APPENDICES

TABLE OF CONTENTS

APPENDIX A

United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued September 25, 2024
Decided December 17, 2024

No. 23-5200

VANDA PHARMACEUTICALS, INC.,
APPELLANT

v.

UNITED STATES FOOD AND DRUG
ADMINISTRATION, ET AL.,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 1:22-cv-01432)

Paul W. Hughes argued the cause for appellant. With him on the briefs were *Andrew Lyons-Berg* and *Tyler L. Bishop*.

Steven A. Myers, Attorney, U.S. Department of Justice, argued the cause for appellees. On the brief were *Brian M. Boynton*, Principal Deputy Assistant Attorney General, *Daniel Tenny* and *Anna M. Stapleton*, Attorneys, *Samuel Bagenstos*, General

Counsel, U.S. Department of Health and Human Services, and *James Allred*, Associate Chief Counsel, U.S. Food and Drug Administration.

Before: KATSAS and CHILDS, *Circuit Judges*, and EDWARDS, *Senior Circuit Judge*.

Opinion of the Court filed by *Senior Circuit Judge* EDWARDS.

EDWARDS, *Senior Circuit Judge*: Companies seeking to market drugs in the United States must first obtain approval from the Food and Drug Administration ("FDA"). 21 U.S.C. § 355(a). Seeking to expedite this process, Congress enacted a "fast track" approval program, pursuant to which the FDA shall "facilitate the development and expedite the review" of a new drug if it "demonstrates the potential to address unmet medical needs" for a serious disease or condition. 21 U.S.C. § 356(b)(1). The dispute in this case concerns a fast track request filed by Vanda Pharmaceuticals, Inc. ("Vanda") with the FDA for tradipitant, an investigational new drug product that Vanda is developing for the treatment of gastroparesis. Vanda claims that the FDA's denial of fast track designation for tradipitant was contrary to law, and arbitrary and capricious agency action.

Before Vanda's fast track request was filed, the FDA had placed its drug on a partial clinical hold, as authorized by 21 U.S.C. § 355(i)(3). The clinical hold prevents any long-term clinical studies on Vanda's drug until long-term animal studies have been completed to assess its toxicological effects. When the FDA later assessed Vanda's eligibility for fast track, the clinical hold was a significant factor that led the agency to deny Vanda's request. The FDA essentially determined that, without long-term studies, Vanda could not "demonstrate" that its drug had the

"potential to address" the unmet need for long-term treatment of gastroparesis.

Vanda challenges the FDA's denial as arbitrary, capricious, and contrary to law under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A). It contends that the FDA erred in considering the clinical hold as a factor, improperly defined the "unmet medical need" at issue to constitute long-term treatment only, and adopted a view of the fast track program that was at odds with agency practice.

The District Court granted summary judgment for the FDA and Vanda sought review in this court. While this appeal was pending, Vanda also filed a complete New Drug Application ("NDA") for its drug, which the FDA has since denied in its current form. This complete filing, the FDA argues, has mooted the question presented here. We disagree, and affirm the District Court's decision on the merits. The FDA properly considered the drug's development plan in assessing whether it qualified for fast track, and its denial of Vanda's fast track application was neither contrary to law nor arbitrary and capricious.

I. BACKGROUND

A. Statutory and Regulatory Framework

Before a new drug may be marketed in the United States, the FDA must first confirm that it is safe and effective. Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(d). The FDA process generally takes approximately ten months. Manufacturers seeking to better study their drugs before filing a marketing application may submit an Investigational New Drug Application ("IND") to the FDA. *Id*. § 355(i)(1), 21 C.F.R. § 312.20(a). The IND allows manufacturers to run clinical trials before obtaining marketing

approval. However, if the FDA finds that the drug in question "represents an unreasonable risk to the safety" of test subjects, it may impose a clinical hold on such studies. 21 U.S.C. § 355(i)(3)(B). A clinical hold halts any further studies or trials until the manufacturer cures the issues that give the FDA pause.

Aiming to "hasten research of the safety and effectiveness of drugs" in some cases, Congress has enacted several programs to expedite the FDA's review process. *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 699, n.4 (D.C. Cir. 2007). One such program, for instance, designates a drug as a "breakthrough therapy" if "preliminary clinical evidence" indicates that the drug offers a "substantial improvement over existing therapies." 21 U.S.C. § 356(a)(1). Another expedited review pathway is "accelerated approval," which may be granted if the FDA determines that the drug in question "has an effect" that is "reasonably likely to predict clinical benefit" for a condition, considering its "severity, rarity, or prevalence" and the "lack of alternative treatments." *Id*. § 356(c)(1).

At issue here is the specific expedited program known as "fast track." Enacted as part of the FDA Modernization Act of 1997, the fast track statute provides that the FDA "shall take such actions as are appropriate to expedite the development and review" of a drug that is intended "for the treatment of a serious or life-threatening disease or condition" if the drug in question "demonstrates the potential to address unmet medical needs for such a disease or condition." *Id*. § 356(b)(1), (b)(3).

A fast track designation offers two main benefits to a drug manufacturer. First, the FDA will "facilitate the development" of the drug, usually by providing

feedback in ongoing discussions with the manufacturer. *Id*. § 356(b)(1); FDA, *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, Joint Appendix ("J.A.") 672. Second, fast track drugs are reviewed on an expedited schedule, and are considered for expedited review programs. These include the accelerated approval program under section 356(c) and "rolling review," in which the FDA provides feedback to the manufacturer on individual portions of the application so that the developer may make any revisions before filing a complete NDA. 21 U.S.C. § 356(d)(1).

Applicants may request a fast track designation "concurrently with, or at any time after" their IND submission. *Id*. § 356(b)(2). In reviewing requests for fast track, the FDA requires that manufacturers list their drug's proposed indication in the application. Where a drug may have more than one indication, applicants may file multiple fast track requests or list multiple indications in the same application.

B. Factual Background

In 2016, Vanda submitted an IND to begin studying its drug tradipitant for the treatment of gastroparesis, a chronic stomach condition with persistent symptoms that include abdominal pain, vomiting, and nausea. Vanda reported that preliminary studies on gastroparesis patients in a four-week drug trial showed that tradipitant had a statistically significant effect on one of the "core" symptoms of gastroparesis, nausea.

There are two kinds of gastroparesis: idiopathic and diabetic. The FDA currently recognizes one approved drug for diabetic gastroparesis, which is only indicated for short-term use of up to three months due to risks of serious side effects after 12 months of use. There are no FDA-approved drugs

specifically for idiopathic gastroparesis, although the treatment of its symptoms – including nausea – is the same as for diabetic gastroparesis.

Vanda's relevant discussions with the FDA regarding tradipitant began in April 2018, when it submitted a proposal to extend its four-week clinical trial of the drug by 12 months. The FDA denied this proposal, requiring a nine-month animal study to assess the drug's long-term toxicity before Vanda could proceed with long-term studies in humans. Vanda refused to conduct such studies, citing its ethical opposition to nonrodent testing that requires sacrificing the animal. As a result of this refusal, the FDA imposed a partial clinical hold, as authorized by 21 U.S.C. § 355(i)(3), which prevents further long-term clinical studies until Vanda conducts the required animal studies. While the hold is in place, Vanda can still conduct short-term clinical studies. In a separate litigation, Vanda sought judicial review of the clinical hold and the District Court upheld the FDA's order. *Vanda Pharm., Inc. v. FDA* ("Vanda I"), 436 F. Supp. 3d 256 (D.D.C. 2020). Vanda did not appeal this decision.

In March 2019, Vanda requested that tradipitant be designated a "breakthrough therapy" for the treatment of gastroparesis under 21 U.S.C. § 356(a). Pointing to issues with the study's conclusions and its findings of the drug's effectiveness on nausea symptoms, the FDA denied this request. The FDA also advised Vanda that it was "considering an indication for the short-term relief of nausea in gastroparesis" and encouraged Vanda to "further evaluate tradipitant for this use" in future submissions. Letter from FDA Director Julie Beitz to Vanda Denying Appeal of Denial of Breakthrough Therapy Designation for Tradipitant (Feb. 28, 2020)

[*hereinafter* FDA Letter Affirming Breakthrough Therapy Designation Denial], J.A. 657.

Finally, in 2021, Vanda filed the fast track application that is the subject of this litigation. Rather than taking the FDA's recommendation to tailor its application to short-term relief, Vanda once again framed tradipitant's indication as for the symptoms of gastroparesis broadly. As with its previous applications, Vanda's fast track request described the symptoms of gastroparesis as "chronic" and "persistent," with most patients "requir[ing] long-term medications." Vanda Pharma., Inc., Request for Fast Track Designation 8-11 (Sep. 28, 2021), J.A. 177-80.

The FDA denied Vanda's fast track request. While it conceded that gastroparesis is a serious condition with an unmet medical need, the agency found that the partial clinical hold prevented Vanda from demonstrating that its drug could address that need. This was because, being unable to conduct long-term studies, Vanda could not obtain the data necessary to demonstrate the product's potential for the indication as described in its application – i.e., to treat the symptoms of gastroparesis, which are chronic, rather than to provide short- term symptomatic relief.

In a contemporaneous internal memorandum, the FDA elaborated that the unmet medical need tradipitant purported to address was the long-term treatment of nausea symptoms, but that no data on the drug's effectiveness for this indication could be generated while the clinical hold was in place. The FDA further observed that the approach to treating nausea in patients was the same whether the gastroparesis was diabetic or idiopathic. The FDA also noted issues with Vanda's study's methodology, including the use of rescue medication, which the FDA

was concerned may have tainted the results of Vanda's study. These internal notes, although not originally disclosed to Vanda, mirror feedback that Vanda had previously received from the FDA in connection with its breakthrough designation application.

The FDA's memo also included an internal checklist that the FDA uses to assess fast track applications. The checklist contains six main items, including whether the condition is serious/life-threatening, and whether the product's development program was designed to demonstrate an effect on a serious aspect of the condition. For these two items – items 1 and 2 – the FDA marked "yes" when assessing Vanda's fast- track application. But it marked "no" as to items 3 and 4, which ask if the product development plan addresses an unmet medical need and if the product shows potential to address an unmet medical need. Also relevant is item 5, which asks whether the data supporting the request comes from trials that are on clinical hold. Here, the FDA marked "yes." The checklist then recommends that, for fast track approval, items 1 through 4 must be answered "yes," and that, if item 5 is marked "yes," – *i.e.*, if there is a clinical hold in place – the fast track application may not be granted.

