UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

LIQUIDIA TECHNOLOGIES, INC., *Plaintiff*, v. UNITED STATES FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of the Food and Drug Administration; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; and XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services, *Defendants*.	Case No. 24-cv-02428 Honorable John D. Bates **HEARING REQUESTED**

MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFF LIQUIDIA TECHNOLOGIES, INC.'S MOTION FOR A PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff Liquidia Technologies, Inc. ("Liquidia") seeks immediate injunctive relief from an August 16, 2024 decision (the "Exclusivity Decision" or "Decision") issued by Defendant U.S. Food and Drug Administration[1] ("FDA") in which the FDA has refused (for a second time in the past three years) to grant full approval of Liquidia's first drug product, Yutrepia, despite findings by the agency on two occasions that Yutrepia is a safe and effective drug that warrants approval. FDA's Exclusivity Decision is both contrary to law and arbitrary and capricious, and it is causing Liquidia irreparable harm. Thus, it should be enjoined.

In a tentative approval ("TA") letter issued to Liquidia on August 16, 2024, FDA confirmed (again) that Yutrepia, a dry powder treprostinil treatment for patients with two incurable conditions, pulmonary arterial hypertension ("PAH") and pulmonary hypertension associated with interstitial lung disease ("PH ILD"), meets ***all*** Federal Food Drug & Cosmetic Act ("FDCA") and FDA requirements, including safety and efficacy as a treatment for its intended uses. FDA, however, determined that a monopoly held by United Therapeutics Corporation ("UTC") over treprostinil treatments should continue for yet ***another nine months*** because of exclusivity based on a purportedly "new clinical investigation" ("NCI exclusivity") for Tyvaso DPI. In awarding NCI exclusivity to UTC for Tyvaso DPI, the latest addition to UTC's franchise of treprostinil products, FDA manufactured yet another extension of UTC's monopoly and blocked the launch of Yutrepia for any patients. FDA's decision to award this exclusivity to another dry powder treprostinil drug submitted for FDA approval ***after*** Liquidia filed its New Drug Application ("NDA") for Yutrepia violates the Hatch-Waxman Amendments that authorize FDA to grant NCI

[1] Liquidia has also sued Robert M. Califf, M.D., in his official capacity as Commissioner of FDA, U.S. Department of Health and Human Services ("HHS"), and Xavier Becerra, in his official capacity as Secretary of HHS. References to "FDA" include these Defendants.

exclusivity under the FDCA for the purpose of rewarding innovation. 21 U.S.C. § 355(c)(3)(E)(iii). Here, UTC is being rewarded for copying Liquidia's innovation and then slowing approval for Liquidia's drug through meritless patent litigation, not any actual innovation by UTC. Meanwhile the true innovator, Liquidia, is penalized.

The Exclusivity Decision is the latest FDA action refusing to give full approval to Yutrepia because of UTC. In a TA letter that FDA issued in November 2021, FDA indicated that Yutrepia was blocked from the market solely because of stays and injunctions issued in connection with patent litigation initiated by UTC against Liquidia in which Liquidia was ultimately found not to have infringed any valid claims of the patents asserted by UTC. The last of those stays and injunctions was lifted in March 2024. FDA nevertheless delayed making any decision on Liquidia's NDA for Yutrepia until August 2024 when FDA issued the Exclusivity Decision.

The Exclusivity Decision not only exceeds FDA's authority under the FDCA, but also it contradicts a prior FDA decision on this very issue. In May 2022, at the same time FDA approved Tyvaso DPI, FDA concluded that ***no*** "new clinical investigations" supported that approval, and thus Tyvaso DPI was ineligible for NCI exclusivity. Ex. E at 1.[2] Yet, on August 16, 2024, FDA reversed course and awarded the precise exclusivity it found inapplicable at the time of approval in 2022. Ex. A at 1.

FDA's Exclusivity Decision allows UTC to maintain a decades-long monopoly over treprostinil in violation of clear congressional intent to allow NCI exclusivity only in limited circumstances not present here. In extending this exclusivity to Tyvaso DPI, FDA violated statutory limitations and its own regulations by improperly crediting a study that cannot, as a matter

[2] All Exhibits ("Ex.") are Exhibits to the Declaration of Sonia W. Nath, filed concurrently with this motion.

of law, support NCI exclusivity for Tyvaso DPI. It further prevents Liquidia—who was the first to conduct a clinical study with a dry powder treprostinil formulation, the first to submit such a formulation for FDA approval, and the sponsor of the first dry powder treprostinil formulation found by FDA to be a safe and effective drug warranting approval—from reaching patients. FDA's Exclusivity Decision is an affront to patients in need of safe and effective treatments, the drug development process itself, and the intent of Congress, and it cannot lawfully stand. Thus, Liquidia seeks a preliminary injunction on its claims under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2), to prevent substantial and irreparable harm from FDA's unlawful Exclusivity Decision. Each preliminary injunction factor weighs decisively in favor of granting injunctive relief. *See Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008).

First, Liquidia has a strong likelihood of success on the merits of its claims that FDA has violated the APA. "Congress ... enacted the APA 'as a check upon administrators whose zeal might otherwise have carried them to excesses not contemplated in legislation creating their offices.'" *Loper Bright Enters. v. Raimondo*, 144 S. Ct. 2244, 2261 (2024) (citation omitted). That check is critical here because FDA exceeded its specific and limited authority under the FDCA in granting the contested award of NCI exclusivity. FDA has routinely defended its interpretations of the FDCA by relying on the judicially created deference doctrine established in *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984), but now "*Chevron* is overruled," *Loper Bright*, 144 S. Ct. at 2273, and this Court "must exercise [its] independent judgment in deciding whether [the] agency has acted within its statutory authority, as the APA requires." *Id*. In addition to FDA's statutory excesses, FDA contravened its own regulations governing NCI exclusivity and ran afoul of the APA's fundamental requirement mandating reasoned agency decision-making.

Specifically, in issuing the Exclusivity Decision, FDA exceeded its statutory authority under the FDCA and acted contrary to the FDCA and FDA regulations as follows:

- FDA unlawfully extended NCI exclusivity to Tyvaso DPI in violation of the FDCA and FDA regulations limiting eligibility for such exclusivity to drugs supported by new clinical investigations other than bioavailability studies. The single study on which FDA relied for the Exclusivity Decision, the BREEZE Study, was a bioavailability study—as FDA recognized over two years ***before*** the Exclusivity Decision—that was categorically ineligible for NCI exclusivity. FDA's determination that BREEZE was not "solely" a bioavailability study is contrary to the FDCA and FDA regulations, which do not permit FDA to rely on such a study. Moreover, BREEZE could not qualify as a new clinical investigation because its results duplicated and confirmed those of prior studies.

- FDA unlawfully extended NCI exclusivity to Tyvaso DPI in violation of the FDCA and FDA regulations limiting eligibility for NCI exclusivity to new clinical investigations "essential" to the approval of a prior drug application. BREEZE was ***not*** essential to FDA's approval of Tyvaso DPI. FDA admits it relied on safety and efficacy data from previously submitted treprostinil NDAs to approve Tyvaso DPI.

- FDA exceeded its authority under the FDCA and acted contrary to FDA regulations by awarding Tyvaso DPI broad NCI exclusivity that does not correspond to the "conditions of approval" supported by the BREEZE Study.

FDA also violated the APA's fundamental requirement that an agency must engage in reasoned decisionmaking. FDA's determination that BREEZE was a new clinical investigation contradicts a 2022 finding by the agency when it approved Tyvaso DPI where it reached the ***opposite*** conclusion. FDA failed to articulate any satisfactory reason for how the "conditions of approval" supported by the BREEZE study were "innovative." And FDA departed from its own prior practice of limiting NCI exclusivity to the patient populations actually studied by a new clinical investigation when FDA refused to address how BREEZE could support an NCI exclusivity that would block ***all of Yutrepia's indications*** even though BREEZE did not study the use of treprostinil inhalation powder in PH-ILD patients, one of Yutrepia's (blocked) indications.

Second, injunctive relief is necessary to prevent the immediate and clear threat of irreparable harm to Liquidia from FDA's Exclusivity Decision. Absent injunctive relief, the

Exclusivity Decision prohibits Liquidia from lawfully marketing Yutrepia for at least nine additional months, *i.e.*, until May 2025. This represents nine months of market participation Liquidia cannot recover, and nine months during which Liquidia is unable to generate any revenue from its first and currently only approvable product. This additional prohibition is on top of over two and a half years of delay resulting from UTC's meritless patent litigation and FDA's delays in taking action on Liquidia's application after the legal impediments to approval were removed. As a result, Liquidia faces monetary losses it can never recover from FDA due to sovereign immunity. A preliminary injunction is necessary to prevent these irremediable harms to Liquidia.

Third, the equities and the public interest decisively weigh in Liquidia's favor. Because Liquidia is likely to succeed on its claims that the Exclusivity Decision violates the APA, "a preliminary injunction would serve the public interest because there is generally no public interest in the perpetuation of unlawful agency action." *Shawnee Tribe v. Mnuchin*, 984 F.3d 94, 102 (D.C. Cir. 2021) (internal brackets and quotation marks omitted). Injunctive relief would not harm FDA because the government is not harmed by being required to comply with the law. Nor would UTC suffer any creditable harm, let alone harm that could outweigh the substantial irreparable harm Liquidia faces, as UTC is "a large company with more than $2 billion in annual revenue and two decades on the market." *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. CV 23-975, 2024 WL 2805082, at *13 (D. Del. May 31, 2024). And, as of 2023, UTC stated that it expected its double-digit growth rate would remain solid even with the possibility of new FDA approvals for Liquidia. The prospect of competition to UTC's products cannot foreclose injunctive relief for Liquidia, particularly when UTC could not have expected any NCI exclusivity for Tyvaso DPI.

Fourth, in light of Liquidia's strong showing on the preliminary injunction factors, the remaining question is the scope of the preliminary injunction. At a minimum, the Court should

immediately enjoin the effectiveness of the Exclusivity Decision, which would eliminate that unlawful obstacle to Yutrepia. Liquidia also requests that the Court require FDA to give full approval to Yutrepia immediately or, alternatively, full approval for the PH-ILD indication.

