UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

LIQUIDIA TECHNOLOGIES, INC.,
419 Davis Drive, Suite 100
Morrisville, NC 27560,

Plaintiff,

v.

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

ROBERT M. CALIFF, M.D., in his official capacity as COMMISSIONER OF FOOD AND DRUGS,
10903 New Hampshire Avenue,
Silver Spring, MD 20993;

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, SW,
Washington, DC 20201; and

XAVIER BECERRA, in his official capacity as SECRETARY OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, SW,
Washington, DC 20201,

Defendants.

Case No. 1:24-cv-2428

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Liquidia Technologies, Inc. ("Liquidia") brings this action for declaratory and injunctive relief against Defendants U.S. Food and Drug Administration ("FDA"), Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Department of Health and Human Services ("HHS"), and Xavier Becerra, in his official capacity as Secretary of HHS (collectively, "Defendants" or "FDA"). In support thereof, Liquidia states as follows:

INTRODUCTION

1. Liquidia challenges FDA's unlawful decision to extend market exclusivity to United Therapeutics Corporation ("UTC"), the incumbent manufacturer of a drug for treating pulmonary hypertension called treprostinil, and prohibit competition from Liquidia's Yutrepia, a safe and effective alternative treatment for patients with pulmonary hypertension. FDA's action is contrary to law and arbitrary and capricious. It improperly allows UTC to maintain its decades-long monopoly in violation of clear congressional intent permitting exclusivity only in strictly limited circumstances involving innovation. FDA exceeded its statutory mandate by improperly crediting a single study that fails to justify any exclusivity at all, and by granting UTC broad exclusivity for far more than the "innovation" the study purportedly covered, encompassing unstudied indications, patient populations, drug-device combination products, and formulations. FDA's decision should be vacated, and Liquidia must be allowed to bring Yutrepia to market for the benefit of patients.

2. The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (Sept. 24, 1984) (the "Hatch-Waxman Amendments") amended the Federal Food, Drug, and Cosmetic Act of 1938 ("FDCA") to provide sponsors of new drug applications ("NDA"), under certain conditions, with limited periods of protection from competition for the innovation represented by the sponsor's approved drug. These are known as exclusivity periods.

3. This case involves one specific type of exclusivity in the FDCA, three-year new clinical investigation exclusivity ("NCI exclusivity"), which is afforded only where FDA finds a new clinical investigation essential to the approval of a new drug and that a competitor drug shares the same "conditions of approval." 21 U.S.C. § 355(c)(3)(E)(iii).

4. Notably, the FDCA limits the scope of NCI exclusivity for the new drug solely to the innovative change supported by the "new clinical investigation[]" that was "essential" to the FDA's decision to approve the NDA in the first instance. *Id.* This statutory limitation on the scope of NCI exclusivity serves the congressional purpose of the Hatch Waxman Amendments aimed at encouraging innovation in drug development while also accelerating patient access to affordable alternatives to such drugs through competition. *See AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 85 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (limiting "[NCI] exclusivity for significant innovations" furthers the FDCA's "careful balance between providing exclusivity rights to promote innovation and making generic alternatives available to patients").

5. FDA's decision to award NCI exclusivity to UTC's new drug, Tyvaso Dry Powder Inhalation ("Tyvaso DPI") (the "Exclusivity Decision"), is not supported by any new clinical investigation, as defined and required by the FDCA and FDA regulations. Moreover, FDA's Exclusivity Decision improperly ascribed a broad scope to the "conditions of approval" supported by the one and only study—the BREEZE Study—it cites as "new" in its Exclusivity Decision.

6. The result of FDA's Exclusivity Decision is that, contrary to congressional direction and FDA's own mission of allowing safe and effective products to reach the market, patients suffering from pulmonary hypertension ("PH") will be denied access to an additional safe and effective treprostinil treatment for pulmonary arterial hypertension ("PAH") and pulmonary hypertension associated with interstitial lung disease ("PH-ILD").

7. Liquidia filed an NDA seeking FDA approval for Yutrepia, its dry powder inhalation form of treprostinil to treat patients with PAH, on January 24, 2020, more than a year *before* UTC submitted its NDA for Tyvaso DPI, the drug blocking full approval of Yutrepia, on

April 16, 2021. On July 24, 2023, Liquidia amended its Yutrepia NDA to treat patients with PH-ILD as well.

8. FDA's Exclusivity Decision, and its asserted scope of that NCI exclusivity, block FDA's full approval for Yutrepia's distribution to patients suffering from PAH and PH-ILD, contravene the plain text of the FDCA and FDA regulations, and constitute a final agency action that violates the Administrative Procedure Act ("APA").

9. Liquidia is entitled to declaratory and injunctive relief in the form of (i) a ruling declaring FDA's Exclusivity Decision unlawful because it exceeds FDA's statutory authority; (ii) a vacatur setting aside FDA's Exclusivity Decision; and (iii) preliminary and permanent injunctive relief requiring FDA to grant full approval to Yutrepia's NDA, or at minimum, limiting FDA's Exclusivity Decision to apply only to PAH patients thereby requiring FDA to grant full approval to Yutrepia's NDA for PH-ILD patients.

PARTIES

10. Plaintiff Liquidia is a clinical biopharmaceutical startup that develops life-saving therapies for patients, including those with rare diseases. Liquidia is organized under the laws of the State of Delaware. Its registered office is 251 Little Falls Drive, Wilmington Delaware 19808, and its principal place of business is 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560. The first product developed by Liquidia is Yutrepia, an inhaled dry powder treprostinil formulation that safely and effectively treats patients with two kinds of PH—PAH and PH-ILD. Liquidia is the sponsor for the Yutrepia NDA.

11. Defendant FDA is an administrative agency of the United States government and a component of HHS charged with implementing the FDCA and responsible for the Exclusivity Decision described in this Complaint. FDA's headquarters and principal place of business are

located at 10903 New Hampshire Ave., Silver Spring, MD 20903. Its governmental activities occur nationwide.

12. Defendant Robert M. Califf, M.D., is the Commissioner of Food and Drugs and head of FDA, and is sued in his official capacity only. Commissioner Califf is responsible for administering the FDCA, and for overseeing FDA's actions described in this Complaint. He oversees governmental activities that occur nationwide.

13. Defendant HHS is a cabinet-level department of the United States government that oversees FDA and the actions described in this Complaint. Its headquarters and principal place of business are located at 200 Independence Avenue, S.W., Washington, DC 20201. Its governmental activities occur nationwide.

14. Defendant Xavier Becerra is Secretary of Health and Human Services and head of HHS, and is sued in his official capacity only. Secretary Becerra is ultimately responsible for activities at HHS and FDA, including administering the FDCA, and for overseeing the actions described in this Complaint. He maintains an office and carries out official duties in this district, and he oversees governmental activities that occur nationwide.

JURISDICTION AND VENUE

15. This action arises under and asserts violations of the FDCA, 21 U.S.C. § 301 *et seq.*, and the APA, 5 U.S.C. § 551 *et seq.* The Court has subject-matter jurisdiction of this action pursuant to 28 U.S.C. §§ 1331, 1346, and 1361.

16. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e). HHS is located in this district, and Secretary Becerra maintains his office and performs his official duties in this district.

17. Sovereign immunity has been waived for the declaratory and injunctive relief sought in this Complaint. 5 U.S.C. § 702. This Court is authorized to grant Liquidia's request for declaratory relief pursuant to the Declaratory Judgment Act. 28 U.S.C. §§ 2201–2202.

18. FDA's Exclusivity Decision is a final agency action reviewable under the APA. *See* 5 U.S.C. § 704.

19. This dispute is ripe for judicial review because the issues presented are fit for judicial decision and Liquidia would incur substantial hardship were judicial review withheld.

