IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VANDA PHARMACEUTICALS, INC.
2200 Pennsylvania Avenue, N.W.
Suite 300E
Washington, DC 20037,

Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Avenue
Silver Spring, MD 20993,

SCOTT GOTTLIEB, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993,

and

ALEX M. AZAR II,
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201,

Defendants.

Civ. No. _____

COMPLAINT TO SET ASIDE AGENCY ACTION AND FOR DECLARATORY RELIEF

Plaintiff Vanda Pharmaceuticals, Inc. ("Vanda") brings this Complaint against Defendants and alleges as follows:

NATURE OF THE ACTION

1. Through this Complaint against the Food and Drug Administration ("FDA"), Vanda Pharmaceuticals, Inc. ("Vanda") challenges the FDA's imposition of a partial clinical hold that prohibits it from continuing past 90 days its successful study in humans of the safety and efficacy of tradipitant in relieving symptoms of gastroparesis. Gastroparesis is a serious, chronic gastrointestinal disease for which there are currently no FDA-approved safe and effective long-term treatments. In contrast to the current standard treatments, which carry serious adverse health risks, initial studies of tradipitant, in both animals and humans, have shown no safety signal of concern for humans. Studies of other drugs in the same class have likewise shown no troubling safety signal in humans. Despite this evidence of tradipitant's safety, as well as evidence regarding the ineffectualness of conducting additional non-rodent animal toxicity studies of tradipitant, FDA reflexively imposed an order to cease studies in humans past 90 days until Vanda had completed further chronic toxicity studies in dogs, which would require sacrificing the dogs, without any specific scientific justification. In so doing, FDA violated the Administrative Procedure Act ("APA"). FDA is only statutorily authorized to impose a clinical hold by demonstrating an "unreasonable risk to the safety of the persons who are the subjects of the clinical investigation," taking into account certain considerations set forth in the statute with respect to the specific drug at issue (hereafter, "Unreasonable Risk Determination"), or by relying upon a requirement set forth in a duly promulgated regulation. Here, FDA instead merely cited as binding authority a "requirement" that has never been subjected to notice-and-comment rulemaking, but was instead

issued as a recommendation in non-binding "guidance." FDA's action is therefore arbitrary, capricious, and contrary to law.

2. Vanda is a specialty pharmaceutical company focused on the development and commercialization of novel therapies to address high priority unmet medical needs and thereby improve the lives of patients.

3. In 2012, Vanda in-licensed tradipitant, a novel neurokinin-1 ("NK-1") antagonist, from Eli Lilly and Company ("Lilly"). Tradipitant has been studied by Vanda for efficacy and safety in both animals and humans for multiple indications, including for gastroparesis from November 22, 2016 until January 7, 2019. Nonclinical animal studies have included multiple three-month canine chronic toxicity studies, and multiple acute and chronic rodent toxicity studies, including three- and six-month studies. Not one of these animal studies has identified clinically relevant safety signals for use of tradipitant in humans. The primary toxicity findings from these studies—which involved dosing of the drug at concentrations many times higher than would be used in humans—do not raise safety concerns because the toxicities identified in the animal studies are not expected to occur in humans or are not considered to be adverse in humans.[1] Similarly, clinical testing of tradipitant in more than 600 patients to date at various doses has shown no clinically relevant safety signals.

4. Gastroparesis is a chronic digestive disorder in which the stomach cannot empty food into the small intestines. Gastroparesis predominantly affects women, with one study reporting approximately 80% of patients were female.[2] Symptoms include nausea, vomiting, and

---

[1] *See* Vanda, Tradipitant Investigator's Brochure (May 14, 2018), at 43-44 [hereinafter "Investigator's Brochure"].

[2] *See* Enrique Rey et al., *Prevalence of Hidden Gastroparesis in the Community: The Gastroparesis "Iceberg"*, 18 Journal of Gastroenterology & Motility 34, 39 (2012).

abdominal pain, seriously decreasing quality of life. Gastroparesis is particularly threatening to patients with diabetes, and can result in recurrent hospitalization. Metoclopramide, the only medication available in the United States that is FDA-approved to relieve gastroparesis symptoms, was approved almost forty years ago. It presents severe side effect risks and, because of such risks, carries a warning against its use for longer than twelve weeks.[3] There is one unapproved drug that is currently available in the United States for use in gastroparesis by submitting and obtaining FDA approval of a request for single patient expanded access (also referred to as "compassionate use") as an investigational new drug, but that drug is associated with serious risks of cardiac arrhythmias, cardiac arrest, and sudden death.[4]

5. Until January 7, 2019—when the last patient completed treatment in an 8-week open-label extension of Study VP-VLY-686-2301 ("Study 2301"), a Phase II study originally initiated on November 22, 2016—Vanda was actively evaluating tradipitant's safety and efficacy in relieving symptoms of gastroparesis.

6. In April 2018, Vanda submitted to FDA a proposed protocol to extend Study 2301 by adding a 52-week, open-label extension period. Vanda's request for the extension was driven in part by requests from participating clinicians and patients who did not want to cycle off the drug because of the relief they had obtained from taking the drug and the lack of good alternatives, and by Vanda's commitment to helping those patients with their unmet need for safe and effective medical treatments in gastroparesis.

---

[3] *See* Reglan, Highlights of Prescribing Information (Aug. 2017).

[4] *See* FDA, How to Request Domperidone for Expanded Access Use, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm368736.htm.

7. Beginning with a May 15, 2018 teleconference between Vanda and senior officials in FDA's Division of Gastroenterology and Inborn Error products (the "Division") and continuing throughout the year, FDA repeatedly took the position that Vanda was "required" to conduct an additional, nine-month non-rodent toxicity study before FDA would approve the extension that would permit Vanda to continue to provide the drug to study subjects.

8. FDA at no time made an Unreasonable Risk Determination relating to tradipitant that warranted an additional canine or other non-rodent study of such extended duration, nor did FDA identify any statutory or regulatory requirement mandating the additional study. Instead, FDA simply cited a non-binding "Guidance for Industry, M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (Jan. 2010) (the "ICH Guidance"), developed by an international, non-governmental organization, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH"), and then adopted by FDA as its own guidance document.

9. FDA at no time responded substantively to Vanda's arguments that: (1) the nine-month canine study was not scientifically justified in light of the extensive nonclinical safety testing that had already been done of tradipitant as well as other related compounds; (2) scientific research and regulatory developments subsequent to the ICH Guidance support the view that such a study in canines is unlikely to identify additional toxicities that would be clinically relevant to humans and materially relevant to FDA's decisionmaking; and (3) requiring such an additional study, which would result in the death of every canine participant, was inhumane and unethical in the absence of any expectation that it would lead to any clinically relevant findings.

10. FDA repeatedly rebuffed Vanda's efforts to engage the agency in a review of the specific safety record for tradipitant and the scientific literature regarding the ineffectualness of

further chronic non-rodent toxicity studies as predictors of toxicity in humans. Despite FDA's affirmative agreement with Vanda that preclinical studies of tradipitant had not raised any safety concerns, FDA continuously reverted to asserting that the ICH Guidance's recommendation to conduct nine-month, non-rodent toxicity studies was a binding requirement. FDA refused to engage in any discussion of whether its policy should change as a general matter, or whether (as contemplated by the ICH Guidance itself) tradipitant might present a case in which the combination of strong efficacy findings and the lack of safety signals supported Vanda's conclusion that it was reasonable, in light of the specific record of clinical testing and safety information for the drug together with supporting data for the related class of compounds, to conduct the proposed open-label extension. *See* 21 U.S.C. § 355(i)(1); 21 C.F.R. § 312.23(a)(8).

11. In addition, FDA has engaged in a pattern of bureaucratic conduct that has caused Vanda significant and unreasonable delay in the development of tradipitant. In May 2018, FDA told Vanda that it would impose a clinical hold on Vanda's tradipitant protocol unless Vanda withdrew the amendment proposing the extension study and first conducted the required nine-month non-rodent study or, alternatively, limited its proposed protocol to an extension of no more than eight weeks after the four-week double-blind portion of the study. Vanda informed FDA that it wished to challenge such a hold based on the scientific record. In order to avoid the threatened clinical hold that Vanda feared would apply to the ongoing four-week and eight-week open-label extension study, however, Vanda acceded to FDA's demand and withdrew the 52-week extension protocol. Vanda amended the protocol again, substituting an eight-week extension for the 52-week extension. Yet, when Vanda submitted a Formal Dispute Resolution Request ("FDRR") challenging FDA's insistence that a nine-month non-rodent animal study was required in order to conduct a 52-week clinical study, FDA rejected the FDRR on the ground that a request for formal

dispute resolution was not appropriate "at this time" because a protocol for a clinical trial exceeding three months in duration had "not been submitted" by Vanda. In short, FDA told Vanda to withdraw the protocol, and when Vanda followed FDA's instructions, the agency used that withdrawal as the basis to ignore Vanda's arguments in the FDRR by asserting, astonishingly, that a protocol that had been submitted but then withdrawn had "not been submitted."

12. Through its actions, FDA made it clear that the only way Vanda could engage in substantive discussion with the agency was to resubmit the protocol for a 52-week open-label extension study, which FDA would then put on clinical hold, at which point Vanda could again submit an FDRR. In September 2018, Vanda again sought to engage the agency on this issue by submitting a protocol for a new clinical study, Study VP-VLY-686-2302 ("Study 2302"), proposing a twelve-month open-label extension study for patients who complete Study 2301. Vanda submitted Study 2302 so that, if FDA put Study 2302 on hold, it would not jeopardize the rest of Vanda's study of tradipitant. In its submission, Vanda again explained that, based on tradipitant's safety profile in both animals and humans, a nine-month canine toxicity study should not be required because it was unlikely to uncover new clinically relevant safety data that had not been discovered already.

13. On December 19, 2018, however, approximately ninety days after Vanda submitted and was authorized by regulation to proceed with Study 2302, FDA imposed the partial clinical hold (the "Clinical Hold") via teleconference (the "Clinical Hold Call") on both Study 2302 and the proposed 52-week open-label extension phase of Study 2301, which Vanda had filed on December 11, 2018. On December 21, 2018, FDA sent a letter (the "Clinical Hold Letter") documenting the clinical hold. In both the Clinical Hold Call and the Clinical Hold Letter, FDA emphasized that the Division had already consulted with FDA's Medical Policy and Program

Review Council ("MPPRC"), and that MPPRC unanimously agreed that "non-rodent toxicity studies of 9 months duration are ***required*** for the conduct of [Vanda's] proposed clinical investigations of 52 weeks (12 months) duration, ***per*** the ICH *Guidance for Industry*[.]" Clinical Hold Letter at 2 (emphases added). FDA stressed that Vanda would be required to "submit satisfactory results from a chronic toxicity study of 9 months duration in a non-rodent species, ***per*** ICH M3(R2) guidance prior to conducting a clinical trial exceeding 3 months (12 weeks) in duration." *Id.* (emphasis added). Thus, the Clinical Hold Letter stated, Vanda "may continue Study 2301 up to 3 months (12 weeks) of treatment with tradipitant, limiting the study to the completed 4-week, double blind trial and the 8-week, open-label extension phase of the trial," but that Study 2302 "may not be initiated or continued beyond 12 weeks, if it has been started." *Id.* at 1-2.

14. That same day, Vanda's Chief Executive Officer requested reconsideration of the Clinical Hold from Janet Woodcock, M.D., the Director of FDA's Center for Drug Evaluation and Research ("CDER"), and Defendant Dr. Gottlieb. On January 4, 2019, Dr. Peter Stein, Director of the Office of New Drugs within CDER, communicated by telephone to Vanda's Chief Executive Officer that the request for reconsideration had been referred to him, that he and Dr. Woodcock had conferred, and that FDA would not reconsider its decision to impose the Clinical Hold. Dr. Stein noted that he had participated in the MPPRC decision, which unanimously endorsed imposing the ICH Guidance's recommendation to conduct an additional nine-month study as a requirement on Vanda.

