UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

LIQUIDIA TECHNOLOGIES, INC.,

Plaintiff,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*,

Defendants,

and

UNITED THERAPEUTICS CORPORATION,

Intervenor-Defendant and Cross-Claimant.

REDACTED

Case No. 1:24-cv-02428-TJK

Honorable Timothy J. Kelly

ORAL ARGUMENT REQUESTED

PLAINTIFF LIQUIDIA TECHNOLOGIES, INC.'S REDACTED CONSOLIDATED OPPOSITION TO FEDERAL DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND REPLY IN SUPPORT OF ITS RENEWED MOTION FOR A PRELIMINARY INJUNCTION AND MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

Two years ago, on the same day it approved Tyvaso DPI's NDA, FDA correctly determined that the drug failed to qualify for NCI exclusivity under the FDCA and FDA regulations. FDA did so because it found that Tyvaso DPI's NDA contained only ineligible studies—two studies previously submitted to FDA, and three bioavailability studies that merely confirmed what FDA already knew about inhaled treprostinil.

But on August 16, 2024, FDA abruptly changed course. Without justification for reversing its original decision denying exclusivity to Tyvaso DPI, FDA determined that the same evidence it had reviewed two years earlier now justified NCI exclusivity for all inhalation powder dosage forms of treprostinil for chronic use for all indications. FDA's erroneous decision blocks full approval for Liquidia's competing treprostinil drug, Yutrepia, which FDA has already found safe and effective for treating PAH and PH-ILD. FDA's reversal flouted the agency's statutory limitations by rewriting the FDCA and awarding exclusivity that sweeps beyond the limited scope of BREEZE, the sole study FDA cites as the basis for Tyvaso DPI's NCI exclusivity.

BREEZE was a three-week, 51-patient, bioavailability and confirmatory study—categorically ineligible for NCI exclusivity under the FDCA and FDA regulations. Moreover, BREEZE did not study any dry powder other than Tyvaso DPI's specific FDKP formulation, did not study PH-ILD patients at all, and did not study any patients other than PAH patients who were already stable on treprostinil. And because the study ran for just three weeks, BREEZE did not (and could not) study chronic use. Yet FDA overlooked each of these specific limitations when it granted broad NCI exclusivity based on BREEZE, improperly extending UTC's treprostinil monopoly and depriving PAH and PH-ILD patients of drug choice and access to Yutrepia.

FDA's arguments are premised on one overarching assumption: that it acted within a "zone of reasonableness" when it belatedly concluded that Tyvaso DPI qualifies for NCI exclusivity. But the Exclusivity Decision was neither "reasonable" nor authorized under its governing statute, its own regulations, or precedent because it found that: (1) BREEZE was a "new clinical investigation," whereas it was actually a bioavailability and confirmatory study ineligible for NCI exclusivity, as FDA itself concluded two years earlier; (2) BREEZE was "essential to approval" of Tyvaso DPI, whereas FDA had found to the contrary, i.e., that BREEZE duplicated the prior findings of TRIUMPH and INCREASE on the safety and efficacy of inhaled treprostinil; and (3) BREEZE qualified Tyvaso DPI for NCI exclusivity over the entire dosage form of dry powder treprostinil for chronic use and for all indications, ignoring BREEZE's limited patient population and indication (stable-switching PAH patients), formulation (an FDKP/treprostinil dry inhalation powder), and short-term duration (three weeks).

Nothing in FDA's briefing changes the fact that the Exclusivity Decision contravenes the FDCA and FDA regulations, or that FDA's flip-flop was arbitrary, capricious, and contrary to law under the APA. The Court should grant summary judgment for Liquidia, deny FDA's Cross-Motion, set aside the Exclusivity Decision, and order FDA to grant full approval for Yutrepia.

ARGUMENT

I. FDA UNLAWFULLY GRANTED NCI EXCLUSIVITY TO TYVASO DPI.

The FDCA and FDA regulations prohibit FDA from granting NCI exclusivity to Tyvaso DPI. To qualify for NCI exclusivity under the FDCA, FDA agrees that an NDA must (1) contain "reports of new clinical investigations (other than bioavailability studies)" that are (2) "essential to the approval of the application." 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108(a); FDA Br.

5-6.[1] Here, however, Tyvaso DPI is categorically ineligible for exclusivity because its NDA contained two previously-submitted studies (TRIUMPH and INCREASE), and three bioavailability studies (TIP-PH-102, MKC-475-001, and BREEZE). Moreover, the one bioavailability study upon which FDA seeks to base NCI exclusivity, BREEZE, was not essential to approval.

FDA struggles to fit BREEZE's square peg into a round hole, defaulting to an argument that even duplicative bioavailability studies like BREEZE can qualify as new clinical investigations. FDA Br. 18-19. But the clear terms of the FDCA and FDA regulations do not support FDA's arguments. Rather, they support FDA's original exclusivity decision made concurrently with Tyvaso DPI's approval in 2022, in which FDA correctly determined that BREEZE was not a new clinical investigation, but a bioavailability study offering "only" "bioavailability or bioequivalence data," and "confirmatory efficacy information" already known to FDA, and therefore Tyvaso DPI was ineligible for NCI exclusivity. FDA-000453-459 ("Original Exclusivity Summary").

Moreover, even if Tyvaso DPI were eligible for exclusivity based on BREEZE (it is not), FDA unlawfully granted overbroad exclusivity encompassing the entire dosage form of dry powder treprostinil, far exceeding the scope of BREEZE's supposed "innovations presented to the FDA in the new clinical investigation[] that led to the FDA's approval of the first-in-time 505(b) NDA." *Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104, 121 n.16. (D.D.C. 2015). As FDA precedent demonstrates, Tyvaso DPI was ineligible for the broad NCI exclusivity FDA awarded because BREEZE failed to study, and thus offered no "innovations" for, treprostinil dry powder formulations other than Tyvaso DPI's specific formulation of treprostinil and FDKP excipient (i.e.,

[1] FDA's and UTC's memorandum for its opposition and cross motion for summary judgment ("Cross-Motion") is referred to as "FDA Br." and "UTC Br." Liquidia's memorandum in support of its renewed preliminary injunction motion and motion for summary judgment is referred to as "Liquidia Br." For ease of reference, citations in this Brief to the FDA and UTC Briefs are paginated by the page numbers appearing in those briefs, not their ECF pagination.

dry powder treprostinil products formulated with a different excipient), on other patient populations and indications (e.g., PH-ILD patients and treatment naïve PAH patients), or for chronic use. By awarding this broad exclusivity, FDA exceeded its authority under the FDCA and, as a result, has blocked wholly distinct formulations of dry powder inhalation treprostinil—even those like Yutrepia that do not share conditions of approval with Tyvaso DPI.

In implicit recognition that its arguments are unsupported by the plain language of the FDCA and FDA regulations, and FDA's own precedent, FDA asserts that its Exclusivity Decision should nevertheless be upheld because it falls within an undefined "zone of reasonableness" beyond this Court's review. FDA Br. 13 (quoting *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021)). But the "zone of reasonableness" cannot excuse FDA's erroneous statutory and regulatory interpretations. This court is more than capable of fulfilling its "basic judicial task of 'say[ing] what the law is.'" *Loper Bright Enters. v. Raimondo*, 144 S. Ct. 2244, 2271 (2024) (quoting *Marbury v. Madison*, 1 Cranch 137, 177 (1803)); *see Genus Med. Techs. LLC v. FDA*, 994 F.3d 631, 637 (D.C. Cir. 2021) (rejecting FDA's reading based on the FDCA's clear text). Applying the law to the facts here, the Exclusivity Decision must be vacated and the agency must issue full approval to Yutrepia.

A. FDA's Determination that BREEZE Qualified as a New Clinical Investigation Violated the FDCA and FDA Regulations, and Was Arbitrary and Capricious.

BREEZE was a bioavailability study that also duplicated the findings of prior studies on inhaled treprostinil. Studies like BREEZE fail to qualify as new clinical investigations because the FDCA expressly limits NCI exclusivity to NDAs that "contain[] reports of ***new*** clinical investigations (***other than bioavailability studies***)." 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added); 21 C.F.R. § 314.108(a) ("Bioavailability study means a study to determine the bioavailability or the pharmacokinetics of a drug."); *see* FDA-000415 ("Bioavailability data

provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug."). Not only is BREEZE an ineligible bioavailability study, but it is also separately ineligible because it "duplicate[d] the results of []other investigation[s] that w[ere] relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product"—i.e., TRIUMPH and INCREASE. 21 C.F.R. § 314.108(a).