BACKGROUND

I. STATUTORY AND REGULATORY BACKGROUND

A. The New Drug Approval Process.

The FDCA requires FDA to approve new drugs before they may be distributed in interstate commerce. 21 U.S.C. § 355(a). In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments"), which, among other changes, amended the FDCA to provide new abbreviated pathways for FDA drug approval under sections 505(b)(2) and 505(j). Public Law 98-417 (1984). The Hatch-Waxman Amendments reflected Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions. House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

The FDCA contemplates three types of drug applications 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. An NDA must include 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.

Under section 505(b)(1), an NDA applicant must, among other requirements, submit full reports of investigations made to show whether the drug is safe for use and effective. 21 U.S.C. § 355(b)(1)(A). By contrast, under section 505(b)(2), an applicant may submit an NDA for a new drug by relying on all or part of the prior safety and/or effectiveness data for a listed drug that FDA has already approved. *Id*. § 355(b)(2); 21 C.F.R. § 314.54(a)(1)(iii).

FDA has three ways to resolve an NDA: (1) denial (or delay), (2) tentative approval ("TA"), or (3) approval. First, FDA may deny the NDA. *See* 21 C.F.R. § 314.125. Grounds for denial include, among other reasons, lack of adequate studies on safety and efficacy or test results showing that the drug is unsafe for its intended uses. *Id*. § 314.125(b). Second, "FDA will issue a [TA] letter if an NDA ***otherwise meets the requirements for approval under the*** [***FDCA***], but cannot be approved" for certain reasons. 21 C.F.R. § 314.105(a) (emphasis added). Among the reasons that will prevent full approval are a patent stay pursuant to 21 C.F.R. § 314.107(b)(3), or "because there is a period of exclusivity for the listed drug under [21 C.F.R.] § 314.108." 21 C.F.R. § 314.105(a). By definition, under FDA's regulations, a drug that receives a TA satisfies ***all*** requirements for approval under the FDCA as of the date of the TA—including safety and efficacy requirements. *Id.* A drug that receives TA "is not an approved drug and will not be approved until FDA issues an approval after any necessary additional review of the NDA." *Id.* Third, "FDA will approve an NDA and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the NDA applies." *Id.* Final approval allows the applicant to market the drug immediately.

An applicant also must propose labeling for its drug product as part of the approval process. Among the labeling requirements is a requirement that the applicant must identify the "[i]ndications and usage" of the drug. 21 C.F.R. § 201.57(c)(2). An indication reflects that "the

drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or conditions, or for the relief of symptoms associated with a recognized disease or condition." *Id*.

B. Marketing Exclusivities Under the FDCA.

The Hatch-Waxman Amendments amended the FDCA to provide statutory periods of exclusivity for drugs approved by FDA. These exclusivities apply only if specific statutory requirements are met and have varying lengths of exclusivity depending on the degree of innovation. *See* 21 U.S.C. § 355. Among the FDCA's exclusivities are (1) orphan drug exclusivity ("ODE"), a seven-year period, (2) new chemical entity ("NCE") exclusivity, a five-year period, and (3) NCI exclusivity, a three-year period. "Through the Hatch-Waxman Amendments, even while creating new incentives for the development of generic drugs, Congress sought to encourage innovation. To this end, pioneer drug companies are entitled to certain periods of marketing exclusivity." *AstraZeneca Pharms. LP v. FDA*, 850 F.Supp.2d 230, 234 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013).

NCI exclusivity is the focus here, and it creates a temporal relationship between an approved drug and later drugs with the same "active moiety" as the first approved drug. Under the FDCA, NCI exclusivity extends to the first approved drug whose application "contain[ed] reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii).[3] If the first approved drug is eligible for NCI exclusivity because its application contained reports

[3] The FDCA defines "bioavailability" as "the rate and extent to which the active ingredient or [active moiety] therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action." 21 U.S.C. § 355(j)(8)(A)(i). FDA regulations have a similar definition. 21 C.F.R. § 314.3 (defining "[b]ioavailability" 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").

of a qualifying new clinical investigation essential to FDA's approval of the drug, the FDCA prohibits FDA from giving full approval to a second drug in an application submitted under section 505(b) for a specified period of time "for the conditions of approval" of the first approved drug if the applicant for the second drug did not conduct the investigations on which the applicant is relying to show the safety and efficacy of the second drug and "has not obtained a right of reference or use from the person by or for whom the investigations were conducted." *Id*.

C. FDA's Regulatory Framework for NCI Exclusivity.

FDA has promulgated regulations to implement the FDCA's provisions on NCI exclusivity. Like the FDCA, the regulations exclude bioavailability studies from the clinical investigations eligible for the exclusivity. 21 C.F.R. § 314.108(a) (defining "clinical investigation" to mean "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects"). FDA regulations define a "bioavailability study" as "a study to determine the bioavailability or the pharmacokinetics of a drug." *Id*.

FDA's implementing regulations define the phrase "new clinical investigation" as follows:

> ***[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(a) (emphasis added). The regulation further provides that "[e]ssential to approval means, with regard to an investigation, that there are no other data available that could support approval of the [application]." *Id.*

FDA has not promulgated a regulation that defines the phrase "conditions of approval." Nor is the phrase defined in the FDCA. However, FDA's longstanding view, as applied by the

courts, is that the FDCA sets up a "logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [product], and the scope of any resulting three-year exclusivity." *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104, 120–21 (D.D.C. 2015); *AstraZeneca*, 872 F. Supp. 2d at 81. According to FDA's established interpretation, 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." *Veloxis*, 109 F. Supp. 3d at 121 n.16.

II. FACTUAL BACKGROUND

A. Treprostinil Treatment for PH Patients.

PH is a condition that causes elevated blood pressure in the pulmonary arteries, which can worsen over time and may lead to heart failure.[4] A person with PH suffers from reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death.

The identification of various PH subtypes has led to the development of improved and differentiated treatment strategies. 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. FDA considers each WHO Group a distinct disease or condition.[5] Thus, a drug approved for one PH indication is not necessarily approved for other PH indications.

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

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[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.

activities.[6] While the WHO/NYHA classification is separate from the WHO Groups of PH, it is used to help characterize the severity of symptoms experienced by patients with PH, and has been referenced in the approved indications for several UTC treprostinil products. As relevant here, PAH is designated within WHO Group 1, and is characterized by higher pulmonary arterial pressure, among other things.[7] A hallmark of PAH patients is limited exercise capacity.[8] Pulmonary Hypertension Due to Lung Disease and/or Hypoxia, also known as WHO Group 3, is associated with several other diseases, including Interstitial lung disease ("ILD"), a particularly devastating form of PH. ILD 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. PH-ILD is a subset of WHO Group 3.

Treprostinil is a drug that mimics a naturally occurring substance in the body that affects dilation of blood vessels. The drug dilates narrowed blood vessels in the lungs, which decreases lung pressure and reduces the stain on the heart.

B. UTC's Nearly 20-Year Market Exclusivity for Treprostinil Products.

UTC has maintained a monopoly 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 ODE and three-year NCI exclusivity periods, which altogether span more than 20 years.[9] UTC's treprostinil drugs include Remodulin, Orenitram, Tyvaso, and Tyvaso

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[6] *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.

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

[8] *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.

[9] 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.

DPI.

Remodulin. On May 21, 2002, FDA approved UTC's Remodulin 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.[10]

Orenitram. On December 20, 2013, FDA approved UTC's Orenitram for the treatment of PAH (WHO Group I), and received ODE for PAH to improve exercise capacity. The ODE period for Orenitram began on December 20, 2013 and expired on December 20, 2020.[11] 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), which ends on October 18, 2026.[12]

Tyvaso. While it had ODE for Remodulin, UTC submitted an NDA for Tyvaso Inhalation Solution ("Tyvaso") on June 27, 2008, and received FDA approval on July 30, 2009, for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with NYHA Class III symptoms, to increase walk distance.[13]

FDA granted an ODE period to UTC's Tyvaso (treprostinil) on June 17, 2010, and limited that exclusivity to patients with NYHA Class III symptoms to increase walk distance, a subset of WHO Group 1. The ODE period for Tyvaso began on July 30, 2009, and expired on July 30, 2016.[14] The efficacy of inhaled treprostinil for the treatment of PAH (WHO Group 1) was

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§ 527(c); 21 C.F.R. Part 316. ODE is not relevant to this case, except to the extent that it offers context for inapplicable or already-expired ODE periods held by UTC's other drugs.

[10] *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).

[11] *Id.*

[12] *Id.*

[13] FDA, Center for Drug Evaluation and Research ("CDER"), NDA No. 22-387 (Tyvaso Inhalation Solution) Approval Letter (July 30, 2009), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022387s000ltr.pdf.

[14] *Id.*

demonstrated by one clinical study, the TRIUMPH 001 study ("TRIUMPH"),[15] submitted in support of the Tyvaso NDA.[16]

On June 1, 2020, UTC submitted a supplemental NDA for Tyvaso to add a new indication for treatment of PH-ILD (WHO Group 3) to improve exercise ability, which FDA approved on March 31, 2021.[17] (UTC and FDA subsequently relied on TRIUMPH and the INCREASE study ("INCREASE") to establish the safety and efficacy of Tyvaso DPI for PAH and PH-ILD.[18]) FDA's approval of this supplemental NDA based on INCREASE triggered a three-year period of NCI exclusivity for Tyvaso, which expired on March 31, 2024. According to UTC, this exclusivity also applied to Tyvaso DPI.

C. Liquidia Sought FDA Approval of Yutrepia Over Four Years Ago.

On January 24, 2020, Liquidia submitted its NDA for Yutrepia (treprostinil inhalation powder) for treatment of PAH under section 505(b)(2) of the FDCA. Ex. D. This was well before UTC submitted the Tyvaso DPI NDA to FDA on April 16, 2021. *Contrast id.*, *with* Ex. C. In the Yutrepia NDA, Liquidia referenced the safety and efficacy data that UTC had previously submitted to FDA for Tyvaso, and did not rely on any other listed drug.