15. In neither the Clinical Hold Letter nor in other communications did FDA provide any basis for its insistence that Vanda conduct the additional, nine-month study, other than referring to the ICH Guidance "requirement," citing the single scientific article from 1999 on

which the ICH Guidance relied for determining the recommended duration of non-rodent, chronic toxicity studies, and stating that, as a general matter, "sometimes things show up in nine-month studies that don't show up in three-month studies." Throughout, FDA made clear that its decision had nothing to do with an Unreasonable Risk Determination related to tradipitant, but instead relied upon the ICH Guidance as a generally applicable binding regulatory requirement.

16. Throughout 2018, including in the Clinical Hold Letter and in Vanda's conversations with Dr. Stein, FDA made clear that, one way or another, Vanda would be obligated to conduct the nine-month study "per" the ICH Guidance, even though FDA had not identified any specific scientific reason for why such a study should be conducted in this instance.

17. Although the Clinical Hold Letter described a single "potential option to continue your clinical program" prior to completing the entire 9 month non-rodent study, and referenced discussing "a path forward with the Division," FDA made it clear, both in the Clinical Hold Letter and other communications, that further discussions would not alter FDA's position that a nine-month non-rodent study was "required" as a precondition to lifting the Clinical Hold. In fact, the Agency's "potential option" described in the Clinical Hold Letter, which would have allowed Vanda to start further human studies sooner, was no "option" at all: FDA would still ultimately require Vanda to conduct the additional, nine-month study, and would furthermore require the sacrifice of *even more* canine subjects than the purported ICH "requirement." *Id.* at 2 (noting inclusion of "additional animals to provide for interim sacrifice"). The "option" would therefore not only fail to address Vanda's objections, including to the unnecessary and unethical sacrifice of animals in a scientifically unjustified study, it would have *exacerbated* the problems to which Vanda objected.

18. To be clear, Vanda does not categorically object to the sacrifice of animals in the course of scientific research when developing new human medications. Vanda understands the importance of preclinical animal research in identifying potential toxicities in humans. Vanda is, however, opposed on principle to engaging in the sacrifice of animals—typically young beagles—where such sacrifice is not scientifically justified.

19. On January 7, 2019, pursuant to FDA's Clinical Hold—which cut off further treatment with tradipitant after an extension of only eight weeks—the last participant in Study 2301 was forced to cease taking tradipitant.

20. FDA's imposition of the Clinical Hold represents final agency action, as it is clear that the agency has set forth its final position and that position has an immediate effect on Vanda, forcing it to discontinue its longer-term study of tradipitant in humans for the relief of gastroparesis symptoms. At the same time, the Clinical Hold had an immediate impact on patients, forcing them to discontinue a treatment that, to date, had provided significantly greater symptom relief than other available options, with considerably less risk.

21. FDA's action violates the APA. Although the Federal Food, Drug, and Cosmetic Act ("FDCA") unambiguously provides FDA authority to impose a clinical hold in certain circumstances, the statute requires FDA either to make a showing that the drug involved "represents an unreasonable risk to the safety" of study subjects or to determine that the clinical hold should be issued for reasons FDA has established "by regulation." 21 U.S.C. §§ 355(i)(3)(B)(i), (ii). The FDCA does not authorize FDA to impose a clinical hold simply by reference to a non-binding guidance document, without establishing an "unreasonable risk to the safety" of subjects. FDA made no attempt to undertake an individualized determination of "unreasonable risk" in this case, and the "requirement" it invoked was not one adopted "by

regulation." As a consequence, FDA's action was arbitrary, capricious, and otherwise contrary to law.

22. The APA requires administrative agencies to respond meaningfully to evidence presented by regulated parties. *Tesoro Alaska Petroleum Co. v. FERC*, 234 F.3d 1286, 1294 (D.C. Cir. 2000). FDA acted arbitrarily and capriciously by imposing the requirements of the ICH Guidance on Vanda reflexively, without offering any reasoned, tradipitant-specific scientific rationale for so doing, and by refusing to engage substantively in any way with the various arguments Vanda presented as to why an additional, nine-month toxicity study in dogs was unnecessary based on the specific facts and circumstances of tradipitant.

23. The APA also requires administrative agencies to publish within the Federal Register a "[g]eneral notice of proposed rulemaking" before adopting substantive rules, and to "give interested persons an opportunity to participate in the rule making[.]" 5 U.S.C. § 553(b), (c). By treating the ICH Guidance as a binding requirement, despite not having submitted the ICH Guidance to notice-and-comment procedures, FDA violated its obligations under the APA.

24. FDA's actions have harmed and continue to harm Vanda, as well as patients suffering from gastroparesis. Restricting Vanda's ability to conduct its proposed clinical studies has not only harmed Vanda's commercial interests, but has also inhibited Vanda's ability to advance its mission of bringing to market treatments that fulfill important and unmet medical needs.

25. Vanda is committed to responsible, scientifically justified animal testing, and refuses to undertake the unnecessary sacrifice of young beagles that would be used in non-rodent studies. FDA's inflexible demand that dozens of dogs, or other non-rodent mammals, be killed at the conclusion of a further, nine-month toxicology study lacks scientific basis or legal authority,

and would force Vanda to violate its sincerely held ethical principles that animal sacrifice for scientific study should be limited where possible, and done only when justified. Here, FDA has not identified any action that it might take that is likely to be informed by further animal testing beyond the extensive testing that has already taken place. Vanda is harmed by FDA's prohibition, without legal authority, against Vanda continuing its clinical study program for tradipitant beyond 12 weeks unless it conducts such unnecessary additional animal testing.

26. Vanda brings this suit to set aside the Clinical Hold, so that Vanda may continue its successful clinical evaluation of tradipitant, in keeping with good science and ethical practice.

PARTIES

27. Plaintiff Vanda Pharmaceuticals, Inc. is a global biopharmaceutical company focused on the development and commercialization of innovative therapies to address high unmet medical needs and improve the lives of patients. Vanda is incorporated in Delaware and maintains its principal place of business in Washington, DC.

28. Defendant Food and Drug Administration is an agency of the United States Government within the Department of Health and Human Services with offices at 200 Independence Avenue, SW, Washington, DC, and 10903 New Hampshire Avenue, Silver Spring, MD. The Secretary of Health and Human Services has delegated to FDA the authority to administer the relevant provisions of the FDCA.

29. Defendant Scott Gottlieb, M.D., is Commissioner of Food and Drugs and is the senior official of the FDA. He is sued in his official capacity. Dr. Gottlieb maintains offices at 200 Independence Avenue, SW, Washington, DC, and 10903 New Hampshire Avenue, Silver Spring, MD.

30. Defendant Alex M. Azar II is Secretary of Health and Human Services and the official charged by law with administering the FDCA. He is sued in his official capacity. Secretary Azar maintains an office at 200 Independence Avenue, SW, Washington, DC.

JURISDICTION AND VENUE

31. This action seeks declaratory relief under the Federal Declaratory Judgment Act, 28 U.S.C. § 2201.

32. This action arises under the FDCA, 21 U.S.C. § 301, *et seq*., and the APA, 5 U.S.C. §§ 551, *et seq*., as Vanda seeks judicial review of certain FDA actions that are "in excess of statutory jurisdiction, authority, or limitations," "without observance of procedure required by law," and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."

33. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331, because all causes of action arise under the laws of the United States.

34. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e).

35. An actual justiciable controversy, requiring resolution by this Court, currently exists between the parties concerning whether FDA may restrict Vanda from conducting its proposed clinical studies through the reflexive, unconsidered, and unexplained application of a non-binding guidance document that was originally prepared by a non-U.S. entity and which has not undergone notice-and-comment rulemaking.

36. Setting aside the Clinical Hold and providing declaratory relief will resolve this controversy and eliminate the harm to Vanda that FDA's Clinical Hold currently imposes.

LEGAL AND REGULATORY FRAMEWORK

A. Investigational New Drug Applications

37. Under the FDCA, a new drug may not be introduced into interstate commerce without FDA approval. *See* 21 U.S.C. §§ 355(a), 331(d); *see also*, *e.g.*, *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 761 (D.C. Cir. 2010).

38. In order to permit the study of new drugs for the purpose of determining their safety and efficacy prior to approval, the FDCA creates a limited exception to the prohibition against the introduction of unapproved new drugs into interstate commerce, exempting "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. § 355(i)(1).

39. The FDCA contemplates that FDA will promulgate regulations to implement this exception for investigational new drugs, which may condition such exception on, among other things, the submission of "reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing." *Id.*

40. FDA regulations implementing 21 U.S.C. § 355(i)(1) require the sponsor of a new drug to submit an investigational new drug application ("IND") to FDA, which must become effective before clinical trials in the United States may begin. *See* 21 C.F.R. § 312.20. The IND becomes active 30 days after the IND is submitted to FDA, unless FDA imposes a "clinical hold." 21 U.S.C. § 355(i)(2), (3).

41. Among other things, an IND must contain information on the drug's chemistry and manufacturing, information on the pharmacological and toxicological effects of the drug from animal studies and *in vitro* testing, information on any previous human experience, and a protocol for each planned study. *See* 21 C.F.R. § 312.23.

42. Once an IND is active, clinical trials generally are conducted in three phases. *See* 21 C.F.R. § 312.21. Phase I involves the initial introduction of a new drug into human subjects, may be conducted in patients or healthy volunteer subjects, and is "designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness." 21 C.F.R. § 312.21(a)(1). Phase II studies are "typically well controlled, closely monitored, and conducted in a relatively small number of patients" and are used to evaluate "effectiveness of the drug for a particular indication . . . and to determine the common short-term side effects and risks associated with the drug." 21 C.F.R. § 312.21(b). Phase III studies are expanded trials, usually including several hundred to several thousand subjects, designed to "gather . . . 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." 21 C.F.R. § 312.21(c).

43. During the clinical trial process, a drug sponsor is required to provide ongoing reports to FDA, and in some cases study investigators and Institutional Review Boards (*i.e.*, third party entities, the composition and duties of which are established in 21 C.F.R. Part 56, which provide ethical oversight over clinical studies carried out under an IND), among other things, to seek review and approval of new and amended protocols, submit required safety reports, submit significant findings from other clinical and nonclinical studies of the drug, and submit annual reports summarizing specified categories of information from the past year. *See* 21 C.F.R. §§ 312.30–312.33.

44. When a drug sponsor wishes to conduct a study that is "not covered by a protocol already contained in" an existing IND, that new study may begin as soon as two conditions are met: (1) the sponsor must submit the protocol to FDA for its review; and (2) an Institutional

Review Board ("IRB") with responsibility for the study must review and approve the protocol in accordance with the requirements of 21 C.F.R. Part 56. *See* 21 C.F.R. § 312.30(a). A drug sponsor must also submit to FDA any amendment to a Phase 2 or 3 protocol that "affects the safety of subjects, the scope of the investigation, or the scientific quality of the study" and the protocol change can be made provided the same two conditions are met. *Id.* § 312.30(b).

B. Imposition of Clinical Holds

45. At any time during the clinical development of a new drug, including prior to commencing clinical studies under an IND, FDA "may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a 'clinical hold')." 21 U.S.C. § 355(i)(3)(A). Under the FDCA, a clinical hold may be imposed only if the FDA determines either that (1) "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation" or (2) "the clinical hold should be issued for such other reasons as the Secretary [of the Department of Health and Human Services, who has delegated such authority to the Commissioner of the FDA] may by regulation establish." 21 U.S.C. §§ 355(i)(3)(B)(i), (ii).