1. BREEZE Was an Ineligible Bioavailability Study.

a. Under the FDCA, Bioavailability Studies like BREEZE Are Not New Clinical Investigations

Under the FDCA, "bioavailability studies" are ineligible for NCI exclusivity. 21 U.S.C. § 355(c)(3)(E)(iii). On this point, all parties agree. *See, e.g.*, FDA Br. 5; UTC Br. 2. BREEZE studied bioavailability as a study endpoint. On this point, all parties also agree. *See, e.g.*, FDA-000426-427 (BREEZE studied "PK assessments," and those "PK assessments" were a BREEZE study endpoint); FDA Br. 16; UTC Br. 20 (BREEZE "report[ed] data on bioavailability"); UTC Br. 21 (bioavailability was a BREEZE endpoint); *id.* at 22 (BREEZE "did assess pharmacokinetics"); *id.* at 23 (BREEZE had "[p]harmacokinetic assessments," i.e., "pharmacokinetic analyses for plasma concentrations of treprostinil"); *see* 21 U.S.C. § 355(j)(8)(A)(i) (defining "bioavailability" as "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug [product] and becomes available at the site of drug action"). Therefore, BREEZE is a bioavailability study.

Where the parties diverge, however, is whether the FDCA permits BREEZE to qualify as a new clinical investigation ***despite the fact that it indisputably studied bioavailability***. FDA and UTC insist that a bioavailability study like BREEZE can still qualify as a new clinical investigation because it did not "***solely***" study bioavailability as an endpoint and also studied other endpoints

like safety and tolerability. FDA-000432; *see* FDA Br. 18-19; UTC Br. 22. According to FDA, any bioavailability study can remain a new clinical investigation eligible for NCI exclusivity, so long as it does not "solely" study bioavailability. FDA Br. 19; *see* FDA-000432.

FDA's interpretation cannot be reconciled with the FDCA or even its own regulations. Based on the plain text of the FDCA, BREEZE was undoubtedly a "bioavailability study" that cannot qualify as a "new clinical investigation" because this statutory provision specifically defines "clinical investigations" and "bioavailability studies" in ***disjunctive terms***—clinical investigations are human studies "other than" bioavailability studies. 21 U.S.C. § 355(c)(3)(E)(iii). Consequently, according to this FDCA provision governing NCI exclusivity, a study is either a clinical investigation ***or*** it is a bioavailability study.[2] It cannot be both.

Even as FDA claims that its reading falls within the nebulous "zone of reasonableness," in practical effect, FDA has asked this Court to uphold its Exclusivity Decision by jamming the word "solely" into FDCA's phrase "other than bioavailability studies" so that it reads "other than [studies that are ***solely***] bioavailability studies." FDA Br. 19; *see Util. Air Regul. Grp. v. EPA*, 573 U.S. 302, 328 (2014) ("We reaffirm the core administrative-law principle that an agency may not rewrite clear statutory terms to suit its own sense of how the statute should operate. . . . [T]he need to rewrite clear provisions of the statute should have alerted EPA that it had taken a wrong interpretive turn. Agencies are not free to 'adopt . . . unreasonable interpretations of statutory provisions and then edit other statutory provisions to mitigate the unreasonableness.'"); *Eagle Pharms., Inc. v. Azar*, 2018 WL 3838265, at *6 (D.D.C. June 8, 2018) (Kelly, J.) *aff'd*, 952 F.3d 323 (D.C. Cir. 2020) ("'[N]either courts nor federal agencies can rewrite a statute's plain text to

[2] *See* Other Than, Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/other%20than ("other than" means "with the exception of" or "except for").

correspond to its supposed purposes.'" (quoting *Landstar Express Am., Inc. v. Fed. Mar. Comm'n*, 569 F.3d 493, 498 (D.C. Cir. 2009))).

In an attempt to find support for its dismissive treatment of the FDCA's clear limitations on bioavailability studies, FDA argues that Liquidia waived its bioavailability arguments, presents a view of bioavailability studies irreconcilable with the FDCA and its own regulations, and deflects with unfounded policy arguments. FDA Br. 16-17, 20. None of these arguments has merit.

Flawed Waiver Argument. In a specious attempt to deflect from its own about-face in the Exclusivity Decision, FDA ironically argues that Liquidia's bioavailability arguments are an "about-face" from arguments that Liquidia made in a July 2021 letter that somehow preclude Liquidia from challenging FDA's determination that BREEZE is not a bioavailability study under the FDCA and FDA regulations. FDA Br. 16-17. FDA is wrong on multiple fronts.

First, FDA's argument improperly seeks to prevent the Court from performing its judicial function. As the Supreme Court instructed, under the APA, "courts, not agencies, will decide '***all relevant questions of law***' arising on review of agency action." *Loper Bright*, 144 S. Ct. at 2261 (quoting 5 U.S.C. § 706) (emphasis added). Whether a bioavailability study like BREEZE is ineligible for NCI exclusivity under the FDCA is squarely a question of law before this Court, and the Court must set aside FDA's determinations that are "inconsistent with the law." *Id.*

Second, FDA's arguments are also premised on a purported "principle of administrative law" that FDA claims can be found in a series of cases. FDA Br. 17. But FDA's reference to *Hill Dermaceuticals, Inc. v. FDA* does not support its arguments. 709 F.3d 44, 46 n.1 (D.C. Cir. 2013) (per curiam). *Hill* says nothing about a party being precluded from asserting an argument in court. Similarly, FDA's reliance on *Southern Pacific Transportation Co. v. ICC*, is misplaced because the issue in that case was whether the petitioner was "aggrieved" by agency action for the purposes

of asserting challenges to the agency action under the Hobbs Act, a statute that does not apply here. 69 F.3d 583, 587–88 (D.C. Cir. 1995). FDA's reliance on *Delaware Department of Natural Resources and Environmental Control v. EPA*, 895 F.3d 90, 96 (D.C. Cir. 2018) also does not help FDA's cause. There, the court ***rejected*** the agency's view that the petitioner had taken a position opposite to the one it advanced before the agency because its earlier position was "ambiguous or equivocal" and "did not even address—let alone contradict—the legal arguments" made in court. *Id*. And unlike plaintiff in *Archiocese of Washington v. Washington Metropolitan Area Transit Authority*, who had expressly "conceded" an argument in court, FDA does not argue that Liquidia has ever conceded that BREEZE is not a bioavailability study before this Court. 897 F.3d 314, 322 (D.C. Cir. 2018).

Third, FDA cannot accuse Liquidia of waiving an argument that FDA itself ***credited***. *See Wash. Ass'n for Television & Child. v. FCC,* 712 F.2d 677, 681 (D.C. Cir. 1983) ("[I]t is not always necessary for a party to raise an issue, so long as the Commission in fact considered the issue."). FDA had every opportunity to consider Liquidia's argument earlier because FDA's Original Exclusivity Summary issued in May 2022 denied NCI exclusivity to Tyvaso DPI using the same reasoning that Liquidia is advancing—i.e., BREEZE was a bioavailability and confirmatory study that failed to qualify as a new clinical investigation. FDA-000453-459.

Fourth, FDA's argument is factually incorrect. In the July 2021 letter on which FDA relies, Liquidia stated unequivocally that "Tyvaso DPI is ***not eligible*** for three-year exclusivity because its pending [NDA] does not contain any 'new clinical investigations' that are 'essential to approval' of the reformulated treprostinil product." FDA-000001 (emphasis added); *see also* FDA-000008 (arguing that BREEZE "does not qualify for three-year exclusivity"). In support of that argument, Liquidia argued that "a bioavailability study ***cannot*** be used to confer [NCI]

exclusivity on a new drug product." FDA-000008 (emphasis added). Liquidia further argued BREEZE studied "***PK*** of Tyvaso DPI compared to Tyvaso Inhalation Solution." FDA-000007 (emphasis added). These are precisely the arguments Liquidia makes here to challenge FDA's unlawful grant of NCI exclusivity on the basis of BREEZE. Consistent with its arguments here, Liquidia further argued that BREEZE "does little more than help to ***confirm*** the general safety of Tyvaso DPI in the existing PAH patient population currently taking Tyvaso Inhalation Solution." FDA-000010 (emphasis added). Therefore, the record confirms that Liquidia repeatedly raised these issues with the FDA, even though it was not required to do so.