In the face of the fast track denial and of the partial clinical hold, Vanda could then pursue one of two courses of action. First, it could file a new fast track application, tailored to the short-term treatment of gastroparesis symptoms, as the FDA suggested it do. Alternatively, it could conduct the required animal studies to lift the clinical hold and proceed with long-term studies to treat gastroparesis broadly. Vanda chose to pursue neither of these options, which have remained open in the course of this litigation. Instead, it filed suit in federal court challenging the fast track

denial as arbitrary and capricious under the APA. While the District Court's decision on cross- motions for summary judgment was pending, Vanda then submitted a complete NDA, requesting marketing approval of its drug – once again, indicated broadly to treat gastroparesis symptoms. The District Court granted summary judgment in favor of the FDA. This appeal followed.

After this appeal was filed, the FDA reviewed Vanda's NDA and issued a Complete Response Letter denying the application in its current form, finding that Vanda does not provide substantial evidence of effectiveness for tradipitant for the treatment of either symptoms of gastroparesis more broadly or nausea specifically.

II. ANALYSIS

A. Standard of Review

This Court reviews appeals from summary judgments *de novo*, applying the standards set forth in Federal Rule of Civil Procedure 56(a). *See, e.g., Celotex Corp v. Catrett*, 477 U.S. 317, 322 (1986). Under Rule 56(a), summary judgment is warranted if the movant shows that "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law."

When reviewing agency decisions under the APA, we set aside agency actions if we determine that they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). An agency "acts arbitrarily or capriciously if it 'has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it

could not be ascribed to a difference in view or the product of agency expertise.'" *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 997- 98 (D.C. Cir. 2008) (quoting *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)).

Where the question is whether the agency action was consistent with statutory authorization, our task is to determine whether the agency acted consistently with the "best reading" of the statute. *Loper Bright Enterprises v. Raimondo*, 144 S. Ct. 2244, 2263 (2024). This judicial inquiry includes a determination as to whether the statute in question "delegates discretionary authority" to the agency and whether the agency "engaged in reasoned decisionmaking within [the] boundaries" of that statutory delegation. *Id*. (internal quotation marks and citations omitted).

B. Finality and Mootness

As a threshold matter, it is not clear that the denial of fast track review is a final action that is subject to judicial review. *See Bennett v. Spear*, 520 U.S. 154, 177-78 (1997). This is because normally "[a] preliminary, procedural, or intermediate agency action or ruling" is only "subject to review on the review of the final agency action." *Yaman v. U.S. Dep't of State*, 634 F.3d 610, 613 (D.C. Cir. 2011) (per curiam) (quoting 5 U.S.C. § 704).

This final order rule codifies the understanding that "[p]remature review squanders judicial resources," and that litigants are generally "best served by a system which prohibits piecemeal appellate consideration of rulings that may fade into insignificance by the time proceedings conclude." *CSX Transp., Inc. v. Surface Transp. Bd.*, 774 F.3d 25, 31 (D.C. Cir. 2014) (internal quotation marks and citations omitted). Thus, we normally "reserv[e] judicial review until the end of an adjudication," when

a judgment has been rendered on the merits of the matter before the agency – in this case, until the final completed NDA is ultimately denied. *Id.; see also Holistic Candlers & Consumers Ass'n v*. FDA, 664 F.3d 940, 943 (D.C. Cir. 2012) (finding that FDA warning letters are not reviewable final agency actions because they "neither mark the consummation of the agency's decisionmaking process nor determine the appellants' legal rights or obligations").

Neither party contends that the FDA's Complete Response Letter denying the NDA in its current form is a final agency action, as it "simply afford[s] [Vanda] the opportunity to provide additional information before the agency makes a final decision on the application." *Nostrum Pharms., LLC v. FDA*, 35 F.4th 820, 825 (D.C. Cir. 2022) (holding that a "complete response letter is an interim step in the FDA's consideration of an application" and, therefore, not a final agency action under 21 U.S.C. § 355(h)). Indeed, the Complete Response Letter is not at issue in this case.

It is thus unclear under applicable law whether the FDA's denial of fast track review of Vanda's application, on its own, is a final order. We leave this question for another day, however, because the FDA does not claim the disputed action taken on Vanda's fast track request was not a final action subject to judicial review. As finality is not jurisdictional under the APA, we therefore need not decide this matter. *See Marcum v. Salazar*, 694 F.3d 123, 128 (D.C. Cir. 2012). Rather than challenge finality, the FDA alleges a different justiciability bar, contending that the fast track issue should be dismissed as moot. We disagree.

We are "obliged to address the issue" of mootness because it "goes to the jurisdiction of this court." *Row 1 Inc. v. Becerra*, 92 F.4th 1138, 1143 (D.C. Cir. 2024)

(internal quotation marks and citation omitted). A claim is moot when "the issues presented are no longer 'live' or the parties lack a legally cognizable interest in the outcome." *Already, LLC v. Nike, Inc.*, 568 U.S. 85, 91 (2013) (quoting *Murphy v. Hunt*, 455 U.S. 478, 481 (1982) (*per curiam*)). Intervening events may moot a claim if they "make it impossible to grant the prevailing party effective relief." *Lemon v. Geren*, 514 F.3d 1312, 1315 (D.C. Cir. 2008) (internal quotation marks and citation omitted). While the party invoking mootness "bears the initial burden of proving that no live controversy exists," *N. Am. Butterfly Ass'n v. Wolf*, 977 F.3d 1244, 1258 (D.C. Cir. 2020) (internal quotation marks and citation omitted), this court still has the "independent obligation to ensure that appeals before us are not moot." *Planned Parenthood of Wis., Inc. v. Azar*, 942 F.3d 512, 516 (D.C. Cir. 2019) (internal quotation marks and citation omitted).

The FDA contends that the denial of fast track review is not a live issue at this juncture because any benefits of fast track are inapplicable once the complete NDA has been filed. But fast track is not an "all or nothing" package: that Vanda cannot at this stage benefit from all of the features of the fast track program, such as rolling review, does not mean it has no concrete interest in the program. Because Vanda can still benefit from other advantages the program confers, including expedited review and facilitation opportunities, it retains a "legally cognizable interest" in the resolution of the question before us here. *Already*, 568 U.S. at 91.

First, now that the FDA has denied Vanda's NDA in its current form, Vanda may continue to discuss how to move forward with its application, and will benefit from facilitation of the drug's development in these negotiations. We see no reason why a fast track

designation would confer no relief in this ongoing process, and why it would therefore be "impossible for a court to grant any effectual relief" to Vanda if we determine that it should prevail on the merits. *Knox v. Serv. Emps. Int'l Union, Loc*. 1000, 567 U.S. 298, 307 (2012) (internal quotation marks and citation omitted). Even if the benefits of such facilitation discussions are marginal in the face of the substantial feedback Vanda has already received, this concrete interest, "however small," means that the case is not moot. *Id*.

Second, while the application is in continued revision, fast track status would still confer the concrete benefit of expedited "review of the application" under section 356(b). Should Vanda prevail on the merits, it would thus obtain the "opportunity to pursue a benefit" of expedited review of its application, which is a "constitutionally cognizable" interest. *CC Distribs., Inc. v. United States*, 883 F.2d 146, 150 (D.C. Cir. 1989).

The FDA argues that completed NDAs are only reviewable in an expedited fashion under "priority review," a separate review program which assesses whether the drug in question would provide a significant improvement in safety and effectiveness. It points to the fact that in filing its NDA, Vanda concurrently requested priority review of its application. But the fact that a complete NDA may benefit from priority review does not necessarily mean that it cannot also qualify for fast track. In fact, fast track applications may be filed "any time after" the IND is submitted. 21 U.S.C. § 356(b)(2). Nor are these two expedited review pathways interchangeable because, as the FDA acknowledges, an application meeting the criteria for fast track would not necessarily qualify for priority review. Thus, Vanda

could still receive the benefit of expedited review "of the application" if it meets the fast track statutory criteria, which are different from those for priority review.

Finally, even if the fast track status were a moot issue, the facts here involve an agency action "capable of repetition yet evading review." *Del Monte Fresh Produce Co. v. United States*, 570 F.3d 316, 322 (D.C. Cir. 2009). This exception to the mootness doctrine applies "where (1) the challenged action is in its duration too short to be fully litigated prior to cessation or expiration, and (2) there is a reasonable expectation that the same complaining party will be subject to the same action again." *Kingdomware Techs., Inc. v. United States*, 579 U.S. 162, 170 (2016) (cleaned up).

Because fast track applications must be reviewed within 60 days, 21 U.S.C. § 356(b)(3), the challenged action here is "too short to be fully litigated prior to its cessation or expiration." *Del Monte*, 570 F.3d at 322 (noting that "agency actions of less than two years' duration cannot be 'fully litigated' prior to cessation or expiration"). And because the FDA has made it clear that it invites Vanda to submit a modified application for tradipitant indicated for short-term symptoms of gastroparesis, there is "a reasonable expectation that" any subsequent fast track applications will be subject to the same assessment process that Vanda alleges is improper here. *Id*.

We therefore proceed to the merits of Vanda's claim.

C. The FDA's Denial of Vanda's Fast Track Application Was Not Contrary to Law

Vanda first argues that the text of section 356(b) prohibits the FDA from considering a clinical hold or

other elements of the drug's development program when assessing a fast track application. We disagree.

There are some provisions in the FDCA that are relatively clear in indicating how the FDA should designate certain products. *See, e.g., Genus Med. Techs. LLC v. FDA*, 994 F.3d 631, 633 (D.C. Cir. 2021) (interpreting FDCA provisions for designation of products as "drugs" or "devices" where the statute defined each term and rejecting the FDA's interpretation as inconsistent with the relevant statutory definitions). The same is not true with respect to the fast track provision in the FDCA. Rather, the statute leaves it for the FDA to determine whether a drug "demonstrates the potential to address unmet medical needs," 21 U.S.C. § 356(b)(1), (b)(3), and it does not define these terms. The statute merely encourages the FDA to "utilize innovative and flexible approaches to the assessment of products" that address "unmet medical needs." *Id*. § 356(e)(1).

Vanda contends that the FDA could not consider the clinical hold because the statute's text allows the FDA to only consider the "drug," not the drug's development program. In other words, Vanda argues that because the statutory language requires the FDA to assess whether *the drug* demonstrates the potential to address unmet medical needs, the FDA impermissibly deviated from the statute when it considered the drug's *development program*, including whether a clinical hold was in place. This is an untenable distinction.