20. Liquidia has standing to challenge this action because FDA's Exclusivity Decision, and its corresponding decision to deny full approval to Yutrepia, have deprived Liquidia of its right to lawfully distribute Yutrepia to patients nationwide. Had Liquidia received FDA's full approval for Yutrepia on August 16, 2024, as anticipated and required by law, Liquidia would have launched distribution of Yutrepia to patients nationwide within days of FDA's decision. In light of FDA's Exclusivity Decision, Liquidia's inability to distribute Yutrepia, which would have been Liquidia's sole commercial product, is causing irreparable injury to Liquidia and to patients with PAH and PH-ILD. *See* Liquidia, SEC Form 10-Q (Aug. 7, 2024).[1]

GENERAL ALLEGATIONS

I. STATUTORY AND REGULATORY BACKGROUND

21. Under the FDCA, FDA must conclude a new drug is safe and effective before it can be introduced lawfully into interstate commerce. 21 U.S.C. § 355(a). The FDCA contemplates three types of drug applications to FDA for small molecule (*i.e.*, non-biological) drugs: (1) a full NDA under section 505(b)(1) of the FDCA, (2) an abbreviated NDA under section 505(j) of the FDCA, and (3) an intermediate form of NDA under section 505(b)(2) of the FDCA.

[1] *See* https://www.sec.gov/ix?doc=/Archives/edgar/data/1819576/000155837024011206/lqda-20240630x10q.htm.

22. An NDA must include, among other things, adequate studies to show that the drug will be safe, and "substantial evidence" that the drug will be effective under the conditions of use prescribed, recommended, or suggested in its labeling. "Substantial evidence" is a term of art meaning one or more (usually at least two) adequate and well-controlled clinical trials conducted by qualified experts. 21 U.S.C. § 355(d); *see* 21 C.F.R. § 314.126.

23. Under section 505(b)(1) of the FDCA, a sponsor may seek approval for a drug by providing FDA with full reports of investigations of safety and effectiveness. 21 U.S.C. § 355(b)(1). This type of application requires the applicant to conduct clinical and non-clinical studies to demonstrate the safety and effectiveness of the proposed new drug for its intended use.

24. Under section 505(b)(2)'s intermediate pathway (applicable to the Yutrepia NDA), the sponsor may submit an application to change or modify a "listed drug" for which the FDA already has made a finding of safety and effectiveness. 21 U.S.C. § 355(b)(2).

25. While a section 505(b)(2) NDA "must directly demonstrate that the proposed drug product is safe and effective," *Veloxis Pharmaceuticals, Inc. v. FDA*, 109 F. Supp. 3d 104, 108 (D.D.C. 2015), the section 505(b)(2) NDA sponsor need not conduct all the clinical studies itself and can rely, wholly or in part, "on clinical studies that were previously submitted to FDA in support of another drug" by a different sponsor. *Id.* at 109 (modified); 21 U.S.C. § 355(b)(2).[2] This is because, as Congress and FDA have recognized, it is duplicative and wasteful to carry out studies to reiterate what is already known about a drug. Consequently, a section 505(b)(2) NDA contains full reports of clinical studies demonstrating the safety and effectiveness of the proposed

[2] *See also Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, FDA (Feb. 11, 2016), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity (Section 505(b)(2) "expressly permits FDA to rely for approval of an NDA, on data not developed by the applicant such as published literature or the agency's finding of safety and effectiveness of a previously approved drug.").

drug, but differs from a section 505(b)(1) NDA because it may draw on safety and/or efficacy data from previously approved drugs, or from published studies. Section 505(b)(2) NDAs must identify the "listed drug" on which their sponsor relies in seeking approval. 21 C.F.R. § 314.54(a)(1)(iii).

26. After it has reviewed an NDA, FDA typically (1) grants final approval, allowing immediate distribution subject to proper notice and labeling for the drug's approved indication(s); (2) grants tentative approval, indicating that the drug is safe and effective for use but that FDA must delay final approval for some reason, such as due to another drug's ongoing exclusivity period; or (3) provides a complete response letter, in which FDA notifies the NDA sponsor of deficiencies that preclude FDA from approving the NDA in its present form.

27. Under the Hatch-Waxman Amendments, following approval of an NDA, the FDCA allows for a three-year NCI exclusivity period only if specific statutory requirements are satisfied.

28. ***First***, the FDCA requires that the drug's NDA "contain[] reports of new clinical investigations (other than bioavailability studies) . . . conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii).

29. FDA has promulgated regulations implementing this statutory provision. Like the FDCA, FDA regulations exclude bioavailability studies from the clinical investigations eligible for NCI exclusivity. 21 C.F.R. § 314.108(a) (Clinical investigation means "any experiment other than a bioavailability study."). FDA regulations define "bioavailability" as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action." 21 C.F.R. § 314.3.

30. Critically, for purposes of this case, FDA regulations expressly limit what may constitute a "new clinical investigation" to:

> ***[A]n investigation in humans the results of which*** have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and ***do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product***. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

21 C.F.R. § 314.108 (emphases added).

31. ***Second***, FDA must find that those "new clinical investigations" were "essential to the approval of the application." 21 U.S.C. § 355(c)(3)(E)(iii).

32. ***Third***, FDA must "identif[y] the relevant conditions of approval shared between [the drug receiving NCI exclusivity and the competitor drug's NDA]." *Veloxis*, 109 F. Supp. 3d at 120; *see* 21 U.S.C. § 355(c)(3)(E)(iii).

33. As explained in *Veloxis*, FDA's identification of the "conditions of approval" "can be no broader than the innovations presented to the FDA in the new clinical investigations that led to the FDA's approval of the first-in-time 505(b) NDA." *Id.* at 121 n.16.

34. The FDCA also requires a "logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting three-year [NCI] exclusivity." *See AstraZeneca*, 872 F. Supp. 2d at 80.

35. This aligns with FDA's historical interpretation of the limited scope of the term "conditions of approval." *See* FDA, Center for Drug Evaluation and Research ("CDER"), NDA No. 206406 (Envarsus XR) General Advice Letter 21 (Jan. 15, 2015) ("Veloxis Letter"), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206406Orig1s000AdminCorres.pdf ("[C]onditions of approval" means only the "***innovative change*** that is supported by the new clinical investigations" that entitled the first-approved drug to NCI exclusivity) (emphasis added); 1989 Preamble to the Proposed Rule Implementing Title 1 of the Drug Price Competition and

Patient Term Restoration Act, Abbreviated New Drug Application, Proposed Rule, 54 Fed. Reg. 28872, 28899 (July 10, 1989) ("1989 Preamble").[3] And as FDA regulations make clear, "[i]f the innovation is a new use, then exclusivity protects only that labeling claim and ***not the active ingredients, dosage form, or route of administration***." 1989 Preamble (emphasis added).

36. Once FDA has identified the narrow scope of NCI exclusivity derived from the innovative change studied in a new clinical investigation, FDA may only block a competitor's NDA for those specific "conditions of approval" (*e.g.*, indications or patient populations) for which NCI exclusivity was granted.

37. Otherwise, a drug sponsor could simply publish successive "new" studies every three years—with no innovation—showing that a new drug containing the same ingredients functions similarly to its older drugs (whose exclusivity periods have already expired) and demand that FDA tack on another exclusivity period—preserving its monopoly and precluding the very competition the FDCA intended by limiting NCI exclusivity to three years. This is precisely what FDA has unlawfully countenanced in its Exclusivity Decision here.

II. FACTUAL AND PROCEDURAL BACKGROUND

A. Treprostinil Is a Proven Treatment for PH Patients.

38. PH is a condition that causes elevated blood pressure in the pulmonary arteries. The increased strain that this elevated blood pressure places on the right ventricle of the heart can

[3] *See also Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, FDA (Feb. 11, 2016), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity ("Exclusivity provides the holder of an approved [NDA] limited protection from new competition in the marketplace for the innovation represented by its approved drug product.").

lead to right ventricular failure and death.[4] There are many potential causes of PH, and it is a comorbid condition for many other diseases.