All clinical studies necessarily include safety data. FDA attempts to challenge Liquidia's reasoning by suggesting that there should be no limits on bioavailability studies remaining eligible for NCI exclusivity as long as they have "***a*** purpose other than measuring bioavailability," claiming that all studies collect bioavailability data. FDA Br. 20 (emphasis added). *First*, FDA is wrong because Liquidia's interpretation properly limits the types of studies eligible for NCI exclusivity in accordance with the FDCA and clear Congressional intent. *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 85 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013); 1989 Preamble to the Proposed Rule Implementing Title 1 of the Drug Price Competition and Patient Term Restoration Act, Abbreviated New Drug Application, Proposed Rule, 54 Fed. Reg. 28872, 28899 (July 10, 1989) ("1989 Preamble"). *Second*, under FDA's flawed interpretation, ***all*** studies would remain eligible for exclusivity, including bioavailability studies, because all studies necessarily include some safety data, which must be reported to FDA. 21 C.F.R. § 312.32(b). *Third*, FDA never explains how, under its interpretation, it lawfully selected BREEZE rather than TIP-PH-102 and/or MKC-475-001 for NCI exclusivity when all three of those studies expressly studied pharmacokinetics, safety, and tolerability as separate endpoints.

To the extent FDA asserts that such determinations should be left to the agency, this is the precise type of legal question that this Court should determine in the first instance. *Loper Bright*, 144 S. Ct. at 2262 (The APA "incorporates the traditional understanding of the judicial function, under which courts must exercise independent judgment in determining the meaning of statutory provisions."). This Court, not FDA, can reasonably determine whether to follow the plain text of the FDCA that limits NCI exclusivity to studies that do not study bioavailability—such as TRIUMPH or INCREASE, for which UTC received NCI exclusivity, both of which did not study bioavailability as an endpoint—or whether to rewrite the statute to add a word that does not exist ("solely") as FDA suggests.[3] FDA-000472-473 (showing that TRIUMPH and INCREASE did not study bioavailability or pharmacokinetics as study endpoints). So contrary to FDA's alarmist arguments, the record here shows that numerous studies can and do qualify as new clinical investigations (and not bioavailability studies) consistent with Liquidia's straightforward reading of the FDCA and FDA regulations. Liquidia's argument is simply that the statute, and not FDA, prescribes the contours of studies that qualify for NCI exclusivity. The FDCA is clear that bioavailability studies are ineligible.

Flawed Policy Argument. Finally, in the absence of textual grounding for its arguments, FDA alleges that Liquidia's purportedly "novel interpretation" of the FDCA "would also be contrary to the protection of public health." FDA Br. 20. According to FDA, "to preserve their eligibility for exclusivity, sponsors might study pharmacokinetics only in separate studies," which would lead to "additional, unnecessary testing on human subjects in direct contravention of FDA

[3] *See* Vallerie V. McLaughlin et al., *Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension* (TRIUMPH), J. Am. Coll. Cardiol. (May 4, 2010), https://pubmed.ncbi.nlm.nih.gov/20430262/; Aaron Waxman et. al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease* (INCREASE), NEW ENGLAND J. OF MED., Vol 384(4) (Jan 13, 2021), https://www.nejm.org/doi/full/10.1056/NEJMoa2008470.

regulations." *Id.* (citing 21 C.F.R. § 320.25(a)(1)). This is nonsensical. Sponsors will still design studies to generate data to support NDA approval. The only question is whether the FDCA permits FDA to credit bioavailability studies as new clinical investigations for NCI exclusivity. Congress unequivocally answered this question, and FDA is now trying to unlawfully exceed its statutory authority by extending exclusivity to ineligible studies. The net effect of FDA's misguided policy argument is to ***stifle*** competition and deny patients to otherwise safe and effective medications, contrary to the public health and Congressional intent. *See AstraZeneca*, 872 F. Supp. 2d at 85.

Further, FDA's appeals to policy are irrelevant. "Courts interpret statutes" "based on the traditional tools of statutory construction, not individual policy preferences . . . that ha[ve] not made it into the statute." *Loper Bright*, 144 S. Ct. at 2268; *see also Eagle Pharms.*, 2018 WL 3838265, at *6 ("The Court starts, as it must, with the text of the statute as it stood at the time of the FDA's decision . . . ."). While FDA may think its atextual approach is preferable as a policy matter, that preference cannot redeem FDA's misreading of the FDCA or override Congress's clear intent to exclude "bioavailability studies" from NCI exclusivity. Moreover, FDA's argument appears nowhere in the Exclusivity Decision. *See Michigan v. EPA*, 576 U.S. 743, 758 (2015) ("[A] court may uphold agency action only on the grounds that the agency invoked when it took the action."). It is hard to see how FDA's (unfounded) policy concerns override the proper classification of BREEZE as an ineligible bioavailability study.

b. FDA Regulations Similarly Classify BREEZE as an Ineligible Bioavailability Study.

Given the weakness in its statutory argument, FDA leans into its regulations in an attempt to salvage its Exclusivity Decision. But those regulations are just as clear as the FDCA. FDA's regulation defines a "bioavailability study" as a "study to determine the bioavailability or the pharmacokinetics of a drug," which BREEZE most certainly did and is undisputed. 21 C.F.R.

§ 314.108(a); FDA-000426–427 (documenting FDA's understanding that BREEZE studied "PK assessments," and that those "PK assessments" were an endpoint for BREEZE); FDA-000712 (BREEZE "was designed to evaluate the pharmacokinetics" of Tyvaso DPI); FDA-000838 (pharmacokinetics, or "exposure of TreT," was a BREEZE endpoint); FDA-000842 (finding TIP-PH-102's bioavailability data similar to BREEZE's bioavailability data and displaying a table summarizing data from BREEZE's bioavailability endpoint); UTC Br. 20–23 (repeatedly conceding that bioavailability and pharmacokinetics were a BREEZE endpoint). BREEZE is unquestionably a bioavailability study under this plain regulatory definition.

In an effort to shore up its flawed interpretation, FDA strangely amalgamates the regulatory definitions for "bioavailability study" and "clinical investigation." FDA Br. 18 (arguing that "clinical investigation" should be read as "an[] experiment other than a [study *to determine* the bioavailability or the pharmacokinetics of a drug] in which a drug is administered or dispensed to, or used on, human subjects.") (brackets and emphasis in original). This argument, however, still does not alter the fact that BREEZE was undoubtedly a "study to determine the bioavailability or the pharmacokinetics" of Tyvaso DPI. 21 C.F.R. § 314.108(a).

Lastly, without using the word "deference," FDA essentially asks this Court for deference for a definition not found in its regulations and that FDA advances here solely to defend the Exclusivity Decision. But deference is unwarranted "unless, after exhausting all the 'traditional tools' of construction, . . . the regulation is genuinely ambiguous." *Kisor v. Wilkie*, 588 U.S. 558, 574 (2019). FDA does not argue that its regulation defining "clinical investigation" and "bioavailability study" are ambiguous. Nor can it. These definitions clearly provide that BREEZE falls squarely in the definition of bioavailability study. FDA-000151 (BREEZE "evaluate[d]: (1) the systemic exposure and pharmacokinetics of treprostinil when delivered as Tyvaso Inhalation

Solution and Tyvaso DPI . . . ."); FDA-000712–713 (BREEZE "was designed to evaluate the pharmacokinetics" and "systemic exposure and pharmacokinetics" was a BREEZE endpoint).

FDA's interpretation of its regulation is further unreasonable because FDA has not consistently applied it. FDA argues that the distinction between what qualifies as a "new clinical investigation" as opposed to a "bioavailability study" turns on whether the study characterized its bioavailability or pharmacokinetic endpoints as "primary" or "secondary." FDA Br. 17. Curiously, FDA never used that reasoning in its Exclusivity Decision, nor is it consistent with even its own flawed, rewritten definitions of a "new clinical investigation" and "bioavailability study" in which it argues that a "bioavailability study" must study ***solely*** bioavailability. FDA's shifting arguments are mere *post hoc* justifications. *See Michigan*, 576 U.S. at 758 (Courts "may uphold agency action only on the grounds that the agency invoked when it took the action."); *Kisor*, 588 U.S. at 579 (Courts "decline to defer to a merely 'convenient litigating position' or '*post hoc* rationalizatio[n] advanced' to 'defend past agency action against attack.'") (citation omitted).

Perhaps FDA never introduced this reasoning in its Exclusivity Decision because it would render the FDCA's categorical exclusion for bioavailability studies meaningless. Under FDA's flawed view, any sponsor (or FDA) retains unilateral power to obtain (or award) NCI exclusivity simply by labeling the study's bioavailability endpoint as "secondary" instead of "primary"—regardless of whether bioavailability or pharmacokinetics were studied. There is nothing in the statute nor FDA regulations that allow sponsors or FDA to cherry pick which studies it deems to be "bioavailability studies" and which other studies that indisputably investigate bioavailability as study endpoints still remain eligible for NCI exclusivity. FDA's position here would give FDA and drug sponsors unfettered discretion, render the express limitations prescribed by the FDCA and FDA regulations toothless, and upend the "careful balance" Congress struck "between

providing exclusivity rights to promote innovation and making generic alternatives available to patients." *AstraZeneca*, 872 F. Supp. 2d at 85.