The statute places the burden on an applicant to "demonstrate" that its drug meets the fast track criteria. To assess whether this standard is met, the FDA obviously must consider how the application puts forth the drug's capacity to address the indicated need. In doing so, the FDA may consider past studies

that have been conducted and how future studies may further offer evidence of the drug's efficacy. *See Prohibition Juice Co. v. FDA*, 45 F.4th 8, 26 (D.C. Cir. 2022) (explaining that the FDA shall deny an application where the statute "requires that applicants make a certain showing before their products can be approved" and the "applicant[s] fail[] to make that showing"). Vanda points to no statutory language to the contrary. Moreover, the fast track provision requires the FDA to assess not only whether the drug currently addresses unmet needs, but whether it has the "potential" to address them. This language mandates an inherently prospective analysis. *See Potential*, OXFORD ENGLISH DICTIONARY (2d ed. 1989). The drug's development plan, including what past and future studies may demonstrate about the potential of the drug, are plainly relevant and permissible considerations.

Vanda's self-serving interpretation of the statute is both under- and overinclusive. It would preclude the FDA from considering a drug's development plan at all, even where it might be lenient to an applicant whose drug has yet to show results and who can only demonstrate its potential through a development plan that may in the future prove the drug's effectiveness. Simultaneously, Vanda would require that the FDA grant fast track to all applications that show that the drug might in the future serve an unmet need, even if current studies do not show that it is effective and future studies cannot be conducted. Such a construction of the statute would render superfluous the FDA's role in determining whether a drug "demonstrates" the potential defined by the statute, as it would make virtually all drugs intended for treating the qualifying conditions eligible for fast track. *See Donnelly v. FAA*, 411 F.3d 267, 271 (D.C. Cir. 2005)

("We must strive to interpret a statute to give meaning to every clause and word, and certainly not to treat an entire subsection as mere surplusage.").

The best reading of the statute indicates that, in enacting the fast track, Congress intended to benefit drugs that are not yet fully effective but that can demonstrate their potential effectiveness in addressing an unmet medical need in the future. Assessing the drug's development plan, including whether future studies may be conducted to demonstrate its potential or cure current data issues, is perfectly consistent with that goal. By considering all available evidence, the FDA thus lives up to the statutory mandate that it "utilize innovative and flexible approaches" to determine whether to grant fast track status, especially where current data on the drug's effectiveness may be scarce at the time the FDA is evaluating it for fast track. 21 U.S.C. § 356(e)(1).

The FDA previously informed Vanda of numerous concerns it had about its tradipitant study. In the face of such issues with existing data, the agency's consideration of whether future studies might cure those problems is entirely consistent with the statute's mandate. It was equally reasonable for the FDA to conclude that Vanda's decision not to conduct additional studies required to lift the partial clinical hold meant that Vanda would not cure those issues and, thus, could not demonstrate tradipitant's potential to address the unmet need that Vanda's application identified.

D. The FDA Did Not Act Arbitrarily and Capriciously in Denying Vanda's Fast Track Application

On the record before us, we also conclude that the FDA did not act arbitrarily or capriciously in assessing Vanda's fast track application.

First, it was permissible for the FDA to assess tradipitant as indicated for long-term symptoms of gastroparesis. The record – including Vanda's own filings with the FDA – makes clear that gastroparesis is a chronic disease. Indeed, the fact that Vanda had previously sought to extend its clinical trials to 12 months indicates that it was interested in tradipitant's long- term effects. And, even after the FDA advised Vanda that it should tailor its future submissions more narrowly to short- term symptoms, Vanda did not do so, continuing to list tradipitant's indication as for the treatment of symptoms of gastroparesis broadly. The fact that Vanda chose not to follow that recommendation does not place the burden on the FDA to divine a more specific indication for the drug than what Vanda described in its application.

Moreover, as Vanda itself acknowledged in its application, there is already a FDA-approved short-term treatment for gastroparesis. In light of this alternative treatment and of Vanda's own description of the condition it set out to treat, the FDA was reasonable in defining the unmet medical need as the need for long-term treatment of gastroparesis symptoms. And, because the clinical hold precludes Vanda from demonstrating that its drug will be an improvement on the current treatment's toxic long-term side effects, it was also reasonable for the FDA to conclude that tradipitant could not demonstrate that it had the potential to meet that need.

Second, it was also reasonable for the FDA not to address tradipitant's indication to treat *idiopathic* gastroparesis separately, because the version of the disease is irrelevant to the drug's effectiveness to treat chronic nausea symptoms. Vanda contends that, because idiopathic gastroparesis in particular has no

FDA-approved treatment, the FDA should have granted fast track to tradipitant for that narrower indication. But the lack of any approved idiopathic gastroparesis treatment does not mean that tradipitant necessarily meets that need. In fact, the record shows that tradipitant's only statistically significant effects are on the symptom of nausea, which manifests the same way in both idiopathic and diabetic gastroparesis. The FDA's concerns with Vanda's nausea findings and with the clinical hold's foreclosure of long-term studies apply just as compellingly to an indication for idiopathic gastroparesis as they do for gastroparesis generally.

Finally, Vanda argues that the FDA had already previously indicated that tradipitant had "potential," and had already approved it for treatment in some circumstances, so the fast track denial was an arbitrary contradiction of the agency's prior positions. This claim is without merit. An agency acts unreasonably when it deviates from prior positions "in similar situations," which is plainly not the case here. *Gen. Motors Corp. v. Nat'l Highway Traffic Safety Admin.*, 898 F.2d 165, 174 (D.C. Cir. 1990).

Vanda first points to a letter in which an FDA director, while affirming the FDA's denial of breakthrough therapy designation under the separate standard governed by section 356(a), states that she saw "a potential therapeutic role for tradipitant, particularly for the short-term relief of nausea in gastroparesis patients." FDA Letter Affirming Breakthrough Therapy Designation Denial, J.A. 657. But this non-binding statement assessed tradipitant's merits under the separate standard of section 356(a), and thus cannot indicate a shift in agency position with regards to whether tradipitant met the different criteria for fast track under section 356(b). *See Gen.*

Motors Corp., 898 F.2d at 174; *Muwekma Ohlone Tribe v. Salazar*, 708 F.3d 209, 216 (D.C. Cir. 2013) (finding no inconsistency where the agency's positions did not involve treating "similar situations differently").

In any event, the FDA's denial of both requests reflects a consistent position, as the agency asserted many of the same issues with the drug's studies in both decisions. Immediately after the language Vanda quotes, the FDA director observed that "additional data would be needed" to support a breakthrough therapy designation. FDA Letter Affirming Breakthrough Therapy Designation Denial, J.A. 657. The director also added that Vanda's application was for a broader indication than its data supported, as it was "for 'the treatment of gastroparesis', not for the treatment of a single symptom associated with gastroparesis." *Id*. Instead, the agency advised that Vanda "should not submit a request for Breakthrough Therapy Designation to treat 'gastroparesis' based on a treatment effect for nausea alone." *Id*. The FDA's denial of Vanda's fast track application is therefore consistent with its prior feedback to Vanda, including that its current data did not demonstrate the potential for tradipitant to treat gastroparesis symptoms generally.

Vanda's second contention of a prior inconsistent agency position is equally unpersuasive. Vanda refers to the FDA's prior approval of expanded access for tradipitant, which is not only governed by a different statutory standard under 21 U.S.C. § 360bbb(b)(2), but is also wholly unrelated to expedited approval. The expanded access program allows physicians, subject to certain conditions, to request manufacturers to provide an unapproved, investigational drug for the treatment of specific patients, whom the physician in question will monitor. *Id*. § 360bbb(b). Unlike

breakthrough therapy, accelerated approval, and fast track, expanded access does not expedite a drug's approval process. It merely authorizes its use for certain patients in certain conditions if "the Secretary determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug" in the unique case of each petitioning patient. *Id*. § 360bbb(b)(2).

Vanda argues that because the FDA had already granted expanded access for tradipitant to eight individuals, some of whom have used the drug for over a year, tradipitant's "potential" under section 356(b) is met, and the FDA's fast track denial was therefore inconsistent with the expanded access grant. But authorization for expanded access takes no position on the drug's marketing approval, likelihood of success, or potential to treat patients on a broader scale. There is no inconsistency between the FDA's grant of expanded access and its denial of fast track where these two programs operate under different statutory standards and objectives.

Finally, Vanda's ethical objections to the required animal studies to lift the clinical hold, principled though they may be, are beside the point. Having fully litigated the propriety of the clinical hold in *Vanda I*, Vanda is estopped from raising any new challenges to the hold that it could have raised earlier. *See Ashbourne v. Hansberry*, 894 F.3d 298, 302 (D.C. Cir. 2018). Vanda attempts to circumvent res judicata by raising the novel argument that the FDA Modernization Act 2.0, Pub. L. No. 117-328, enacted after *Vanda I*, now renders the clinical hold unreasonable. But we do not reach this claim because Vanda raises it for the first time on appeal, even though the relevant statute was enacted before the District Court reached its decision. *See Zevallos v.*

Obama, 793 F.3d 106, 114 (D.C. Cir. 2015). Vanda is welcome to raise this argument before the FDA as it continues to discuss tradipitant's approval, as the FDA is better positioned to assess the reasonableness of scientific methodology than this court. *See Smith v. Berryhill*, 587 U.S. 471, 488 (2019) ("[A] federal court generally goes astray if it decides a question that has been delegated to an agency if that agency has not first had a chance to address the question.").

In light of the evidence before it, the FDA reasonably interpreted Vanda's fast track application as targeting the chronic symptoms of gastroparesis, which necessarily requires that tradipitant meet the unmet need for long-term treatment. The FDA's focus on the drug's effects on chronic symptoms is wholly consistent with the record and demonstrates a "rational connection between the facts found and the choice made." *State Farm*, 463 U.S. at 43 (internal quotation marks and citation omitted); *see also Growth Energy v. EPA*, 5 F.4th 1, 16 (D.C. Cir. 2021) (*per curiam*) ("[B]ecause the agency examined the relevant data and articulated a satisfactory explanation for its action, we uphold its decision." (internal quotation marks and citation omitted)). We therefore find that the FDA's denial of Vanda's fast track application was neither arbitrary nor capricious.