46. By regulation, FDA defines a clinical hold as "an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation." 21 C.F.R. § 312.42(a). A clinical hold may apply to one or more investigations covered by an IND. *Id.* When a "proposed study" is placed on clinical hold, "subjects may not be given the investigational drug." *Id.* When an "ongoing study" is placed on clinical hold, "no new subjects may be recruited to the study and placed on the investigational drug [, and] patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety." *Id.*

47. FDA regulations list specific circumstances under which clinical studies under an IND may be placed on clinical hold. 21 C.F.R. § 312.42(b). A clinical hold may be imposed if "[h]uman subjects are or would be exposed to an unreasonable and significant risk of illness or injury" or "[t]he IND does not contain sufficient information required under [21 C.F.R. §] 312.23 [(discussed below)] to assess the risks to subjects of the proposed studies." 21 C.F.R. §§ 312.42(b)(1)(i), (iv); 21 C.F.R. § 312.42(b)(2)(i). However, FDA regulations do not list particular study requirements. By contrast, certain other federal regulatory agencies, like the Environmental Protection Agency ("EPA"), include detailed animal toxicology study requirements in regulations. For example, EPA has a detailed "toxicology data requirements table" that indicates the specific "toxicology data requirements" required by EPA "for a particular pesticide product," and includes where applicable "specific conditions, qualifications, or exceptions to the designated test." 40 C.F.R. § 158.500(a). While some FDA guidance documents *recommend* particular study requirements, FDA—unlike EPA—has not implemented those recommendations as binding regulatory requirements.

48. Prior to imposing a clinical hold, FDA regulations require that "unless patients are exposed to immediate and serious risk, [FDA will] attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." 21 C.F.R. § 312.42(c). When a clinical hold order is issued, the order "will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action . . . and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold." 21 C.F.R. § 312.42(d).

49. A clinical trial subject to a clinical hold order "may only resume after FDA . . . has notified the sponsor that the investigation may proceed." 21 C.F.R. § 312.42(e).

C. Nonclinical Toxicity Studies

50. Under FDA regulations, one of the grounds for imposing a clinical hold order is if the "IND does not contain sufficient information required under [21 C.F.R. §] 312.23 to assess the risks to subjects of the proposed studies." 21 C.F.R. § 312.42(b)(1)(iv); 21 C.F.R. § 312.42(b)(2)(i).

51. Under 21 C.F.R. § 312.23(a)(8), an IND must include "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations."

52. Nowhere do FDA's regulations specify that chronic toxicity studies must be conducted in non-rodent species; that such studies must be conducted in particular non-rodent species; or that such studies must have a specified duration. Rather, FDA's regulations contemplate that the "kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8). With regard to toxicity studies specifically, FDA regulations contemplate that the appropriate toxicity studies will vary depending on the drug and clinical development program at issue. The relevant regulation states, "[d]epending on the nature of the drug and the phase of the investigation," the IND must include "the results of acute, subacute, and chronic toxicity tests[.]" 21 C.F.R. § 312.23(a)(8)(ii).

53. Rather than detailing any requirements for toxicity studies, FDA's regulations note that "[g]uidance documents are available from FDA that describe ways in which these requirements *may* be met." 21 C.F.R. § 312.23(a)(8) (emphasis added). In other words, FDA regulations make clear that guidance documents provide flexible options rather than binding rules.

54. FDA has adopted the ICH Guidance as a *non-binding* guidance document addressing nonclinical safety studies to support the conduct of human clinical trials and marketing authorization for pharmaceuticals. *See* FDA, Guidance for Industry: M3(R2) *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (Jan. 2010).

55. The ICH Guidance was not developed by FDA, but rather was "prepared under the auspices of" the ICH. *See* International Conference of Harmonisation; Guidance on M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; Availability, 75 Fed. Reg. 3471 (Jan. 21, 2010).

56. The ICH is an international association, organized under Swiss Law,[5] to "provide an opportunity for . . . harmonization initiatives to be developed with input from both regulatory and industry representatives." *Id.* The "ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States." *Id.* at 3471-72. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health, Labor, and Welfare, the Japanese Pharmaceutical Manufacturers Association, the FDA, and the Pharmaceutical Research and Manufacturers of America. *Id*.

57. With respect to chronic toxicity studies in rodents and non-rodents, the ICH Guidance provides that "[t]he recommended duration of the repeated-dose toxicity studies is usually related to the duration, therapeutic indication, and scope of the proposed clinical trial," and "[i]n principle, the duration of the animal toxicity studies conducted in two mammalian species

[5] International Conference of Harmonisation, *History*, http://www.ich.org/about/history (last visited Jan. 15, 2019).

(one nonrodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies." ICH Guidance at 7.

58. The ICH Guidance clarifies that "[i]n circumstances where significant therapeutic gain has been shown, trials can be extended beyond the duration of supportive repeated-dose toxicity studies on a case-by-case basis." *Id.*

59. The ICH Guidance further provides that "[s]ix-month rodent and 9-month nonrodent studies generally support dosing for longer than 6 months in clinical trials," with certain exceptions. *Id.* These exceptions include a general exception for the EU, where "studies of 6 months' duration in non-rodents are considered acceptable," and the following "examples" where "nonrodent studies of up to 6 months' duration can also be appropriate for Japan and the United States": when immunogenicity or intolerance confounds conduct of longer term studies; drugs with repeated short-term drug exposure, even if the trial duration exceeds six months (e.g., treatment of migraine); and drugs for indications with short life expectancy or for reducing the risk of recurrence of cancer. *Id.* at 8.

60. The current ICH Guidance is a revision of guidance originally developed by the ICH and published by FDA as draft guidance on May 2, 1997, and final guidance on November 25, 1997. *See* International Conference on Harmonisation; Draft Guideline on the Timing of Nonclinical Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, 62 Fed. Reg. 24,320 (May 2, 1997) (draft guidance); International Conference on Harmonisation: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, 62 Fed. Reg. 62,922 (Nov. 25, 1997) (final guidance).

61. The nine-month recommended duration of chronic toxicity studies in non-rodents embodied in the ICH Guidance represents a compromise position adopted by the ICH not based

on a particular scientific rationale but rather "so as to avoid duplication and to follow a single development plan for chronic toxicity testing of new medicinal products" across the U.S., E.U., and Japan. International Conference on Harmonisation; Draft Guidance on the Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing); Availability, 62 Fed. Reg. 61,513, 61,515 (Nov. 18, 1997); *see also* International Conference on Harmonisation; Guidance on the Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing); Availability, 64 Fed. Reg. 34,259, 34,260 (June 25, 1999) (same).[6] To support this recommendation, regulatory authorities in the European Union, Japan, and the United States undertook a joint evaluation of chronic toxicity studies to compare studies with "6 versus 12 months data." 62 Fed. Reg. 61,513, 61,514.

62. This evaluation by the ICH was limited in its consideration of the meaningfulness of toxicological findings in chronic non-rodent toxicity studies, "focus[ing] primarily on toxicological outcome, and less weight was given to the potential human significance of the findings, or the influence of the findings on marketing and labeling[.]" Joseph J. DeGeorge et al., *The Duration of Non-Rodent Toxicity Studies for Pharmaceuticals*, 49 Toxicological Sci. 142, 145 (1999).

63. In addition, as described by the FDA,

> In some of the cases analyzed . . . there were no additional [toxicity] findings at 12 months. For some other cases, there was not complete agreement among the

[6] The version of the ICH Guidance adopted by FDA in November 1997 referenced a separate ICH guidance document for the recommended duration of chronic toxicity studies in non-rodents, "ICH Topic S4 Document: Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)" ("S4 Guidance"). Notably, while the S4 Guidance provides that chronic toxicity testing of new products may employ a six-month study in rodents and a nine-month study in non-rodents, the S4 Guidance cites to no scientific data to support its recommendations regarding study duration. The cited Federal Register notice is from FDA's issuance of the draft S4 Guidance on November 18, 1997, which discusses the basis for the ICH's recommendation of a nine-month duration for chronic toxicity studies in non-rodents.

> regulators with respect to the comparability in study design and conduct to allow assessment of whether there were differences in the findings at 6 and 12 months due to duration of treatment alone. In a number of cases there were findings observed by 12 months, but not by 6 months. It was concluded that these would, or could, have been detected in a study of 9 months duration. Varying degrees of concern for the differences in findings detected between the studies of different durations were expressed. An agreement on the clinical relevance of these findings could not be reached. Studies of 12 months duration are usually not necessary and studies of shorter than 9 months duration may be sufficient.

62 Fed. Reg. 61,514-15; *see also* 64 Fed. Reg. 34,260.

64. Ultimately, in light of these disagreements, driven in part by "regional differences in regulatory history, statutes, policies, and perspectives," a harmonized nine-month standard was selected, not due to scientific consensus but rather to administrative convenience. *See supra* para. 62 DeGeorge et al., at 154 (1999); *see also* 62 Fed. Reg. 61,514-15. In particular, this compromise would prevent "excessively burdensome" and "extensive consultation by industry with the regulatory authorities in all regions." DeGeorge et al., at 154 (1999).

65. To the extent the intent behind the ICH Guidance was to provide regulatory certainty and global harmonization by reducing case-by-case variation across jurisdictions, fulfilling that purpose would have required FDA to adopt the ICH standard as a binding rule. To apply the ICH Guidance as a *requirement*, FDA would have been required to adopt the ICH recommendations, including the 9-month non-rodent toxicity study, as a regulation through notice-and-comment rulemaking. FDA chose, however, to implement the ICH Guidance instead only as a non-binding guidance document.

D. Revisions to Environmental Protection Agency Policy

66. At least one other federal administrative agency with responsibilities analogous to those of FDA, the EPA, has shifted its approach significantly in recent years to adjust for updated scientific consensus on nonclinical toxicity studies. EPA has done so through binding regulations, which it has revised in light of new scientific understanding.

67. Pesticides, like pharmaceutical products, pose direct risks to human health through sustained exposure. In fact, pesticides pose much greater risks, as significantly greater numbers of people are exposed to pesticides—on produce and because they are sprayed across large swaths of territory where people live and work—and without the informed consent that participants in clinical studies receive. Because of human and animal exposure to pesticides through ingestion and other means, EPA data requirements for pesticide registration—similar to FDA requirements for pharmaceutical products—typically include extensive laboratory and animal studies, including toxicity studies. *See* 40 C.F.R. Part 158.

68. EPA's regulations governing data requirements for pesticide registration spell out in detail the type and duration of required animal toxicity studies and the conditions under which they are required. *See* 40 C.F.R. Part 158. By contrast, FDA's regulations provide comparably little detail on data requirements for investigational new drug applications, including preclinical animal toxicity studies, in keeping with FDA's practice of relying on non-binding guidance documents.

69. EPA initially issued regulations governing data requirements for pesticide registration in 1984. *See* 40 C.F.R. § 158.135 (1984); 49 Fed. Reg. 42,856, 42,892-93 (Oct. 24, 1984). The 1984 regulations identified a chronic feeding study in both a rodent and non-rodent species as "required" for all pesticides used on food crops and "conditionally required" for pesticides used in non-food settings if use of the pesticide product is likely to result in repeated human exposure over a significant portion of the human life-span. 40 C.F.R. § 158.135 (1984); 49 Fed. Reg. 42,856, 42,892-93 (Oct. 24, 1984). The regulations specified that the chronic toxicity study in a non-rodent species should be conducted in dogs for a minimum twelve-month duration. *Id.*

70. EPA issued the 1984 regulations requiring the conduct of twelve-month, non-rodent chronic toxicity studies based on its belief at the time that such studies provide "scientifically defensible data to assess the non-oncogenic chronic effects of a pesticide,"[7] "that [the] recommended time periods . . . satisfactorily harmonize [EPA's] requirements with those published by other governmental agencies and international groups," and "that use of the rodent (rat) and nonrodent species (dog) in the chronic studies allows a better evaluation of non-oncogenic chronic effects[.]" 49 Fed. Reg. 42,856, 42,869 (Oct. 24, 1984).