This Court need look no further than the other bioavailability studies submitted with the Tyvaso DPI NDA to see the absurdity of FDA's argument. BREEZE's so-called "primary" safety assessments and endpoints replicated the safety assessments and endpoints studied in TIP-PH-102 and MKC-475-001. *Compare* FDA-000426 (stable PAH patients studied in BREEZE underwent "PK assessments" and "safety assessments (including incidence and severity of reported ***adverse events, vital signs, clinical laboratory tests, electrocardiograms, and physical examinations***)" (emphasis added), *with* FDA-000429 ("During the [TIP-PH-102] study, subjects underwent PK and safety assessments . . . . Safety assessments included ***adverse events, vital signs, clinical laboratory tests, 12-lead ECGs, and physical examinations***." (emphasis added) *and* FDA-000473 (MKC-475-001 studied the "pharmacokinetics" of Tyvaso DPI and conducted "[s]afety assessments includ[ing] incidence and severity of reported ***adverse events, as well as changes from screening in vital signs, clinical laboratory tests, electrocardiograms (ECGs), and physical examinations***." (emphasis added).

And yet, somehow FDA allowed BREEZE to escape designation as a bioavailability study because it characterized safety as a "primary" endpoint, whereas TIP-PH-102 designated safety as "secondary." *See* FDA-000429; FDA-000505 (arguing that "BREEZE was the sole non-BA study submitted to support approval considered by the division to be essential to approval"). Even worse, MKC-475-001, indisputably a bioavailability study, had the same primary endpoint as BREEZE. FDA-000713 (identifying "safety and tolerability" as a primary endpoint of MKC-475-001); UTC Br. 16 (conceding MKC-475-001 and TIP-PH-102 were "bioavailability studies"). For the same reason both TIP-PH-102 and MKC-475-001 were bioavailability studies ineligible for

exclusivity—i.e., they studied bioavailability as an endpoint—BREEZE is likewise ineligible. *See Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) (FDA had to treat "similar products in the same way" or "provide a rational basis" for different treatment). FDA's dissimilar treatment of these three bioavailability studies fails as a matter of law. *Indep. Petrol. Ass'n of Am. v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996) ("An agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.").

c. BREEZE Was a Duplicative, Confirmative Study that Is Not a New Clinical Investigation Under FDA's Regulations.

Not only is BREEZE ineligible as a bioavailability study, BREEZE is also independently ineligible for NCI exclusivity because it merely confirmed what FDA already knew about inhaled treprostinil. FDA's regulations instruct that the phrase "new clinical investigation" excludes studies that "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). In the Exclusivity Decision, FDA claimed that BREEZE qualified as a new clinical investigation by simply parroting the regulatory language without any analysis of whether BREEZE duplicated or confirmed studies like TRIUMPH and INCREASE that were submitted to support prior NDAs. FDA-000431–432 (citing 21 C.F.R. § 314.108(a)).

FDA's Original Exclusivity Summary clearly confirms this aspect of BREEZE, explaining that BREEZE "provided ***confirmatory*** efficacy information only," by echoing the preexisting data from TRIUMPH and INCREASE that UTC submitted with the Tyvaso Inhalation Solution NDA, which UTC then cross-referenced in Tyvaso DPI's NDA. FDA-000453 (emphasis modified); FDA-000878.[4] TRIUMPH first studied efficacy and tolerability of inhaled treprostinil in PAH

[4] In FDA's own words, the approach UTC took for the Tyvaso DPI NDA—i.e., cross-referencing studies submitted with its earlier Tyvaso Inhalation Solution NDA—bears striking "similar[ities] to one that might be used by a 505(b)(2) applicant." FDA-000424. While UTC could apply

patients, and INCREASE first studied safety and efficacy of inhaled treprostinil in PH-ILD patients. FDA-000132–133, 137–142; FDA-000876–877 ("Substantial evidence of effectiveness for the drug product treprostinil administered by inhalation has been previously concluded based on" TRIUMPH and INCREASE.). Unlike INCREASE and TRIUMPH, however, BREEZE did not study a new patient population or a new indication, but rather simply studied PAH patients already taking stable doses of Tyvaso Inhalation Solution who then switched to Tyvaso DPI. FDA-000777. Thus, BREEZE was not a new clinical investigation. *See* 21 C.F.R. § 314.108(a).

Despite its failure to advance any reasoning in the Exclusivity Decision to support its "new clinical investigation" determination, FDA now argues BREEZE is a new clinical investigation because, according to FDA, only BREEZE addressed "the tolerability of multiple doses daily of treprostinil in the new inhalation powder dosage form to support approval for chronic use." FDA Br. 22. But BREEZE did not. It was designed to evaluate bioavailability, safety, and tolerability of Tyvaso DPI in PAH patients already treated with Tyvaso Inhalation Solution over just three weeks. FDA-000712; FDA-000760, 763. At most, the sum of what can properly be concluded from BREEZE in terms of safety and tolerability appears in FDA's labeling recommendation, where FDA indicated that UTC may use the comparable dose criteria from BREEZE to transition patients to Tyvaso DPI, and that UTC should include the adverse event rates from BREEZE for patients transitioned to Tyvaso DPI. FDA-000903 (showing FDA's view that the only change to Tyvaso DPI's label based on BREEZE was showing "adverse event rates from the BREEZE (TIP-

using the 505(b)(1) pathway because it owned the older cross-referenced studies, UTC took advantage of the same approach to develop Tyvaso DPI that Liquidia did for Yutrepia, including by relying on TRIUMPH and INCREASE previously-submitted with the Tyvaso Inhalation Solution NDA. Tyvaso DPI was such a negligible enhancement over Tyvaso Inhalation Solution that UTC did not change its name, even when it had done so with previous novel changes to treprostinil for which it previously received exclusivity (e.g., Remodulin, Orenitram, Tyvaso).

PH-101) for patients transitioned from Tyvaso [Inhalation Solution] to Tyvaso DPI").

Tellingly, this is the full extent to which BREEZE is referenced in the Tyvaso DPI label—only to show its comparability to Tyvaso Inhalation Solution, which was determined by studying systemic exposure and pharmacokinetics to show comparable bioavailability of Tyvaso Inhalation Solution and Tyvaso DPI. *Id.* BREEZE, also known as TIP-PH-101, was essentially the "other half" of the TIP-PH-102 bioavailability study. FDA-000842. As acknowledged in FDA's Clinical Review, BREEZE's efficacy data, measured by the 6-Minute Walking Distance test, was wholly irrelevant. FDA-000903 ("BREEZE (TIP-PH-101) was not a pre-specified efficacy study and results of the 6MWD and patient-reported outcomes measures ***do not merit reporting*** in Section 14 of the label") (emphasis added); FDA-000878 ("No additional studies evaluating the effectiveness of the treprostinil inhaled powder formulation [other than TRIUMPH I and INCREASE] were submitted for the current review."). Further, none of these objectives address the tolerability of multiple daily doses of Tyvaso DPI to support approval for chronic use.

FDA further argues that BREEZE did not duplicate the results of another study because its results "provided assurance that there was no significant change in safety or tolerability with the new inhalation powder dosage form as compared to [the] approved inhalation solution (Tyvaso)." FDA Br. 21 (quoting FDA-000439). It is hard to imagine what could be more confirmatory and duplicative than a bioavailability study like BREEZE that merely "provided ***assurance*** that there was ***no significant change***" from one inhaled treprostinil drug to another inhaled treprostinil drug.

As the record demonstrates, the only aspect of Tyvaso DPI that concerned FDA was its excipient, FDKP. This is clear from the 2017 pre-IND meeting minutes, where FDA inquired whether FDKP particles in Tyvaso DPI differed in physicochemical properties from Afrezza and, if so, their impact on inhalation toxicity. FDA-000685-698 (three of the five questions raised

during FDA's meeting involved FDKP). FDA's Clinical Review addresses these concerns, not with findings from BREEZE, but with repeated references to the Afrezza NDA. FDA-000881 ("The safety of the excipient fumaryl diketopiperazine (FDKP) in TYVASO DPI™ was comprehensively evaluated as part of the approved (AFREZZA®) inhaled human insulin powder application."). FDA's argument is also irrelevant because it fails to apply the regulatory standard, which focuses on whether the results of the study of a particular active moiety duplicate the results of another study on which FDA relied. 21 C.F.R. § 314.108(a). As discussed above, BREEZE's results were duplicative of the results of prior studies, namely TRIUMPH and INCREASE, that inhaled treprostinil is safe and effective as well as data from the Afrezza NDA that had already demonstrated the safety of FDKP as an excipient. FDA-000876–878, 881.