III. CONCLUSION

For the reasons set forth above, we affirm the District Court's grant of summary judgment to the FDA. Vanda remains free to continue its negotiations with the agency, including to file an amended application pursuing a short-term indication for its drug, or to proceed to lift the partial clinical hold.

So ordered.

APPENDIX B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VANDA PHARMACEUTICALS, INC., *Plaintiff*, v. FOOD AND DRUG ADMINISTRATION, et al., *Defendants*.	Civil Action No. 1:22-cv-01432 (CJN)

MEMORANDUM OPINION

Vanda Pharmaceuticals, Inc., a biopharmaceutical company developing a new drug called tradipitant, submitted a request for fast track designation under the Food, Drug, and Cosmetic Act. The FDA denied the request, citing the agency's bar on long-term clinical testing of the drug. Vanda challenges that decision as arbitrary and capricious under the Administrative Procedure Act. For the following reasons, the Court concludes that the FDA's decision was not arbitrary or capricious.

I. Background

A. Statutory and Regulatory Framework

The Food, Drug, and Cosmetic Act generally prohibits the distribution of a new drug in interstate commerce absent the FDA's final marketing approval. 21 U.S.C. § 355(a); *see* 21 U.S.C. § 331(d). Final marketing approval requires the FDA to determine, among other things, that the drug is "safe for use" and

that there is "substantial evidence that the drug will have the effect it purports or is represented to have." *Id*. § 355(d).

An exception to the ban on the distribution of unapproved drugs exists in 21 U.S.C. § 355(i), which allows those drugs to be used for the purpose of investigating their "safety and effectiveness." *Id*. § 355(i)(1). There are two broad categories of investigations: (1) clinical tests, involving human patients as subjects, and (2) nonclinical tests, defined as "test[s] conducted in vitro, in silico, or in chemico," or "nonhuman in vivo test[s]." *Id*. § 355(z).[1] The investigation process contemplates that sufficient animal toxicity studies or other nonclinical tests, designed to indicate potential adverse effects in humans, will occur before clinical testing takes place. *See id*. § 355(i)(1)(A).

To conduct a clinical test, a sponsor or manufacturer of a drug must submit an Investigational New Drug Application (IND). 21 C.F.R. §§ 312.20(a), 312.23. FDA regulations set out the required contents of an IND, which include the "rationale" for the drug or study; "the indication(s) to be studied"; "the general approach to be followed in evaluating the drug"; the nature of the clinical trials to be performed; and "any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs." *Id*. § 312.23(a)(3)(iv). Clinical tests cannot take place until an applicant has submitted "adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations

[1] Congress has enacted two (z) subsections in 21 U.S.C. § 355. The Court refers to the first of the two here.

from nonclinical tests or human studies." 21 U.S.C. § 355(i)(2)(B).

Without affirmative approval from the FDA, clinical investigations may begin 30 days after the FDA's receipt of an IND. *Id*. § 355(i)(2). "At any time," however, the FDA may prohibit clinical tests by issuing a "clinical hold"—an order "to delay a proposed clinical investigation or to suspend an ongoing investigation." *Id*. § 355(i)(3)(A); 21 C.F.R. § 312.42(a). The agency may impose a clinical hold upon determining that "the drug involved represents an unreasonable risk to the safety" of the subjects of the investigation, or that "the clinical hold should be issued for such other reasons" established by regulation. 21 U.S.C. § 355(i)(3)(B). For instance, FDA regulations provide that the agency may issue a clinical hold when "[t]he IND does not contain sufficient information" based on "toxicological data in animals or prior studies in humans with the drug or related drugs" to "assess the risks to subjects of the proposed studies." 21 C.F.R. §§ 312.23(a)(3)(iv), 312.42(b)(1)(iv), 312.42(b)(2)(i).

A clinical investigation is "generally divided into three phases." *Id*. § 312.21. Phase 1 marks "the initial introduction of an investigational new drug into humans," with studies that generally involve 20 to 80 subjects and that are "designed to determine the metabolism and pharmacologic actions of the drug in humans" and "the side effects associated with increasing doses," as well as to gain any "early evidence on effectiveness." *Id*. § 312.21(a)(1). At phase 2, "controlled clinical studies" that usually involve "no more than several hundred subjects" are "conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the

common short-term side effects and risks associated with the drug." *Id*. § 312.21(b). Phase 3 studies are "expanded controlled and uncontrolled trials," usually involving "several hundred to several thousand subjects," that are "performed after preliminary evidence suggesting effectiveness of the drug has been obtained" and are "intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling." *Id*. § 312.21(c).

Several FDA programs exist "to facilitate and expedite development and review of new drugs." Administrative Record ("AR") at 3910, ECF Nos. 23-3 & 25. Those programs include the fast track program and breakthrough therapy designation. Another feature of the development process, meant to increase access to new drugs before final approval rather than expedite the approval process, is called expanded access. Each of these programs is relevant to the development of the drug at issue in this case, tradipitant.

1. Fast Track Program

Congress established the fast track program through the Food and Drug Administration (FDA) Modernization Act of 1997; the program is designed to expedite the study and approval of drugs intended to treat serious and life-threatening conditions. FDA Modernization Act of 1997, Pub. L. No. 105-115, § 112, 111 Stat. 2296, 2309–10 (codified as amended at 21 U.S.C. § 356); see AR at 3918. As amended, the statute requires the FDA to "facilitate the development and expedite the review" of a new drug if (a) "it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition," and (b) "it

demonstrates the potential to address unmet medical needs for such a disease or condition." 21 U.S.C. § 356(b)(1); *see also* 21 U.S.C. § 356(b)(3) (stating that "the Secretary shall designate the drug as a fast track product" if "the Secretary finds that the drug meets the criteria" listed in § 356(b)(1) and requiring the Secretary to "take such actions as are appropriate to expedite the development and review of the application for approval of such product"). A sponsor can obtain fast track status for a new drug by requesting that designation "concurrently with, or at any time after" submission of an IND. *Id*. § 356(b)(2).

In the FDA's non-binding *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* ("Expedited Programs Guidance"), AR at 3906–45, the agency elaborates on the statutory criteria for fast track designation and other features of the program. The agency defines a "serious" disease or condition as one "associated with morbidity that has substantial impact on day-to-day functioning." *Id*. at 3911 (quotation omitted). The term "life-threatening" encompasses "[d]iseases or conditions where the likelihood of death is high unless the course of the disease is interrupted" as well as those "with potentially fatal outcomes, where the end point of clinical trial analysis is survival"; a disease or condition that meets this definition is also "serious" for purposes of fast track designation. *Id*. at 3912; 21 C.F.R. § 312.81(a).

The Expedited Programs Guidance describes an "unmet medical need" as a "condition whose treatment or diagnosis is not addressed adequately by available therapy." AR at 3913. For example, an unmet medical need exists if "there is no available therapy for a serious condition." *Id*. at 3914. Even if other therapy is available, the FDA will still consider a new drug to

"address an unmet medical need" if, for instance, it "[p]rovides efficacy comparable to those of available therapy" while avoiding the toxicity associated with available therapy. *Id*. The Guidance further explains that "[t]he type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development at which fast track designation is requested." *Id*. at 3918. In early stages of development, "a nonclinical model, a mechanistic rationale, or pharmacologic data" could demonstrate the necessary potential. *Id*. Later, that potential should be demonstrated by "available clinical data." *Id*.

The Guidance also addresses the content of a fast track request. It states that "[f]ast track designation applies to the drug . . . and the specific use for which it is being studied." *Id*. "If a sponsor's drug development program is granted fast track designation for one indication and has subsequently obtained data to support fast track designation for another indication, the sponsor should submit a separate request." *Id*. at 3937. Relatedly, the FDA recommends that a designation request include the "proposed indication(s)" for the drug. *Id*. at 3937–38.

The Guidance also explains some of the benefits of fast track designation, which are set out by statute. *See id*. at 3918–19. Two of those benefits are most relevant here. First, the Guidance describes that fast track status comes with "opportunities for frequent interactions with the review team for a fast track product," including "pre-IND meetings, end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers." *Id*. at 3918. In addition, "[o]ther meetings may be scheduled as appropriate," to discuss

"critical issues" like "the structure and content" of a New Drug Application (NDA). *Id*. These benefits correspond with the statutory requirement that the agency "take such actions as are appropriate to expedite the development and review of the application for approval" of fast track products. 21 U.S.C. § 356(b)(3). Second, a fast track product is eligible for rolling review, meaning that the FDA "may consider reviewing portions of a marketing application before the sponsor submits the complete application." AR at 3919. The corresponding statutory provision for rolling review states that the agency "shall evaluate for filing" and "may commence review of portions of" an application for approval "before the sponsor submits a complete application," if the applicant provides a schedule for submission of the complete application and pays any required fee. 21 U.S.C. § 356(d)(1). The agency must engage in this evaluation if it "determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective." *Id*.

2. Breakthrough Therapy Designation

In 2012, through the Food and Drug Administration Safety and Innovation Act (FDASIA), Congress added breakthrough therapy designation as an additional pathway for expedited development. FDASIA, Pub. L. No. 112-144, § 902(a), 126 Stat. 993, 1086–87 (2012) (codified at 21 U.S.C. § 356(a)). For breakthrough therapy designation, the drug must be "intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition," and "preliminary clinical evidence" must indicate that "the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early

in clinical development." 21 U.S.C. § 356(a)(1). If the agency grants breakthrough therapy designation, it must, as for fast track products, "expedite the development and review" of the drug. *Compare id*. (breakthrough therapies), with *id*. § 356(b)(3) (fast track products).

3. Expanded Access

Along with the fast track program, the FDA Modernization Act enacted a mechanism for individual patients to access investigational drugs before they are finally approved for interstate distribution. § 561, 111 Stat. at 2365–67 (codified at 21 U.S.C. § 360bbb). The expanded access program allows drug manufacturers or distributors to provide a physician with an investigational drug "for the diagnosis, monitoring, or treatment of a serious disease or condition" if, among other things: (1) the physician "determines that the person has no comparable or satisfactory alternative therapy available" and that the "probable risk" that the drug carries "is not greater than the probable risk from the disease or condition"; and (2) the agency "determines that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug" for that individual patient. 21 U.S.C. § 360bbb(b).