39. The identification of various PH subtypes has led to the development of improved and differentiated treatment strategies.

40. PH subtypes are classified into five different groups ("WHO Groups") based on shared histology, pathophysiology, clinical presentation, and treatment strategy, pursuant to a World Health Organization ("WHO") symposium in 2013.

41. FDA considers each of these five WHO Groups distinct diseases or conditions.[5] Thus, a drug approved for one PH indication is not necessarily approved for other PH indications.

42. PAH, also known as WHO Group 1, is characterized by increased mean pulmonary arterial pressure and pulmonary vascular resistance due to changes in pulmonary vasculature. PAH may be idiopathic, heritable, toxin-induced, or caused by other diseases or disorders such as connective tissue disorders and HIV, among other causes.[6] A hallmark of PAH patients is limited exercise capacity.[7]

43. Pulmonary Hypertension Due to Lung Disease and/or Hypoxia, also known as WHO Group 3, is associated with chronic obstructive pulmonary disease ("COPD"), interstitial lung disease ("ILD"), and other pulmonary diseases with similar presentation.[8]

---

[4] *See, e.g.*, J.R. Sysol & Roberto F. Machado, *Classification and Pathophysiology of Pulmonary Hypertension*, CONTINUING CARDIOLOGY EDUCATION (July 27, 2018), https://onlinelibrary.wiley.com/doi/epdf/10.1002/cce2.71.

[5] *Orphan Drug Designation: Disease Considerations*, FDA (last updated Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-designation-disease-considerations.

[6] Sysol & Machado, *supra* note 4.

[7] *See, e.g.*, Robin M. Fowler, Kevin R. Gain & Eli Gabbay, *Exercise Intolerance in Pulmonary Arterial Hypertension*, PULMONARY MEDICINE (June 10, 2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377355/pdf/PM2012-359204.pdf.

[8] Sarah Beshay, Sandeep Sahay & Marc Humbert, *Evaluation and Management of Pulmonary Arterial Hypertension*, PUBMED (Aug. 19, 2020), https://pubmed.ncbi.nlm.nih.gov/32829182/.

44. PH-ILD is a subset of WHO Group 3. Interstitial lung disease describes a group of diseases that cause scarring and inflammation of the lungs, which can result in difficulty breathing and poor exchange of oxygen between the lungs and blood vessels. Arteries in the lungs tighten to allow blood to travel to the areas of the lungs receiving the most oxygen, leading to high blood pressure and ultimately pulmonary hypertension as a result of the interstitial lung disease.

45. Pulmonary hypertension can worsen over time and may lead to heart failure. Both WHO and the New York Heart Association ("NYHA") have a classification system to describe the stages of heart failure based upon patient symptoms when performing physical activities.[9] While the WHO/NYHA classification is separate from the WHO Groups of PH, it is used to further characterize the severity of symptoms experienced by patients with PH, and has been referenced in the approved indications for several UTC treprostinil products.[10]

46. Class I patients have no limitations on physical activity. Patients in Classes II–III are considered to have intermediate heart failure and have limitations in their physical activities. As patients progress from Class II to Class III, they are likely to experience fatigue, shortness of breath, and other symptoms that limit physical activity. Patients in Class IV suffer from symptoms of heart failure even when at rest and physical discomfort with any amount physical activity.

---

[9] *See, e.g.*, *Classes and Stages of Heart Failure*, AMERICAN HEART ASSOCIATION (last reviewed Jun. 7, 2023), https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure.

[10] *See, e.g.*, Orenitram Label at 1 (revised Nov. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203496Orig1s013lbl.pdf ("The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms…"); Tyvaso Label at 1 (revised July 2009), https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022387LBL.pdf ("Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.").

47. Treprostinil is a prostacyclin analog that causes direct vasodilation of pulmonary and systemic vascular beds to reduce pulmonary arterial pressure.[11]

48. FDA has consistently found that treprostinil effectively treats PAH and PH-ILD.

B. UTC Has Enjoyed Over Twenty Years of Market Exclusivity for Its Treprostinil Products to Date.

49. UTC has maintained monopoly power over treprostinil drugs for treatment of PAH and PH-ILD by reformulating treprostinil and splicing the patient populations for the drugs to claim eligibility for successive seven-year orphan drug exclusivity ("ODE") and three-year NCI exclusivity periods spanning more than twenty years.[12]

50. For example, on May 21, 2002, FDA approved UTC's Remodulin (treprostinil) injection for general treatment of PAH (WHO Group 1). The ODE period for Remodulin began on May 21, 2002 and expired on May 21, 2009.[13]

51. While it was enjoying ODE for Remodulin, UTC submitted an NDA for Tyvaso Inhalation Solution on June 27, 2008, and received approval on July 30, 2009, for the treatment of PAH (WHO Group 1) in patients with NYHA Class III symptoms, to increase walk distance.[14]

52. FDA granted an ODE period to UTC's Tyvaso Inhalation Solution (treprostinil) on June 17, 2010, and limited that exclusivity to patients with NYHA Class III symptoms to increase

---

[11] *See, e.g.*, Pegah Zare & Daniel Heller, *Treprostinil*, NATIONAL LIBRARY OF MEDICINE (last updated May 8, 2023), https://www.ncbi.nlm.nih.gov/books/NBK545152/.

[12] Under the Orphan Drug Act and FDA regulations, the FDA may confer a seven-year ODE period for certain drugs that treat rare conditions. A drug that has already been approved for the given disease or condition may not receive ODE again after that ODE period has elapsed. 21 U.S.C. § 360cc; 21 C.F.R. Part 316. ODE is not at issue in this case, except to the extent that it offers context for previous exclusivity periods enjoyed by UTC for treprostinil.

[13] *Search Orphan Drug Designations and Approvals*, FDA ("Orphan Drug Database"), https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=105197 (last accessed Aug. 20, 2024).

[14] FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Approval Letter (July 30, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022387s000ltr.pdf.

walk distance, a subset of PAH (WHO Group 1). The ODE period for Tyvaso Inhalation Solution began on July 30, 2009 and expired on July 30, 2016.[15]

53. The efficacy of inhaled treprostinil was demonstrated by one clinical study, the TRIUMPH 001 study (the "TRIUMPH Study"),[16] submitted in support of the Tyvaso Inhalation Solution NDA.[17] On June 1, 2020, UTC submitted a supplemental NDA for Tyvaso Inhalation Solution to add a new indication for treatment of PH-ILD (WHO Group 3) to improve exercise ability, which FDA approved on March 31, 2021.[18] UTC and FDA subsequently relied on the same TRIUMPH Study to establish the safety and efficacy of Tyvaso DPI for PH-ILD.[19]

54. On December 20, 2013, FDA approved UTC's Orenitram (treprostinil) for treatment of PAH (WHO Group 1), and UTC received ODE for PAH to improve exercise capacity. The ODE period for Orenitram began on December 20, 2013 and expired on December 20, 2020.[20]

55. On October 18, 2019, FDA approved a second ODE period for Orenitram for a subset of WHO Group 1 patients, those treated to delay disease progression only. Notably, while the label for Orenitram states that the drug is indicated to treat PAH (WHO Group 1) to improve exercise capacity based on a study that established effectiveness predominately for patients with

---

[15] *Id*.
[16] Vallerie V. McLaughlin *et al.*, *Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension*, J. AM. COLL. CARDIOL. (May 4, 2010), https://pubmed.ncbi.nlm.nih.gov/20430262/; *see also Clinical Investigation Into Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension (PAH) (TRIUMPH)*, CLINICALTRIALS (last updated Jan. 2, 2024), https://www.clinicaltrials.gov/study/NCT00147199.
[17] *See*, FDA, CDER, NDA No.22-387 (Tyvaso Inhalation Solution) Clinical Review at 20 (Apr. 3, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022387s000MedR.pdf.
[18] FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Supplemental Approval Letter (Mar. 31, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022387Orig1s017ltr.pdf.
[19] *See, e.g.*, FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Multi-Discipline Review at 7, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/022387Orig1s017.pdf.
[20] Orphan Drug Database, *supra* note 13.