Unable to defend against BREEZE's status as a confirmatory study ineligible for NCI exclusivity under its regulations, FDA next turns to its "longstanding policy" that interpreted NCI exclusivity to be "***limit*[*ed*]** . . . to changes in a drug product that are significant enough to require human safety or effectiveness studies for approval." FDA Br. 22; 54 Fed. Reg. 28,872, 28,899 (July 10, 1989). Under that policy, FDA has stated 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). This policy favors Liquidia's interpretation rather than FDA's because BREEZE ***did not*** study an expanded patient population to support a "broader use" of treprostinil than these prior studies. FDA Br. 22. No additional patients were studied in BREEZE who were not already taking inhaled treprostinil via Tyvaso Inhalation Solution, and therefore it did not study a "broader use." FDA-000876–877. Moreover, the test for awarding NCI exclusivity does not turn on whether a drug's approval "represent[s] an additional treatment option" upon approval, but

whether the study for which FDA awards NCI exclusivity is eligible.

As for the specific population that BREEZE studied, BREEZE did not establish that Tyvaso DPI was safer than Tyvaso Inhalation Solution. FDA recognized in October 2021 that "[t]he safety profile in [BREEZE] is ***indistinguishable*** from that for the inhaled liquid." FDA-000913 (emphasis added). FDA found that "[n]o new risks associated with treprostinil formulated as an inhaled powder (Tyvaso DPI™) were identified in . . . BREEZE." FDA-000312. Nor did BREEZE support a broader use of the FDKP excipient. As FDA determined, "[t]he exposure to the excipient FDKP by the treprostinil inhaled powder formulation appears acceptable" because its dose was lower than the "Afrezza® maximal dose of co-administered FDKP." FDA-000879. Because BREEZE's results duplicated and were indistinguishable from the results of prior studies on which FDA relied to demonstrate effectiveness or safety of previously approved drugs, FDA unlawfully concluded that BREEZE qualified as a new clinical investigation under the FDCA and FDA regulations. 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108(a).

2. FDA Irrationally Departed from Its Original Exclusivity Summary, which Found that BREEZE Is an Ineligible Bioavailability Study.

On May 23, 2022, FDA approved Tyvaso DPI's NDA. But that is not all it did. That same day, FDA also issued its Original Exclusivity Summary, in which FDA expressly found that TRIUMPH, INCREASE, TIP-PH-102, MKC-475-001, and BREEZE were ineligible for NCI exclusivity. FDA-000455. The Original Exclusivity Summary—reflecting FDA's reasoning and conclusions denying Tyvaso DPI NCI exclusivity—was signed by Dr. Norman Stockbridge, Director of FDA's Division of Cardiology and Nephrology on May 23, 2022, in accordance with the authority delegated to him by the Commissioner of Food and Drugs. FDA-000459; *see* FDA Staff Manual Guides, Volume II – Delegations of Authority 1410.104(1)(C).

In its Original Exclusivity Summary, FDA first asked whether the Tyvaso DPI NDA, which

included TRIUMPH, INCREASE, TIP-PH-102, MKC-475-001, and BREEZE, "contain[ed] reports of clinical investigations? (***The Agency interprets 'clinical investigations' to mean investigations conducted on humans other than bioavailability studies.***)" (emphasis added). FDA-000455. In response, FDA unequivocally concluded: "NO." *Id.* BREEZE was "conducted on humans" and so, pursuant to FDA's interpretation of the FDCA that "clinical investigation[]" has only two criteria (1) an "investigation[] conducted on humans" (2) "other than bioavailability studies," FDA's conclusion that BREEZE did ***not*** qualify as a "clinical investigation[]" necessarily turned on its finding that BREEZE was an ineligible bioavailability and confirmatory study. *Id.*

Further dispelling any doubt that FDA viewed BREEZE as an ineligible bioavailability study for NCI exclusivity, when FDA then asked itself whether the Tyvaso DPI NDA "require[d] the review of clinical data other than to support a safety claim or change in labeling related to safety? (***If it required review only of bioavailability or bioequivalence data, answer "no."***)" (emphasis added), FDA again concluded: "NO." FDA-000453. FDA made this finding because BREEZE studied bioavailability, and merely duplicated and confirmed the "expected known safety profile of Tyvaso Inhalation Solution." FDA-000853 (documenting FDA's understanding that TRIUMPH and INCREASE had already established the "safety" and "tolerability" of inhaled treprostinil, including Tyvaso Inhalation Solution and Tyvaso DPI).

The Original Exclusivity Summary then instructed FDA to elaborate only if FDA "believe[s] the study is a bioavailability study and, therefore, not eligible for exclusivity," and to then "EXPLAIN why it is a bioavailability study." FDA-000453. FDA readily provided that explanation. *Id.*; *see* UTC Br. 25. In the space provided immediately below, FDA documented its finding that, for Tyvaso DPI's NDA, FDA's "basis of approval is the safety, tolerability, and bioavailability established in two studies." FDA-000453. FDA pulled no punches when

characterizing BREEZE's duplicative, confirmatory, and ultimately nonessential findings: "The safety and tolerability study provided ***confirmatory efficacy information only***." *Id.* (emphasis added). Notably, FDA would not have had to "EXPLAIN" had it viewed BREEZE as anything other than "a bioavailability study and, therefore, not eligible for exclusivity." *Id.* FDA thus made abundantly clear that it considered BREEZE a bioavailability study and that it considered its "confirmatory" findings "only." *Id.*

In sum, the Original Exclusivity Summary underscores FDA's understanding contemporaneous with its approval of the Tyvaso DPI NDA that BREEZE was a bioavailability study that merely duplicated and confirmed UTC's other studies.

Despite this, more than two years later, FDA suddenly cast aside its Original Exclusivity Summary and concluded that BREEZE was not "solely" a bioavailability study, such that it could qualify for NCI exclusivity—***without*** persuasively distinguishing, or even displaying awareness of, its earlier Original Exclusivity Summary that reached the opposite conclusion. *See Me. Lobstermen's Ass'n v. Nat'l Marine Fisheries Serv.*, 70 F.4th 582, 599 (D.C. Cir. 2023) ("The Service displayed no awareness of its own flip flop. This was 'arbitrary and capricious,' . . . ."). FDA argues for the first time here that it did not flip flop because the Original Exclusivity Summary was merely an "initial assessment." FDA Br. 14–16. According to FDA, its "final determination" on Tyvaso DPI's exclusivity was made only once "when its Director signed the Orange Book's Exclusivity Eligibility Evaluation" on August 14, 2024. *Id*. 16 (citing FDA-000506). FDA's revisionist claim that the Original Exclusivity Summary was merely an "initial assessment" falters under even an ounce of scrutiny. FDA Br. 15.

First, FDA's argument squarely contradicts its letter response and production of the Original Exclusivity Summary pursuant to Liquidia's FOIA request in 2022. ECF No. 13-8

(Liquidia's FOIA request and FDA's response). Liquidia filed a FOIA request seeking, in FDA's own words, "***the Agency's decision*** whether to award three-year exclusivity to Tyvaso DPI (treprostinil) inhalation powder (NDA 214324)." *Id.* (emphasis added). If the Original Exclusivity Summary were simply an "initial assessment" and not the agency's decision, as FDA now alleges, then the deliberative process exemption would have applied and FDA would not have produced the Original Exclusivity Summary at all. *See* 5 U.S.C.§ 552(b)(5); 21 C.F.R. § 20.62 ("Interagency or intra-agency memoranda or letters that would not be available by law to a party other than an agency in litigation with the [FDA] may be withheld from public disclosure . . . ."); *Renegotiation Bd. v. Grumman Aircraft Eng'g Corp.*, 421 U.S. 168, 184 (1975) (The privilege "distinguish[es] between predecisional memoranda prepared in order to assist an agency decision-maker in arriving at his decision, which are exempt from disclosure, and postdecisional memoranda setting forth the reasons for an agency decision already made, which are not."). In response to Liquidia's FOIA request, however, FDA produced the Original Exclusivity Summary, thereby confirming that it did indeed reflect "the Agency's decision," as FDA itself characterized it. ECF No. 13-8.

Second, FDA cannot seriously contest the decisional nature of the Original Exclusivity Summary. FDA's certified index of the administrative record labeled the two divergent exclusivity determinations the "***Original*** Exclusivity Summary" and "***Superseding*** Exclusivity Summary." ECF No. 42-1 (Amended Index of Administrative Record) (emphasis added). If an earlier exclusivity decision were never made in the first place, it cannot be "supersed[ed]." And common sense dictates that if the FDA's exclusivity summary were predecisional, it certainly could not be called the "***Original*** Exclusivity Summary."

