do not even attempt a substantive rebuttal.

That the Federal Circuit's law to the contrary is entrenched does not make it "settled." Opp. 18. Rather, the Court should consider whether the Federal Circuit's approach—which stands at odds with this Court's own precedent and that of the regional circuits—is correct.

3. The question presented is undeniably important.

Proper calibration of the obviousness standard is essential to the patent system. *Pfaff*, 525 U.S. at 63. As *amici* have described, the appropriate rule is necessary to ensure the development of new and innovative pharmaceutical treatments—especially those for

rare diseases that affect discrete, small, and underserved patient populations. Patients' Amicus Br. 15; Salix Amicus Br. 9.

Respondents implicitly agree; it is hard to imagine that future innovators will invest the enormous sums required, only to experience the "commercial disaster" that respondents describe. Opp. 3. Distorting the necessary incentive for innovators, as the Federal Circuit's reasonable-expectation standard does, will inevitably stall pharmaceutical innovation for patient populations that need it most. Patients' Amicus Br. 10-15.

Respondents—generic drug manufacturers who have enormous incentive to invalidate innovators' patents—thinly veil the benefits they reap from the Federal Circuit's erroneous standard. Patent challengers are increasingly using government-mandated clinical trial disclosures as prior art before any results demonstrating promise are released. Pet. 27-28 & n.8 (collecting cases). The Federal Circuit just again used "expect[ing]" a clinical trial "to be a success" as reason to vacate a nonobviousness finding. *Janssen Pharms., Inc.* v. *Teva Pharms. USA, Inc.*, __ F.4th __, 2024 WL 1355733, at *15 (Fed. Cir. Apr. 1, 2024). Yet respondents agree that the outcomes of clinical trials are not predictable (Opp. 29)—it would be hard to argue otherwise. The standard makes all the difference.

Beyond wrong, the Federal Circuit's precedent puts pharmaceutical innovators in an impossible bind. As the petition explained, the Court reiterated in *Amgen Inc.* v. *Sanofi* that a drug innovator cannot patent its novel methods without possessing sufficient detail to explain the scope of the invention, which often requires the results of clinical trials. Pet. 29; Salix Amicus Br. 4. The Federal Circuit's recent decision in *Biogen International GMBH* v. *Mylan Pharma-*

ceuticals Inc., which held that the written description requirement in 35 U.S.C. § 112 requires proof of safety and efficacy, only enhances this problem. 18 F.4th 1333, 1343 (Fed. Cir. 2021).[1]

Respondents' only retort (Opp. 35) is that *Amgen* involved enablement under Section 112, not obviousness under Section 103. But that is exactly the point. After *Amgen*, pharmaceutical innovators face impossibility: It will be too early to patent pharmaceutical method claims prior to obtaining the results of clinical trials for enablement and written description purposes, but once clinical trials are announced, it will be too late to patent those inventions because the existence of the trial will tend to render obvious the resulting invention. See Salix Amicus Br. 4.

The patent laws are supposed to incentivize innovation by granting a limited monopoly. The Federal Circuit's misaligned standard produces an improper calibration of the incentives to innovate, particularly in the pharmaceutical space. Whatever answer the Court ultimately reaches, the question is exceedingly important.

B. This is an appropriate vehicle.

The decision below turned on the Federal Circuit's obviousness standard. See, *e.g.*, Pet. App. 8a. Indeed, the court of appeals underscored the centrality of that reticulated standard to this case, stating that "[o]bviousness does not require certainty—it requires a reasonable expectation of success." *Id.* at 15a. This is thus

[1] Respondents' citation (Opp. 35) to a Federal Circuit case predating *Amgen* and *Biogen* for the highly general proposition that a patent may be secured before a clinical trial is complete surely does not override the holdings in *Amgen* and *Biogen*.

an appropriate vehicle to resolve whether that standard is correct.

Application of the correct standard may well be a task for the court of appeals on remand. See, *e.g.*, *Illinois Tool Works Inc.* v. *Independent Ink, Inc.*, 547 U.S. 28, 46 (2006). In any event, there is a substantial likelihood—if not certainty—that the proper standard will change the outcome here. And because all parties agree on the scope and content of the prior art, there are no—contrary to respondents' claim (at 30)—contested "factual issues." The dispute instead centers on the proper legal standard to assess that art.

As for the RE604 patent, the method of administering 20mg of tasimelteon to entrain a Non-24 patient's circadian rhythm, the Federal Circuit reasoned that "the evidence is sufficient to support the district court's finding that the tasimelteon prior art would have given a skilled artisan a reasonable expectation of success of entrainment with 20mg." Pet. App. 8a. But the evidence the court relied upon is telling: Hardeland, which summarized a clinical trial by Rajaratnam, did *not* produce "statistically significant phase shift" for doses less than 100mg, and its conclusion—that lower doses "*may* be useful"—was self-evidently speculative. *Id*. at 6a (emphasis added). The '244 publication merely summarized Rajaratnam; it provided no independent basis for substantiating the efficacy of a 20mg dose. *Id*. at 7a. That is why the Federal Circuit intentionally and expressly relied on Lankford—which described the "*then-ongoing* phase III trial of tasimelteon" that was testing a 20mg dose. *Ibid*. (emphasis added).