71. Subsequently, an extensive analysis of toxicity studies in dogs that compared findings from three-month studies against findings in twelve-month studies found that twelve-month studies "did not provide additional essential toxicity information." 72 Fed. Reg. 60,934, 60,940-41 (Oct. 26, 2007). In 2007, on the basis of that analysis, EPA revised its regulations to eliminate the requirement to conduct chronic toxicity studies in dogs. *Id.*; 40 C.F.R. § 158.500. Specifically, under the revised regulations, a chronic non-rodent study (i.e., a 1-year dog study) is required only if EPA "finds that a pesticide chemical is highly bioaccumulating and is eliminated so slowly that it does not achieve steady state or sufficient tissue concentrations to elicit an effect during a 90-day study," and "appropriate tier II metabolism and pharmacokinetic studies to evaluate more precisely bioavailability, half-life, and steady state" indicate a chronic dog toxicity study is needed. 40 C.F.R. § 158.500(e)(36). This finding must be made with respect to a particular pesticide chemical in order for the study requirement to be applied. In the preamble to the final rule, EPA noted with regard to circumstances under which EPA may require a chronic

[7] "Oncogenic" means tending to cause tumors. *Oncogenic*, Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health (7th ed. 2003).

toxicity study in dogs that it "anticipates that this situation will be infrequent." 72 Fed. Reg. 60,934, 60,941 (Oct. 26, 2007).

72. In issuing its revised regulations in 2007, EPA explained that it conducted an "extensive analysis of dog toxicity studies on 110 chemicals representing over 50 different classes of pesticides[8]. . . [and] concluded from this analysis that extending a dog toxicity study beyond a 13-week duration does not provide additional essential toxicity information." *Id.* Indeed, in only 2% of the cases analyzed were additional toxic effects identified in the 1-year study that were not observed in the 13-week dog study or in longer-term rodent studies.[9] And, even in the small number of cases where results differed slightly in the 1-year dog studies, "[i]n no case, did these small differences have a regulatory impact on pesticide risk assessments." *Id.* This analysis followed a previous retrospective analysis that had similar findings.[10]

---

[8] *See* U.S. EPA, Health Effects Division, Office of Pesticide Programs, *Length of Dog Toxicity Study(ies) that is Appropriate for Chronic RfD Determinations of Pesticide Chemicals* (Mar. 20, 2006) (reporting the results of EPA's 2006 assessment of chronic toxicity studies in dogs cited in support of the 2007 revisions to EPA's regulations to remove the requirement to conduct chronic toxicity studies in dogs). *See also* Vicki L. Dellarco et al., *A Retrospective Analysis of Toxicity Studies in Dogs and Impact on the Chronic Reference Dose for Pesticide Chemicals*, 40 Critical Rev. in Toxicology 16 (Jan. 2010) (describing the results of EPA's 2006 review of toxicology studies and outlining additional supportive evidence from other retrospective analyses of pesticide and drug toxicity studies that support removing the requirement to conduct a 12-month dog study); Karl P. Baetcke et al., U.S. EPA, Health Effects Division, Office of Pesticide Programs, *A Comparison of the Results of Studies on Pesticides from 12- or 24-Month Dog Studies with Dog Studies of Shorter Duration* (May 2005) (This paper describes a 2005 EPA assessment of 77 chronic toxicity studies in dogs, which was referred to the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") Scientific Advisory Panel for consideration prior to EPA finalizing its amended regulations in 2007).

[9] *See supra* n.8 Dellarco, et al. (2010) (This is an article authored by EPA personnel, reporting the results of EPA's 2006 analysis supporting the 2007 regulatory update to eliminate the requirement to conduct chronic toxicity studies in dogs).

[10] *See supra* n.8 Baetcke et al. (2005).

73. Based on its comprehensive analysis, EPA concluded that "reliance on the required chronic rodent studies, 2-generation rat reproductive study, and the 13-week dog toxicity study provides an adequate basis for chronic reference dose ("RfD") derivation in pesticide risk assessment." 72 Fed. Reg. 60,934, 60,941 (Oct. 26, 2007).

74. EPA's conclusion that chronic toxicity studies in a non-rodent species should not be routinely required for pesticides is supported not only by the EPA's own extensive retrospective analysis of toxicity studies in dogs, but has also been confirmed by other retrospective analyses.[11]

75. In supporting its decision to eliminate the non-rodent chronic toxicity study requirement, EPA also relied on retrospective analyses conducted in the analogous context of pharmaceutical toxicity studies, which it determined were likewise "supportive of the overall conclusion that long term toxicity studies in the dog rarely provide either qualitatively new toxicological information or quantitative information not already gained from other required

[11] *See, e.g.*, Horst Spielmann & Ulrich Gerbracht, *The Use of Dogs as Second Species in Regulatory Testing of Pesticides, Part II: Subacute, Subchronic, and Chronic Studies in the Dog*, 75 Archives of Toxicology 1, 1 (2001) (A comprehensive analysis of data submitted to the Federal Institute of Health Protection of Consumers and Veterinary Medicine (Germany) from dog studies on 216 pesticides demonstrated that "chronic long-term studies (52/104 weeks) in dogs do not provide specific additional information to 26-week studies in the same species."); Rainer J. Box & Horst Spielmann, *Use of the Dog as Non-rodent Test Species in the Safety Testing Schedule Associated with the Registration of Crop and Plant Protection Products (Pesticides): Present Status*, 79 Regulatory Toxicology 615 (2005) (describing the results of the Spielmann & Gerbracht 2001 retrospective analysis as well as the results of additional retrospective analyses of chronic toxicity studies); Werner Kobel, et al., *A 1-Year Toxicity Study in Dogs is No Longer a Scientifically Justifiable Core Data Requirement for the Safety Assessment of Pesticides* 40 Critical Rev. in Toxicology 1 (2010) (reporting the results of a review of peer-reviewed publications assessing the need for 1-year toxicity studies in dogs and concluding that "routine inclusion of a 1-year dog study as a mandated regulatory requirement for the safety assessment of pesticides is no longer justifiable").

studies."[12] And, while EPA recognized that there are differences between the drug and pesticide contexts, they noted with respect to drugs that "there appear to be few examples in the literature reports where 'new findings' affected the margins of safety." *Id.*

FACTUAL BACKGROUND

A. Treatment of Gastroparesis with Tradipitant

76. Gastroparesis is a serious chronic digestive disorder of gastric motility. Patients with gastroparesis suffer from nausea, vomiting, early satiety, postprandial fullness, and abdominal pain. The estimated number of patients with confirmed gastroparesis in the United States is approximately 70,000-80,000, with a roughly 4-to-1 ratio of affected females to males.[13] The actual prevalence of gastroparesis in the U.S. population, including undiagnosed cases, is expected to be significantly higher, with estimates that it may affect roughly 1.8% of the U.S. population (or approximately 5.9 million individuals).[14]

77. There currently are no long-term medication treatment options for gastroparesis symptoms in the United States. There are two drugs that are potentially available, each of which

---

[12] *See supra* n.8 Baetcke et al. (citing C.E. Lumley, et al., *An International Appraisal of the Minimum Duration of Chronic Toxicity Studies*, 11 Human and Experimental Toxicology 155 (1992); J.F. Contrera, et al., *A Retrospective Comparison of the Results of 6 and 12 Month Non-Rodent Toxicity Studies*, 12 Adverse Drug Reactions and Toxicological Rev. 63 (1993); C. Parkinson, et al., *The Value of Information Generated by Long-Term Toxicity Studies in the Dog for the Nonclinical Safety Assessment of Pharmaceutical Compounds*, 25 Fundamental and Applied Toxicology 115 (1995); *see supra* at para. 62 DeGeorge et al., at 143 (1999)).

[13] *See* Hye-kyung Jung et al., *The Incidence, Prevalence and Outcomes of Patients with Gastroparesis in Olmsted County, Minnesota from 1996-2006*, 136 Gastroenterology 1225, Table 4 (2009) (reporting an observed prevalence of definite gastroparesis in Olmsted County of 37.8 in women and 9.6 in men per 100,000 persons, with an overall observed prevalence of 24.2 per 100,000). Using a U.S. population estimate of 325 million, it can be estimated that there are between 70,000 to 80,000 confirmed cases of gastroparesis in the U.S based on this epidemiology study.

[14] *See supra* n. 2 Rey, et al. (2012).

is associated with serious adverse reactions. Reglan (metoclopramide) is FDA-approved, but the drug's FDA-approved label bears a boxed warning—FDA's most serious warning—regarding the risk of developing tardive dyskinesia ("TD"), a serious movement disorder which is untreatable and often irreversible, and which specifically recommends avoiding treatment for longer than 12 weeks because of the risk of developing TD with longer-term use. Reglan is also subject to a Risk Evaluation and Mitigation Strategy ("REMS") requiring that a medication guide for patients be distributed with the drug.[15] A REMS is necessary when a particular risk or risks associated with a medication may outweigh its benefits in the view of FDA staff, and it is determined that additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[16]

78. Domperidone is the second possible option. It is not FDA-approved, but it is potentially available pursuant to an expanded access (or "compassionate use") investigational new drug application. However, Domperidone is associated with serious cardiovascular risks, including sudden cardiac death.[17]

79. Vanda is currently studying tradipitant, a novel NK-1 antagonist to treat the symptoms of gastroparesis. Vanda in-licensed tradipitant from Lilly in 2012.

---

[15] FDA, Reglan Highlights of Prescribing Information (2017), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017854s062lbl.pdf; Letter from Joyce Korvick, FDA, to Mary Alonso, Alaven Pharm. (Sept. 4, 2009), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/017854s052_021793s005ltr.pdf.

[16] FDA, Frequently Asked Questions (FAQs) about REMS, available at https://www.fda.gov/Drugs/DrugSafety/REMS/ucm592627.htm.

[17] FDA, How to Request Domperidone for Expanded Access Use, https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm368736.htm.

80. Although not approved for use in gastroparesis, other NK-1 modulators have been shown to reduce symptoms and symptom severity in patients with symptoms such as nausea and vomiting, without serious side effects. One such example is EMEND (aprepitant), FDA-approved for chemotherapy-induced and post-operative nausea and vomiting, which contains neither a boxed warning nor a REMS.[18]

81. Tradipitant is not approved for any indication in the United States, but has previously been investigated to treat social anxiety disorder, anxiety-related functional gastrointestinal disorders, and alcohol dependence.

82. Multiple non-clinical (*i.e.*, animal) studies have been conducted with tradipitant, first by Lilly and then by Vanda. These studies include: a single-dose study in rats; a thirteen week repeat-dose study in mice; one-, three-, and six-month repeat-dose studies in rats; one- and three-month repeat-dose studies in dogs; a fertility and embryo-fetal development study in rats; an embryo-fetal development study in rabbits; and *in vitro* and *in vivo* genetic tests.[19]

83. The results of these studies with tradipitant are consistent with studies of other NK-1 antagonists that detected no serious side effects, showing that other NK-1 antagonists are safe and well-tolerated in animals.[20]

---

[18] FDA, EMEND Highlights of Prescribing Information (2010), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021549s027,207865s001lbl.pdf; *see also* P.J. Pasricha et al., *Aprepitant Has Mixed Effects on Nausea and Reduces Other Symptoms in patients with Gastroparesis and Related Disorders*, 154 Gastroenterology 65-76 (2018).

[19] Investigators Brochure at 43-63.