Third, even assuming that the Original Exclusivity Summary were simply an "initial assessment" as FDA insists (it was not), the APA still requires FDA to account for and persuasively

distinguish that "initial assessment." But FDA's Exclusivity Decision does not even refer to—much less explain or distinguish—the findings and reasoning in its Original Exclusivity Summary that contradict its Exclusivity Decision. *See Endo Par Innovation Co., LLC v. Becerra*, 2024 WL 2988904, at *4 (D.D.C. June 10, 2024) (Kelly, J.) (FDA acted arbitrarily and capriciously because "it is obvious that the FDA offered no such explanation" for its action). Indeed the Exclusivity Decision reads as though the Original Exclusivity Summary ***never existed***. That is the definition of arbitrary and capricious. *Id.*; *Brady Campaign to Prevent Gun Violence v. Salazar*, 612 F. Supp. 2d 1, 18 (D.D.C. 2009) ("[A]n agency's decision to reverse its position in the face of a precedent it has not persuasively distinguished is quintessentially arbitrary and capricious.") (cleaned up).

Fourth, FDA's assertion that it required an additional ***two years*** after approving Tyvaso DPI to decide whether it was entitled to a ***three-year*** period of NCI exclusivity, even with the benefit of the Original Exclusivity Summary in 2022, is simply not credible. When FDA reviewed and approved Tyvaso DPI's NDA and denied NCI exclusivity to Tyvaso DPI in 2022, FDA already had on-hand the Yutrepia NDA as well as INSPIRE, Liquidia's clinical investigation that studied dry powder treprostinil in both treatment naïve and treatment stable populations. ECF No. 1 (Complaint), ¶¶ 69, 70. Liquidia submitted this data to FDA more than a year before UTC filed its NDA for Tyvaso DPI, *id.* ¶¶ 69–71, and FDA tentatively approved the Yutrepia NDA, finding it safe and effective, for the first time in November 2021—***before*** it approved the Tyvaso DPI NDA in May 2022. ECF No. 30 (UTC Answer), ¶¶ 59, 72. In other words, FDA knew no later than November 2021 that there was another NDA requiring it to make an NCI exclusivity determination, which is why it did so with its Original Exclusivity Summary in May 2022.

3. BREEZE Was Not "Essential to Approval" of the Tyvaso DPI NDA.

FDA regulations define "essential to approval" to mean "with regard to an investigation, that there are ***no other data available*** that could support [NDA] approval." 21 C.F.R. 314.108(a)

(emphasis added); *see Nat'l Env't Dev. Ass'n's Clean Air Project v. EPA*, 752 F.3d 999, 1009 (D.C. Cir. 2014) ("[A]n agency is not free to ignore or violate its regulations while they remain in effect.") (cleaned up); *Accrediting Council for Indep. Colls. & Schs. v. Devos*, 303 F. Supp. 3d 77, 104 (D.D.C. 2018) ("[T]he Secretary's violation of . . . the regulations . . . independently support findings that the APA was violated.").

Here, BREEZE answered no unique previously unanswered clinical questions because data from TRIUMPH and INCREASE had already confirmed the safety and/or efficacy of inhaled treprostinil. 21 C.F.R. § 314.108(a); FDA-001247 (FDA's "essential to approval" analysis "ask[s] what ***unique, previously unanswered*** clinical question(s) about the safety and/or efficacy of [the ***active moiety***] for the relevant use . . . the new clinical investigations essential to [the drug's] approval answered.") (emphasis added). The FDCA limits NCI exclusivity to only new clinical investigations "essential to approval," and so a nonessential bioavailability and confirmatory study like BREEZE could not qualify Tyvaso DPI for NCI exclusivity. 21 U.S.C. § 355(c)(3)(E)(iii).

Despite the agency's reliance on data from TRIUMPH and INCREASE, FDA now argues that "[t]he BREEZE study—and only the BREEZE study—provided data on multiple-dose use of treprostinil inhalation powder that was necessary to support approval" for both PAH and PH-ILD indications. FDA Br. 22, 24 (citing FDA-000447). But FDA erroneously conflated the operative legal question question—whether BREEZE answered any ***unique, previously unanswered questions*** about the safety and efficacy inhaled treprostinil for the very first time—with whether the clinical data supporting Tyvaso DPI NDA, which included TRIUMPH, INCREASE, TIP-PH-101, TIP-PH-102 (BREEZE) and MKC-475-001, were ***sufficient*** to support approval. Tyvaso DPI's approval is not contested here, only the NCI exclusivity FDA awarded to it for BREEZE.

Because FDA focused on the wrong doctrinal question, it necessarily reached the wrong

conclusion, namely that BREEZE entitles Tyvaso DPI to NCI exclusivity because it was part of the clinical package that supported Tyvaso DPI's approval. But this is not the law. *Veloxis*, 109 F. Supp. 3d at 120–21 ("The FDCA sets up a 'logical relationship between the changes in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting three-year exclusivity.'" (quoting *AstraZeneca*, 872 F. Supp. 2d at 80)); *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, 29–30 (D.D.C. 2019).

FDA's collapsing of the NCI exclusivity standard into the drug approval standard has resulted in FDA giving credit to BREEZE for data available from other ineligible studies. For example, as FDA recognized, the available data for use of Tyvaso DPI in PH-ILD patients came from INCREASE, as BREEZE did not study PH-ILD patients because it was limited to "Subjects with [PAH] Currently Using Tyvaso [Inhalation Solution]." FDA-000529 (italics omitted). And the available data for Tyvaso DPI's use in treatment naïve patients did not come from BREEZE either. BREEZE patients, by design, were already stable and taking Tyvaso Inhalation Solution for at least three months. FDA-000529. The only studies in the Tyvaso DPI NDA that studied the use of Tyvaso DPI in treatment naïve populations were MKC-475-001 and TP-PIH-102, the other two ineligible bioavailability studies submitted with the NDA. FDA-000473.

Given BREEZE's limitations, FDA necessarily relied on data available from other studies to establish the safety and efficacy of inhaled treprostinil to approve Tyvaso DPI. In what is perhaps FDA's most telling concession, FDA candidly acknowledges that it was not BREEZE but the "relative bioavailability study [TIP-PH-102] that ***justified*** extrapolation of the safety and effectiveness data from the TRIUMPH I and INCREASE studies to Tyvaso DPI." FDA Br. 8 (citing FDA-000425-426, 429-430) (emphasis added). That is fatal to FDA's claim that BREEZE was "essential to the approval" under the regulatory definition. 21 C.F.R. § 314.108(a). Where,

as here, a study "might be determined not to be essential to [NDA] approval because [it] merely reestablish[es] something that has been shown by the previous approvals" (FDA-001246–1247), FDA may not lawfully confer NCI exclusivity—and particularly not based on the *post hoc* rationalizations FDA offered for Tyvaso DPI. *Braeburn*, 389 F. Supp. 3d at 29–30, 30 n.13.

To the extent FDA argues that BREEZE was necessary to show no new tolerability issues, that argument is unavailing. FDA already knew that inhaled treprostinil may present tolerability issues. FDA-000433. In evaluating the Tyvaso DPI NDA, FDA drew on what it already knew about inhaled treprostinil from the results of prior studies, and in fact rightly minimized BREEZE's supposed innovations as "indistinguishable" from prior studies on treprostinil and FDKP. FDA-000913. For example, as FDA's Tyvaso DPI Clinical Review found, "[t]he safety profile in [BREEZE] is ***indistinguishable*** from that for the inhaled liquid . . . ." *Id.* (emphasis added). FDA similarly found that "[***n***]***o new*** risks associated with treprostinil formulated as an inhaled powder (Tyvaso DPI™) were identified in . . . BREEZE." FDA-000312. FDA's Office of Clinical Pharmacology confirmed that "[p]atient tolerability, as assessed by incidence of new adverse events following transition to Tyvaso DPI, was consistent with the ***expected known safety profile*** of Tyvaso Inhalation Solution."). FDA-000853. And as FDA's clinical reviewers surmised: "Treprostinil is approved in an inhaled liquid formulation (with no FDKP), so ***little beyond demonstrating bioavailability was necessary*** for Tyvaso DPI." FDA-000913 (emphasis added).

The key issue that FDA raised during Tyvaso DPI's development according to the record was Tyvaso DPI's use of its excipient, FDKP, which is known to have safety concerns. FDA 000685-689. But as FDA's brief concedes and the record reveals, these clinical questions were already answered by the Afrezza NDA years prior. FDA Br. 22 n.11 ("While Tyvaso DPI also contains FDKP, FDA did not consider the BREEZE study as necessary to establish the safety of

that excipient."); FDA-000878–879, 881–882 (basing its benefit-risk determination on FDKP exposure from Tyvaso DPI by comparing it to Afrezza, and concluding that "[t]he exposure to the excipient FDKP by the treprostinil inhaled powder formulation appears acceptable, as the AFREZZA® maximal dose of coadministered FDKP is [redacted] and the co-administered dose of FDKP in [Tyvaso DPI] is [redacted]."). Thus, the record confirms that FDA recognized there were ample data available on inhaled treprostinil and FDKP, thanks to TRIUMPH and INCREASE and the Afrezza NDA, such that BREEZE was not essential to approval. BREEZE's finding that there were "no new risks" as expected is insufficient to justify NCI exclusivity under FDA regulations.