Liquidia conducted its own clinical investigations for Yutrepia. During investigational

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[15] 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.

[16] *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.

[17] FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Supplemental Approval Letter (Mar. 31, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/022387Orig1s017ltr.pdf.

[18] *See, e.g.*, FDA, CDER, NDA No. 22-387 (Tyvaso Inhalation Solution) Multi-Discipline Review at 7 (Feb. 26, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/022387Orig1s017.pdf.

studies, Yutrepia was known as LIQ861.[19] Liquidia's studies included two Phase 1 studies in healthy volunteers, as well as a Phase 3, open-label, multicenter trial called INSPIRE, the primary objective of which was to assess the safety and tolerability of Yutrepia in patients naïve to prostacyclin therapy and those transitioning from Tyvaso.[20] Liquidia completed INSPIRE in November 2019,[21] and released the final results from Phase 3 of INSPIRE in April 2020.[22]

D. UTC's Patent Suit Against Liquidia Blocks Full Approval of Yutrepia.

Less than six months after Liquidia's submission of the Yutrepia NDA to FDA, UTC filed a patent infringement suit against Liquidia, alleging infringement of several UTC patents for Tyvaso. *See* Complaint, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-cv-755 (D. Del. June 4, 2020), ECF No. 1. UTC's lawsuit triggered an automatic stay under the FDCA, which barred FDA from approving the Yutrepia NDA for a specific period of time.[23] On November 4, 2021, FDA issued a TA to Liquidia for Yutrepia for the treatment of PAH to improve exercise ability in patients with NYHA functional Class II-III symptoms based upon the primary endpoints of the INSPIRE Study and comparable bioavailability to Tyvaso. Ex. D. FDA did not grant full approval for Yutrepia solely due to the stay triggered by UTC's patent suit. *Id.*

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[19] *See* Press Release, Liquidia, *FDA Grants Tentative Approval for Liquidia's YUTREPIA™ (Treprostinil) Inhalation Powder* (Nov. 8, 2021), https://liquidia.com/node/9416/pdf.

[20] Nicholas S. Hill *et al.*, *INSPIRE: Safety and Tolerability of Inhaled Yutrepia (treprostinil) in Pulmonary Arterial Hypertension (PAH)*, PUBMED (July 1, 2022), https://onlinelibrary.wiley.com/doi/epdf/10.1002/pul2.12119.

[21] *See Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil (INSPIRE)*, CLINICALTRIALS (last updated July 30, 2024), https://clinicaltrials.gov/study/NCT03399604.

[22] *See* Press Release, Liquidia, *Liquidia Releases Final LIQ861 Results from Pivotal Phase 3 INSPIRE Study in Patients with Pulmonary Arterial Hypertension* (Apr. 30, 2020), https://investors.liquidia.com/node/7836/pdf.

[23] Because of the statutory patent stay, FDA could not approve Yutrepia until the earlier of the expiration of the patent, resolution of the lawsuit, or 30 months after a patentee has received notice from an NDA applicant that a patent that claims the drug is invalid, unenforceable, or will not be infringed by the drug. 21 U.S.C. § 355(c)(3)(C); 21 C.F.R. § 314.107(b)(3)(viii).

E. UTC Submits the Tyvaso DPI NDA and Receives FDA Approval.

During the pendency of Liquidia's Yutrepia NDA and several months after bringing its patent suit against Liquidia, UTC submitted an NDA for Tyvaso DPI, a powder inhalation form of treprostinil, under section 505(b)(1) of the FDCA on April 16, 2021. UTC requested three years of exclusivity for its NDA. Ex. E at 2.

The Tyvaso DPI NDA included no new clinical investigations involving patients with PAH except patients who switched from Tyvaso, and it included no new clinical investigations involving patients with PH-ILD. Instead, the NDA consisted of: (1) safety and efficacy data resubmitted from UTC's earlier TRIUMPH Study and INCREASE Study, which were submitted to FDA with the Tyvaso NDA as evidence for treprostinil when administered by inhalation, Ex. F[24], and (2) bioavailability data to justify extrapolation of the previously submitted data for Tyvaso to Tyvaso DPI.[25] The studies on which the Tyvaso DPI NDA relied were:

- ***TRIUMPH***: A 12-week randomized, double-blind, placebo-controlled study to investigate the efficacy and tolerability of Tyvaso in 235 patients with PAH already receiving other PAH treatments. The primary endpoint was change in 6-minute walk distance ("6MWD") at week 12 compared to baseline.[26]

- ***INCREASE***: A 16-week randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of Tyvaso 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.[27]

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[24] FDA, CDER, NDA No. 214324 (Tyvaso DPI) Clinical Review at 10 ("Tyvaso DPI Clinical Review") (Sept. 23, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214324Orig1s000MedR.pdf.

[25] 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"), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9063953/pdf/PUL2-12-e12063.pdf.

[26] Vallerie V. McLaughlin *et al.*, *supra* note 15; *see also* Ex. A at 12–13 (Exclusivity Decision).

[27] 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.

- ***TIP-PH-102*:** A 6-treatment crossover study of Tyvaso and Tyvaso DPI in 36 healthy subjects, which was used to estimate bioavailability in the target patient population.

- ***BREEZE***: 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." Ex. G at 2.[28] Secondary endpoints were assessment of pharmacokinetics following administration, efficacy based upon 6MWD and patient evaluation of PAH symptoms, and a preference questionnaire. Of the 51 patients enrolled, 49 completed the three-week treatment phase. The study excluded patient diagnosed with PH for reasons other than PAH (WHO Group 1), such as PH-ILD patients. *Id.*

BREEZE—which became the basis for FDA's Exclusivity Decision at issue in this case—began in September 2019.[29] The results of the study duplicated those of prior studies UTC submitted for its earlier drug applications, as FDA itself recognized. *See* Ex. E at 1 (May 2022 Exclusivity Summary noting that BREEZE "provided confirmatory efficacy information only"). For example, BREEZE observed that adverse events ("AEs") were "consistent with studies of [Tyvaso] in patients with PAH, and there were no study drug-related serious AEs." Ex. G at 2. FDA's May 23, 2022 clinical review of Tyvaso DPI confirmed that the prevalence of AEs in BREEZE was similar to those reported in TRIUMPH. Ex. F at 12. FDA's review expressly noted that UTC and FDA did ***not*** rely on BREEZE to establish Tyvaso DPI's safety and effectiveness, which was already proven by INCREASE and TRIUMPH. *Id*. FDA's review further made clear that, other than TRIUMPH and INCREASE, which were submitted with the Tyvaso NDA, "[n]o additional evidence for effectiveness was submitted as part of the [Tyvaso DPI NDA]." *Id*.

On July 15, 2021, following the submission of the Tyvaso DPI NDA, Liquidia submitted a letter to FDA to request that FDA deny or limit any award of three-year exclusivity to Tyvaso DPI.

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[28] The BREEZE Study, *supra* note 25.
[29] *See 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.

On May 23, 2022, FDA approved the Tyvaso DPI NDA for the treatment of PAH (WHO Group 1) and PH-ILD (WHO Group 3), to improve exercise ability. Ex. C at 1. In an Exclusivity Summary finalized on the same date FDA granted full approval for Tyvaso DPI, FDA determined that the drug was ***not*** eligible for NCI exclusivity. Ex. E at 1. FDA determined that the Tyvaso DPI "required review only of bioavailability or bioequivalence data." *Id*. FDA explained the basis for approval "is the safety, tolerability, and bioavailability established in studies," but "[t]he safety and tolerability study provided confirmatory efficacy information only." *Id*. Thus, FDA concluded Tyvaso DPI was ***ineligible*** for NCI exclusivity. *Id*.

Unaware that FDA had already determined that Tyvaso DPI was ineligible for NCI exclusivity, Liquidia submitted a supplemental letter to FDA on July 25, 2022, to support its request that FDA deny or limit any award of NCI exclusivity to Tyvaso DPI.

F. UTC Sues to Block FDA's Approval of Yutrepia for the PH-ILD Indication and Liquidia's Anticipated Launch of Yutrepia for that Indication.

On July 24, 2023, while its NDA was pending approval with FDA, Liquidia submitted an amendment to the Yutrepia NDA to add a new indication: treatment of PH-ILD.[30] FDA had previously confirmed that Liquidia would not need to submit new clinical data for the PH-ILD indication.[31] FDA accepted the amendment for review in September 2023. *Id.*

Following FDA's acceptance of Liquidia's amendment to the Yutrepia NDA for the PH-ILD indication, UTC responded on multiple fronts. On February 20, 2024 (nearly a month before the March 31, 2024 expiration of the NCI exclusivity based on INCREASE that FDA granted to Tyvaso for the use of inhaled treprostinil to treat PH-ILD patients), UTC sued FDA in a lawsuit

[30] Press Release, Liquidia, *Liquidia Submits Amendment to Add PH-ILD Indication to Tentatively Approved NDA for YUTREPIA™ (trepostinil) Inhalation Powder* (July 27, 2023), https://www.liquidia.com/node/10556/pdf.

[31] *See* Press Release, Liquidia, *FDA Accepts Submission to Add PH-ILD to YUTREPIA™ Label* (Sept. 25, 2023), https://www.liquidia.com/node/10646/pdf.

challenging FDA's acceptance of Liquidia's amendment to the Yutrepia NDA to add the PH-ILD indication. *See* Complaint, *United Therapeutics Corp. v. FDA*, No. 24-cv-484-JDB (D.D.C. Feb. 20, 2024), ECF No. 1. Thereafter, on March 4, 2024, UTC moved to enjoin FDA from granting final approval to Yutrepia. Motion for Temporary Restraining Order & Preliminary Injunction (Mar. 4, 2024), ECF No. 14. This Court denied that motion on March 29, 2024.

Separately, UTC sued to challenge Liquidia's launch of Yutrepia for the PH-ILD indication, which UTC argued infringed new UTC patents. *See* Complaint, *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 23-cv-00975 (D. Del. Sept. 5, 2023), ECF No. 1. UTC moved for a preliminary injunction, which the district court denied. *United Therapeutics*, 2024 WL 2805082, at *1. Among other things, the court noted that UTC "has not shown that it would be irreparably harmed absent an injunction" because it "is a large company with more than $2 billion in annual revenue and two decades on the market" and was "prepared to compete with [Liquidia's] Yutrepia product." *Id.* at *13.