WHO functional Classes II–III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue, only this latter patient population, namely those who have disease and are treated to delay disease progression, are covered by Orenitram's second ODE period, which began on October 18, 2019 and ends on October 18, 2026.[21]

56. In addition to these ODE periods, Tyvaso Inhalation Solution and Tyvaso DPI received a three-year NCI exclusivity period limited to treatment of PH-ILD, which expired earlier this year, on March 31, 2024. As UTC represented to investors in an SEC filing, the "three-year [NCI] exclusivity for the treatment of PH-ILD" that "covered both Tyvaso DPI and nebulized Tyvaso [Inhalation Solution] for the treatment of PH-ILD, and precluded the FDA from approving a PH-ILD indication for Yutrepia prior to the expiration of clinical trial exclusivity," had "expired in March 2024." UTC, SEC Form 10-Q (May 1, 2024).[22]

57. Leading up to FDA's Exclusivity Decision granting yet another period of NCI exclusivity to Tyvaso DPI, the UTC's treprostinil drugs (including Tyvaso DPI itself) had finally exhausted all their exclusivity periods that could otherwise bar FDA's full approval of Yutrepia to treat patients with PAH and PH-ILD. FDA nevertheless decided to grant another round of broad NCI exclusivity to Tyvaso DPI covering treatment of both PAH and PH-ILD—duplicating Tyvaso DPI's already-expired NCI exclusivity for PH-ILD.

C. Tyvaso DPI Relied on the Same Data Package as Tyvaso Inhalation Solution to Demonstrate Safety and Effectiveness.

58. Both Tyvaso Inhalation Solution and Tyvaso DPI are administered through oral inhalation. While Tyvaso Inhalation Solution must be used in conjunction with an inhalation system nebulizer that aerosolizes a liquid medication solution into respirable particles, Tyvaso DPI

[21] *Id*.
[22] *See* https://www.sec.gov/ix?doc=/Archives/edgar/data/1082554/000108255424000025/uthr-20240331.htm.

utilizes a different drug delivery mechanism to aerosolize a dry powder formulation of treprostinil into respirable particles. The inhalation system nebulizer for Tyvaso Inhalation Solution is battery powered, so patients periodically charge the battery.[23] To nebulize treprostinil, the system also requires patients to fill a reservoir with water, and relies on ampules with the drug product.[24] Tyvaso DPI on the other hand uses cartridges that deliver treprostinil to a more-compact Tyvaso DPI inhaler compared to the Tyvaso inhalation system and does not require batteries to operate because it is not electronically powered.[25]

59. UTC submitted an NDA for Tyvaso DPI under section 505(b)(1) of the FDCA on April 16, 2021, and received approval by FDA on May 23, 2022 for the treatment of PAH (WHO Group 1) and PH-ILD (WHO Group 3), to improve exercise ability.[26] FDA considered the Tyvaso DPI NDA under section 505(b)(1) because, although it relied on previously-submitted safety and efficacy data submitted to FDA for the Tyvaso Inhalation Solution NDA, UTC owns the rights to all such data such that Tyvaso DPI did not need to apply under the 505(b)(2) pathway.

60. The NDA for Tyvaso DPI consisted of: (1) safety and efficacy data resubmitted from UTC's earlier TRIUMPH Study and the INCREASE Study, which were submitted to FDA with the Tyvaso Inhalation Solution NDA; (2) bioavailability data to justify extrapolation of the previously submitted data for Tyvaso Inhalation Solution to Tyvaso DPI; and (3) the BREEZE Study.[27]

---

[23] *See* Tyvaso Inhalation System Instructions for Use Manual (revised Aug. 2022), https://www.tyvaso.com/pdf/TD300_instructions_for_use.pdf.
[24] *Id.* at 31.
[25] *See* Tyvaso DPI Instructions for Use (revised Nov. 2023), https://www.tyvaso.com/pdf/TYVASO-DPI-instructions-for-use.pdf.
[26] FDA, CDER, NDA No. 214324 (Tyvaso DPI) Approval Letter (May 23, 2022), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/214324Orig1s000ltr.pdf.
[27] Leslie A. Spikes et al., *BREEZE: Open-label clinical study to evaluate the safety and tolerability of treprostinil inhalation powder as Tyvaso DPI™ in patients with pulmonary arterial hypertension*, PULMONARY CIRCULATION 2 (Apr. 12, 2022) (the "BREEZE Study"),

61. The Tyvaso DPI NDA relied upon the TRIUMPH Study and INCREASE Study as evidence of the safety and effectiveness of treprostinil when administered by inhalation.[28]

62. The TRIUMPH Study was a 12-week randomized, double-blind, placebo-controlled study to investigate the efficacy and tolerability of Tyvaso Inhalation Solution in 235 patients with PAH already receiving other PAH treatments. The primary endpoint was the change in 6-minute walk distance ("6MWD") at week 12 compared to baseline.[29] The INCREASE Study was a 16-week randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of Tyvaso Inhalation Solution in 326 patients with PH-ILD. The primary efficacy endpoint was the change in 6MWD at peak exposure of the drug from baseline to week 16.[30]

63. For the Tyvaso DPI NDA, UTC also submitted relative bioavailability data based on (1) the TIP-PH-102 study, a 6-treatment crossover bioavailability study of Tyvaso Inhalation Solution and Tyvaso DPI in 36 healthy subjects, and (2) the BREEZE Study.[31]

64. The BREEZE Study was a three-week open-label study with a primary objective of "evaluat[ing] the safety and tolerability of treprostinil inhalation powder (TreT) in patients currently treated with treprostinil inhalation solution."[32] Secondary endpoints were assessment of

---

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9063953/pdf/PUL2-12-e12063.pdf; *see also Open-label, Clinical Study to Evaluate the Safety and Tolerability of TreT in Subjects With PAH Currently Using Tyvaso (BREEZE)*, CLINICALTRIALS (last updated Jan. 24, 2024), https://clinicaltrials.gov/study/NCT03950739?term=BREEZE&cond=PAH&rank=1.

[28] FDA, CDER, NDA No. 214324 (Tyvaso DPI) Clinical Review 10 ("Tyvaso DPI Clinical Review"), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214324Orig1s000MedR.pdf.

[29] Vallerie V. McLaughlin *et al.*, *supra* note 16.

[30] Aaron Waxman *et. al.*, *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, NEW ENGLAND J. OF MED., Vol 384(4) (Jan 13, 2021), https://www.nejm.org/doi/full/10.1056/NEJMoa2008470; *see also Safety and Efficacy of Inhaled Treprostinil in Adult PH with ILD Including CPFE*, CLINICALTRIALS (last updated July 27, 2022), https://www.clinicaltrials.gov/study/NCT02630316.

[31] *Id.* at 18.

[32] The BREEZE Study, *supra* note 27.

pharmacokinetics following administration, efficacy based upon 6MWD and patient evaluation of PAH symptoms, and a preference questionnaire.[33] Of the 51 patients enrolled, 49 completed the three-week treatment phase. Notably, the study excluded patients diagnosed with PH for reasons other than PAH (WHO Group 1), such as PH-ILD patients.[34]

65. The BREEZE Study failed to produce clinically-valid findings because it was an open-label study with a number of patients too small to render statistically-significant results. To the extent the BREEZE Study offered any observations, they were duplicative of the prior studies. For example, the BREEZE Study observed that adverse events ("AEs") were "consistent with studies of [Tyvaso Inhalation Solution] in patients with PAH, and there were no study drug-related serious AEs." FDA's clinical review of Tyvaso DPI also observed the prevalence of AEs in the BREEZE Study was similar to those reported in the TRIUMPH Study.[35] Crucially, FDA's review expressly noted that UTC and FDA did not rely at all on the BREEZE Study to establish Tyvaso DPI's efficacy, which was already assumed given the prior studies.[36] As FDA's Tyvaso DPI clinical review made clear: Other than the TRIUMPH and INCREASE Studies submitted with the Tyvaso Inhalation Solution NDA, "[n]o additional evidence for effectiveness was submitted as part of the [Tyvaso DPI NDA]."[37]

66. The most charitable reading of the BREEZE Study is that PAH patients already using stable dosing of Tyvaso Inhalation Solution faced no worse outcomes for the first three weeks when switching to equivalent doses of Tyvaso DPI. This is not an "innovative change" warranting exclusivity under the statute and FDA regulations.