Sensing that Liquidia exposed a hole in the Exclusivity Decision, FDA offers a single, fleeting reference to "scientific deference," arguing that it "is especially suited to determine what conclusions can be extrapolated from the BREEZE study results, and its conclusions are entitled to deference." FDA Br. 25 (citing *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996)). But FDA cannot assert scientific deference because that was not the basis for its Exclusivity Decision—which contains ***zero*** references to "deference" or "discretion," and no explanation of ***how*** that deference was applied between two otherwise reasonable alternative paths. FDA-000460–497.

Nor does it excuse FDA's failure to provide adequate reasoning in its Exclusivity Decision. *See Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221 (2016) ("One of the basic procedural requirements of administrative rulemaking is that an agency must give adequate reasons for its decisions."); *Int'l Union, United Mine Workers of Am. v. Dept. of Lab.*, 358 F.3d 40, 45 (D.C. Cir. 2004) ("[T]he MSHA failed to provide an adequate explanation for its decision to withdraw the Air Quality proposal."). "Absent such an explanation, the agency's action was arbitrary and capricious." *Id.* In any event, scientific deference does not excuse FDA from complying with its own regulation. *See Nat'l Env't Dev.*, 752 F.3d at 1009 ("[A]n agency is not free to ignore or

violate its regulations while they remain in effect.") (cleaned up).

In an attempt to resuscitate its Exclusivity Decision, FDA doubles down on its fabricated "theory"—raised for the very first time in the Exclusivity Decision, and ***nowhere else***—that "an inhalation powder might present a risk of getting stuck in the throat or might cause a sensation of something stuck in the throat." FDA Br. 25-26 (quoting FDA-000433). Telling, in making this argument FDA refers to only the Exclusivity Decision because no other evidence in the record suggests that FDA had concerns about throat blockage or similar sensations. That supposed concern did not manifest in the 2017 pre-IND meeting minutes, in FDA's Original Exclusivity Summary, in FDA's CDTL, OCP, or Clinical Reviews, or anywhere else in the record—other than in the Exclusivity Decision. *See* FDA-000691; FDA-000453–459; FDA-000881–882. FDA's *post hoc* justification cannot stand under the APA. *See DHS v. Regents of the Univ. of Cal.*, 591 U.S. 1, 20 (2020) ("It is a foundational principle of administrative law that judicial review of agency action is limited to the grounds that the agency invoked when it took the action.") (cleaned up).

FDA strenuously tries, but fails, to shore up its belated throat blockage rationale by citing a few phrases from the 2017 meeting minutes and Clinical/Decisional Memorandum. FDA Br. 26 (citing FDA-000690–691 & FDA-000921). The significance of those cites, however, is far from clear. They merely show that FDA was supportive of UTC conducting BREEZE and that BREEZE offered generalized bioavailability and safety data; crucially, the meeting minutes do not convey any concerns whatsoever about throat blockage or sensations. FDA-000690–691; FDA-000921. And not once did FDA raise throat blockage concerns in the context of the Tyvaso DPI NDA or the Yutrepia NDA, another dry powder treprostinil product. To the extent there was any concern with coughing, throat irritation, or pharyngolaryngeal pain, FDA already had the data it needed on those potential adverse events from TRIUMPH. FDA Br. 25 n.14 (acknowledging that TRIUMPH

data had already shown that patients on inhaled treprostinil may experience coughing, headaches, throat irritation or pharyngolaryngeal pain, and nausea) (citing FDA-000433 & FDA-000640). In other words, contrary to FDA's belated contentions, the record evidence echoes Liquidia's correct understanding that throat blockage reflects a *post hoc* justification for FDA's characterization of BREEZE as essential to approval. *See McDonnell Douglas Corp. v. Dep't of Air Force*, 375 F.3d 1182, 1188 (D.C. Cir. 2004) (rejecting "*post hoc* rationale for upholding an agency's action").

Nor is there any evidence showing that BREEZE was designed to or did address FDA's novel safety concern. BREEZE did not collect any data as to whether patients experienced a sensation of the powder becoming stuck in their throats or whether the powder did in fact deposit in patients' throats. Nor did BREEZE show that Tyvaso DPI reduced those risks. The only references to "sensation of foreign body" or "globus pharyngeus" in the record demonstrate that, rather than study those patients, BREEZE ***withdrew*** all patients who experienced those issues. FDA-000827; FDA-000878, 894, 900 (same). It defies logic that FDA could deem BREEZE essential to approval because it supposedly addressed a specific safety concern when patients experiencing that same concern were withdrawn, such that their data for the duration of the three-week study was not before FDA to evaluate with the Tyvaso DPI NDA. *See* FDA-000720 (patients were "withdrawn if necessary, to protect their health and safety or the integrity of the study data").

FDA then advances the strawman argument that "Liquidia's argument is in tension with its own apparent position about the role of the tolerability data in the Yutrepia application." FDA Br. 23. FDA's argument appears to be that Liquidia must have regarded the data available from the Tyvaso Inhalation Solution NDA insufficient to show the tolerability of a dry powder treprostinil because Liquidia studied the tolerability of Yutrepia in INSPIRE, a study that FDA contends was "similar in many respects to the BREEZE study." *Id.* The tension that FDA attempts to conjure

is a red herring because Liquidia never sought NCI exclusivity for INSPIRE. In a misguided effort to attack Liquidia's arguments, FDA inadvertently confirms once again that it has conflated what is ***sufficient*** for NDA approval with the much higher bar of what is ***necessary*** for NCI exclusivity. In any event, INSPIRE was conducted ***before*** BREEZE and thus BREEZE was "similar" to Liquidia's study, not the other way around.

Next, FDA contends that BREEZE was "essential to approval" because it addressed previously unanswered clinical questions about dry powder treprostinil for "chronic use." FDA Br. 24. But up until the Exclusivity Decision, not once did FDA characterize BREEZE as studying "chronic use," instead appropriately characterizing it as "short-term (~2 to 3 weeks)." FDA-000685. When it came time for FDA to describe precisely ***how*** a three-week study could answer any unique, previously-unanswered clinical questions about chronic use of inhaled treprostinil, FDA bafflingly points to Tyvaso DPI's drug labeling for "two indications," PAH and PH-ILD, as well as FDA's conclusory extrapolation that BREEZE "supports the safety of Tyvaso DPI" in PAH and PH-ILD, without discussing the actual findings of BREEZE, much less how they support those conclusions or its "chronic use." FDA Br. 24–25; *but see* FDA Br. 8 (conceding that it was TIP-PH-102 that "justified extrapolation of the safety and effectiveness data from the TRIUMPH I and INCREASE studies to Tyvaso DPI," not BREEZE).

Lurking just below the surface of FDA's overbroad reading of BREEZE is the undisputed fact that TRIUMPH and INCREASE had already answered the clinical questions of whether inhaled treprostinil is safe and effective for chronic use by all types of PAH and PH-ILD patients. FDA-000471–472 ("Specifically, safety and efficacy of inhalational treprostinil in the treatment of PAH (WHO Group 1) to improve exercise ability and PH-ILD (WHO Group 3) to improve exercise ability were demonstrated in the TRIUMPH I study and the INCREASE study, which

were submitted to the Tyvaso NDA."). Standing alone, BREEZE answered no such questions for the first time and, as FDA had previously found, "provided confirmatory . . . information only." FDA-000453.[5] In short, the record clarifies that BREEZE was not a new clinical investigation essential to the approval of Tyvaso DPI within the meaning of the FDCA and FDA regulations. FDA's contrary determination was unlawful.

B. The Conditions of Approval for Tyvaso DPI Cannot Block Yutrepia.

Even assuming that BREEZE could qualify as a new clinical investigation other than a confirmatory bioavailability study that was essential to approval of Tyvaso DPI (it cannot), the Exclusivity Decision cannot stand. In the Decision, FDA determined that Tyvaso DPI has NCI exclusivity until May 23, 2025, for all "inhalation powder dosage form[s] of the active moiety treprostinil for chronic use." FDA-000450. That sweeping scope of exclusivity—which covers unstudied patient populations (de novo PAH patients and all PH-ILD patients), unstudied dosage form (all dry powder treprostinil, even those without the FDKP excipient) and an unstudied type of use (chronic use)—far exceeds the FDCA's limitations on the outer boundaries of NCI exclusivity that may attach to a drug on the basis of an eligible new clinical investigation given the limited patient population, indication, duration, and the FDKP/treprostinil formulation that BREEZE studied. FDA's determination is further contrary to its own prior precedents.