G. FDA Issues the Exclusivity Decision and Refuses Full Approval of Yutrepia.

On August 16, 2024, notwithstanding FDA's conclusion on May 23, 2022 that BREEZE—a study submitted with the Tyvaso DPI NDA—was a bioavailability study that did not warrant NCI exclusivity, Ex. E at 1, FDA relied entirely on BREEZE to justify NCI exclusivity. Ex. A at 38. FDA determined that Tyvaso DPI has NCI exclusivity until May 23, 2025, for all "inhalation powder dosage form of the active moiety treprostinil for chronic use." *Id*. FDA granted such exclusivity even though it had previously found that TRIUMPH and INCREASE had provided sufficient evidence of safety and effectiveness of treprostinil when administered by oral inhalation.

In the Exclusivity Decision, FDA conceded that UTC had "relied on safety and efficacy data submitted in the Tyvaso NDA and provided relative bioavailability data to justify extrapolation of the previously submitted data to Tyvaso DPI." *Id*. at 12. That safety and efficacy

data was specifically from TRIUMPH and INCREASE. *Id.* The logical inference is that UTC submitted BREEZE as relative bioavailability data. In the Decision, FDA acknowledged that BREEZE provided bioavailability data supporting the Tyvaso DPI NDA, since the bioavailability and safety profiles of Tyvaso and Tyvaso DPI are similar (though they differ in dosage form and certain features of use). Nevertheless, FDA determined that BREEZE was "not considered to be ***solely*** a bioavailability study." *Id.* at 20 (emphasis added). FDA did not identify any support in the FDCA or its regulations for the conclusion that a study must be ***solely*** a bioavailability study to qualify as a bioavailability study under the FDCA. 21 U.S.C. § 355(c)(3)(E)(iii). Nor did FDA acknowledge its determination over two years earlier that Tyvaso DPI did not qualify for NCI exclusivity because there were no new clinical studies provided with the Tyvaso DPI NDA and the NDA merely required review of bioavailability data (*i.e.*, BREEZE ***was*** a bioavailability study). *Compare* Ex. A, *with* Ex. E.

The Exclusivity Decision delays approval of Yutrepia for both the PAH and PH-ILD indications—*i.e.*, the specific conditions for which Yutrepia is intended as a treatment option for patients—for at least nine months. Ex. A at 38. Thus, although FDA has found Yutrepia is safe and effective to treat patients with PAH and PH-ILD, and included drug labeling for Yutrepia covering both the PAH and PH-ILD indications, Liquidia cannot lawfully launch Yutrepia for ***any*** indication because of the NCI exclusivity that FDA erroneously awarded to Tyvaso DPI on the basis of BREEZE. *Id*. at 19.

H. FDA's Exclusivity Decision Will Cause Irreparable Harm to Liquidia.

FDA's award of NCI exclusivity to Tyvaso DPI, and its resulting failure to provide full approval for Yutrepia on that basis, poses immediate and substantial harm to Liquidia. Absent relief from this Court, Liquidia faces substantial harm from the Exclusivity Decision. Had FDA granted full approval to distribute Yutrepia effective August 16, 2024, Liquidia was ready to

launch marketing by early September 2024. Declaration of Mike Kaseta ("Kaseta Decl.") ¶ 10. Now, as a result of the Exclusivity Decision, Liquidia is deprived of the opportunity to market Yutrepia for at least nine months—time that Liquidia can ***never*** get back. *Id*. ¶¶ 9–10. The permanent loss of that marketing opportunity prevents Liquidia from realizing any economic gain for at least three quarters in a market for inhaled treprostinil that has an estimated current run rate of $1.5 billion and the potential to grow in excess of $3 billion in the coming years. *Id*. ¶ 10. FDA's Exclusivity Decision deprives Liquidia's salesforce of the ability to carry out their duties and responsibilities to secure sales of Yutrepia and generate revenue from those sales for at least nine months. *Id*. ¶¶ 11. By depriving Liquidia of the opportunity to market Yutrepia immediately, the Exclusivity Decision also threatens Liquidia's operations by depriving Liquidia of revenue that Liquidia would use to alleviate operating losses and jeopardizing funding of Liquidia's research and development programs. *Id*. ¶¶ 12–14. Full approval of Yutrepia effective immediately for any of its intended uses would prevent these harms to Liquidia. *Id*. ¶ 15.

LEGAL STANDARD

The issuance of a preliminary injunction is within this Court's sound discretion, *Bayer Healthcare, LLC v. FDA*, 942 F. Supp. 2d 17, 23 (D.D.C. 2013), and is appropriate when (1) the movant is likely to succeed on the merits, (2) the movant is likely to suffer irreparable harm absent relief, (3) the balance of equities tips in the movant's favor, and (4) issuance of an injunction is in the public interest. *Winter*, 555 U.S. at 20. Liquidia satisfies each factor.

ARGUMENT

I. LIQUIDIA HAS A STRONG LIKELIHOOD OF SUCCESS ON THE MERITS OF ITS APA CLAIMS CHALLENGING FDA'S UNLAWFUL EXCLUSIVITY DECISION.

The likelihood of success on the merits is the "most important factor" in evaluating a preliminary motion injunction. *See Aamer v. Obama*, 742 F.3d 1023, 1038 (D.C. Cir. 2014).

"[T]he APA delineates the basic contours of judicial review of such action." *Loper Bright*, 144 S. Ct. at 2261. Under the APA, a court must "hold unlawful and set aside agency action, findings, and conclusions found to be … arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," or "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2), (A), (C). Liquidia has a strong likelihood of success on the merits of its APA claims challenging FDA's Exclusivity Decision.

A. FDA Exceeded Its Statutory Authority and Acted Contrary to Law.

At this preliminary juncture, Liquidia's APA claims require this Court to determine whether FDA likely exceeded its statutory authority and acted contrary to the FDCA and FDA regulations. The method by which this Court must review the APA issues raised in this case was recently settled by the Supreme Court. As the Court instructed in *Loper Bright*, under the APA, "courts, not agencies, will decide '***all relevant questions of law***' arising on review of agency action." 144 S. Ct. at 2261 (citing 5 U.S.C. § 706) (emphasis added). The APA "prescribes ***no*** deferential standard … to employ in answering … legal questions." *Id.* (emphasis added). Instead, "[c]ourts ***must*** exercise their independent judgment in deciding whether an agency has acted within its statutory authority, as the APA requires." *Id.* at 2273 (emphasis added).

In performing its review, the court must "police the outer statutory boundaries" of any authority delegated to the agency to "ensure that agencies exercise their discretion consistent with the APA." *Id.* at 2268. Thus, unlike every prior case addressing NCI exclusivity (which relied on now-abrogated *Chevron* deference), this Court must determine the "best reading of the statute and resolve the ambiguity" in a statutory provision, if any. *Id*. at 2266. *Loper Bright* confirmed what the D.C. Circuit has long recognized, that under the APA "[t]he judiciary remains the final authority with respect to questions of statutory construction and must reject administrative agency actions which exceed the agency's statutory mandate or frustrate congressional intent," *American*

Financial Services Association v. FTC, 767 F.2d 957, 968 (D.C. Cir. 1985), and that agency action is contrary to law "[i]n the absence of statutory authorization for its act." *Hikvision USA, Inc. v. FCC*, 97 F.4th 938, 944 (D.C. Cir. 2024) (quoting *Atl. City Elec. Co. v. FERC*, 295 F.3d 1, 8 (D.C. Cir. 2002)).

As for FDA's application of its regulations governing NCI exclusivity, agency action is contrary to law when the agency acts contrary to its own regulations. *See Nat'l Env't. Dev. Ass'ns Clean Air Project v. EPA*, 752 F.3d 999, 1009 (D.C. Cir. 2014) ("[An] agency is not free to ignore or violate its regulations while they remain in effect.") (internal quotation marks and citation omitted); *Accrediting Council for Indep. Colls. & Schs. v. Devos*, 303 F. Supp. 3d 77, 104 (D.D.C. 2018) ("the Secretary's violation of the [statute] and the regulations … independently support findings that the APA was violated").

This Court reviews an agency's interpretation of its own regulations pursuant to the framework in *Kisor v. Wilkie*, 585 U.S. 558, 607 (2019). Under this framework, the court cannot afford deference to FDA's interpretation of its regulations "unless, after exhausting all the 'traditional tools' of construction, … the regulation is genuinely ambiguous." *Id.* at 574. Even if a court determines a regulation is ambiguous, *Kisor* requires that the agency's interpretation must be ***reasonable***, 588 U.S. at 575-76, and even then "countervailing reasons" may "outweigh" deference. *Id.* at 573.

Applying these standards, Liquidia has a strong likelihood of success on its APA claims that FDA exceeded its authority and acted contrary to law because Tyvaso DPI is ineligible for NCI exclusivity based on BREEZE. Even if any NCI exclusivity could attach (it could not), FDA has exceeded the bounds of its authority under the FDCA by extending NCI exclusivity beyond the narrow scope of any exclusivity BREEZE could possibly provide for Tyvaso DPI.

1. Tyvaso DPI Was Ineligible for NCI Exclusivity Because BREEZE Was Not a New Clinical Investigation.

FDA Exclusivity's Decision fails at the outset because BREEZE—the sole study underlying FDA's Exclusivity Decision awarding NCI exclusivity to Tyvaso DPI—fails threshold statutory and regulatory requirements. 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108(a).

a. BREEZE Is a Bioavailability Study that Cannot Support NCI Exclusivity as a Matter of Law.

FDA's determination that Tyvaso DPI was eligible for NCI exclusivity was contrary to law because BREEZE is a bioavailability study that cannot support NCI exclusivity as a matter of law.