---

[33] *Id.*
[34] *Id.*; BREEZE Clinical Trials, *supra* note 27.
[35] *Id.*
[36] Tyvaso DPI Clinical Review, *supra* note 28, at 12.
[37] *Id.*

67. It is undisputed that the Tyvaso DPI NDA included no new clinical investigations involving patients with PAH who did not switch from Tyvaso Inhalation Solution, and no new clinical investigations involving patients with PH-ILD.

68. Tyvaso Inhalation Solution and Tyvaso DPI previously received three-year NCI exclusivity limited to treatment of PH-ILD, which began on March 31, 2021, and expired three years later, on March 31, 2024. According to UTC's SEC filing from earlier this year, the "three-year [NCI] exclusivity for the treatment of PH-ILD . . . covered both Tyvaso DPI and nebulized Tyvaso [Inhalation Solution] for the treatment of PH-ILD, and precluded the FDA from approving a PH-ILD indication for Yutrepia prior to the expiration of clinical trial exclusivity." That NCI exclusivity period, according to UTC, "expired in March 2024." UTC, SEC Form 10-Q (May 1, 2024).[38]

D. Liquidia's NDA for Yutrepia and Related Litigation.

69. On January 24, 2020, long before UTC filed its Tyvaso DPI NDA, Liquidia submitted to FDA NDA 213005 for Yutrepia (treprostinil inhalation powder) for treatment of PAH. Per section 505(b)(2) of the FDCA, the Yutrepia NDA referenced the previously-submitted safety data from Tyvaso Inhalation Solution in support of its NDA. The Yutrepia NDA relied on no other listed drug in its NDA.

70. Liquidia also conducted its own clinical investigations, including two Phase 1 studies in healthy volunteers, as well as a Phase 3, open-label, multicenter trial (the "INSPIRE Study"), which assessed the safety and tolerability of Yutrepia both in patients (1) new to prostacyclin therapy, and (2) those transitioning from Tyvaso Inhalation Solution.[39]

---

[38] *See supra* note 22.

[39] Nicholas S. Hill *et al.*, *INSPIRE: Safety and Tolerability of Inhaled Yutrepia (treprostinil) in Pulmonary Arterial Hypertension (PAH)*, PubMed (July 1, 2022), https://pubmed.ncbi.nlm.nih.gov/36034402/.

71. Liquidia submitted these clinical investigations with Yutrepia's NDA in 2020 more than a year before UTC filed Tyvaso DPI's NDA in 2021.

72. In November 2021, FDA initially issued a tentative approval ("TA") for Yutrepia for the treatment of PAH to improve exercise ability in patients with NYHA functional Classes II–III symptoms based upon the primary endpoints of the INSPIRE Study and comparable bioavailability to Tyvaso Inhalation Solution. At the time, FDA did not grant full approval solely due to a 30-month stay and injunction resulting from Hatch-Waxman litigation between UTC and Liquidia, which ultimately proved to be meritless.[40]

73. UTC submitted to FDA the Tyvaso DPI NDA for treatment of PAH and PH-ILD to improve exercise ability on April 16, 2021.

74. On July 24, 2023, Liquidia submitted an amendment to the still-pending Yutrepia NDA to add treatment of patients with PH-ILD to improve exercise ability consistent with guidance received from FDA. FDA accepted Yutrepia's NDA amendment for review in September 2023 and the FDA targeted January 2024 as the timeframe by which Liquidia could expect FDA's determination regarding the Yutrepia NDA, as amended.

75. On March 28, 2024, the District Court in Delaware lifted the injunction that effectively prohibited FDA from issuing full approval of the Yutrepria NDA until expiration of the underlying patent. *See United Therapeutics Corp. v. Liquidia Techs., Inc.*, 2024 WL 2805082 (D. Del. May 31, 2024). This ruling eliminates the FDA's stated justification for denying full approval to Yutrepia, as the NCI exclusivity for PH-ILD for Tyvaso Inhalation Solution and Tyvaso DPI expired on March 31, 2024.

[40] FDA, CDER, NDA No. 213005, Tentative Approval Letter (Mar. 28, 2024) ("NDA 213005 Tentative Approval"), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213005Orig1s000TAltr.pdf.

76. On February 20, 2024, UTC sued FDA, challenging FDA's decision to allow Liquidia to amend its NDA to add the PH-ILD indication. Complaint, *UTC v. FDA*, No. 24-484 (D.D.C. Feb. 20, 2024), ECF No. 1. On March 29, 2024, UTC's motion for a temporary restraining order and/or preliminary injunction was denied by the United States District Court for the District of Columbia. Minute Entry, *UTC v. FDA*, No. 24-484 (D.D.C. Mar. 29, 2024).

77. Had Liquidia received FDA's full approval for Yutrepia on August 16, 2024, rather than a tentative approval, it had planned to lawfully distribute Yutrepia to patients within days of receiving that approval.

78. FDA's decision to improperly grant sweeping NCI exclusivity for Tyvaso DPI bars access to patients nationwide who stand to benefit from Yutrepia's safe and effective treatment of PAH and PH-ILD.

79. In addition, FDA's erroneous decision further delays competition in the treprostinil market, reinforcing UTC's twenty-year monopoly and denying vulnerable patients choice and access to affordable drug alternatives to treat PAH and PH-ILD.

E. FDA's August 16, 2024 Tyvaso DPI Exclusivity Decision and the Yutrepia Tentative Approval Letter.

80. On August 16, 2024, FDA concluded that the Yutrepia NDA demonstrated safety and effectiveness in treating patients with PAH and PH-ILD, and provided complete labeling for Yutrepia covering both indications. FDA, however, decided only to grant tentative approval for Yutrepia in a letter to Liquidia dated August 16, 2024 ("Yutrepia Tentative Approval Letter"). The Yutrepia Tentative Approval Letter denied Yutrepia full approval because FDA had found

pursuant to its Exclusivity Decision that Tyvaso DPI qualifies for three-year NCI exclusivity and that such exclusivity delays the approval of Yutrepia for both PAH and PH-ILD indications.[41]

81. According to FDA, the TRIUMPH Study and the INCREASE Study provided sufficient evidence of safety and effectiveness of treprostinil when administered by oral inhalation. Therefore, to the extent the BREEZE Study provided any safety data regarding inhaled treprostinil, this data was duplicative of prior studies.

82. Further, FDA acknowledged that the BREEZE Study provided bioavailability data supporting the Tyvaso DPI NDA, since the bioavailability and safety profiles of Tyvaso Inhalation Solution and Tyvaso DPI are similar even though they differ in dosage form and certain features of use. Thus, the data from the BREEZE Study is either duplicative of those prior studies or is a bioavailability study categorically excluded from the definition of a new clinical investigation under the FDCA and FDA regulations. 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108.

83. Notably, while both Circuit precedent and FDA's longstanding interpretation of "conditions of approval" limit three-year NCI exclusivity to the innovative change that the new clinical investigations are essential for NDA approval, FDA never articulated the innovative change investigated in the BREEZE Study for Tyvaso DPI.[42]

84. Since any grant of NCI exclusivity is tied to, and limited by, the innovative change for that drug known only through the new clinical investigation, FDA disregarded the FDCA and

[41] *See* Press Release, Liquidia, *U.S. FDA Grants Tentative Approval of YUTREPIA™ (treprostinil) Inhalation Powder for Patients with Pulmonary Arterial Hypertension (PAH) and Pulmonary Hypertension Associated with Interstitial Lung Disease (PH-ILD)* (Aug. 19, 2024), https://www.liquidia.com/node/11366/pdf.