B. Development of Tradipitant

In September 2016, Vanda submitted an IND to begin clinical trials of its drug tradipitant for the treatment of gastroparesis. *See* AR at 3122. Gastroparesis is a "medical condition characterized by delayed gastric emptying associated with symptoms of nausea, vomiting, bloating, fullness after meals, and abdominal pain." *Id*. at 12. In 2018, after Vanda proposed clinical trials of 12 months' duration, the FDA imposed a partial clinical hold preventing

clinical trials longer than 12 weeks. *Id*. at 272–73. Though tradipitant had undergone nonclinical trials of up to 6 months' duration in rodents and 3 months' duration in dogs, the agency explained that "non-rodent toxicity studies of 9 months duration are required" before clinical trials could be extended beyond 12 weeks. *Id*. at 272–73, 287–89. Vanda objected to conducting the required non-rodent studies on the ground that they "would have resulted in the needless killing of the test-subject dogs."[2] Pl.'s Mem. in Support of Mot. for Summ. J. ("Pl.'s Mot.") at 12, ECF No. 16-1.

Vanda then submitted a request for breakthrough therapy designation in March 2019, with a proposed indication "for the treatment of gastroparesis." AR at 397. The FDA denied that request, explaining that while "gastroparesis meets the criteria for a serious or life-threatening disease or condition," the preliminary clinical data that Vanda submitted "does not indicate that the drug may demonstrate substantial improvement over existing therapies." *Id*. at 446. Results for symptoms of gastroparesis such as fullness, early satiety, vomiting, and abdominal pain "were small in magnitude and of unclear meaningfulness to patients." *Id*. at 447. For the symptom of nausea, "the improvement seen for tradipitant over placebo was small" and "difficult to interpret"; moreover, there were already "multiple products available to treat this one symptom." *Id*. at 446–47.

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[2] Vanda unsuccessfully challenged the partial clinical hold in this court. *See Vanda Pharmaceuticals, Inc. v. FDA*, 436 F. Supp. 3d 256 (D.D.C. 2020) (Bates, J.). After that decision, Vanda also unsuccessfully challenged the partial clinical hold within the FDA. *See* AR at 341–89.

Citing the "significant therapeutic benefit" observed in one of its phase 2 studies, VP-VLY-686-2301 ("Study 2301"), Vanda requested that the agency reconsider its denial of breakthrough therapy designation and submitted an amended request. *Id*. at 480. For similar reasons as before, the agency denied both the amended request and an administrative appeal. *Id*. at 721–22, 3017.

The FDA provided an explanation for denying the appeal, which also came with "recommendations for a possible path forward." *Id*. at 3017. The agency noted that Vanda had described tradipitant's use as for "the treatment of gastroparesis," rather than the treatment of any singular symptom of gastroparesis. *Id*. at 3026 (internal quotation marks omitted). If Vanda sought breakthrough therapy designation for the effect of tradipitant on nausea alone, the agency explained, the request should be tailored to that symptom. *Id*. The agency stated that in the context of "ongoing discussions" regarding tradipitant's development program, it was "considering an indication for the short-term relief of nausea in gastroparesis," and it "encourage[d]" Vanda "to further evaluate tradipitant for this use in appropriately designed clinical trials to support future submissions requesting Breakthrough Therapy Designation." *Id*.

Describing Vanda's "path forward," the agency remarked that it "see[s] a potential therapeutic role for tradipitant, particularly for the short-term relief of nausea in gastroparesis patients." *Id*. Before breakthrough therapy designation on that basis could be possible, "additional data would be needed," namely, clinical data assessing "the effect of tradipitant on nausea in a sufficiently symptomatic gastroparesis population . . . treated for at least 12 weeks (to assess durability of effect)." *Id*. The agency

prompted Vanda to discuss, "in advance," its "approach to obtaining new clinical data to support a future request" for breakthrough therapy designation. *Id*. at 3027. After receiving this feedback, Vanda began a phase 3 study focusing mostly on the symptom of nausea. *See id*. at 37, 171; Pl.'s Mot. at 13, 35 n.6.

In October 2021, "rather than wait for further clinical data to resubmit a Breakthrough Therapy designation request," Vanda submitted a request for fast track designation "for the treatment of the symptoms of gastroparesis." Pl.'s Mot. at 13; AR at 1, 9–10. In line with the statutory requirements for fast track designation under 21 U.S.C. § 356(b)(1), Vanda's request stated that "[g]astroparesis is a serious or life-threatening disease or condition" and that "treatment of the symptoms of gastroparesis represents a significant unmet medical need." AR at 10 (internal quotation marks omitted). Vanda explained that for one type of the condition (*idiopathic* gastroparesis), there is no approved drug product, and for a second type (*diabetic* gastroparesis), the only available drug, Reglan (metoclopramide), carries with it a risk of serious side effects including a movement disorder called tardive dyskinesia. *Id*. at 10–11. Because there is "no available therapy" for idiopathic gastroparesis, Vanda proffered that tradipitant "has the potential to address that unmet need." *Id*. (quotation omitted). For diabetic gastroparesis, tradipitant showed potential in that its existing efficacy and safety data indicated that it could "provide an effective treatment without the tardive dyskinesia risk associated with metoclopramide." *Id*. at 11.

To show tradipitant's potential, Vanda highlighted the results of Study 2301, its four-week phase 2 study, as demonstrating "improvements in nausea, vomiting,

and overall gastroparesis symptoms with tradipitant." *Id*. at 11, 18–37; *see* Pl.'s Mot. at 9–10. Vanda also reported positively on the expanded access protocol opened for multiple patients: each patient was approved for tradipitant dosing in six-month increments, with the longest-treated patient in their third approval cycle (amounting to 12 to 18 months of treatment).[3] AR at 11.

In February 2022, the FDA denied Vanda's fast track request in a two-page letter. *Id*. at 167–68. The agency explained that "[a]lthough gastroparesis is a serious condition with an unmet medical need," the information that Vanda submitted as part of its request did not "demonstrate the potential for tradipitant to address an unmet medical need." *Id*. at 167. In addition, tradipitant's "overall development plan" would not "currently enable" Vanda "to obtain the data necessary to evaluate the safety and efficacy" of the drug "for the indication as described in the Fast Track Designation Request." *Id*. Because of "the lack of necessary safety data and the resulting partial clinical hold," the FDA concluded that tradipitant's "drug development program is not able to provide the data necessary to demonstrate the product's potential to address an unmet medical need." *Id*.

C. Procedural History

This lawsuit followed. In a four-count complaint, Vanda alleges that the FDA's denial of fast track designation for tradipitant was arbitrary and capricious agency action. *See* Compl. at 29–33, ECF No. 1. According to Vanda, the agency: (1) used an

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[3] In a post-hearing notice, Vanda informed the Court that the number of patients receiving treatment through expanded access has grown to roughly 30, with many patients receiving treatment for over a year. Pl.'s Post-Hr'g Notice at 1 n.1, ECF No. 27.

improper standard when applying the fast track statute by supplementing the criteria listed in 21 U.S.C. § 356(b)(1); (2) failed to consider relevant evidence and provide a reasoned explanation when denying the fast track request; (3) failed to follow or explain its departure from previous actions respecting tradipitant; and (4) treated similarly situated applicants differently by granting certain fast track requests to other drugs. *Id*. The parties dispute these issues in cross-motions for summary judgment. And while Vanda asks the Court to readjudicate its fast track request in the first instance (under what it contends is the proper standard) before remanding to the FDA, the FDA wants the Court to abstain from reviewing its decision at all on the basis that Vanda lacks standing.

II. Legal Standards

When reviewing final agency action under the APA, the Court "sits as an appellate tribunal," where "[t]he entire case on review is a question of law." *Rempfer v. Sharfstein*, 583 F.3d 860, 865 (D.C. Cir. 2009) (quotations omitted). The APA provides that reviewing courts must "hold unlawful and set aside agency action" that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). The Court's review under this standard is limited; so long as an agency "examine[s] the relevant data and articulate[s] a satisfactory explanation for its action including a rational connection between the facts found and the choice made," the Court may not "substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (quotation omitted). The Court will not disturb the challenged action if the agency considered

the relevant factors and did not commit a "clear error of judgment." *Id*. (quotation omitted).

III. Analysis

A. Vanda Has Standing to Challenge the Denial of Fast Track Status

As in all cases, the Court must ensure that it has subject-matter jurisdiction before proceeding to the merits. See Grocery Mfrs. Ass'n v. EPA, 693 F.3d 169, 174 (D.C. Cir. 2012). Plaintiffs must satisfy three elements to meet the "irreducible constitutional minimum" of standing—they "must have (1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision." *Spokeo, Inc. v. Robins*, 578 U.S. 330, 338 (2016) (quotation omitted). The required injury in fact must be "concrete and particularized" and "actual or imminent, not conjectural or hypothetical." Lujan v. Defs. of Wildlife, 504 U.S. 555, 560 (1992) (quotations omitted). The FDA argues that Vanda has not satisfied these requirements.

This stance is somewhat surprising; after all, a plaintiff's "standing to seek review of administrative action is usually self-evident" when "the complainant is an object of the action (or foregone action) at issue." *Bonacci v. TSA*, 909 F.3d 1155, 1159 (D.C. Cir. 2018) (quotations and brackets omitted); *see Lujan*, 504 U.S. at 561–62. The thrust of the FDA's argument is that Vanda has not been "injured" by the agency's refusal to grant fast track status, because the main benefit of that designation is more frequent meetings with the agency during the drug development process, yet Vanda has "already received every meeting with [the] FDA that it requested." Defs.' Mem. in Opp'n to Pl.'s Mot. for Summ. J. & in Support of Cross-Mot. for Summ. J. ("Defs.' Mot.") at 2, ECF No. 17-1; see AR at

3918. Vanda disputes that factual claim, but in any event, the FDA's *discretion* to grant meetings during the development process does not equate to the agency's *obligation* to facilitate the development of fast track products. *See* 21 U.S.C. § 356(b)(1). Engaging with the agency through meetings is just one manifestation of the "facilitate[d]" development and "expedite[d]" review obligation that attaches to fast track products. *Id*. Another statutory benefit of fast track status, which the agency addresses only in passing, is eligibility for rolling review. *See id*. § 356(d)(1). Vanda's ineligibility for rolling review, and its failure to qualify for facilitated development and expedited review more generally, provide a basis for standing in this case.