The text of the FDCA is the starting point. *Cmty. for Creative Non-Violence v. Reid*, 490 U.S. 730, 739 (1989). The FDCA unambiguously instructs that NCI exclusivity is limited to a drug application that "contains reports of new clinical investigations (***other than bioavailability studies.***)" 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). The plain language of this provision means that—whatever the scope of the statutory phrase "new clinical investigations" (which is discussed below, *see infra* Part I.A.1.b)—"bioavailability studies" are categorically ***excluded*** from the types of NCIs that could legally support exclusivity. FDA's regulations similarly define "[c]linical investigation" to mean "any experiment ***other than a bioavailability study*** in which a drug is administered or dispensed to, or used on, human subjects." 21 C.F.R. § 314.108(a) (emphasis added). Thus, like the FDCA, FDA regulations categorically exclude bioavailability studies from clinical investigations that could trigger NCI exclusivity.

There can be no serious question that BREEZE is a bioavailability study ineligible for NCI exclusivity. First, FDA itself recognized that BREEZE is a bioavailability study in May 2022 when it approved Tyvaso DPI. *See* Ex. E at 1. Indeed, over two years before it issued the Exclusivity Decision, FDA prepared an exclusivity summary for Tyvaso DPI in which FDA had already deemed BREEZE a bioavailability study. *Id.* Second, BREEZE evaluated the absorption

in patients of Tyvaso DPI, which alone would render the study a bioavailability study under the FDCA's statutory text.[32] Third, in the Exclusivity Decision, FDA itself repeatedly recognized that BREEZE's endpoints were bioavailability endpoints. *See* Ex. A at 14 (recognizing that an "endpoint" of the study was "PK assessment[] after administration of each treatment"). Because BREEZE was a bioavailability study, FDA could not rely on it as the basis for NCI exclusivity. This alone renders the Exclusivity Decision in excess of FDA's statutory authority, and contrary to the FDCA and FDA regulations.

FDA's assertion in the Exclusivity Decision that it did not consider BREEZE to be "solely" a bioavailability study cannot salvage the Decision. *Id.* at 20. The FDCA ***categorically excludes*** "bioavailability studies" from the types of new clinical investigations eligible for NCI exclusivity. 21 U.S.C. § 355(c)(3)(E)(iii). FDA regulations similarly exclude "a bioavailability study" from the definition of a "clinical investigation" that can trigger NCI exclusivity. 21 C.F.R. § 314.108(a). There is ***no*** exception for bioavailability studies that also include other endpoints that would not be treated as a bioavailability study if taken in isolation. FDA's interpretation in the Exclusivity Decision improperly inserts the word "solely" into the FDCA and FDA regulations. But FDA has ***no*** authority to rewrite the statute. *See ASARCO, Inc. v. EPA*, 578 F.2d 319, 327 (D.C. Cir. 1978) ("The agency has no authority to rewrite the statute in this fashion."). Nor can FDA "constructively rewrite the regulation … through internal memoranda or guidance directives that incorporate a totally different interpretation and effect a totally different result." *Nat'l Family Planning & Reprod. Health Ass'n, Inc. v. Sullivan*, 979 F.2d 227, 236 (D.C. Cir. 1992); *see also Zhang v. U.S. Citizenship & Immigr. Servs.*, 344 F. Supp. 3d 32, 58 (D.D.C. 2018) ("[A] policy that adds a requirement not found in the relevant regulation is a substantive rule that is invalid

[32] *See* The BREEZE Study, *supra* note 25.

unless promulgated after notice and comment."). This, too, renders the Exclusivity Decision in excess of statutory authority and contrary to law.

b. BREEZE Was Not a New Clinical Investigation.

FDA's determination that Tyvaso DPI was eligible for NCI exclusivity was further contrary to law because BREEZE was not a new clinical investigation, but rather a "confirmatory" study that duplicated the results of ***prior*** investigations whose results UTC had submitted to FDA to demonstrate the safety and efficacy of Tyvaso.

The FDCA unambiguously states that NCI exclusivity is limited to a drug application that "contains reports of ***new*** clinical investigations (other than bioavailability studies)." 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). The FDCA does not define the phrase "new clinical investigations," but FDA regulations do. In the FDA regulation that implements the FDCA's NCI exclusivity provision, FDA defines the statutory phrase "[n]ew clinical investigation" as "an 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." 21 C.F.R. § 314.108(a) (emphasis added).

BREEZE fails to meet the threshold requirement of a "new clinical investigation" because its results duplicated TRIUMPH and INCREASE—studies that UTC had previously provided FDA and on which FDA had relied to approve Tyvaso DPI. Specifically, BREEZE was "conducted in 51 [PAH] patients on stable doses of Tyvaso who switched to a corresponding dose of Tyvaso DPI." Ex. G at 3. BREEZE compared these patients' baselines prior to the switch to three weeks after starting Tyvaso DPI and ultimately found "comparable systemic exposure [of treprostinil] between the two formulations." *Id.* at 2. Thus, at most, BREEZE merely confirmed

that ***PAH patients already taking Tyvaso*** would not face adverse consequences when taking an equivalent dose of treprostinil in dry powder format. The duplicative nature of BREEZE's results is the very reason why FDA has repeatedly stated that BREEZE was merely a "***confirmatory*** study." Ex. E at 1 (emphasis added); Ex. F at 13 (FDA's May 2022 clinical review for Tyvaso DPI concluded that BREEZE merely identified "[n]o new risks associated with treprostinil formulated as an inhaled powder (Tyvaso DPI) were identified in the BREEZE study."); Ex. A at 15 (FDA's conclusion in the Exclusivity Decision that "[n]o new risks associated with treprostinil formulated as an inhaled powder (Tyvaso DPI) were identified in the BREEZE study."). Because BREEZE merely duplicated the results of TRIUMPH and INCREASE, it cannot qualify as a "new clinical investigation" under FDA's regulations. Thus, FDA's determination was contrary to law.

2. Tyvaso DPI Was Ineligible for NCI Exclusivity Because BREEZE Was Not Essential to the Approval of Tyvaso DPI.

FDA's grant of NCI exclusivity was also unlawful because the BREEZE Study was not "essential" to the approval of Tyvaso DPI. Even if a study qualifies as a new clinical investigation, the FDCA requires that the investigation must be "essential to the approval of the application." 21 U.S.C. § 355(c)(3)(E)(iii). The FDCA does not define the phrase "essential to approval." Consistent with the FDCA's intent to reward innovation through the Hatch-Waxman Amendments, FDA's regulations define the phrase "essential to approval" to mean, "with regard to an investigation, that there are no other data available that could support approval of the NDA." 21 CFR § 314.108(a). BREEZE does not satisfy this regulatory requirement.

BREEZE was not "essential" to the approval of Tyvaso DPI because there were "other data that could [and did] support approval of the NDA." Ex. A at 10. UTC had already established the required safety and efficacy criteria essential to FDA approval with TRIUMPH and INCREASE. And because there was already data available, BREEZE was simply a "confirmatory study"

corroborating that the safety results for "patients with PAH currently treated with treprostinil inhalation solution [Tyvaso]" that were switched to Tyvaso DPI had comparable outcomes at the three-week mark. Ex. G at 4. Merely "confirming" that equivalent doses of treprostinil (via Tyvaso DPI) would not harm PAH patients who switched from the same dosing of treprostinil (via Tyvaso) cannot satisfy the regulatory standard for a study that is "essential to the approval" of an NDA. This independently renders Tyvaso DPI ineligible for NCI exclusivity based on BREEZE under the FDCA and FDA regulations.

3. FDA's Exclusivity Decision Exceeds the Limited Scope of NCI Exclusivity that the FDCA Allows for the "Conditions of Approval."

Liquidia also is likely to prevail on its APA claims that FDA exceeded its statutory authority and acted contrary to law in granting NCI exclusivity to Tyvaso DPI that exceeds the narrow scope of exclusivity permitted by the FDCA. FDA acted contrary to law by applying NCI exclusivity for Tyvaso DPI to block Yutrepia entirely, let alone for each indication.

a. Under the FDCA, the "Conditions of Approval" Must Be Linked to the Innovative Change Presented by the New Clinical Investigation that Makes a Drug Eligible for Exclusivity.

The FDCA prohibits FDA from granting boundless NCI exclusivity even if a drug is eligible for such exclusivity. The FDCA unambiguously provides that NCI exclusivity attaches only "for the ***conditions of approval*** of such drug." 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). Thus, the "conditions of approval" of the first NDA delineate the outer boundaries of NCI exclusivity that FDA may lawfully extend to a drug without running afoul of the FDCA. After identifying the "conditions of approval" of the first NDA, the next step is to "identif[y] the relevant conditions of approval ***shared*** between [the drug receiving NCI exclusivity and the competitor drug's NDA]," as NCI exclusivity covers only the overlap between the conditions of approval. *Veloxis*, 109 F. Supp. 3d at 120 (emphasis added).

In determining the meaning of the FDCA's undefined phrase "conditions of approval," it is the role of this Court to determine its plain meaning and, if it is ambiguous, to "use every tool at [its] disposal to determine the best reading of the statute and resolve the ambiguity." *Loper Bright*, 144 S. Ct. at 2266; *cf. Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, 23 (D.D.C. 2019) ("Section 355(c)(3)(E)(iii)'s ambiguity is not a license for the FDA to adopt any interpretation it chooses.").

As FDA has acknowledged, and courts have made clear, "the scope of [NCI] exclusivity … 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 … NDA." *Veloxis*, 109 F. Supp. 3d at 121 n.16 (emphasis added). This is the best reading of the FDCA's NCI exclusivity provision, and it aligns with prior decisions in this district. Specifically, in *Braeburn*, the court opined that the most plausible meaning of "conditions of approval" in the FDCA is "tied to the specific characteristics of the drug that warranted exclusivity in the first instance," *i.e.*, "the novel indications or patient populations for which the drug product may be used." 389 F. Supp. 3d at 22–23. As *Braeburn* noted, this interpretation "serv[es] the Hatch-Waxman Amendments' objective of finding an equilibrium that protects research and leaves room for market competition." *Id.* at 23. Similarly, the court in *AstraZeneca*, held that the FDCA's "conditions of approval" require 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." 872 F. Supp. 2d at 80.