[20] *See* FDA, EMEND (aprepitant) Pharmacology Review, 178 (2003) (describing the results of toxicology studies, including 39-week and 52-week studies in dogs, and concluding that aprepitant "appears to have low toxicity profiles in the rodent and non-rodent animals"), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-549_Emend_pharmr_P4.pdf; FDA, VARUBI Pharmacology Review (2015), 134, 229 (describing findings from a 39-week

84. In addition to these nonclinical studies, tradipitant has been administered to human patients in multiple clinical studies, including Phase 1 and Phase 2 studies of tradipitant for various conditions: one for the treatment of irritable bowel syndrome ("IBS"), one for treatment of social anxiety disorder, two for the treatment of alcohol cravings and dependence, and one for the treatment of chronic pruritus in patients with atopic dermatitis. One of the Phase 2 studies examined the effects of tradipitant compared to placebo in reducing alcohol cravings or alcohol consumption in 183 alcohol-dependent outpatients over 12 weeks.[21] Safety data is available in humans from nine Phase 1 studies and six Phase Ib/II studies in patients and volunteers aged 18 to 65. Overall, 627 people have been treated with tradipitant at various doses. In all of those studies, no deaths have been observed and a total of six serious adverse events were identified in a total of two study subjects, one of whom may have been predisposed to the serious adverse events observed and should have been excluded from study participation based on the protocol's exclusion criteria.[22]

B. Vanda's Initial Phase 2 Clinical Trial of Tradipitant as a Treatment for Gastroparesis

85. On August 17, 2016, Vanda submitted its original protocol for Study 2301, a multicenter, randomized, double-blind placebo-controlled study of subjects diagnosed with gastroparesis. The study was initiated on November 22, 2016.

86. Vanda subsequently submitted several protocol amendments to FDA. Under Protocol Amendment #5, submitted on December 15, 2017, Study 2301 consisted of 150 subjects,

---

toxicity study in cynomolgus monkeys and identifying the highest dose tested, which is approximately 2.9 times the recommended human dose, as the no-observed-adverse-effect-level).

[21] Investigator's Brochure at 18-19.

[22] *Id.* at 92-93.

aged 18-70 years, who were diagnosed with idiopathic or diabetic gastroparesis with moderate to severe nausea. Study 2301 patients were randomized into one of two treatment arms to receive oral capsules of either 85 mg of tradipitant or placebo, and were studied during a 4-week screening phase, followed by a 4-week evaluation phase. The primary endpoint in Study 2301 measured change from baseline to Day 28 in average daily individual nausea severity scores.

87. On April 10, 2018, Vanda submitted Protocol Amendment #6 for FDA's review to extend Study 2301 to add a 52-week, open-label extension period. In addition to providing scientifically valuable information on the effect of tradipitant in patients with gastroparesis, Vanda sought the extension, among other reasons, because patients and clinicians were requesting that Vanda continue the study due to patients' desire to stay on the drug as a direct result of the relief they had experienced in the study and the lack of alternative treatments.

88. The submission included, among other materials, a survey examining the burdens, concerns, and quality of life of 1,423 adults in the general community diagnosed with gastroparesis. The survey contained responses about participant symptoms and severity, as well as treatments and satisfaction with treatments for gastroparesis. The submission also included a letter from a patient currently enrolled in the tradipitant study voicing strong support for the open-label extension. This patient explained that tradipitant had changed his life by allowing him to "go from taking multiple doses of rescue medications for nausea to only taking 4 over the course of a month" and allowing him to "go back to playing rugby and going to the gym, which was incredible."[23]

89. During a May 14, 2018 teleconference with Maureen Dewey, FDA's Senior Regulatory Project Manager assigned to Study 2301, about the possibility of an open-label

[23] Letter from Anonymous to FDA (July 28, 2017).

extension, Vanda informed FDA that the company had already completed both a three-month canine chronic toxicity study and a six-month rat chronic toxicity study of tradipitant, both of which supported tradipitant's safety for human use. During this teleconference, FDA did not ask whether Vanda had completed any other chronic toxicity studies, and agreed to a subsequent discussion the following day.

C. FDA's Nine-Month Study Requirement and Reliance on the ICH Guidance

90. During a May 15, 2018 teleconference involving Dr. Lisa Soules, Associate Director for the Division, and Dewey, FDA informed Vanda that, despite the extensive toxicity and other nonclinical data collected for tradipitant, the Division would require Vanda to complete a repeated-dose non-rodent toxicity study lasting nine months before FDA would permit Vanda to conduct human dosing on tradipitant for more than three months. FDA cited the nine-month study as a "requirement" under the ICH Guidance. During the call, Vanda asserted that the ICH guidance is a recommendation only, but FDA made clear that, if Vanda did not agree to conduct the nine-month study, FDA would place a clinical hold on Vanda's proposed open-label extension.

91. When Vanda told FDA it intended to pursue formal dispute resolution procedures in order to object to a clinical hold, no one at FDA informed Vanda that when it submitted an amended protocol limiting treatment to no longer than three months, it would be forfeiting its right to challenge FDA's position regarding the 9-month nonclinical rodent study "requirement" through the formal dispute resolution process.

92. Although Vanda strongly disagreed with FDA's decision, on May 22, 2018, Vanda submitted an amended protocol limiting Study 2301 to a treatment duration of no longer than three months in order to avoid being placed on clinical hold and jeopardizing not only Protocol Amendment #6 but the entirety of Study 2301. Vanda did so based on the persistent insistence from FDA that Vanda withdraw Protocol Amendment #6 as soon as possible.

93. On May 24, 2018, FDA sent Vanda a letter agreeing to the amendment. The letter stated that while Vanda's proposed modification was "accepted based on the currently available nonclinical data," FDA would consider imposing a "clinical hold under 21 CFR 312.42" should Vanda again seek to extend the protocol to provide tradipitant to human subjects for longer than three months based on the view that, because Vanda had not completed the nine-month study recommended by the ICH Guidance, Vanda necessarily lacked "adequate nonclinical safety data to support clinical trials beyond 3 months duration."

94. Understanding that the FDRR process was the prescribed method for challenging the agency's reliance on the ICH Guidance, Vanda worked diligently to contest the underlying basis of FDA's assertions in both the May 15 teleconference and May 24 letter. Vanda proceeded to work with an international law firm with a highly regarded FDA law practice over the next several months to prepare an FDRR challenging FDA's position.

95. On August 1, 2018, Vanda submitted the FDRR to FDA. The FDRR explained that tradipitant's safety profile is supported by a wealth of data from toxicity, nonclinical, and clinical studies. The FDRR also showed that the scientific community has recognized that nine-month animal studies are unlikely to demonstrate any adverse health effects not seen in shorter studies. Furthermore, the FDRR articulated the view that companies and FDA alike have a moral imperative to limit studies requiring the death of animal participants.

96. On August 16, 2018, FDA rejected the FDRR on the ground that a request for formal dispute resolution was not appropriate "at this time" because a protocol for a clinical trial exceeding three months in duration "has not been submitted to [Vanda's] application."

97. On September 26, 2018, Vanda submitted a new clinical study protocol, the Study 2302 protocol, to FDA in yet another effort to engage with FDA on the underlying science behind

tradipitant and the good faith reasons Vanda believed the nine-month non-rodent toxicity study FDA claimed to be required by the ICH Guidance was not warranted. Like the proposed extension to Study 2301, Study 2302 is a planned twelve-month open label extension study of tradipitant in patients with gastroparesis who were previously enrolled in Study 2301. Vanda submitted Study 2302 due to its concern that FDA might impose a clinical hold that would apply to Study 2301 in its entirety (as opposed to just the proposed extension).

98. Because, under 21 C.F.R. § 312.30(a), a new protocol to an existing IND can be implemented immediately upon its submission to FDA, provided the sponsor ensures adherence to other FDA requirements for clinical trials, CDER has established within its internal Manual of Policies and Procedures ("MAPP") a section that provides a process for the agency to conduct a quick review of such protocols for potential safety issues that might warrant the imposition of a hold.[24] The MAPP states that, within seven business days of receipt of a new phase 2 protocol, "a [r]eviewer [or] team leader should screen [the submission] to determine priority status; potential clinical hold issues; and need for consult [with] quality, clinical pharmacology (including pharmacogenomics and pharmacometrics), or other disciplines." MAPP 6030.9 at 37. To the extent a written safety or efficacy review is needed, the MAPP recommends a 60-day review period and communication with the sponsor as needed during that period. *Id.* Under the MAPP, a protocol change should be reviewed within 30 days for safety issues, and within 60 days for development concerns, and written reviews are recommended by the appropriate discipline(s) for

[24] *See* CDER Manual of Policies and Procedures (MAPP) 6030.9, *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review* (Effective Date 04/29/13) ("MAPP 6030.9") https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM349907.pdf.

safety concerns as well as other changes, with communication with the sponsor on an as needed basis. *Id.* at 38.

99. FDA did not respond to Vanda's submission of Study 2302 for almost 90 days, strongly signaling that FDA did not have specific concerns with Vanda's proposal. Assuming FDA followed its own good review practices, as outlined in the MAPP, had FDA been significantly concerned about safety, such concerns should have been caught within the seven day screening period, and a hold communicated to VANDA promptly, so that study subjects would not be unnecessarily put at risk.

100. In November 2018, Vanda contacted FDA via email to confirm that FDA was comfortable with the extension study, because there was no reason to begin study implementation if a clinical hold was imminent. Dewey inquired in response as to how many individuals were participating in Study 2302, implying that FDA by then believed the new protocol was already ongoing.

101. Assuming FDA had changed its mind and no longer had concerns about safety, because no hold had issued and Dewey seemed to think the study had already been initiated, Vanda submitted a protocol amendment on December 11, 2018, to add a 12-month open label extension to Study 2301. As amended, the open label extension phase of Study 2301 is similar to Study 2302 in structure, visit number, and in efficacy and safety assessments measured.

D. Vanda's Arguments that the Nine-Month Study is Unnecessary

102. Throughout its engagement with FDA, including by telephone and in its August 1 FDRR, Vanda has sought to engage substantively with FDA on the underlying science and ethics motivating the nine-month study recommendation. Vanda has repeatedly explained to FDA that the science does not support the view that an additional, nine-month non-rodent study would lead to the discovery of additional toxicities that would be relevant to humans, and that if FDA were to

insist on additional canine studies, Vanda would like the opportunity to present a study option that would result in less animal sacrifice than the protocol demanded by FDA.

103. Extensive nonclinical studies, including toxicity studies, have been conducted with tradipitant and other NK-1 inhibitors. These studies include a single-dose toxicity study in rats, a thirteen-week repeat-dose toxicity study in mice, definite one-, three-, and six-month repeat-dose toxicity studies in rats, definitive one-and three-month repeat-dose toxicity studies in dogs, a fertility and embryo-fetal development study in rats, and an embryo-fetal development study in rabbits. Both the six-month rat study and the three-month dog study included clinical examinations, physical examinations, neurological evaluations, and complete necropsies for all animals. The three-month dog study also included urinalysis evaluations and measured electrocardiograms and heart rates for animals in the study. In all of these studies, no treatment-related mortality or marked toxicity were observed up to, and including, a dosage level approximately 300 times the highest dosage level contemplated for administration to humans in the open-label extension study that is currently on hold.[25]

104. The toxicity profiles seen in rodents and non-rodents from the studies described above were limited and similar to each other, as evidenced through the six-month rat and three-month canine studies. The lack of significant safety findings in these studies was consistent with results of chronic toxicity studies in approved NK-1 antagonists, aprepitant and rolapitant, which did not identify any clinically relevant toxicity with those compounds, as evidenced by the absence of information on chronic toxicity studies in these products' FDA-approved labeling.[26] And, the

[25] *See* Investigator's Brochure at 43-63.