The FDA argues in its reply that Vanda cannot rely on ineligibility for rolling review to support standing because relevant allegations are missing from Vanda's complaint and Vanda "asserts this injury for the first time in its response." Defs.' Reply at 6, ECF No. 22 (citing *La Asociacion de Trabajadores de Lake Forest v. City of Lake Forest*, 624 F.3d 1083, 1089 (9th Cir. 2010)). The FDA has not supported this position with any authority requiring this kind of precision. *See La Asociacion de Trabajadores*, 624 F.3d at 1089 (stating that a plaintiff "may not effectively amend its Complaint by raising a *new theory of standing* in its response to a motion for summary judgment" (emphasis added)). Vanda alleges in its complaint that it was denied fast track designation for tradipitant, and by statute, ineligibility for rolling review flows from that decision. Compl. ¶ 8; *see* 21 U.S.C. § 356(d)(1) (limiting rolling review eligibility to "fast track product[s]"). A party cannot rest on "general factual allegations of injury" when responding to a summary judgment motion,

Lujan, 504 U.S. at 561, but the record makes clear that Vanda has been denied both fast track status and, consequently, the opportunity for rolling review.

"[A] plaintiff suffers a constitutionally cognizable injury by the loss of an *opportunity to pursue a benefit* . . . even though the plaintiff may not be able to show that it was *certain to receive* that benefit had it been accorded the lost opportunity." *CC Distribs., Inc. v. United States*, 883 F.2d 146, 150 (D.C. Cir. 1989); *see Teton Historic Aviation Found. v. U.S. Dep't of Def.*, 785 F.3d 719, 724–25 (D.C. Cir. 2015). Although standing will not follow from a lost opportunity "if there is no realistic possibility" of receiving the benefit, tradipitant is not clearly unqualified for rolling review on any other basis besides its lack of fast track status. *Albuquerque Indian Rts. v. Lujan*, 930 F.2d 49, 56 (D.C. Cir. 1991); *see CC Distribs*., 883 F.2d at 151 (assessing whether an opportunity would be "illusory"); *see also* 21 U.S.C. § 356(d)(1) (requiring as a criterion for rolling review, in addition to fast track status, that the agency "determine[], after preliminary evaluation of clinical data submitted by the sponsor," that the "product may be effective").

The FDA's next response—that "Vanda has not claimed that it is ready, or will imminently be ready," to submit a portion of its NDA and thus to potentially receive rolling review—is no answer. Defs.' Reply at 6. Vanda states in its opposition to the FDA's cross-motion that it "has begun preparing an NDA for tradipitant, which will take several months and expenditure of resources to complete entirely." Pl.'s Reply in Support of Mot. for Summ. J. & Opp'n to Defs.' Cross-Motion for Summ. J. ("Pl.'s Reply") at 14, ECF No. 20; Pl.'s Ex. 17 at 1, ECF No. 20-3 (describing communication from Vanda in August 2022 regarding its intent to submit an NDA). While standing "must

be assessed as of the time a suit commences," *Food & Water Watch v. U.S. Dep't of Agric.*, 1 F.4th 1112, 1117 (D.C. Cir. 2021) (quotation omitted), the record amply supports that Vanda intended to apply for final approval throughout this litigation. After all, final approval is the goal of drug development, and even the FDA has described tradipitant as being in "the late stage of its drug development program." Defs.' Reply at 1, 8. If tradipitant were designated as a fast track product, Vanda's application for final approval could undergo rolling review once a portion of it is ready for submission, and Vanda has, at this point, offered a months-long estimate for its completion of the *entire* application. Pl.'s Reply at 14; see 21 U.S.C. § 356(d)(1). Vanda's preparation of just a portion would naturally take less time, and in any event, is not so speculative as to fail the injury-in-fact requirement. *See Union of Concerned Scientists v. U.S. Dep't of Energy*, 998 F.3d 926, 929 (D.C. Cir. 2021).

In addition to its imminence, Vanda has shown the concreteness of its injury resulting from the fast track denial by tying the adverse agency action to monetary harm, a "traditional tangible harm[]" that "readily qualif[ies]" as concrete. *TransUnion LLC v. Ramirez*, 141 S. Ct. 2190, 2204 (2021). The loss of eligibility for rolling review corresponds with a substantial likelihood that a drug developer would "waste resources preparing an application with deficiencies that [the] FDA could have warned of ahead of submission." Pl.'s Reply at 13–14.

Similar reasoning underlies the Court's conclusion that the harm resulting from the general loss of facilitation through the fast track program is also an imminent and concrete injury. Unlike rolling review, which is contingent upon the submission of a portion of tradipitant's NDA, the FDA could "facilitate

the development" of a fast track product at any pre-NDA stage. 21 U.S.C. § 356(b)(1). The denial of fast track status creates a significant risk of added expense due to increased time and resources spent on the development process. *See* Pl.'s Reply at 12 (stating that "Vanda would save substantial costs . . . if tradipitant received Fast Track designation because of the efficiencies Vanda would achieve through FDA's increased engagement with essential drug development issues").

Finally, the FDA argues that Vanda's injuries would not likely be redressed by the reversal of its fast track decision because fast track status guarantees neither additional meetings nor rolling review. The question for standing purposes, however, is not whether fast track status would likely result in rolling review for tradipitant, but whether it would likely provide "just that *opportunity* the loss of which constitutes the[] injury." *CC Distribs*., 883 F.2d at 151 (emphasis added). Here, the loss of an opportunity to qualify for rolling review, and the corresponding substantial risk of monetary harm, would likely be redressed by the removal of the barrier that caused the loss of opportunity. Likewise, the more direct monetary harm that arises from unfacilitated development would likely be redressed by the award of fast track status, which, again, requires facilitation of the development process and expedited review. *See* 21 U.S.C. § 356(b)(1).

Vanda fits the mold of the usual object of challenged agency action, where standing poses "little question." *Children's Health Def. v. FCC*, 25 F.4th 1045, 1049 (D.C. Cir. 2022) (quotation omitted). The Court therefore proceeds to the merits of Vanda's claims.

B. The FDA Did Not Improperly Apply Statutory Fast Track Criteria

Turning to the merits, Vanda first argues that the FDA's fast track denial is "irreconcilable with the statutory text." Pl.'s Mot. at 16. The text at issue, 21 U.S.C. § 356(b)(1), states in relevant part:

> The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition . . . .

Because the parties agree that tradipitant is intended for the treatment of "a serious or life- threatening disease or condition" (gastroparesis), their dispute centers around whether tradipitant "demonstrates the potential to address unmet medical needs" for gastroparesis. *See* AR at 167, 171.

Vanda contends that the FDA has improperly "supplemented the statute's two criteria with four of its own" by implementing a six-part checklist for the consideration of the fast track criteria. Pl.'s Mot. at 17. In an internal agency memorandum, the agency lists the following six questions:

1. Is the condition serious/life-threatening?
2. Is the product development program designed to demonstrate an effect on a serious aspect of the condition?
3. Does the product development plan address an unmet medical need?

4. Does the product show potential (given its stage of development) to address an unmet medical need?
5. Are the data supporting the FTD [(Fast Track Determination)] request coming from trials/INDs on clinical hold?
6. Was the FTD request submitted to a PIND?

AR at 171–72. These questions are followed by a "[r]ecommendation": "For fast track designation to be granted, questions 1-4 must all be answered 'Yes.' If questions 5 or 6 are answered yes, then the [fast track] may not be granted." *Id*. at 172. When evaluating Vanda's fast track request for tradipitant, the FDA answered "Yes" to Questions 1, 2, and 5, and "No" to Questions 3, 4, and 6. *Id*. at 171–72.

Vanda says—at first—that the FDA has "attempt[ed] to legislate via checkbox" by demanding *six* prerequisites for fast track designation instead of the statutory *two*. Pl.'s Mot. At 17. But Vanda really takes issue with the substance of only two of these six prerequisites—the third (looking to the drug's development plan) and the fifth (considering whether supporting data came from trials on clinical hold). Though Vanda frames its issues with respect to these two prerequisites somewhat differently, they share a common foundation that leads the agency to justify them in similar ways.

Vanda contends that the FDA's focus on the drug's development plan in Question 3, rather than on the drug itself, contravenes the statutory text. From Vanda's perspective, assessing whether the development plan demonstrates potential to address an unmet medical need inappropriately requires that the plan produce "the data necessary to evaluate the safety and efficacy required to achieve final marketing

approval." *Id*. at 18 (quoting AR at 167) (internal quotation marks and citation omitted). Such an approach would amount to frontloading the requirements of final marketing approval at the fast track stage. *Id*. at 18–19.

The FDA responds that Vanda has mischaracterized its reasoning for looking to the drug's development plan. Rather than requiring that Vanda submit *existing* studies showing that tradipitant is safe and effective to treat the symptoms of gastroparesis, as would be necessary to achieve final marketing approval, see 21 U.S.C. § 355(d), the FDA assessed whether Vanda could—in the future—produce safety and efficacy data showing its capability to address the unmet medical need. *See* Defs.' Mot. at 27. It could not, the FDA determined, because the partial clinical hold prevents studies lasting longer than 12 weeks. AR at 175. And that showing was necessary, in the context of the fast track request for tradipitant, because the FDA determined that the relevant "unmet medical need is for therapies that are *safe* and *effective* for the chronic treatment of the core signs and symptoms of gastroparesis." *Id*. at 173 (emphasis added). This framing of the unmet medical need aligned with Vanda's fast track request, which stated that "there is a significant unmet need for a safe and effective treatment for the symptoms of gastroparesis." *Id*. at 15. To this, Vanda counters that the FDA is not authorized to import safety and effectiveness requirements into the definition of an unmet medical need—and that the agency cannot blame Vanda for exceeding its statutory authority.

The Court agrees with the agency. Defining an "unmet medical need" is a "scientific judgment" within the agency's "area of expertise," and the Court gives it a "high level of deference." *Rempfer*, 583 F.3d at 867

(quotations omitted). The agency rationally relied on Vanda's own characterization of the unmet medical need, especially given the existing therapeutic options for gastroparesis symptoms. Vanda proposed tradipitant as an improvement over metoclopramide, the only existing drug for the treatment of diabetic gastroparesis, in part because of tradipitant's enhanced safety profile. AR at 11 (stating that unlike metoclopramide, "tradipitant has not been shown to increase the risk [of] any serious adverse event such as tardive dyskinesia"). And while no drug exists for idiopathic gastroparesis, the FDA reasonably saw no unmet medical need for therapies that are ineffective or unsafe. The inability of a drug's development plan to produce data necessary to assess the drug's safety and efficacy directly undermines a sponsor's claim that the drug has the potential to serve as a safe and effective treatment. The FDA's examination of the development plan, at the very least in the context of responding to Vanda's fast track request for tradipitant, was not arbitrary or capricious.