Thus, the scope of NCI exclusivity, if any, must be limited to the innovative changes presented by the new clinical investigation that were necessary for approval of the application. *See id.* at 83 (opining that the "substantive relationship between new clinical studies and changes in the [NDA] ... dictates what changes receive exclusivity"); *see also* 54 Fed. Reg. 28872, 28896

(July 10, 1989) ("Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product."). A study showing a drug's active ingredient is safe and effective for a given indication or use cannot justify NCI exclusivity if FDA previously approved an NDA based on a study showing the safety and effectiveness of the same active ingredient for the same indication or use. Only an NDA with "new clinical investigations" and new safety and efficacy findings for "new indications or uses of the already approved pioneer drug" may receive NCI exclusivity—and only for those "new indications or use." *AstraZeneca*, 872 F. Supp. 2d at 64, 85.

b. FDA's Exclusivity Decision Flouts the FDCA's Boundaries.

The Exclusivity Decision flouts the FDCA's boundaries limiting the scope of NCI exclusivity to the innovation supported by a new clinical investigation. The Exclusivity Decision improperly confers sweeping NCI exclusivity to Tyvaso DPI across the entire "inhalation powder dosage form for the active moiety treprostinil for chronic use," Ex. A at 30, for both the PAH and PH-ILD indications. This sweeping exclusivity was unlawful because BREEZE, a 3-week confirmatory study, was not designed to study "chronic use." FDA exceeded its statutory authority and acted contrary to law when it awarded NCI exclusivity to Tyvaso DPI for this broad use rather than the limited set of "conditions of approval" that BREEZE could support.

First, the Tyvaso DPI NDA did not actually contain an innovation that could justify an award of NCI exclusivity. In the Exclusivity Decision, FDA asserted that "the innovation represented by Tyvaso DPI for which a new clinical investigation [the BREEZE Study] was essential is the inhalation powder dosage form for the active moiety treprostinil for chronic use." Ex. A at 30. But Liquidia—not UTC—was the true innovator of this form of treprostinil. As FDA recognized in the Decision, "Yutrepia is a proposed treprostinil inhalation powder for chronic use." *Id.* at 38. Liquidia submitted an NDA for an inhalation powder dosage form of treprostinil (*i.e.*,

Yutrepia) in 2020. *Id.* at 18. And as FDA recognized, FDA gave Liquidia tentative approval to Yutrepia on November 4, 2021. *Id.* Thus, the purportedly innovative change reflected in Tyvaso DPI was ***already*** the subject of NDA submitted by a different applicant (*i.e.*, Liquidia) nearly a year and a half ***before*** FDA approved the Tyvaso DPI on May 23, 2022.

Second, even if Tyvaso DPI's inhalation powder dosage form were deemed an innovative change, the Exclusivity Decision flouts the FDCA because BREEZE did not adequately study that change, let alone in any way that could justify an award of NCI exclusivity. According to FDA, "the BREEZE study answered for the first time whether the active moiety treprostinil administered as an inhalation powder is safe and tolerable for chronic use." Ex. A at 30. However, as FDA recognized in the Exclusivity Decision, the data BREEZE provided was "***limited***." *Id.* at 15, 21 (emphasis). The purported safety data that FDA highlights in the Decision is from the three-week treatment phrase of BREEZE. *Id.* at 17 (Table 1 graphic). That 3-week period of the study was ***not*** designed to evaluate long-term safety; that issue was for the optional extension phase in the study "**[*a*]*fter*** completing the 3-week treatment phase."[33] Even accounting for the results from BREEZE's optional phase along with the treatment phase, none of BREEZE's findings were adequate to address chronic use of treprostinil administered as an inhalation powder. BREEZE was merely "an open-label, unblinded study with short follow-up and without a control group and was ***not*** designed to show improvement in efficacy."[34] Thus, by its very design, BREEZE could not generate meaningful answers to the purported question for which FDA claimed a new clinical investigation was necessary.

Third, even if BREEZE's defects were ignored (and they should not be), FDA's grant of

[33] The BREEZE Study, *supra* note 25 at 3 (emphasis added).
[34] *Id.* at 12 (emphasis added).

NCI exclusivity to Tyvaso DPI for PAH and PH-ILD patients was unlawful. It is undisputed that the Tyvaso DPI NDA had ***no*** clinical investigations with PAH patients who did ***not*** switch from Tyvaso to Tyvaso DPI. Instead, BREEZE studied a narrow patient population—PAH patients who were already taking stable doses of Tyvaso. *Id.* at G at 2. As FDA explained, BREEZE 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. *Id.* at 4. BREEZE ***excluded*** all other PAH patients (*i.e.*, patients not already taking stable doses of Tyvaso). It is also undisputed that BREEZE, by design, ***excluded*** PH-ILD patients. FDA could not lawfully grant Tyvaso DPI any NCI exclusivity for treatment of PAH patients who did not switch from Tyvaso or lawfully grant Tyvaso DPI any NCI exclusivity for treatment of PH-ILD patients because neither could have been a "condition of approval" for Tyvaso DPI due to BREEZE's narrow design. FDA's contrary determination reaches beyond the boundaries set by the FDCA and FDA regulations and grants NCI exclusivity for "conditions of approval" BREEZE does not establish.

B. FDA's Exclusivity Decision Is Arbitrary and Capricious.

Liquidia is likely to prevail on its claim that FDA's application of the statutory and regulatory standards in the Exclusivity Decision was arbitrary and capricious. An agency acts arbitrarily or capriciously if it "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). An agency also acts arbitrarily and capriciously when it "decides to change" course but fails to "supply a reasoned analysis indicating prior policies are being deliberately changed, not casually ignored." *Nuclear Energy Inst., Inc. v. EPA*, 373 F.3d 1251, 1296 (D.C. Cir. 2004) ("If an agency decides to change

course we require it to supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored." (internal quotation marks and citation omitted)). FDA's Exclusivity Decision cannot survive arbitrary and capricious review here.

1. FDA's Novel Determination that BREEZE Is a New Clinical Investigation Contradicted FDA's Prior Conclusions.

FDA's novel determination in the Exclusivity Decision that BREEZE can justify NCI exclusivity for Tyvaso DPI is arbitrary and capricious because it contradicts FDA's prior conclusions over two years ago—conclusions that FDA failed even to acknowledge. First, FDA's determination in the Exclusivity Decision that "[t]he BREEZE study … qualifies as a *new* clinical investigation," Ex. A at 20 (emphasis in original), contradicts FDA's contrary conclusion years earlier. On May 23, 2022, the same day FDA gave final approval to Tyvaso DPI, FDA issued an Exclusivity Summary in which it determined that the Tyvaso DPI contained ***no*** reports of clinical investigations. Ex. E at 3. On that basis alone, contemporaneous with FDA's approval of Tyvaso DPI, FDA determined that the studies provided with the Tyvaso DPI could ***not*** be either "new clinical investigations" or "essential to the approval" of Tyvaso DPI. *Id.* at 3–5. FDA fails to acknowledge in the Exclusivity Decision that its new conclusion contradicts its prior conclusion, let alone explain that reversal. This is the hallmark of arbitrary and capricious agency action.

Second, FDA's determination in the Exclusivity Decision that BREEZE was "considered" to be "an investigation *other than a bioavailability study*," Ex. A at 20 (emphasis in original), contradicts the same 2022 Exclusivity Summary. In fact, FDA recognized in the Exclusivity Summary that BREEZE ***is*** a bioavailability study. Ex. A at 1. The Exclusivity Decision itself also appears to acknowledge that BREEZE is a bioavailability study when it notes that, "[t]o support approval of Tyvaso DPI, [UTC] relied on safety and efficacy data submitted in the Tyvaso NDA and provided ***relative bioavailability data*** [from TIP-PH-102 and BREEZE] to justify

extrapolation of the previously submitted data to Tyvaso DPI." Ex. A at 12 (emphasis added). The Exclusivity Decision's inconsistency with FDA's own prior determination and FDA's related failure to acknowledge that FDA was adopting a new conclusion, is arbitrary and capricious.

2. FDA's Determination in the Exclusivity Decision that BREEZE Was a New Clinical Investigation Was Implausible Under FDA's Longstanding Policy.

FDA's determination that BREEZE qualified as a "new clinical investigation" was arbitrary and capricious because it was implausible under FDA's longstanding policy regarding the types of studies that will be eligible for NCI exclusivity. When it promulgated regulations to implement the Hatch-Waxman Amendments nearly 35 years ago, FDA staked out its position that NCI exclusivity under § 505(c)(3)(E)(iii) is "limit[ed] … to changes in a drug product that are significant enough to require human safety or effectiveness studies for approval." 54 Fed. Reg. at 28899. FDA explained that "most studies qualifying for exclusivity will be ***efficacy studies***," with "occasional clinical investigations qualifying for exclusivity that establish that a product ***is safer*** than originally thought and that ***permit broader use*** of the drug." *Id.* (emphasis added).

BREEZE does not qualify as a new clinical investigation under this policy. BREEZE "was ***not*** designed to show improvement in efficacy." Ex. G at 12 (emphasis added). Nor could BREEZE establish that Tyvaso DPI—the specific product under review in the Tyvaso DPI NDA—was safer than originally thought. While FDA repeatedly asserts in the Exclusivity Decision that BREEZE studied a "broader use of treprostinil," Ex. A at 24 n.87, 25, 26, this conclusory statement is belied by the study's design and results. BREEZE ***did not*** establish that Tyvaso DPI was safer than Tyvaso Inhalation Solution. As discussed above, FDA found only that BREEZE ***confirmed*** the safety profile of treprostinil already known to FDA in the drug's two forms. BREEZE also did not study an expanded patient population to support a "broader use" of treprostinil because it was, in fact, ***limited*** to a population switching from a nebulized solution form of treprostinil (*i.e.*,

Tyvaso) to Tyvaso DPI. As to these patients, FDA has repeatedly recognized that "(BREEZE) provide[d] limited safety data." Ex. F at 32; *see also* Ex. A at 15 (noting that "BREEZE study provided limited safety data"). And, as FDA notes in the Exclusivity Decision, the median overall population change in the patient-reported outcome measure in BREEZE was ***zero***, which suggests that the median patient did not experience any detectable improvement in symptoms. *Id.* at 16. The conclusion that BREEZE did not support "broader use" is further evidenced by the final label for Tyvaso DPI, which covers the ***same*** patient population as the label for Tyvaso.[35] Thus, the Exclusivity Decision cannot be justified under FDA's own interpretation of the types of investigations that may qualify for NCI exclusivity.