[26] *See* EMEND® (aprepitant) U.S. Prescribing Information § 13.1 (2017); VARUBI® (rolapitant) U.S. Prescribing Information § 13.1 (2018); *see also supra* n.18.

tradipitant toxicity studies for gastroparesis are also consistent with the favorable safety profile shown in the fifteen studies that have been conducted with tradipitant to date in humans, including those for other indications.[27]

105. In addition, since FDA's initial adoption of the ICH Guidance in 1997, *see* 62 Fed. Reg. 62922, studies evaluating preclinical animal toxicity studies have found limited additional benefit for long-term toxicity studies in canines. A study analyzing 117 compounds found that, in the large majority of cases analyzed, long-term toxicity studies in canines provided little qualitatively new toxicological information not already gained from a short-term study in canines in conjunction with short- and long-term studies in rodents.[28] Scientific papers have confirmed the limited utility of animal studies generally in predicting toxicity in humans.[29] Furthermore,

---

[27] *See* Investigator's Brochure at 92.

[28] *See* C. Parkinson et al., *The Value of Information Generated by Long-Term Toxicity Studies in the Dog for the Nonclinical Safety Assessment of Pharmaceutical Compounds*, 25 Fundamental and Applied Toxicology (1995); *see also* A. Galijatovic-Idrizbegovic et al., *Role of Chronic Toxicology Studies in Revealing New Toxicities*, 82 Regulatory Toxicology & Pharmacology (2016) (authors reviewed 32 chronic toxicity studies in non-rodents and 27 such studies in rats dosed with Merck compounds to determine the frequency at which additional organ toxicities were observed in the chronic studies as opposed to the sub-chronic studies and concluded that all but six of non-rodent studies failed to identify toxicities not already identified in sub-chronic studies. Of the six chronic non-rodent studies where new toxicities were found, for three of the compounds, the toxicities found did not prevent further clinical development of the drug; Jerrod Bailey et al., *An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety*, 41 ALTA 335-350 (2013) (authors calculated likelihood ratios (LRs) for an extensive dataset of 2,366 drugs with both animal and human data, and found that the absence of toxicity in dogs provided little likelihood that adverse effects would not be seen in humans, that dogs are highly inconsistent predictors of toxic responses in humans, and that the predictions they provide are little better than those that could be obtained by chance.)

[29] Jerrod Bailey et al., *An Analysis of the Use of Animal Models in Predicting Human Toxicology and Drug Safety*, 42 ALTA 181-199 (2014) (authors calculated likelihood rations (LRs) for 2366 drugs with animal (rat, mouse and rabbit) and human data and concluded that the LRS showed that the "absence of toxicity in the animal provides little or virtually no evidential weight that adverse drug reactions will also be absent in humans; and b) that, while the presence of toxicity in these species can add considerable evidential weight for human risk, the LRs are extremely inconsistent, varying by over two orders of magnitude for different classes of compounds and their effects.");

FDA itself has recognized the need to better understand the utility of animal data and to develop new and better ways to predict toxicity in humans, though it has done little to work with companies like Vanda to accomplish this objective.[30] Indeed, in contrast to the EPA's regulatory reforms in this area, FDA has routinely continued to require sponsors to conduct 9-month toxicity studies in non-rodent species and sacrifice those animals at the conclusion of the study.

106. In the context of tradipitant's safety profile and the significant efficacy findings associated with tradipitant, FDA had no scientific or regulatory basis to insist upon a chronic nine-month non-rodent toxicity study as a condition for lifting the Clinical Hold. Even the ICH Guidance, which FDA impermissibly relied upon as though it were a regulation, contemplates exceptions to the nine-month study requirement. Yet FDA never gave Vanda's request for such an exception serious consideration, and articulated no scientific basis for its refusal relative to the existing data for tradipitant.

107. In light of the significant and positive preclinical and clinical efficacy and safety findings regarding tradipitant, increasing scientific evidence supporting the limited value of chronic studies in uncovering new toxicities relevant in humans, and FDA's refusal to provide Vanda with a scientifically justified rationale for conducting an additional study that would result

---

Robert A.J. Matthews, *Medical Progress Depends on Animal Models-Doesn't It?*, 101 Journal of the Royal Society of Med. 95-98 (2008) (questions the statistical methods used in certain previous studies to support claims that animals models were likely to predict toxicity in humans).

[30] *See, e.g.,* Janet Woodcock & Raymond Woolsey, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 Annual Review of Med. 1-12 (2008) ("Animal toxicology tests are very useful for assessing safety for initial human testing; however, they often fail to uncover the types of toxicities seen after widespread human exposure . . . "); FDA, Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Technologies (2004) ("Although traditional animal toxicology has a good track record for ensuring the safety of clinical trial volunteers, it is laborious, time-consuming, requires large quantities of product, and may fail to predict the specific safety problem that ultimately halts development . . . Conversely, some models create worrisome signals that may, in fact, not be predictive of a human safety problem.")

in the sacrifice of all participating dogs, Vanda determined that moving forward with the nine-month chronic canine study FDA demanded based on the ICH Guidance would be unethical. In addition, it would be significantly at odds with the 3Rs (Replacement, Reduction and Refinement) framework for more humane animal research, which Congress embraced in establishing the Interagency Coordinating Committee on the Validation of Alternative Methods ("ICCVAM"), of which FDA is a statutorily required member, to "reduce, refine, or replace the use of animals in testing, where feasible." 42 U.S.C. § 285l-3(b)(5).

108. Among other things, Vanda requested permission to design and run a non-rodent study in parallel with a 6-month to 1-year open label extension to Study 2301 in which non-rodents not exhibiting signs of toxicity would not be sacrificed, or, if sacrifice was mandated, that FDA permit the use of a significantly lower number of dogs.[31] FDA refused to entertain such a protocol. Instead, as noted above, FDA's one suggested "option" was to require the death of yet more dogs, in violation of Vanda's ethical commitment to the humane treatment of animals.

E. FDA's Clinical Hold and Rejection of Vanda's Appeal to Superior Agency Authority

109. Following Vanda's submission of the protocol for Study 2302, Vanda responded to requests for additional information by FDA. For example, on October 12, 2018, Vanda provided the final report on Lilly's Phase 1b clinical study of tradipitant as a treatment for IBS.

110. On December 3, 2018, Vanda forwarded to FDA an announcement of the topline results for Study 2301. Those results indicated that tradipitant met the primary endpoint of the study, and was well tolerated, with comparable rates of adverse events between the study participants receiving tradipitant and those receiving placebo.

[31] FDRR at 7.

111. Then, on December 19, 2018, FDA informed Vanda during the Clinical Hold Call that both protocols (2301 and 2302) had been placed on partial clinical hold. During that teleconference, Dr. Lisa Soule at CDER explained to Vanda that FDA had no concerns about the clinical data or studies that Vanda had presented with respect to tradipitant. Instead, FDA's sole concern was that Vanda had not complied with FDA's demand that Vanda conduct an additional, nine-month toxicity study in a non-rodent species. Dr. Soule stated that this additional study was a requirement imposed by the ICH Guidance, and that Vanda had not complied with that requirement.

112. FDA followed the Clinical Hold Call with the Clinical Hold Letter, issued on December 21, 2018, as required by regulation to provide a written explanation of the clinical hold it had initially communicated orally. 21 C.F.R. § 312.42(d). The Clinical Hold Letter stated that both Study 2301 and Study 2302 were put on clinical hold to the extent they have a duration longer than 3 months. The Clinical Hold Letter also noted that the Division had discussed Vanda's concerns with FDA's MPPRC, and that FDA as an agency was in agreement that "non-rodent toxicity studies of 9-months duration ***are required*** for the conduct of [Vanda's] proposed clinical investigations of 52 weeks (12 months) duration, ***per*** the ICH [Guidance.]" Clinical Hold Letter at 2 (emphases added).

113. The Clinical Hold Letter further explained that "[t]he rationale to support the ICH requirement for the nine-month duration for non-rodent toxicity studies is summarized in the following publication: DeGeorge JJ, Meyers LL, Takahashi M, Contrera JF. *The duration of non-rodent toxicity studies for pharmaceuticals. Toxicol Sci 1999; 49: 143-155*, which noted that later toxicologic findings have been observed in the absence of earlier toxicologic findings." FDA did

not explain its conclusion that this *possibility* justified the imposition of a clinical hold, as opposed to a being a review issue for FDA to consider once it had full data available.

114. The Clinical Hold Letter did not acknowledge or address the scientific arguments raised by Vanda, or Vanda's request that the agency apply the ICH Guidance's exception to the nine-month canine toxicity study requirement. Nor did it square its reflexive treatment of the nine-month study as a requirement with the recognition in the article cited therein that "[s]ome flexibility was still felt to be necessary, since in some cases, shorter duration studies (less than 9 months) might be adequate to detect relevant toxicities[.]" DeGeorge et al., 49 Toxicological Sci. at 154 (1999).

115. While FDA offered Vanda the "potential option" of conducting a staggered canine toxicity study chronologically ahead of the clinical trial, a nine-month study would ultimately still be required, and "that option would require inclusion of additional animals to provide for interim sacrifice" to stay ahead of the clinical trial. Clinical Hold Letter at 2.

116. The Clinical Hold Letter made clear that FDA would give Vanda only one of two feasible choices. Either Vanda would "submit satisfactory results from a chronic toxicology study of 9 months duration in a non-rodent species, ***per ICH M3(R2) guidance*** prior to conducting a clinical trial exceeding 3 months (2 weeks in duration)," or Vanda's clinical studies of tradipitant as a potential treatment option for gastroparesis would be at an end. *Id.* (emphasis added).

117. Because FDA had not responded to any of Vanda's showings of why a nine-month study should not be required, on December 21, 2018, Vanda responded to the Clinical Hold Letter by requesting reconsideration from Janet Woodcock, M.D., the Director of CDER, and Defendant Dr. Gottlieb. Vanda once again reiterated tradipitant's well-documented safety profile and the

more recent retrospective studies questioning whether an extended canine toxicity study was likely to find any significant safety data beyond that found in a three-month study.

118. Vanda further noted that FDA's rote reliance on the ICH Guidance reflects arbitrary decisionmaking and improper treatment of the ICH Guidance as a de facto regulation mandating nine-month non-rodent toxicity studies without complying with notice-and-comment rulemaking requirements.

119. On January 4, 2019, Dr. Peter Stein, Director of CDER's Office of New Drugs, communicated by telephone to Vanda's Chief Executive Officer about Vanda's communication. Dr. Stein explained that he had conferred with Dr. Woodcock about Vanda's concerns. He stated that Vanda's question as to whether the additional nine-month study would yield any additional information that would be meaningful from an FDA regulatory decisionmaking perspective was a thoughtful one, but that FDA would not change its position. Dr. Stein also stated that FDA had considered granting a waiver to Vanda based on its safety data but had decided not to do so because this would imply FDA was changing its policy on the issue.

F. The Partial Clinical Hold's Impact on Vanda's Clinical Program for Tradipitant and its Patients

120. Due to the Clinical Hold, Vanda is unable to continue the open-label portion of Study 2301 beyond 8 weeks. The final patient in Study 2301 completed the 8-week open-label extension on January 7, 2019. Vanda also is unable to commence Study 2302. As a result, the Clinical Hold currently is preventing any patients from receiving tradipitant in either Study 2301 or Study 2302. These patients are directly harmed by FDA's action, as tradipitant is the only option for treating their symptoms of gastroparesis that does not pose the risk of severe side effects.

121. Moreover, Vanda will be forced to conduct what it believes is an unethical and scientifically unnecessary nine-month animal study that would require the company to needlessly

undertake the kind of unjustified killing of dogs that other federal agencies have moved away from. FDA's offer of a potential option, whereby Vanda could conduct a staggered animal study chronologically ahead of the clinical, open-label extension studies, would require killing even more dogs due to the need for interim sacrifice. FDA's presentment of this "potential option" is particularly troubling given that the science has shown that such a study would be extraordinarily unlikely to yield *any* meaningful safety information. Naturally, Vanda could not agree to such an ethically repugnant proposal.