Vanda next argues that the FDA improperly refused fast track status for tradipitant because its IND is on a partial clinical hold, causing the agency to answer "Yes" to Question 5. Allowing a clinical hold to impede fast track designation is unreasonable, Vanda says, because a drug may address unmet patient needs for *acute* treatment of symptoms notwithstanding a hold preventing study for *chronic* use, or the clinical hold may be resolved as the drug progresses through the development process.

The FDA defends Question 5 by arguing that the agency does not, in fact, view the existence of a clinical hold as a per se bar on fast track designation. Instead, it contends that it engages in a fact-specific inquiry, and in the circumstances of this case, the partial

clinical hold limited the agency's ability to assess whether tradipitant had the potential to address an unmet medical need. In other words, even though the "recommendation" after the checklist states that fast track designation "may not be granted" if Question 5 is answered "Yes," what the agency actually means is that a clinical hold gives the agency "discretion to deny fast track designation."[4] Defs.' Mot. at 29. The question, then, is whether the FDA acted arbitrarily or capriciously in determining that the partial clinical hold on tradipitant prevented the agency from finding that the drug has the potential to address an unmet medical need.

For similar reasons as above, including the Court's deference to the agency's characterization of the unmet medical need, the Court concludes that the FDA permissibly considered the effect of the partial clinical hold. Especially key here, the FDA concluded that the relevant unmet need was for "therapies . . . for the chronic treatment of the core signs and symptoms of gastroparesis." AR at 173 (emphasis added). Vanda does not dispute that the partial clinical hold prevents tradipitant's study for *chronic* use. Assuming for purposes of this analysis that the FDA permissibly limited its consideration of Vanda's fast track request to *chronic* as opposed to *short-term* treatment of gastroparesis symptoms, a question that the Court addresses below, the FDA reasonably evaluated whether the partial clinical hold would prevent the production of necessary safety and efficacy data regarding chronic use.

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[4] Though this explanation seems to be an unnatural reading of the recommendation—"may not be granted" most plainly connotes a *denial of permission to grant rather than a grant of permission to deny*—Vanda does not appear to question the FDA's explanation of this language, so the Court takes it at face-value.

At bottom, Vanda asserts that the FDA's consideration of these two criteria relies on a faulty premise: that the FDA is authorized to examine not only the *currently available* data that a drug sponsor submits with its fast track request, but also the sponsor's ability to collect other data in the future. Vanda's position is that the agency is statutorily required to consider only existing data, based on the statute's text and congressional intent. Neither supports its position.

Vanda first emphasizes the word "potential" in 21 U.S.C. § 356(b)(1) as a capacious one, encompassing any possibility no matter how "remote" or "contingent." Pl.'s Mot. at 19 (quoting *James v. United States*, 550 U.S. 192, 207–08 (2007), *overruled on other grounds by Johnson v. United States*, 576 U.S. 591 (2015)) (internal quotation marks omitted). Even assuming the text contemplates this degree of remoteness,[5] it does not follow that the agency's analysis of a drug's potential must rely only on a backward-looking evaluation of the existing data that the sponsor submitted, rather than a forward-looking assessment of the drug's development plan (as impacted by any clinical hold). The term "potential" is inherently prospective—it refers to that which is "[n]aturally and probably expected to come into existence at some future time, though not now existing." *Potential, Black's Law Dictionary* (6th ed. 1990); *see also Potential, Webster's Third New*

[5] In *James v. United States*, the Court interpreted the term "potential risk" and noted that "the *combination* of the two terms suggests that Congress intended to encompass possibilities even more contingent or remote than a simple 'risk.'" 550 U.S. at 207–08 (emphasis added). No similar combination exists in the fast track provision at issue, which may not contemplate remoteness to the same degree.

International Dictionary (3d ed. 1993) ("something that exists in a state of potency or possibility for changing or developing into a state of actuality"). The FDA could therefore reasonably consider whether tradipitant's development plan, affected by the partial clinical hold, limited the drug's potential.

Vanda also points to textual indicators showing that the fast track program encompasses drugs even at early stages of development. Section 356(b)(1) directs the agency to "facilitate the [drug's] development," and that mandate would be less impactful if the designation were limited to drugs that have a clear and short path forward to final marketing approval. 21 U.S.C. § 356(b)(1). Similarly, the statute allows a sponsor to request designation "concurrently with" or after submission of an IND, which means that fast track status could be granted before any clinical data is collected in the first place.[6] *Id*. § 356(b)(2). But the FDA does not dispute that it may grant fast track status to drugs at early stages. The relevant dispute is whether the FDA can appropriately consider a drug's development plan and the clinical data the sponsor is likely (or unlikely) to produce. Nothing about the statute's reach to early-stage drugs forecloses that approach.

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[6] A clinical hold may be imposed "[a]t any time," and clinical investigations cannot begin until 30 days after the submission of an IND. 21 U.S.C. § 355(i)(2), (i)(3)(A). This lapse would afford the agency an opportunity to review the IND and impose a clinical hold before any clinical trials begin. After a fast track request is submitted, the agency has 60 days to make a decision on the request. *Id*. § 356(b)(3). The statutory scheme therefore allows the FDA time to impose a clinical hold, as well as deny fast track designation, even when the fast track request is submitted "concurrently with" the IND. *Id*. § 356(b)(2).

Last, Vanda invokes both implicit and explicit indications of congressional intent, arguing that "Congress's programmatic design" for the fast track program is to "remedy[] FDA regulatory hurdles that slow drug development." Pl.'s Mot. at 18. In the FDASIA, which amended the fast track provisions first enacted in 1997 (though without materially changing the wording at the core of the dispute here), the stated "sense of Congress" was "that the Food and Drug Administration should apply the . . . fast track provisions . . . to help expedite the development and availability to patients of treatments for serious or life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments." FDASIA § 901(a)(2). Omitting the last phrase of that purpose provision (about safety and effectiveness) from its briefing, Vanda argues that the FDA has contravened Congress's intent by imposing the "regulatory hurdles" that Congress sought to remove. Pl.'s Mot. at 6, 19–20, 42; Pl.'s Reply at 20.

The Court is not persuaded. The "sense of Congress," let alone any implicit purposes that Vanda derives from the statute, "does not in any way alter the plain text" of 21 U.S.C. § 356(b). *Fund for Animals, Inc. v. Kempthorne*, 472 F.3d 872, 877 (D.C. Cir. 2006); *see Montanile v. Bd. of Trs. of the Nat'l Elevator Indus. Health Benefit Plan*, 577 U.S. 136, 150 (2016) (stating that "[v]ague notions of a statute's basic purpose" do not "overcome the words of its text regarding the specific issue under consideration" (quotations omitted)). And even if a congressional purpose statement could add to the operative text, the sense of Congress makes clear that the FDA is not to pursue expediting measures at the expense of its "safety and effectiveness standards." FDASIA § 901(a)(2); see also FDASIA § 901(a)(1)(A) (congressional finding that the

FDA "serves a critical role in helping to assure that new medicines are safe and effective"). The Court will not deem the agency's reasonable application of statutory criteria improper solely because the agency did not fully pursue one of multiple congressional goals to the exclusion of others. In the context of Vanda's fast track request, Vanda reasonably applied the statutory fast track criteria.

C. The FDA Did Not Fail to Consider Relevant Evidence or to Provide a Reasoned Explanation

Vanda next claims that the FDA's fast track decision was arbitrary and capricious because the agency failed to "examine the relevant data and articulate a satisfactory explanation for its action." Pl.'s Mot. at 32 (quotation omitted). The precise contours of Vanda's argument are unclear, but as alleged in the complaint, Vanda takes issue with the generalized nature of the letter that the agency sent explaining its decision. *See* Compl. ¶ 152. Vanda also alleges that the FDA "did not address whatsoever the thorough data analysis provided in tradipitant's Fast Track application." *Id*. ¶ 153. Similarly, in its summary judgment motion, Vanda argues that the FDA's "cryptic one-page letter" explaining its decision was a "wholly insufficient agency response," particularly because the agency failed to mention Study 2301, even though Vanda discussed the study at length in its fast track request. Pl.'s Mot. at 34.

"When reviewing agency action under the APA," the Court analyzes "'the whole record or those parts of it cited by a party.'" *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1002 (D.C. Cir. 2008) (quoting 5 U.S.C. § 706); *see Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 420 (1971) (stating that APA review "is to be based on the full administrative record that was

before the Secretary at the time he made his decision"). "The record consists of the order involved, any findings or reports on which that order is based, and the pleadings, evidence, and other parts of the proceedings before the agency." *Am. Wildlands*, 530 F.3d at 1002 (quotation omitted).

The Court's review is therefore not limited to the brief decision letter that the FDA issued to Vanda announcing its fast track denial. *See* AR at 167–68. Instead, the Court reviews the agency's findings in the record supporting that decision, including the agency's eight-page internal "Fast Track Designation (FTD) Determination" memorandum ("Fast Track Memo"). *See id*. at 170–77. The Fast Track Memo is more robust. Unlike the letter, it thoroughly analyzes the results of Study 2301. And in it, the agency concluded, after summarizing data from the study, that "it is unclear from these data whether tradipitant has the potential to address the core symptoms of gastroparesis other than nausea" and that "it is difficult to interpret whether improvements in nausea severity or achieving a nausea-free day would be attributed to tradipitant or rescue medication use." *Id*. at 174. Vanda does not provide any reason to find the agency's explanation insufficient in light of these findings.

Instead, Vanda shifts focus to the scope of the "unmet medical need" that the FDA considered, arguing that the FDA appears to have incorrectly "concluded that a chronic treatment was the only unmet medical need of gastroparesis patients," while neglecting the need for *short-term* treatment. Pl.'s Mot. at 35. But the FDA did not reach that conclusion. Instead, the agency interpreted Vanda's request as seeking fast track designation for tradipitant for the

chronic (as opposed to short-term) treatment of gastroparesis symptoms.

That choice was not arbitrary or capricious. Although Vanda's fast track request stated generally that tradipitant could satisfy an unmet need for "the treatment of the symptoms of gastroparesis,"[7] without specifying either long-term or short-term treatment, the remaining content of the request reasonably caused the agency to evaluate only whether tradipitant could address an unmet need for chronic treatment. AR at 10.