3. FDA's Determination that BREEZE Was Essential to the Approval of Tyvaso DPI Was Irrational and Plainly Contrary to the Evidence.

FDA's determination that BREEZE was essential to the approval of Tyvaso DPI was arbitrary and capricious because it was irrational and contrary to the evidence before the agency.

First, FDA could not rationally conclude that BREEZE "was essential to the approval of treprostinil in a new dosage form, *i.e.*, inhalation powder," Ex. A at 25, given that FDA had ***already*** determined—in November 2021—that Yutrepia satisfied safety and efficacy requirements ***without*** the safety and efficacy data in BREEZE that was purportedly essential. In the Exclusivity Decision, FDA opined that BREEZE "assessed a specific safety question, the tolerability of multiple doses daily over multiple weeks of treprostinil in the new inhalation powder dosage form to support approval for chronic use." *Id.* However, as the Exclusivity Decision recognizes, Yutrepia and Tyvaso DPI are both "inhalation powder" treprostinil drugs intended "for chronic

[35] 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.").

use." *Id.* at 38. And as FDA acknowledges, it provided tentative approval to Yutrepia in November 2021. *Id.* at 37 n.146. FDA gave that tentative approval to Yutrepia—nearly six months ***before*** FDA approved Tyvaso DPI—because FDA determined Yutrepia met ***all*** requirements under the FDCA and FDA regulations for approval, including safety and efficacy requirements. Ex. D. The safety and efficacy data Liquidia referenced in the Yutrepia NDA was the data for the listed Tyvaso drug—the same data UTC also referenced to obtain FDA approval for Tyvaso DPI. Ex. A at 12 (Exclusivity Decision, noting that Tyvaso DPI, though submitted as a 505(b)(1) application, was similar to a 505(b)(2) application in that it relied on data previously submitted to FDA by UTC). Thus, FDA cannot rationally assert that BREEZE was "essential to approval" of a dry powder formulation of treprostinil when FDA had already determined that Yutrepia satisfied safety and efficacy requirements without such data. FDA's Exclusivity Decision fails to acknowledge, let alone explain, its novel and contradictory "essential to approval" finding.

Second, if approval of Tyvaso DPI hinged on the need for data concerning the safety of the drug for chronic use, as FDA asserted in the Exclusivity Decision, *see* Ex. A at 23, BREEZE was not designed to answer that question, let alone with adequate data. *See supra* Part I.A.2.b. As discussed above, the purported safety data that FDA highlights in the Exclusivity Decision comes from the ***three-week*** treatment phrase of BREEZE. Ex. A at 17. That phase was ***not*** designed to evaluate long-term safety; that issue was for the optional extension phase in the study "**[*a*]*fter*** completing the 3-week treatment phase."[36] Even accounting for the optional phase, BREEZE could not generate findings adequate to address the question. BREEZE was merely "an open-label, unblinded study with short follow-up and without a control group and was ***not*** designed to

[36] The BREEZE Study, *supra* n.25 at 3 (emphasis added).

show improvement in efficacy."[37] As FDA itself recognized in the Exclusivity Decision, the data BREEZE provided was "limited." Ex. A at 15, 21. Thus, FDA could not plausibly rely on BREEZE itself as adequate evidence of the safety of Tyvaso DPI for "chronic use," let alone as evidence that could justify an award of NCI exclusivity.

Third, the Exclusivity Decision is also arbitrary and capricious because FDA does not explain how BREEZE was "essential to the approval" of Tyvaso DPI for both the PAH and PH-ILD indications.[38] As noted above, BREEZE did not study use of Tyvaso DPI in the PH-ILD population. The ***only*** safety and efficacy data available before the agency for that indication came from INCREASE, a study that triggered a prior period of NCI exclusivity that expired in March 2024. FDA therefore cannot logically assert that BREEZE was essential to the approval of Tyvaso DPI for the PH-ILD indication because the record plainly shows that BREEZE provided no safety and efficacy data for that indication. This alone renders FDA's "essential to approval" determination arbitrary and capricious for the PH-ILD indication.

4. FDA Failed to Articulate the "Conditions of Approval" for Tyvaso DPI or How Those Conditions Could Block Full Approval of Yutrepia.

FDA's Exclusivity Decision violates the APA because BREEZE does not satisfy FDA's own longstanding interpretation of the statutory phrase "conditions of approval" and, therefore, departs without explanation from FDA's own practices. *See Physicians for Soc. Resp. v. Wheeler*, 956 F.3d 634, 644 (D.C. Cir. 2020) ("Reasoned decision-making requires that when departing from precedents or practices, an agency must 'offer a reason to distinguish them or explain its apparent rejection of their approach.'") (citation omitted); *Dillmon v. NTSB*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009) (reasoned decision-making "necessarily requires the agency to acknowledge

[37] *Id.* at 12 (emphasis added).
[38] Tyvaso Label, *supra* note 35.

and provide an adequate explanation for its departure from established precedent").

FDA has long interpreted the FDCA's NCI exclusivity provision to protect only the ***innovative change*** for which the new clinical investigations are essential to approval. *See supra* Part I.A.2; *see also* Ex. J 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); *Veloxis*, 109 F. Supp. 3d at 121 n.16. ("[C]onditions 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.").

Here, there is no innovative change studied by BREEZE that could support the scope of NCI exclusivity that FDA awarded. The FDA has made no findings based on BREEZE that would be broadly applicable to all dry powder formulations of treprostinil. If Tyvaso DPI presents any innovative change, it could only be found in its specific drug-delivery device or the unique formulation and aerodynamic properties of the powder that allows the drug product to reach the lungs without getting caught in the airways. If the innovative change is attributable to the device, however, then that innovative change has not been supported by any clinical studies examining that device. And if the innovative change is attributable to the specific formulation or aerodynamic properties, then there must be a logical relationship between that change and the study for BREEZE to support an award of NCI exclusivity. At most, BREEZE would support NCI exclusivity limited to the unique formulation and aerodynamics properties of the powder for the specific patient population studied. Thus, FDA's decision to award NCI exclusivity to Tyvaso DPI on the basis of BREEZE ran contrary to FDA's own interpretation of the FDCA's requirement that the scope of such exclusivity must be limited to the "conditions of approval" for the prior drug.

5. FDA Arbitrarily Refused to Limit the "Conditions of Approval" for Tyvaso DPI to the Indications and Uses Studied In BREEZE.

FDA acted arbitrarily and capriciously when it refused to limit the scope of NCI exclusivity for Tyvaso DPI to the patient populations and uses studied in BREEZE. In the Exclusivity Decision, after concluding that BREEZE's purported "innovation" was "answer[ing] for the first time whether the active moiety treprostinil administered as an inhalation powder is safe and tolerable for chronic use," Ex. A at 30, FDA stated without explanation that it was "***not necessary*** to address whether the exclusivity-protected condition of approval is limited by the approved indications," *id*. at 30 n.110 (emphasis added). FDA's refusal to address this issue was arbitrary and capricious as FDA has previously limited the scope of NCI exclusivity to the precise indications covered by new clinical investigations when present (unlike here).

In practice, FDA has limited the scope of NCI exclusivity for a drug by the approved indications, which includes both the patient population and the dosage. For example, in *Veloxis*, FDA determined that two new clinical studies made a drug eligible for NCI exclusivity where the studies addressed "[extended release] dosage form and its once-daily dosing regimen [for *de novo* patients], both of which were changes from the previously approved … drug." 109 F. Supp. 3d at 111 (alterations in original); *see also* Ex. J at 1 (finding that NCI exclusivity for Astagraf XL "is based on the new clinical investigations essential to the approval of the once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients"). In another example, FDA addressed the scope of NCI exclusivity that FDA would recognize for a study conducted by the Teva Pharm for Plan B. *See* Ex. K. There, FDA expressly rejected an overly broad exclusivity request and limited it to "nonprescription use in" specific "populations (women ages 15 and 16 and women ages 14 and below)" because those were the populations actually studied in the new clinical investigation on which Teva relied for approval.

Id. at 6. Thus, again, the actual population in which the applicant conducted the study limited the scope of the NCI exclusivity FDA granted.

The Exclusivity Decision departs from FDA's past practices without explanation. It fails to address the sweeping scope of NCI exclusivity it has granted to Tyvaso DPI or reconcile that scope with its own statement with respect to Astagraf XL that exclusivity does not attach to an indication or to a patient population for which the applicant has not conducted the clinical investigations essential to support the drug's approval. Specifically, FDA acknowledges in its Astagraf XL Exclusivity Decision that the applicant "***did not conduct*** those clinical investigations that would have been necessary to support" use in conversion patients and thus could not receive NCI exclusivity for that use. Ex. J at 41 (emphasis added). Yet, FDA failed to engage in the same analysis of the BREEZE Study and the NCI exclusivity it awarded to Tyvaso DPI, which would have limited any NCI exclusivity to the patient population studied in BREEZE, *i.e.*, PAH patients (not PH-ILD patients) switching from a stable dose of Tyvaso inhalation solution. FDA's omissions here are acutely egregious in the context of treprostinil because the agency has recognized in its previous approvals of this same active moiety that PAH and PH-ILD are ***different*** diseases that warrant different treatment.[39] The record before FDA is clear that BREEZE was ***not*** conducted in the PH-ILD population, one of Yutrepia's intended uses. By failing to consider whether Tyvaso DPI's NCI exclusivity should be limited only to the patients BREEZE studied, FDA arbitrarily allowed Tyvaso DPI to receive exclusivity not supported by the alleged new clinical investigation on which it relied in violation of FDA's own precedents.