LEGAL ARGUMENTS

A. FDA's Imposition of the Clinical Hold Represents Final Agency Action

122. FDA's imposition of the Clinical Hold represents reviewable, final agency action.

123. **First**, the Clinical Hold marks "the 'consummation' of the agency's decision-making process." *Bennett v. Spear*, 520 U.S. 154, 177-78 (1997) (quoting *Chicago & S. Air Lines, Inc. v. Waterman S.S. Corp.*, 333 U.S. 103, 113 (1948)). The Clinical Hold clearly demonstrates that FDA will not allow Vanda to proceed with its proposed open-label extension study without conducting an additional nine-month study, as FDA takes the position that there is a binding "ICH ***requirement*** for the 9-month duration for non-rodent toxicity studies[.]" Clinical Hold Letter at 2 (emphasis added).

124. Indeed, FDA has explicitly refused to reconsider the Clinical Hold. Although Vanda requested reconsideration by Dr. Woodcock, the CDER Director, Dr. Stein communicated that, after consultation with Dr. Woodcock, Vanda's request would not be granted. In each instance, FDA has explicitly treated the ICH Guidance as a "requirement" from which agency officials were not free to depart.

125. The decision underlying the Clinical Hold is therefore not "tentative, open to further consideration, or conditional on future agency action." *City of Dania Beach, Fla. v. FAA*, 485

F.3d 1181, 1187-88 (D.C. Cir. 2007). Instead, the view expressed in the Clinical Hold Letter and denial of rehearing that the ICH Guidance imposes binding legal requirements on regulated parties "admit[s] of no ambiguity" and gives "no indication that [this view is] subject to further agency consideration or possible modification." *Ciba-Geigy Corp. v. EPA*, 801 F.2d 430, 436-37 (D.C. Cir. 1986).

126. FDA's pattern of behavior throughout 2018 further supports the conclusion that the Clinical Hold represents the consummation of its decision making process. Time after time, Vanda has sought to substantively engage with FDA on issues ranging from the science underlying the ICH Guidance's nine-month study recommendation to Vanda's sincere desire to limit any inhumane and needless sacrifice of animals in support of unnecessary testing. Time after time, and most recently in Vanda's January 4 discussion with Dr. Stein, FDA has simply stated that it will not diverge from its interpretation of the ICH Guidance as establishing a binding requirement.

127. The fact that the Clinical Hold Letter suggests that Vanda may "discuss a path forward with the Division," Clinical Hold Letter at 2, does not detract from the finality of the decision Vanda challenges. FDA has made clear that the leadership of CDER will not reconsider the agency's position requiring a nine-month study, and further discussions with the same individuals who have stonewalled Vanda for months would simply be about ways that Vanda could undertake that nine-month study, including by a phased approach involving the sacrifice of more animal subjects. "The mere possibility that an agency might reconsider in light of 'informal discussion' and invited contentions of inaccuracy does not suffice to make an otherwise final agency action nonfinal." *Sackett v. EPA*, 566 U.S. 120, 127 (2012).

128. Indeed, even in cases—unlike this one—where an agency has clearly "issued no formal decision," there is final agency action where an agency "has clearly communicated" its

refusal to reach a determination and instead "[places a regulated party] in a holding pattern—preventing [it] from obtaining any explicitly final determination." *Friedman v. FAA*, 841 F.3d 537, 542 (D.C. Cir. 2016). In *Friedman*, as here, there was final agency action because the agency's "actions suggest [it] has made up its mind, yet it seeks to avoid judicial review by holding out a vague prospect of reconsideration." *Id.* at 543.

129. **Second**, the Clinical Hold also is an agency action "by which 'rights or obligations have been determined.'" *Bennett*, 520 U.S. at 178 (citation omitted).

130. The Clinical Hold plainly affects Vanda's rights and obligations, as it makes clear that until Vanda conducts a further nine-month study, it "may not legally conduct the identified clinical studies [2301 or 2302] under this IND[.]" Clinical Hold Letter at 2 (emphasis added).

131. Absent the Clinical Hold, Vanda would be permitted to continue studying tradipitant. *See* 21 C.F.R. § 312.40(b)(1) ("An IND goes into effect . . . [t]hirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold"). And, Vanda is on plain notice that it may face legal or enforcement action should it proceed without receiving FDA approval.

132. Accordingly, the Clinical Hold "'imposes an obligation, denies a right or fixes [a] legal relationship.'" *Nat'l Ass'n of Home Builders v. U.S. Army Corps of Eng'rs*, 417 F.3d 1272, 1278 (D.C. Cir. 2005) (quoting *Reliable Automatic Sprinkler Co. v. Consumer Prod. Safety Comm'n*, 324 F.3d 726, 731 (D.C. Cir. 2003)). As in past cases, there is "little question" that there is final agency action where Vanda has received a "letter [that] clearly made a legal determination that" its desired activities were unauthorized "and ordered that these operations *must* cease." *Bimini Superfast Operations LLC v. Winkowski*, 994 F. Supp. 2d 106, 114 (D.D.C. 2014) (emphasis in original) (internal quotations omitted).

133. As Vanda's suit is under the APA, "an appeal to 'superior agency authority'" would only be "a prerequisite to judicial review . . . when expressly required by statute or when an agency rule requires appeal before review *and* the administrative action is made inoperative pending that review." *Darby v. Cisneros*, 509 U.S. 137, 154 (1993) (emphasis added).

134. Here, the Clinical Hold is in effect immediately. Accordingly, because there is final agency action, FDA's imposition of the Clinical Hold is reviewable now. *Compare DSE, Inc. v. U.S.*, 169 F.3d 21, 27 (D.C. Cir. 1999) (explaining that because a decision by the Small Business Administration was effective immediately, and thus its "decision [was] not rendered inoperative pending appeal to a superior agency authority," pursuing an internal appeal was not required) (internal quotations omitted) *with Marine Mammal Conservancy, Inc. v. Dep't of Agric.*, 134 F.3d 409, 411 (D.C. Cir. 1998) (finding that plaintiff was required to exhaust internal remedies *because* the relevant regulation "suspend[ed] the finality of ALJ decisions pending appeal to that judicial officer.").

B. FDA's Reflexive Reliance on a Non-Binding Guidance Document is in Excess of its Statutory Authority

135. Under the FDCA, FDA may impose a clinical hold in only one of two prescribed circumstances.

136. First, FDA may impose a clinical hold if "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved." 21 U.S.C. § 355(i)(3)(B)(i).

137. To invoke its authority under this provision of the FDCA, the burden is on the FDA to make an Unreasonable Risk Determination for imposing a clinical hold, based on a specified

analysis of the drug at issue's proposed study design, the disease ("condition") being studied, and the drug's particular safety risk to "the persons who are the subject of the clinical investigation." *Id.* The statutory language makes explicit that a clinical hold imposed under paragraph (B)(i) must be a particularized determination, based on an assessment of the individual facts of the drug and study at issue. It specifies that, in invoking this authority, FDA must "tak[e] into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved[.]" *Id.* There is no such individualized analysis reflected in the administrative record here. FDA's Clinical Hold Letter did not reference any specific concerns with tradipitant or with Vanda's clinical or non-clinical safety data. Indeed, in the Clinical Hold Call on December 19, in which FDA announced that it had imposed the Clinical Hold, Dr. Soule at CDER explained that FDA had "no concerns" with Vanda's data. Accordingly, FDA has not met its burden to impose a clinical hold by making an Unreasonable Risk Determination with respect to tradipitant. *Id.* § 355(i)(3)(B)(i).

138. Alternatively, FDA may impose a clinical hold for "such other reasons as the Secretary may ***by regulation*** establish (including reasons established by regulation before November 21, 1997)." *Id.* § 355(i)(3)(B)(ii) (emphasis added).

139. To invoke its authority under this provision of the FDCA, the burden is on the FDA to establish a broadly applicable substantive rule through notice-and-comment rulemaking. If and only if FDA has established such a regulation, through the statutorily mandated procedures, FDA may then rely on application of that rule to the individual case, rather than the case-specific analysis set forth in paragraph (B)(i).

140. To be sure, in the Clinical Hold Letter, FDA *cited* a regulation as identifying the deficiency that was the basis of its action: "21 CFR 312.42(b)(2)(i): Insufficient information to assess risks to human subjects: because you do not have adequate nonclinical safety data to support clinical trials beyond 3 months." Section 312.42(b)(2)(i) incorporates 21 C.F.R. § 312.42(b)(1)(iv), which in turn allows FDA to impose a clinical hold where the IND application "does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies." As noted above, *see* paras 49-50, *supra*, 21 C.F.R. § 312.23 includes, *inter alia*, a requirement that the IND include "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8). But that regulation disclaims any inflexible rules, stating instead that "[t]he kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations," and refers sponsors generally to "[g]uidance documents." *Id.* Nowhere in any of these regulations has FDA adopted through notice-and-comment rulemaking a substantive rule requiring in all cases a nine-month chronic toxicity study in non-rodent mammals before a study in humans can go beyond ninety days. As reflected in the Clinical Hold Letter itself, that "requirement," to the extent it exists at all, appears only in the ICH Guidance, which has never been adopted as a regulation through notice-and-comment rulemaking.

141. Throughout Vanda's discussions with FDA, FDA has cited the existence of the ICH Guidance as the sole basis for its refusal to allow Vanda to proceed without conducting the nine-month, non-rodent toxicity study. However, the ICH Guidance has not been "by regulation establish[ed]," but is instead a non-binding guidance document. *Id.* Accordingly, FDA cannot

rely on the ICH Guidance as establishing a substantive rule to which sponsors must conform, as contemplated by 21 U.S.C. § 355(i)(3)(B)(ii).

142. Thus, the Clinical Hold fails to satisfy the statutory prerequisites of either 21 U.S.C. § 355(i)(3)(B)(i) or (ii). To the extent FDA contends that it imposed the Clinical Hold due to an Unreasonable Risk Determination with respect to tradipitant, under 21 U.S.C. § 355(i)(3)(B)(i), it acted arbitrarily and capriciously, in violation of the APA, by failing to articulate an adequate scientific basis for that determination or engage with Vanda's scientific arguments to the contrary. To the extent FDA contends that it imposed the Clinical Hold based on standards established "by regulation" under 21 U.S.C. § 355(i)(3)(B)(ii), it acted without observance of procedure required by law, in violation of the APA, because it applied a substantive rule that was never subjected to notice-and-comment rulemaking. FDA may neither rely upon the non-binding ICH Guidance as a binding regulation, nor interpret 21 C.F.R. § 312.42 to incorporate the ICH Guidance's recommendations as binding requirements, without fulfilling its statutory burden to implement the ICH Guidance through requisite notice-and-comment procedures.

143. FDA's reflexive reliance on the ICH Guidance as a binding rule, and the sole basis for its imposition of the Clinical Hold, violates the APA.

COUNT I: THE ADMINISTRATIVE PROCEDURE ACT

FDA's imposition of the Clinical Hold without any consideration of the data or other arguments presented by Vanda is arbitrary and capricious.

144. Vanda hereby incorporates and re-alleges foregoing paragraphs 1–143 as though fully set forth herein.

145. An agency must base its actions "on a consideration of the relevant factors" and "examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n v.*

State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). "An [agency's] failure to respond meaningfully to the evidence renders its decisions arbitrary and capricious." *Tesoro Alaska Petroleum Co. v. FERC*, 234 F.3d 1286, 1294 (D.C. Cir. 2000).

146. Here, as an initial matter, FDA presented no affirmative, situation-specific argument as to why Vanda's proposed 52-week extension presented an "unreasonable risk to the safety of the persons" participating in the study. 21 U.S.C. § 355(i)(3)(B)(i). Its failure to conduct any kind of case-specific analysis, as required by the statutory provision's explicit text, and to instead apply the ICH Guidance in a formalistic, mechanistic manner, is itself arbitrary and capricious.