To start, Vanda did not specifically frame its request in terms of short-term treatment. Vanda emphasized that expanded access patients had received treatment in six-month increments, with the longest treatment cycle lasting up to a year and a half. *Id*. at 11. Vanda described the "symptoms of gastroparesis" as "chronic," "persistent," and "recurrent." *Id*. at 12–13. It supported the long-term nature of gastroparesis symptoms with citations to scientific studies: one study of diabetic gastroparesis showed that "upper GI symptoms in patients with diabetes were unchanging over 12 years," and a survey of 1,423 adult patients with gastroparesis found the average length of symptoms to be 9 years. *Id*. When describing its hopeful expectations for

[7] Vanda insists in a post-hearing notice that the Court should not consider the "proposed indication" that it included in the fast track request. Pl.'s Post-Hr'g Notice at 2–3; *see* AR at 9 ("The proposed indication is for the treatment of the symptoms of gastroparesis."). Unlike the proposed indication that Vanda says it was "obligated" to include in accordance with the FDA's Expedited Programs Guidance, no guidance or regulation obligated Vanda to frame the rest of its application in a way that did not promote short-term use. Pl.'s Post-Hr'g Notice at 3 (citing AR at 3938).

tradipitant's development plan, Vanda stated that "if these robust efficacy results with a well-tolerated safety profile for chronic treatment are further confirmed in future studies, tradipitant has the potential to become a first-line option in the treatment of patients for the symptoms of both diabetic and idiopathic gastroparesis." *Id*. at 29 (emphasis added).

Vanda also compared its drug to the only existing treatment for diabetic gastroparesis, metoclopramide. In addition to highlighting metoclopramide's "high risk of significant side effects," Vanda stated that "the product's labeling advises against use for longer than three months due to the risk of developing tardive dyskinesia with longer-term use." *Id*. at 14. Vanda attempted to demonstrate that tradipitant could "provid[e] a therapeutic benefit over metoclopramide" by "treating the symptoms of diabetic gastroparesis while avoiding the serious toxicity and risk of tardive dyskinesia." *Id*. at 16. Metoclopramide is otherwise inadequate, Vanda described, because, while "this disorder is chronic and necessitates continuous treatment in most patients," the FDA approved metoclopramide "only for short-term treatment of adults with diabetic gastroparesis." *Id*. Vanda also stated that another treatment not approved for gastroparesis, erythromycin, had "limited effectiveness" because "significant tachyphylaxis occurs due to receptor down-regulation after prolonged use," causing erythromycin to "lose[] its effectiveness after a few weeks." *Id*. at 14–15. Given this context, the FDA reasonably interpreted the request as seeking to demonstrate tradipitant's potential to address the unmet medical need for chronic treatment.

In its summary judgment briefing, Vanda frames its fast track request as a direct response to the FDA's

advice at the breakthrough therapy stage regarding tradipitant's potential use "for the short-term relief of nausea in gastroparesis patients." *Id*. at 3026. The only alteration that the record reflects, though, was a shift in the proposed indication from "treatment of gastroparesis" to "treatment of the symptoms of gastroparesis." *Id*. at 11; *compare id*. at 9 (fast track request), *with id*. at 397, 488 (breakthrough therapy requests). The fast track request does not mention any focus on short-term treatment, nor does it invoke the FDA's recommendation about its prospects for that use. Months after Vanda submitted its fast track request, in the context of clarifying its plans for the further development of tradipitant as it continued to pursue final approval, Vanda reported to the FDA that it had decided to rely on the agency's advice from the breakthrough therapy context. *Id*. at 3870, 3882–83. But Vanda does not identify any instance where it sought to inform the agency of a change to its fast track request, and it has declined to submit any amended request during this litigation.[8]

Vanda's main counterpoint is that the fast track statute prohibits the FDA from "choos[ing] a particular unmet medical need when assessing a drug's 'potential.'" Pl.'s Reply at 31. In Vanda's view, the FDA must "consider whether the drug

[8] Whether Vanda's fast track request encompassed short-term treatment was a focal point at the hearing on the cross-motions. As a result, the Court requested that Vanda submit a notice informing the Court whether it intends to submit a new request that more clearly proposes short-term treatment as the unmet medical need that tradipitant has potential to address. Hr'g Tr. at 82–83, ECF No. 26. Vanda then clarified that it has no present intention to do so, despite the FDA's representations that it would consider any new request for fast track designation for short-term use. *See id*. at 50–51; Pl.'s Post-Hr'g Notice at 1; Defs.' Resp. to Order to Show Cause at 1–2, 6, ECF No. 29.

'demonstrates the potential to address' any one of the many 'unmet medical *needs*' (plural) of patients with serious diseases and conditions based on the data presented." *Id*. (quoting 21 U.S.C. § 356(b)(1)). The fast track statute, however, only requires the FDA to act "at the request of the sponsor of a new drug." 21 U.S.C. § 356(b)(1). Consistent with this text, the agency may reasonably limit its consideration to the unmet medical need that the sponsor claims its drug can address.

Based on the entire record, the Court rejects Vanda's claim that the FDA failed to address relevant clinical data or to provide a sufficient explanation for its fast track decision in light of that data. The Court also concludes that the agency reasonably limited the scope of its analysis to tradipitant's potential to address the unmet medical need for chronic treatment for the symptoms of gastroparesis.

D. The FDA Did Not Depart from Its Previous Actions

Vanda next challenges the fast track denial as inconsistent with the way that the agency has previously treated tradipitant in other contexts during the development process. First, when denying breakthrough therapy designation, as described above, the agency stated that it "see[s] a potential therapeutic role" for "the short-term relief of nausea in gastroparesis patients." AR at 3026. Second, the agency approved several expanded access requests for the use of tradipitant. Vanda claims that the denial of fast track designation is "irreconcilable" with these actions. Pl.'s Mot. at 30.

The Court disagrees. An agency must "provide reasoned explanation for its action" when it "changes its position regarding a regulatory matter." *Safari Club Int'l v. Zinke*, 878 F.3d 316, 331 (D.C. Cir. 2017)

(quotation omitted); *see FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("An agency may not, for example, depart from a prior policy *sub silentio* or simply disregard rules that are still on the books."). This case does not involve a rule change, nor has Vanda identified any change in the agency's policy for adjudicating fast track requests.

Further, the other actions that Vanda highlights are not inconsistent with the FDA's fast track denial. The agency's statement that it sees a "potential therapeutic role" for "short-term relief of nausea" was made in the breakthrough therapy context when recommending a "possible path forward" for that type of designation. AR at 3017, 3026. At most, this statement could have *some* predictive value for how the agency might view a fast track request for the short-term relief of nausea, because the criteria for breakthrough therapies and fast track products are similar. *See id*. at 3910–15. As the Court has already concluded, however, the agency reasonably did not interpret Vanda's fast track request to seek designation for short-term treatment. This makes the agency's previous statement about short-term use inapposite.

As for the agency's approval of expanded access, that action does not have much bearing on fast track designation. Expanded access requires only "sufficient evidence of safety and effectiveness to support the use of the investigational drug," where use is predicated on a physician's finding "that the probable risk to the person from the investigational drug" does not exceed "the probable risk from the disease or condition" for a particular patient. 21 U.S.C. § 360bbb(b)(1)–(2); *see also* 21 C.F.R. § 312.305(a)(2) ("FDA must determine that . . . [t]he potential patient benefit justifies the potential risks of

the treatment use and those potential risks are not unreasonable "). In contrast, concluding that tradipitant has the potential to provide safe and effective treatment—as needed for fast track designation here—requires more than just a finding that the risks of gastroparesis are equal to or less than the risks of the drug. The FDA did not depart from its decisions to grant expanded access to individual patients when denying fast track status.

E. The FDA Did Not Treat Tradipitant Differently Than Similarly Situated Drugs

Vanda's last claim is that the FDA arbitrarily evaluated tradipitant differently than other drugs in the fast track setting. "Where an agency applies different standards to similarly situated entities and fails to support this disparate treatment with a reasoned explanation and substantial evidence in the record, its action is arbitrary and capricious and cannot be upheld." *Burlington N. & Santa Fe Ry. Co. v. Surface Transp. Bd.*, 403 F.3d 771, 777 (D.C. Cir. 2005). A necessary component of any claim that an agency acted arbitrarily and capriciously in this respect is that the differently treated entities are, in fact, "similarly situated." *See Anna Jaques Hosp. v. Sebelius*, 583 F.3d 1, 7 (D.C. Cir. 2009).

First, Vanda refers to gastroparesis drugs, including relamorelin and velusetrag, which were designated as fast track products even though they were, in Vanda's view, "less promising"; their fast track requests were submitted "at much earlier stages and with much less data supporting safety and efficacy than tradipitant." Pl.'s Mot. at 39–41. The FDA responds that unlike tradipitant, these drugs demonstrated the potential to address an unmet medical need, in part because there was no clinical hold in place that would prevent the collection of

necessary safety and efficacy data. And as Vanda apparently concedes, the FDA's analysis of a drug's potential should vary depending on its stage of development. *See* Pl.'s Mot. at 24 (noting that Question 4 of the agency's checklist, which asks whether the product "show[s] potential (given its stage of development)," is "consistent with the statute"); Pl.'s Reply at 22 (same); AR at 3918. The Court agrees with the agency that these drugs are not similarly situated.

Second, Vanda identifies other drugs, Emend (aprepitant) and Apokyn (apomorphine), which received fast track designation even though they were intended "to acutely treat a single symptom" of a broader condition or disorder. Pl.'s Mot. at 40–42. Vanda argues that the FDA treated tradipitant differently "by unilaterally limiting its potential indication for Fast Track purposes to a chronic treatment for gastroparesis." *Id*. at 41. Vanda offers no information about how the unmet medical needs were described in those fast track requests, or whether the FDA considered the drugs' potential for acute treatment despite requests oriented more toward chronic treatment (as Vanda's request was). In fact, in its reply, Vanda only provides examples of the FDA approving other drugs for short-term or single-symptom treatment "notwithstanding a sponsor's proposal for a broader indication" at the *final approval* stage, not when making a fast track decision. Pl.'s Reply at 35 & n.12. Vanda has failed to demonstrate that these other drugs were similarly situated in a way that would require justification from the agency.

IV. Conclusion

For these reasons, Vanda's Motion for Summary Judgment is **DENIED**, and the FDA's Cross-Motion

for Summary Judgment is **GRANTED**. An order will issue contemporaneously with this opinion.

DATE: August 2, 2023

[signature]
CARL J. NICHOLS
United States District Judge