[42] *See* FDA, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=214324&Appl_type=N (last visited Aug. 20, 2024) (characterizing Tyvaso DPI's NCI exclusivity period as "NP" or "new product"—even though Tyvaso DPI is not a new product).

FDA regulations when its Exclusivity Decision granted sweeping NCI exclusivity to Tyvaso DPI in the absence of any such innovative findings in the BREEZE Study.

III. FDA'S GRANT OF NCI EXCLUSIVITY TO TYVASO DPI MUST BE VACATED

A. FDA Exceeded Its Statutory Authority Under the FDCA, Violated Its Own Regulations, and Took Action that Was Arbitrary and Capricious, and Contrary to Law When Granting NCI Exclusivity to Tyvaso DPI and Overstating the Scope of that Exclusivity.

85. FDA's Exclusivity Decision and corresponding determination that such exclusivity blocks final approval of Yutrepia violates the FDCA and the APA. For NCI exclusivity to lawfully attach, the Tyvaso DPI NDA must: (1) contain one or more "new clinical investigations (other than bioavailability studies)" whose innovative findings are (2) "essential" to the approval of the NDA. FDA had no authority to recognize NCI exclusivity for Tyvaso DPI based on the BREEZE Study because it is not a new clinical investigation essential to the approval of Tyvaso DPI.

1. The Tyvaso DPI NDA Contained No New Clinical Investigations Other than Bioavailability Studies.

86. FDA improperly concluded that the Tyvaso DPI NDA contained new clinical investigations other than bioavailability studies. According to FDA regulations, a new clinical investigation is "an investigation in humans the results of which have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or safety for a new population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108.

87. FDA has previously stated that most qualifying studies will be efficacy studies, but that safety studies demonstrating a product is safer than originally thought and that permit broader use of the drug may qualify for exclusivity. *See* 1989 Preamble.

88. Under the FDCA and FDA regulations, the TRIUMPH Study and the INCREASE Study fail to qualify as "new clinical investigations" because they were previously submitted by UTC to support the Tyvaso Inhalation Solution NDA in 2008, and supplemental NDA in 2020, respectively, which UTC merely cross-referenced in its Tyvaso DPI NDA filed in 2021.

89. FDA admits that another study in the Tyvaso DPI NDA, the TIP-PH-102 Study, is a "bioavailability study" that cannot form the basis for NCI exclusivity under the FDCA.

90. But neither can the BREEZE Study. The BREEZE Study is not a "new clinical investigation[]"; it was a three-week ***confirmatory*** study conducted in 51 [PAH] patients on stable doses of Tyvaso Inhalation Solution who switched to a corresponding dose of Tyvaso DPI. The BREEZE Study compared patients already taking Tyvaso Inhalation Solution to those taking Tyvaso DPI for three weeks and ultimately found "comparable systemic exposure [of treprostinil] between the two formulations."[43]

91. As FDA concedes, to support approval of Tyvaso DPI, UTC relied on safety and efficacy data submitted in the Tyvaso Inhalation Solution NDA from the TRIUMPH Study and the INCREASE Study and provided ***relative bioavailability data*** from the TIP-PH-102 and BREEZE Studies to justify extrapolation of the previously submitted data to Tyvaso DPI. FDA thus erred by treating the BREEZE Study as a "new clinical investigation" for the purposes of NCI exclusivity, when FDA's own analysis characterizes it as a bioavailability study, which is expressly excluded under the FDCA and its implementing regulations as the type of study to which NCI exclusivity can attach. 21 C.F.R. § 314.108.

92. FDA's clinical review of Tyvaso DPI confirms that UTC's application relied upon the TRIUMPH Study and INCREASE Study to demonstrate the safety and efficacy of treprostinil

[43] The BREEZE Study, *supra* note 27, at 2.

and found that, aside from these previously-submitted studies, UTC submitted no new evidence for efficacy.[44] Thus, under FDA's own findings, the BREEZE Study was not an efficacy study.

93. The BREEZE Study further fails to meet the regulatory definition of a new clinical investigation because the results of that study "duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108. Specifically, the INCREASE Study had already established safety and effectiveness in PH-ILD patients (WHO Group 3), and FDA relied upon that study to approve Tyvaso for that patient population. Thus, to the extent that FDA implicitly and erroneously relied on the BREEZE Study to establish safety and effectiveness of the inhalation powder dosage form for use in PH-ILD patients, even though the study did not specifically investigate use in that patient population, the BREEZE Study clearly duplicates the prior findings of the INCREASE Study. FDA's contrary conclusion without explanation in its Exclusivity Decision fails to satisfy the "new clinical investigation" requirement in the FDCA and FDA regulations, and is arbitrary and capricious, and contrary to law.

94. Significantly, FDA's clinical review for Tyvaso DPI concluded that the BREEZE Study merely identified "no new risks associated with treprostinil formulated as an inhaled powder."[45] So, at most, the BREEZE Study merely duplicated the same findings of the earlier studies and confirmed that PAH patients already taking Tyvaso Inhalation Solution would not face new adverse consequences when taking the equivalent dose of treprostinil in dry powder format.

95. In addition, because the BREEZE Study only studied Tyvaso DPI in PAH patients who were already being treated with stable doses of Tyvaso Inhalation Solution, the BREEZE Study cannot have demonstrated broader use of Tyvaso DPI.

[44] Tyvaso DPI Clinical Review, *supra* note 28, at 12.
[45] Tyvaso DPI Clinical Review, *supra* note 28, at 13.

96. Thus, the BREEZE Study fails to meet the definition of a "new clinical investigation" for safety data. *See* 1989 Preamble ("There may, however, be occasional clinical investigations qualifying for exclusivity that establish that a product is safer than originally thought and that permit broader use of the drug. Studies that establish new risks will not be eligible for exclusivity because protection of the public health demands that all products' labeling contain all relevant warnings.").[46]

97. Additionally, FDA policy in the 1989 Preamble indicates that "broader use of the drug" is associated with new safety findings. Therefore, any argument that the BREEZE Study demonstrated broader use of the drug treprostinil as it allowed patients to more easily carry the drug and device and dispose of the cartridge after—without any finding of broader use, such as for new indications or patient populations—is insufficient to satisfy the definition of "new clinical investigations" under the FDCA, FDA regulations, and Circuit precedent. Moreover, the BREEZE Study did not even study whether patients found the cartridge easier to carry or dispose of.

98. The BREEZE Study was not a new clinical investigation and no other study submitted by UTC qualifies either, and so Tyvaso DPI was statutorily ineligible for NCI exclusivity on this basis alone.

2. The BREEZE Study Produced No Findings Essential to the Approval of Tyvaso DPI's NDA.

99. FDA's grant of NCI further violates the FDCA because the BREEZE Study was not "essential to the approval" of Tyvaso DPI.

100. By its own admission, the BREEZE Study simply switched "patients with PAH currently treated with [Tyvaso] [I]nhalation [S]olution" to Tyvaso DPI and confirmed comparable outcomes at the three-week mark. The BREEZE Study merely "confirm[ed]" that identical doses

[46] 1989 Preamble at 28899.

of treprostinil (via Tyvaso DPI) would not harm PAH patients who switched from equivalent doses of treprostinil (via Tyvaso Inhalation Solution).[47]

101. Indeed, the BREEZE Study's exceedingly narrow scope and the fact that it was not powered to achieve any statistically-significant results meant that it offered ***zero*** clinically-valid findings. By design, it provided ***zero*** efficacy and safety data for patients diagnosed with PH-ILD, ***zero*** findings for PAH patients not already using equivalent doses of Tyvaso Inhalation Solution, ***zero*** clinically-valid findings for treatment of PAH patients beyond the third week of using Tyvaso DPI, and ***zero*** clinically-valid findings for any treprostinil dry powder drug-device combination product, or formulation other than Tyvaso DPI.