II. LIQUIDIA WILL SUFFER IRREPARABLE HARM ABSENT AN INJUNCTION.

Liquidia faces substantial irreparable harm as a result of FDA's Exclusivity Decision. An

[39] *See Orphan Drug Designation: Disease Considerations*, *supra* note 5.

injury warrants injunctive relief when it is "beyond remediation" and is "of such *imminence* that there is a 'clear and present' need for equitable relief to prevent irreparable harm." *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006) (citation omitted). Injunctive relief is necessary here to prevent the certain and irreparable harm Liquidia will suffer if the Exclusivity Decision is not enjoined.

First, absent preliminary injunctive relief, Liquidia will permanently lose the opportunity to market Yutrepia for at least nine months. Kaseta Decl. ¶¶ 9–10. That loss is an irreparable harm that warrants preliminary injunctive relief. *See Torpharm, Inc. v. Shalala*, No. Civ. A. 97-1925, 1997 WL 33472411, at *4 (D.D.C. Sept. 15, 1997) (company showed irreparable harm because it would "be permanently disadvantaged in the market for ranitidine hydrochloride if precluded from entering the market until many months after its competitors").

Second, absent preliminary injunctive relief, Liquidia will suffer substantial economic harm that is unrecoverable due to FDA's sovereign immunity. *See Endo Par Innovation Co. v. Becerra*, No. 24-999, 2024 WL 2988904, at *7 (D.D.C. 2024) (noting that the plaintiff's "economic harm is unrecoverable" because "[i]t cannot recover damages against the FDA for its claims in this suit on account of the FDA's sovereign immunity"); *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 76–77, 77 n.19 (D.D.C. 2010) (same). The Exclusivity Decision prevents Liquidia from generating any revenue from sales of Yutrepia for at least an additional nine months, which Liquidia would use to address operating losses. Kaseta Decl. ¶ 12. The economic harm to Liquidia is irreparable because sovereign immunity shields FDA from monetary liability for the injuries its Exclusivity Decision will cause Liquidia. Thus, the clear and immediate irreparable harm Liquidia will face strongly weighs in favor of granting a preliminary injunction.

III. THE BALANCE OF THE EQUITIES AND PUBLIC INTEREST STRONGLY FAVOR LIQUIDIA.

The balance of the equities and the public interest also weigh heavily in Liquidia's favor.

In addressing these factors, the Court must "balance the competing claims of injury," specifically, "the effect on each party of granting or withholding the requested relief." *Winter*, 555 U.S. at 24. The Court must also consider whether an injunction would harm other interested parties. *See Monument Realty LLC v. Wash. Metro. Area Transit Auth.*, 540 F. Supp. 2d 66, 74 (D.D.C. 2008). Conducting that balance here shows FDA and UTC would not suffer legally cognizable harm from an injunction against FDA's unlawful Exclusivity Decision, in contrast to the immediate and substantial harm Liquidia and the public will suffer absent injunctive relief.

The Public Interest. Liquidia's high likelihood of success on the merits of its APA claims "is a strong indicator that a preliminary injunction would serve the public interest because there is generally no public interest in the perpetuation of unlawful agency action." *Shawnee Tribe*, 984 F.3d at 102 (cleaned up). There is a "substantial public interest in having governmental agencies abide by the federal laws that govern their existence and operations" and "generally no public interest in the perpetuation of unlawful agency action." *League of Women Voters of U.S. v. Newby*, 838 F.3d 1, 12 (D.C. Cir. 2016) (internal quotation marks and citation omitted); *Bayer HealthCare*, 942 F. Supp. 2d at 27 ("The public has an interest in federal agency compliance with its governing statute."); *Torpharm*, 1997 WL 33472411, at *5 ("The public interest … in the correct application of the statute favors issuance of the injunction."). Similarly, injunctive relief here would not harm FDA. *See R.I.L-R v. Johnson*, 80 F. Supp. 3d 164, 191 (D.D.C. 2015) (an agency "cannot suffer harm from an injunction that merely ends an unlawful practice or reads a statute as required").

Furthermore, preliminary injunctive relief in Liquidia's favor would serve the public interest by increasing competition amongst drug companies that offer inhaled treprostinil. The public has an interest in competition. *See Torpharm*, 1997 WL 33472411, at *5. That is particularly true here because granting injunctive relief to Liquidia would help give PH-ILD and

PAH patients access to a new and differentiated treatment option.

No Cognizable Harm to UTC. An order enjoining the Exclusivity Decision and requiring FDA to grant full approval to Yutrepia effective immediately also would not cause any cognizable harm to non-party UTC and certainly would not cause sufficient harm to outweigh the harm to Liquidia from denial of the injunction.

UTC has no protectable interest in the NCI exclusivity that FDA extended in the Exclusivity Decision because, on the merits, Liquidia is likely to show that Tyvaso DPI is ineligible for NCI exclusivity under the FDCA and FDA regulations. *See supra* Part I.A. Nor will UTC face any cognizable harm from the specter of competition from an order allowing Liquidia to market Yutrepia earlier than May 2025. "The mere existence of competition is not irreparable harm, in the absence of substantiation of severe economic impact." *Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 n.3 (D.C. Cir. 1977). It is implausible that UTC will suffer "severe economic impact" from Liquidia's launch of Yutrepia. As another federal district court stated earlier this year when it denied UTC's request to enjoin Liquidia from launching Yutrepia, "[UTC] is a large company with more than $2 billion in annual revenue and two decades on the market." *United Therapeutics*, 2024 WL 2805082, at *13. Notably, UTC had already expected that its "double-digit growth rate remains a solid forecast even with the possibility of new FDA approvals of … Liquidia."[40] That undermines any claim of harm by UTC.

Nor can UTC credibly assert that it would suffer economic harm from injunctive relief that enjoins the unlawful Exclusivity Decision. UTC had ***already*** expected that its exclusivity for Tyvaso for the PH-ILD indication would expire in March 2024, as UTC alleged in a complaint

[40] *See* UTC Q1 2023 Earnings Call Transcript (May 3, 2023), https://www.roic.ai/quote/UTHR/transcripts/2023/1.

filed in this very court. *See* Complaint, *United Therapeutics Corp. v. FDA*, No. 24-cv-484-JDB (D.D.C. Feb. 20, 2024), ECF No. 1, ¶ 42 ("FDA approved UTC's supplemental NDA for PH-ILD in 2021. As a result, UTC was granted a three-year period of new-clinical-study exclusivity until March 31, 2024. That means that FDA cannot approve any 505(b)(2) application to market a treprostinil product for the PH-ILD indication until after that date.").

In short, UTC has held a monopoly on treprostinil drugs for nearly 20 years, and it surely will continue to market Tyvaso and Tyvaso DPI even if the Court issues injunctive relief here. UTC's interests cannot outweigh the substantial irreparable harm to Liquidia.

IV. LIQUIDIA REQUESTS INJUNCTIVE RELIEF THAT IMMEDIATELY REDRESSES THE IRREPARABLE HARM FROM FDA'S UNLAWFUL EXCLUSIVITY DECISION.

Liquidia requests injunctive relief that immediately provides redress to Liquidia for the unlawful Exclusivity Decision.

First, at a minimum, Liquidia requests preliminary injunctive relief immediately to enjoin the effectiveness of the Exclusivity Decision. *See Merck & Co. v. FDA*, 148 F. Supp. 2d 27, 29 (D.D.C. 2001) (noting that the district court had issued temporary restraining order "staying the effectiveness" of an FDA decision on exclusivity). Such relief would clear the sole obstacle to FDA's immediate full approval of Yutrepia.

Second, Liquidia requests an order that requires FDA to grant full approval effective immediately for Yutrepia for both the PAH and PH-ILD indications. There is precedent for the Court to grant such injunctive relief. For example, in *Teva Pharmaceuticals USA, Inc. v. FDA*, the district court determined that the plaintiff was "entitled to immediate final effective approval" for its drug application upon the court's conclusion that the plaintiff had demonstrated that FDA arbitrarily and capriciously interpreted a provision of the FDCA. No. CIV. A. 99-67, 1999 WL 1042743, at *7 (D.D.C. Aug. 19, 1999). In *Torpharm*, the district court similarly granted a

preliminary injunction compelling FDA to approve the plaintiff company's drug application after concluding that FDA had incorrectly applied the FDCA provisions at issue in that case and all other preliminary injunction factors weighed in the plaintiff's favor. 1997 WL 33472411, at *1, *3-5. Similar relief is appropriate here. In light of FDA's determination that Yutrepia already satisfies ***all*** the requirements for final approval, and the significant delays Liquidia has experienced to obtain regulatory approval for Yutrepia, an order that requires FDA to grant final approval is necessary and appropriate.

Third, in the alternative to full approval of Yutrepia for both indications, Liquidia requests an order that requires FDA to grant full approval effective immediately for Yutrepia as to the PH-ILD indication. As shown above, BREEZE did not study patients with this indication, and NCI exclusivity cannot be awarded based on BREEZE for that population as a matter of law.

Fourth, if the Court were not inclined to order FDA to grant full approval to Yutrepia effectively immediately, Liquidia requests in the alternative that the Court remand to FDA so the agency may have "a chance to remedy the explanatory deficiencies" that Liquidia has identified in Part I.B. *See Banner Health v. Price*, 867 F.3d 1323, 1356–57 (D.C. Cir. 2017) ("The Supreme Court has explained that '[i]f the record before the agency does not support the agency action, … the proper course, except in rare circumstances, is to remand to the agency for additional investigation or explanation.'" (citation omitted)); *Merck*, 148 F. Supp. 2d at 31 (noting that "[i]n cases where a reviewing court is unable to make a determination because of the agency's failure to explain the grounds for its decision, the proper remedy is a remand for further proceedings"). In the event the Court would prefer this alternative relief, Liquidia requests that the Court set a very short and specific timeline for FDA to complete its revised analysis, specifically no later than 14 days from the date when the Court issues a decision granting Liquidia a preliminary injunction.

CONCLUSION

For the foregoing reasons, Liquidia requests that the Court grant injunctive relief that (1) immediately enjoins FDA from enforcing its Exclusivity Decision, and (2) immediately enjoins FDA from refusing to grant final approval of Yutrepia pursuant to the Exclusivity Decision either in full or, at the very least, for the PH ILD indication.

Dated: August 27, 2024

By: */s/ Sonia W. Nath*

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