147. Furthermore, FDA has refused to consider any of the evidence Vanda has presented, including: (1) evidence of tradipitant's significant efficacy in treating symptoms of gastroparesis; (2) data showing the lack of serious safety signals in the many animal studies and fifteen clinical studies already conducted with tradipitant, supporting that, in this specific case, an additional study is unlikely to provide any meaningful additional data with respect to tradipitant's safety profile; (3) analyses questioning the utility of 9-month non-rodent toxicity studies for human drugs generally; (4) the example of the EPA's reform in this area; and (5) concerns about animal welfare issues.

148. Agency action must be set aside where, as here, the agency "has failed to 'examine[] [the] relevant data' or failed to 'articulate[] a rational explanation for its actions." *Genuine Parts Co. v. EPA*, 890 F.3d 304, 311-312 (D.C. Cir. 2018) (quoting *Carus Chem. Co. v. EPA*, 395 F.3d 434, 441 (D.C. Cir. 2005)). Agencies, no matter what decision they ultimately reach, "must examine the relevant data." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. "[A]n agency cannot ignore evidence that undercuts its judgment; and it may not minimize such evidence without

adequate explanation." *Genuine Parts Co.*, at 312; *see also Butte Cty. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010) ("[A]n agency cannot ignore evidence contradicting its position"); *Lakeland Bus Lines, Inc. v. NLRB*, 347 F.3d 955, 963 (D.C. Cir. 2003) (holding that the agency could not rely on a "clipped view of the record" to support its conclusion).

149. Here, FDA failed to respond meaningfully to Vanda's submission of safety information on tradipitant, and failed to respond meaningfully to, or address, the retrospective analyses submitted by Vanda questioning the requirement of an extended canine toxicity study prior to extended clinical testing. Indeed, FDA entirely ignored *all* of the evidence that Vanda presented, and instead applied its overly narrow interpretation of the ICH Guidance as a binding, inflexible rule. Failing to assess properly the costs and benefits of an agency action is precisely "the sort of claim that federal courts routinely assess when determining whether to set aside an agency action as an abuse of discretion." *Weyerhaeuser v. U.S. Fish & Wildlife Serv.*, 139 S. Ct. 361, 371 (2018); *see also Judulang v. Holder*, 565 U.S. 42, 53 (2011) ("When reviewing an agency action, we must assess . . . whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment.") (internal quotation marks omitted). Here, FDA's decision did precisely that. Based on its communications with Vanda, FDA appears to have ignored entirely all of Vanda's counterarguments, and failed to consider the relevant factors specific to tradipitant. (Furthermore, even if FDA were to claim that it *did* consider these points, it failed to provide any reasoned explanation of its decision.) FDA's decision was therefore arbitrary and capricious

150. FDA's arbitrary and capricious refusal to consider Vanda's evidence is illustrated by its unwillingness to even consider applying the exceptions *contemplated by the ICH Guidance*. In particular, the text of the ICH Guidance states that "[i]n some circumstances, clinical trials of

longer duration than 3 months can be initiated, provided that," as is the case here, "the data are available from a 3-month rodent and a 3-month nonrodent study, and that complete data from the chronic rodent and nonrodent study are made available . . . before extending dosing beyond 3 months in the clinical trial." The ICH Guidance further explains that flexibility is particularly appropriate "[i]n circumstances where significant therapeutic gain has been shown." ICH Guidance at 7-8. FDA, however, refused to entertain Vanda's request that the flexibility contained in the ICH Guidance be applied, and instead treated the ICH Guidance as imposing a mandatory, inflexible requirement that nine-month, non-rodent toxicology studies must be conducted in all cases, whether entirely preceding an open-label extension study or run in parallel. It therefore applied the ICH Guidance in an arbitrary and capricious manner.

151. FDA's imposition of the Clinical Hold represents final agency action, and Vanda has no adequate remedy at law.

152. Vanda therefore seeks for the Clinical Hold to be set aside, and for entry of a judgment declaring that FDA's imposition of the Clinical Hold on Vanda's proposed twelve-month clinical trials is in violation of the APA because it is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

COUNT II: THE ADMINISTRATIVE PROCEDURE ACT

FDA's reliance on the ICH Guidance violates the Administrative Procedure Act by treating the ICH Guidance as a legislative rule implemented without notice-and-comment rulemaking

153. Vanda hereby incorporates and re-alleges foregoing paragraphs 1-152 as though fully set forth herein.

154. To the extent FDA contends that it imposed the Clinical Hold based on standards established "by regulation" under 21 U.S.C. § 355(i)(3)(B)(ii), it acted without observance of

procedure required by law, in violation of the APA, because it applied a substantive rule that was never subjected to notice-and-comment rulemaking.

155. The APA requires administrative agencies to publish within the Federal Register a "[g]eneral notice of proposed rulemaking" for substantive rules, and to "give interested persons an opportunity to participate in the rule making[.]" 5 U.S.C. § 553(b), (c); *see also Utility Solid Waste Activities Grp. v. EPA*, 236 F.3d 749, 752 (D.C. Cir. 2001) ("[T]here must be publication of a notice of proposed rulemaking; opportunity for public comment on the proposal; and publication of a final rule accompanied by a statement of the rule's basis and purpose.").

156. A new legal standard is considered substantive if it "adopts a new position inconsistent with existing regulations," *Mendoza v. Perez*, 754 F.3d 1002, 1021 (D.C. Cir. 2014), or "'affect[s] individual rights and obligations,'" *Comm. for Fairness v. Kemp*, 791 F. Supp. 888, 893 (D.C. Cir. 1992) (quoting *Chrysler Corp. v. Brown*, 441 U.S. 281, 302 (1979)).

157. By contrast, notice-and-comment rulemaking is not required for "interpretive rules, general statements of policy, or rules of agency organization, procedure, or practice[.]" *Id.* § 553(b)(A). Unlike substantive rules, interpretive rules do not announce new binding legal standards or affect individual rights and obligations.

158. FDA's regulations explicitly state that its "[g]uidance documents do not establish legally enforceable rights or responsibilities" and "do not legally bind the public or FDA." 21 C.F.R. § 10.115(d)(1). Furthermore, FDA regulations also indicate that regulated parties "may choose to use an approach other than the one set forth in a guidance document." *Id.* § 10.115(d)(2). Guidance documents merely "represent the agency's current thinking." *Id.* § 10.115(d)(3).

159. FDA guidance documents carry disclaimers echoing this regulation. For example, the ICH Guidance itself carries a disclaimer noting that it represents only FDA's "current thinking

on this topic," that the ICH Guidance "does not create or confer any rights for or on any person and does not operate to bind FDA or the public," and that regulated parties may "use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."

160. However, when an agency policy purports to allow discretion but is treated in practice as establishing a binding standard to which regulated parties must conform, courts look past the agency's characterization and find that the rule is substantive. *See, e.g.*, *U.S. Tel. Ass'n v. FCC*, 28 F.3d 1232, 1234-35 (D.C. Cir. 1994); *McLouth Steel Prods. Corp. v. Thomas*, 838 F.2d 1317, 1320-21 (D.C. Cir. 1988); *see also Iowa League of Cities v. EPA*, 711 F.3d 844, 865 (8th Cir. 2013) (agency's "pro forma reference to . . . discretion" was "Orwellian Newspeak").

161. Here, despite its own characterization of the ICH Guidance as non-binding, FDA plainly treated the ICH Guidance as a substantive rule. FDA did so by time and again asserting the binding requirement that Vanda comply with the ICH Guidance prior to moving forward with Vanda's proposed twelve-month clinical trials, including by in conversations with Vanda on May 15 and on the December 19 Clinical Hold Call, and by, in the Clinical Hold Letter, interpreting 21 C.F.R. § 312.42(b)(1)(iv) such that the failure of any investigational drug sponsor to comply with the recommendations contained in the ICH Guidance necessarily means that FDA will find there to be insufficient information to assess the risk of a proposed study.

162. FDA may not legally require regulated parties to comply with the requirements of the ICH Guidance without the ICH Guidance first undergoing notice-and-comment rulemaking. *Cf. Coal. for Common Sense in Gov't Procurement v. U.S.*, 576 F. Supp. 2d 162, 170 (D.D.C. 2008) (finding that the Department of Defense likely violated the APA by imposing new requirements of the National Defense Authorization Act for Fiscal Year 2008 via a "Dear Manufacturer letter and related materials" rather than by regulation).

163. FDA's improper use of the ICH Guidance as a substantive rule is particularly troubling in this case, as, in relying on the ICH Guidance, FDA has essentially obligated U.S. companies like Vanda to comply with international standards at risk of serious legal and financial consequences, and has prioritized harmonizing FDA practices with European and Japanese practices over providing U.S. regulated industry and U.S. patients with the fair notice and an opportunity to be heard that the Constitution and APA require.

164. FDA's treatment of the ICH Guidance as a binding rule also means that the American public has not had the opportunity to critique the adverse public policy consequences of FDA's actions, including the unjustified denial of access to patients who would benefit from the medicines under study and the harm inflicted on the public generally, who unwittingly and indirectly participate in the unnecessary sacrifice of animal study participants.

165. FDA's practice runs contrary not only to its statutory authority and well-established principles of administrative law, but also to broader federal policy. For example, Section 1-20.00 of the Justice Manual, administered by the U.S. Department of Justice, is captioned "Limitation on Use of Guidance Documents in Litigation" and explains that "[c]riminal and civil enforcement actions brought by the Department must be based on violations of applicable legal requirements, not mere noncompliance with guidance documents issued by federal agencies, because guidance documents cannot by themselves create binding requirements that do not exist by statute or regulation." as emphasized in recent Department of Justice pronouncements. U.S. Dep't of Justice, Justice Manual § 1-20.000 (2018).

166. In short, FDA may not legally require regulated parties to comply with the requirements of the ICH Guidance without the ICH Guidance first undergoing notice-and-comment rulemaking. FDA's treatment of the ICH Guidance as a substantive rule that affects the

rights and obligations of Vanda is "without observance of procedure required by law." 5 U.S.C. § 706(2)(D).

167. FDA's imposition of the Clinical Hold represents final agency action, and Vanda has no adequate remedy at law.

168. Vanda therefore seeks for the Clinical Hold to be set aside, and for entry of a judgment declaring that FDA's imposition of the Clinical Hold on Vanda's proposed twelve-month clinical trials is in violation of the APA because of FDA's improper reliance on the ICH Guidance, which FDA treated as a binding, substantive rule, though it had not been subjected to the procedural requirements for adopting such a rule.

PRAYER FOR RELIEF

WHEREFORE, Vanda respectfully requests that this Court enter judgment in its favor and that the Court:

1. Set aside FDA's Clinical Hold on Vanda's proposed twelve-month clinical studies of tradipitant.
2. Declare that the FDA may not, under the FDCA and consistent with the APA, impose a clinical hold on Vanda without making an Unreasonable Risk Determination regarding the proposed clinical trials or relying upon a duly enacted regulation.
3. Award Vanda such other and further relief as the Court may deem just and proper.

Dated: February 5, 2019

Respectfully submitted,

/s/ Douglas Hallward-Driemeier
Douglas Hallward-Driemeier
(D.C. Bar No. 994052)
Gregory H. Levine (D.C. Bar No. 456055)

Beth Weinman*
ROPES & GRAY LLP
2099 Pennsylvania Avenue, NW
Washington, D.C. 20006-6807
(202) 508-4600
Douglas.Hallward-Driemeier@ropesgray.com
Gregory.Levine@ropesgray.com
Beth.Weinman@ropesgray.com

Attorneys for Plaintiff

*Not admitted to practice in the District of Columbia; supervised by Ropes & Gray LLP partners who are members of the District of Columbia Bar.