102. In short, attaching NCI exclusivity to Tyvaso DPI based on the BREEZE Study runs counter to the Hatch Waxman Amendments and FDA's own stated policy to award exclusivity only for the "innovative change" investigated in the study. There was *no* innovative change that the BREEZE Study investigated, and FDA's Exclusivity Decision granting broad NCI exclusivity to Tyvaso DPI without any restrictions on its specific formulation, delivery mechanism, indications or the patient populations is contrary to law.

103. ***First***, the BREEZE Study cannot be considered essential to the approval for the PH-ILD indication because the BREEZE Study did not study any PH-ILD patients. As discussed above, PH-ILD is a specific subset of PH, distinct from PAH, with a different etiology—namely increases in pulmonary blood pressure due to poor oxygenation from underlying interstitial lung disease. In other exclusivity contexts involving treprostinil,[48] FDA has indicated that it considers different WHO Groups different diseases or conditions. FDA has not articulated any reason why this would be any different for purposes of NCI exclusivity of treprostinil, where the operative

[47] The BREEZE Study, *supra* note 27, at 4.
[48] *See supra* ¶¶ 49–57.

study rendered zero findings for patients with PH-ILD. Not only did the BREEZE Study fail to confirm safety for PH-ILD patients, those patients were excluded from study participation altogether.

104. ***Second***, to the extent FDA asserts that the BREEZE Study was essential to the approval of Tyvaso DPI to assess tolerability of the new dosage form, FDA did not rely on the BREEZE Study to determine safety and tolerability for the patient population with an underlying respiratory condition, which UTC recognizes "could worsen V/Q matching," which occurs when lungs receive oxygen without blood flow or blood flow without oxygen in patients using pulmonary vasodilators. "PFTs [pulmonary functional tests] (including FVC [forced vital capacity]) and exacerbations of lung disease were included as safety endpoints in the INCREASE study due to the potential risk of V/Q mismatch."[49] But the BREEZE Study did not assess these safety endpoints, or for that matter, any clinically-valid endpoints.

105. As UTC has stated, this potential risk was not addressed in the BREEZE Study, but rather in the INCREASE Study previously submitted for Tyvaso Inhalation Solution. Because the BREEZE Study failed to assess ***any*** safety and tolerability for patients with PH-ILD, and because FDA relied wholly upon the previously-submitted INCREASE Study for safety data for treatment of PH-ILD, the FDCA prohibits FDA's Exclusivity Decision awarding NCI exclusivity to Tyvaso DPI for the BREEZE Study because it was not "essential to approval" of Tyvaso DPI for PH-ILD.

106. ***Third***, FDA's finding of NCI exclusivity for the PH-ILD indication cannot stand for another key reason: FDA previously awarded NCI exclusivity for this indication back in 2021 based on another study, thus, rendering the BREEZE Study duplicative and, once again,

[49] *Study Overview: Increase Was Designed to Access the Efficacy and Safety of TYVASO in Patients with PH-ILD*, UTC (May 2022), https://www.tyvasohcp.com/ph-ild/efficacy-safety/increase-study/.

categorically ineligible for "new clinical investigation" treatment under the FDCA and FDA regulations. As UTC's recent SEC filing noted, Tyvaso Inhalation Solution and Tyvaso DPI's NCI exclusivity period for PH-ILD already expired in March 2024. UTC, SEC Form 10-Q (May 1, 2024).[50] It is contrary to law, therefore, for FDA to allow UTC to further extend its twenty-year monopoly by granting a second NCI exclusivity period covering the exact same indication for the exact same drug for a study that duplicated the findings of previously-submitted studies.

107. Because the BREEZE Study had no innovative findings "essential" to approval of Tyvaso DPI's NDA, Tyvaso DPI was statutorily ineligible for NCI exclusivity.

3. To the Extent the BREEZE Study Could Support NCI Exclusivity for Tyvaso DPI, FDA Unlawfully Blocked Yutrepia from Coming to Market by Overreading the Scope of Any Such Exclusivity.

108. Even if the Tyvaso DPI were somehow eligible for NCI exclusivity (it is not), the FDCA mandates that the scope of any such exclusivity must be limited to the narrow "conditions of approval" actually investigated in the BREEZE Study that are shared by a competitor NDA. Because those conditions do not foreclose both of Yutrepia's indications (for treatment of PAH and PH-ILD), nor Yutrepia's unique drug delivery mechanism or formulation, the scope of the NCI exclusivity recognized by FDA for Tyvaso DPI is impermissibly overbroad under the FDCA and FDA regulations, and cannot lawfully block Yutrepia's full approval.

109. Given the exceedingly narrow scope of the BREEZE Study, the FDCA prohibits FDA from identifying unstudied "conditions of approval" to grant NCI exclusivity in excess of its incremental findings. Under the FDCA, FDA may not rely on unstudied "conditions of approval" to grant broad NCI exclusivity. Thus, FDA could not grant Tyvaso DPI any NCI exclusivity for treatment of PAH patients aside from those already using Tyvaso Inhalation Solution (the narrow

[50] *See supra* note 22.

patient population in the BREEZE Study), nor for PH-ILD patients (because patients with PH-ILD were categorically excluded from the BREEZE Study).

110. FDA interprets "conditions of approval" to be the innovation represented by the approved drug product for which the new clinical investigation was essential. *See* Veloxis Letter, at 21 ("[C]onditions of approval" means only the "innovative change that is supported by the new clinical investigations" that entitled the first-approved drug to NCI exclusivity); *AstraZeneca*, 872 F. Supp. 2d at 121 n.16. ("conditions of approval" "can be no broader than the innovations presented to the FDA in the new clinical investigations that led to the FDA's approval of the first-in-time 505(b) NDA").

111. For example, oral inhalation of treprostinil to improve exercise ability in patients with PAH and PH-ILD had already been established in the TRIUMPH Study and the INCREASE Study, and therefore no new clinical investigation was needed to answer questions about the safety or efficacy of treprostinil for this route of administration or these indications. Moreover, it is difficult to understand how the three-week BREEZE Study furnished any innovative, non-duplicative data on "chronic use" of treprostinil, particularly when FDA already had data from previously-submitted studies and three prior UTC NDAs for this same active moiety.

112. To the extent that FDA focuses on the new dosage form of the inhalation powder as the innovative change, the BREEZE Study fares no better as the source for NCI exclusivity supporting this innovation as it did not study the effectiveness of this route of administration. Rather, the BREEZE Study only examined whether the relative safety of Tyvaso DPI matched that expected for treprostinil based on the AEs reported from patients already taking Tyvaso Inhalation Solution. This argument is also contrary to FDA's tentative approval of Yutrepia's NDA for oral

dry powder inhalation, finding it safe and effective based on its cross-reference to the Tyvaso Inhalation Solution NDA—not the BREEZE Study or the Tyvaso DPI NDA.

113. Given that the safety and efficacy of administering aerosolized particles of medication containing treprostinil had already been well-established by previously-submitted studies, at most, the innovative change represented by Tyvaso DPI is found in its drug-delivery device or the excipients used in the unique formulation of the powder. If the "innovative change" represented by Tyvaso DPI is attributable only to the device, then that innovative change has not been supported by any clinical studies specifically on that device. Any NCI exclusivity based on Tyvaso DPI's proprietary drug-delivery device, therefore, cannot lawfully block full approval of Yutrepia, which is a different alternative drug-device combination product altogether.