Respondents' position falters on two grounds. First, nothing in the court of appeals' decision—nothing at all—remotely supports respondents' claim that

"the patents would be invalid even if the clinical trial protocol had not been available." Opp. 30. The court below surely did not reach such a holding.

Second, the governing standard does all the work here. That Vanda was paying considerable sums for a Phase III trial, in the Federal Circuit's view, supported the conclusion that a skilled artisan might hold a "reasonable expectation of success." But that does not render the result later achieved in the trial "predictable." Articulation and application of the correct standard will alter this outcome.

So too with the drug-drug interaction patents. As for the CYP3A4 inducer, the '910 patent, the prior art reported *only* an interaction between rifampicin and ramelteon, an entirely different compound. Pet. App. 12a. Contrary to respondents' assertion (at 31), the Federal Circuit never held that it was "entirely predictable that co-administration" of tasimelteon and rifampicin should be avoided. Rather, the panel's ultimate conclusion was that a "skilled artisan * * * could not have ruled out an interaction between tasimelteon and a CYP3A4 inducer, like rifampicin." Pet. App. 13a-14a. Finding that a conclusion could not be "ruled out" certainly does not make that result *predictable*. And the same precise analysis applies with respect to the CYP1A2 inhibitor, the '829 patent. Again, the proper standard will change the outcome.

Finally, as for food-effects, the '487 patent, the *only* prior art relied on by the court of appeals was the existence of FDA's 2002 guidance that suggests studying food effects. Pet. App. 9a-11a. There could simply be no prediction one way or another as to whether taking tasimelteon with food would be a successful

method of administering tasimelteon. Pet. 33-34. The standard thus made all the difference.[2]

That the decision is unpublished is no obstacle to review. The Federal Circuit's reasonable-expectation standard is entrenched. See, *e.g.*, *Pfizer Inc.* v. *Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024); *Elekta Ltd.* v. *ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1374 (Fed. Cir. 2023); *Merck*, 808 F.3d at 833. The Court granted review in similar circumstances in *KSR*: Although the Federal Circuit's decision was unpublished (*Teleflex, Inc.* v. *KSR Int'l Co.*, 119 F. App'x 282 (Fed. Cir. 2005)), the Court reviewed—and ultimately reversed—the Federal Circuit's improper approach to obviousness. See also *Oil States Energy Servs., LLC* v. *Greene's Energy Grp., LLC*, 584 U.S. 325 (2018) (reviewing unpublished Federal Circuit summary affirmance); *Octane Fitness, LLC* v. *ICON Health & Fitness, Inc.*, 572 U.S. 545 (2014) (reviewing unpublished Federal Circuit decision). The same is warranted here.

C. Vanda did not waive the question presented.

Respondents' preservation argument (at 17-19) is mistaken. A litigant need not ask a court to overturn circuit precedent—a task a panel is powerless to accomplish—to preserve an argument for this Court's review. Rather, the Court's "traditional rule"

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[2] Respondents' assertion that Vanda's patent is invalid because it does not claim a food effect (Opp. 31-32) is deeply misguided. To start, nothing in the decision below suggests, much less rests, on such a conclusion. More, the purpose of the method of treatment without food is to avoid the negative food effect in order to successfully administer the drug. This necessarily required Vanda to test the impact of food on tasimelteon's bioavailability. See Pet. 33-34.

"precludes a grant of certiorari only when the question presented was not pressed *or passed upon* below." *United States* v. *Williams*, 504 U.S. 36, 41 (1992) (emphasis added). "[T]his rule operates in the disjunctive, permitting review of an issue not pressed so long as it has been passed upon." *Ibid*. See also *Citizens United* v. *FEC*, 558 U.S. 310, 330 (2010) ("Our practice 'permit[s] review of an issue not pressed [below] so long as it has been passed upon.'"); *Lebron* v. *National R.R. Passenger Corp.*, 513 U.S. 374, 379 (1995) (same).[3]

The obviousness standard was certainly "passed upon" below; indeed, it was central to the Federal Circuit's decision. See Pet. App. 15a-16a. To be sure, Vanda attempted to present its case within circuit precedent (see Opp. 27), in recognition that the reasonable-expectation standard presently governs. But this strategy "does not suggest a waiver; it merely reflects counsel's sound assessment that the argument would be futile." *MedImmune, Inc.* v. *Genentech, Inc.*, 549 U.S. 118, 125 (2007). The Court routinely reviews questions passed on below, even when a petitioner did not ask the appellate court to overturn its binding precedent. Compare *Nasrallah* v. *Barr*, 590 U.S. 573 (2020) (reversing unpublished court of appeals decision) with Gov't Br. in Opp. at 18, *Nasrallah*, *supra* (No. 18-1432) (observing that "petitioner asks this Court to grant review on an argument advanced for the first time in his petition").

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The Federal Circuit's departure from this Court's obviousness precedents "distort[s] * * * the carefully calibrated incentives provided by the Patent Act and

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[3] Respondents' precedent confirms our point: Review is warranted on any issue actually "decided below." Opp. 18-19 (citing *Clingman* and *Mendenhall*).

this Court's case law." Patients' Amicus Br. 4. The Court's intervention is warranted "to correct the Federal Circuit's course and ensure the court of appeals applies the invention standard set forth by Congress and this Court." Professor Amicus Br. 13.

CONCLUSION

The Court should grant the petition.

Respectfully submitted.

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