114. Likewise, if the supposedly innovative change from the BREEZE Study is the excipients enabling the powder dosage form, then there must be a logical relationship with the BREEZE Study to support NCI exclusivity. Based on the study design and its lack of relevant affirmative endpoints, however, the BREEZE Study articulates no such relationship between the excipients and its findings. Thus, any NCI exclusivity arising from Tyvaso DPI's unique excipients cannot lawfully block full approval of Yutrepia because the BREEZE Study failed to meaningfully analyze those excipients; and in any event, those excipients differ from Yutrepia's.

115. To the extent that FDA asserted concerns about specific risks presented by the powder dosage form generally, this is merely a post-hoc rationalization. None of the clinical trial endpoints suggest that the study was designed to specifically evaluate potential safety risks specific or unique to a powder inhalation formulation, or indeed any safety or tolerability risk outside of the already known risks of treprostinil for oral inhalation. In fact, the BREEZE Study did not include a placebo population, and so it failed to capture any clinically-valid data upon which to

compare the effect of administering respirable, micron-sized drug particles that are aerosolized from a dry powder (Tyvaso DPI) against the effect of administering respirable, micron-sized drug particles that are aerosolized from a solution (Tyvaso Inhalation Solution). Nor does FDA identify any risks associated specifically with a powder inhalation form within the risk-benefit analysis of its clinical review of Tyvaso DPI.

116. To the extent FDA did seek confirmation regarding the risks of using a dry powder formulation of treprostinil, those questions were already answered by Liquidia's INSPIRE Study for Yutrepia when FDA granted tentative approval for Yutrepia in November 2021, further casting doubt on any supposed innovation from the BREEZE Study.

117. Moreover, "if the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients." 60 Fed. Reg. at 28896–97. Based on the clear limitations of the BREEZE Study, FDA could not find NCI exclusivity for treatment of PAH patients that were not already using Tyvaso Inhalation Solution, nor NCI exclusivity for PH-ILD patients generally.

118. In sum, Yutrepia does not share "conditions of approval"—*i.e.*, the innovative findings of the BREEZE Study "essential" to approval—that form the basis for FDA's asserted NCI exclusivity for Tyvaso DPI.

119. Yutrepia meets all FDA requirements for demonstrating safety and efficacy for its intended use, as acknowledged by FDA, and there are no valid exclusivities or patents that may prevent its full approval.

120. In denying full approval of Yutrepia based upon the NCI exclusivity improperly granted to Tyvaso DPI, FDA has exceeded its statutory authority under the FDCA, and interpreted FDCA Section 505(c)(3)(E)(iii)in a manner that is arbitrary and capricious and contrary to law.

121. Immediate, unconditional approval of Yutrepia is legally and factually mandated by the FDCA, its implementing regulations, FDA policy, and longstanding precedent.

CAUSES OF ACTION

COUNT I
APA—5 U.S.C. § 706(2)(C) & (A)
FDA's Decision to Grant NCI Exclusivity to Tyvaso DPI Exceeds FDA's Statutory Authority and Was Arbitrary, Capricious, An Abuse of Discretion, and Otherwise Not in Accordance with Law

122. Liquidia repeats and realleges the allegations contained in the preceding paragraphs as if fully set forth herein.

123. The APA prohibits FDA from issuing a final decision that is in excess of statutory jurisdiction, authority, or limitations. 5 U.S.C. § 706(2)(C).

124. The APA prohibits FDA from issuing a final decision that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

125. FDA's Exclusivity Decision to grant Tyvaso DPI NCI exclusivity exceeds FDA's statutory authority to award such exclusivity.

126. Under the FDCA, FDA cannot recognize NCI exclusivity for an NDA submitted under section 355(b) unless "such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." FDCA, 21 U.S.C. § 355(c)(3)(E)(iii).

127. FDA's determination that Tyvaso DPI is entitled to NCI exclusivity exceeds FDA's statutory authority because:

(a) The BREEZE Study was not a new clinical investigation within the meaning of the statute and no other study submitted with the Tyvaso DPI NDA qualifies;

(b) The BREEZE Study was not "essential to the approval" of Tyvaso DPI as defined by the FDCA and its implementing regulations; and

(c) Even assuming the BREEZE Study could qualify as a new clinical investigation, the BREEZE Study did not support any of the "condition[s] of approval" shared by Yutrepia and thus should not block FDA's approval of Yutrepia.

128. Liquidia has no other adequate remedy at law.

129. For the foregoing reasons, FDA's grant of exclusivity to Tyvaso DPI exceeds FDA's statutory authority, and is arbitrary and capricious, an abuse of discretion, and contrary to law. Thus, FDA's Exclusivity Decision must be set aside.

COUNT II
APA—5 U.S.C. § 706(2)(C) & (A)
FDA's Interpretation of the Scope of the NCI Exclusivity for Tyvaso DPI Exceeds FDA's Statutory Authority and Was Arbitrary, Capricious, An Abuse of Discretion, and Otherwise Not in Accordance with Law

130. Liquidia repeats and realleges the allegations contained in the preceding paragraphs as if fully set forth herein.

131. The APA prohibits FDA from issuing a final decision that is in excess of statutory jurisdiction, authority, or limitations. 5 U.S.C. § 706(2)(C).

132. The APA prohibits FDA from issuing a final decision that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

133. FDA's Exclusivity Decision granting Tyvaso DPI NCI exclusivity covering all PAH and PH-ILD patients contravenes the FDCA's limitation that the scope of NCI exclusivity can be no broader than the innovations presented in the new clinical investigations essential to the NDA's approval. *Veloxis*, 109 F. Supp. 3d at 121 n.16.

134. FDA's Exclusivity Decision awarding a broad scope of NCI to Tyvaso DPI is also arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the "conditions of approval" for Tyvaso DPI for which it could be awarded exclusivity must be

narrowly limited to only those changes studied in the BREEZE Study, such as the BREEZE Study's specific patient population of PH patients who switched from Tyvaso Inhalation Solution.

135. For the foregoing reasons, FDA's determination regarding the scope of Tyvaso DPI's NCI exclusivity exceed FDA's statutory authority, and is arbitrary and capricious, an abuse of discretion, and contrary to law. Thus, the FDA's Exclusivity Decision must be set aside.

PRAYER FOR RELIEF

WHEREFORE, Liquidia respectfully requests that this Court provide the following relief:

A. An order pursuant to 28 U.S.C. § 2201 declaring that:

i. FDA's Exclusivity Decision for Tyvaso DPI exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law;

ii. FDA's Exclusivity Decision applying Tyvaso DPI's NCI exclusivity to PH-ILD patients exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law;

iii. FDA's failure to immediately issue full approval to the Yutrepia NDA exceeds FDA's statutory authority and is arbitrary, capricious, and contrary to law; and

iv. Yutrepia is entitled to immediate and full approval for one or more indications.

B. Preliminary and permanent mandatory injunctions ordering FDA to grant immediate, full approval of the Yutrepia NDA for one or more indications.

C. An award of costs and reasonable attorney fees to the extent permitted by law, including 28 U.S.C. § 2412; and

D. Such other relief as this Court may deem just and proper.

Respectfully submitted,

Dated: August 21, 2024

By: */s/ Sonia W. Nath*

Sonia W. Nath (DC Bar No. 977095)
David E. Mills (DC Bar No. 401979)
Robby L.R. Saldaña (DC Bar No. 1034981)
Matt K. Nguyen (DC Bar No. 1736777)
COOLEY LLP
1299 Pennsylvania Ave., NW, Suite 700
Washington, DC 20004-2400
Telephone: (202) 842-7800
Facsimile: (202) 842-7899
snath@cooley.com
dmills@cooley.com
rsaldana@cooley.com
mnguyen@cooley.com

Kathleen R. Hartnett (DC Bar No. 483250)
COOLEY LLP
3 Embarcadero Center, 20th Floor
San Francisco, CA 94111-4004
Telephone: (415) 693-2000
Facsimile: (415) 693-2222
khartnett@cooley.com

Counsel for Plaintiff Liquidia Technologies, Inc.