1. FDA Erroneously Granted NCI Exclusivity Covering the Entire Dosage Form of Dry Powder Treprostinil.

The FDCA prohibits FDA from recognizing NCI exclusivity beyond the "conditions of

[5] While BREEZE had an optional extension phase, the Exclusivity Decision and documents in the record refer to BREEZE data only from its ***three-week*** study phrase. *See, e.g.*, FDA-000860 (Sept. 2021 Office of Clinical Pharmacology Review describing outcomes); FDA-000429 (Table 1 graphic). FDA's singular reference to the optional extension phase appears in a footnote without any analysis or findings from that phrase, an apparent concession that the optional extension phase was not relied on for any previously-unstudied innovations on chronic use. FDA Br. 21 n.10.

approval" for the drug application. *See* 21 U.S.C. § 355(c)(3)(E)(iii). To evaluate the scope of NCI exclusivity and its application, FDA must first identify the "conditions of approval" for the first NDA. Second, after identifying the "conditions of approval" of the first NDA, FDA must "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. *Veloxis* clarified that "conditions of approval" means that "the scope of [NCI] exclusivity . . . can be ***no broader than the innovations presented to the FDA in the new clinical investigation[]*** that led to the FDA's approval of the first-in-time . . . NDA." *Id*. at 121 n.16; *see AstraZeneca*, 872 F. Supp. 2d at 83 (the "substantive relationship between new clinical studies and changes in the [NDA] . . . dictates what changes receive exclusivity").

The FDCA requires a "logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting three-year [NCI] exclusivity." *Veloxis*, 109 F. Supp. 3d at 120–21 (quoting *AstraZeneca*, 872 F. Supp. 2d at 80). The "conditions of approval" are "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." *Braeburn*, 389 F. Supp. 3d at 22–23. 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. Thus, the scope of any NCI exclusivity is limited to the innovative change presented by the new clinical investigation necessary for approval of the NDA. It is this understanding of the FDCA's plain language that the Court must police in this case. *Loper Bright*, 144 S. Ct. at 2268 (courts have "obligations under the APA to independently identify and respect such delegations of authority, police the outer

statutory boundaries of those delegations, and ensure that agencies exercise their discretion consistent with the APA").

FDA's erroneously granted NCI exclusivity to Tyvaso DPI on the basis of information already known to FDA that UTC cross-referenced from its Tyvaso Inhalation Solution NDA. FDA determined that the purported "innovation represented by Tyvaso DPI for which a new clinical investigation was essential is the inhalation powder dosage form for the active moiety treprostinil for chronic use." FDA-000442. FDA reiterates the same assertion here. FDA Br. 28.

But it is undisputed that Tyvaso DPI did not innovate the "inhalation powder dosage form" of dry powder. The innovation of dry powders as a dosage form had already been approved by FDA. For example, dry powder as a dosage form with FDKP had previously appeared in the Afrezza NDA approved by FDA years prior. *See* FDA-000878. Nor did Tyvaso DPI innovate inhaled treprostinil. That innovation came from TRIUMPH and INCREASE submitted with the Tyvaso Inhalation Solution NDA. FDA-000472 (efficacy and tolerability of inhaled treprostinil for the treatment of PAH (WHO Group 1) was demonstrated by TRIUMPH); *id.* (safety and efficacy of inhaled treprostinil for the treatment of the PH-ILD indication was demonstrated by INCREASE). FDA's decision to grant NCI exclusivity encompassing innovations that BREEZE never studied and its refusal to limit that exclusivity to only BREEZE supposed innovations flouts the FDCA. *See Hikvision USA, Inc. v. FCC*, 97 F.4th 938, 944 (D.C. Cir. 2024) (courts must reject agency action "[i]n the absence of statutory authorization") (citation omitted); *Am. Fin. Servs. Ass'n v. FTC*, 767 F.2d 957, 968 (D.C. Cir. 1985) (courts "must reject administrative agency actions which exceed the agency's statutory mandate or frustrate congressional intent").

A visual may help to clarify the fatal error in FDA's approach to defining the scope of NCI exclusivity here. In Figure 1 below, the yellow pie slice represents the sole patient population,

indication, FDKP/treprostinil dry powder, and short-term use covered by the data from BREEZE. But rather than define the scope of Tyvaso DPI's NCI exclusivity based on, at most, that narrow sliver (the yellow region)—as required by the FDCA, FDA regulations, and FDA precedent—the Exclusivity Decision awarded NCI exclusivity for BREEZE encompassing the whole pie (the yellow ***and*** red regions), inclusive of all PAH and PH-ILD patients and chronic use from the data and findings from the four other ineligible studies submitted with the Tyvaso DPI NDA.

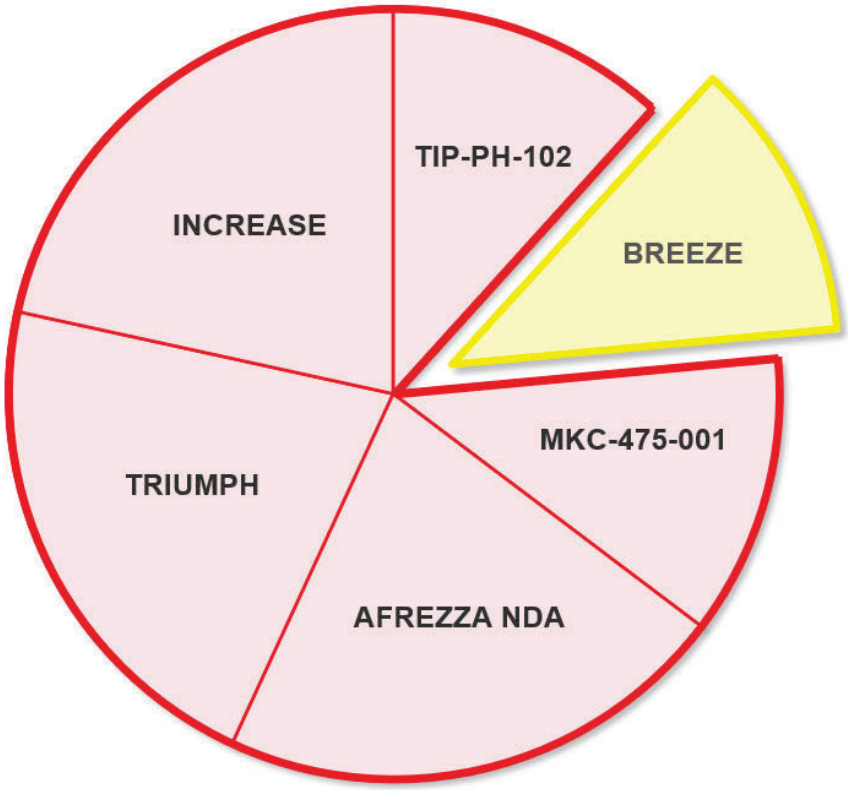

Figure 1: Data Supporting Approval of the Tyvaso DPI NDA

FDA's overbroad interpretation not only exceeded its authority under the FDCA and FDA regulations, but it is also inconsistent with the FDCA's intent to reward innovation while strengthening competition, public health, and patient access to safe and effective treatments. *AstraZeneca*, 872 F. Supp. 2d at 85. The inconsistency of FDA's actions with the FDCA is particularly acute here as FDA has already granted UTC exclusivity for the other pieces of the pie,

including by recognizing prior exclusivity periods for INCREASE and TRIUMPH, which have since expired. UTC Answer ¶¶ 53, 56.

FDA argues that "the scope of exclusivity properly encompassed the PH-ILD as well as the PAH indication" because "[w]ithout the BREEZE study, Tyvaso DPI could not have been approved for *either* indication." FDA Br. 27. This argument, however, is incorrect. Although BREEZE was a component of the Tyvaso DPI NDA, its role in FDA's approval was peripheral and it could not support a sweeping grant of NCI exclusivity covering the inhalation powder dosage form for the active moiety treprostinil for chronic use generally, let alone for all PAH and PH-ILD patients. FDA-000442. BREEZE did not study any novel indications, or new uses for the PAH and PH-ILD populations that UTC had not already studied for Tyvaso Inhalation Solution's NDA. *Compare* FDA-000637 (Tyvaso Inhalation Solution labeling) *with* FDA-000620 (Tyvaso DPI labeling). BREEZE merely studied stable PAH patients who were already taking stable doses of Tyvaso Inhalation Solution. FDA-000762. By granting NCI exclusivity to Tyvaso DPI that was ***not*** tied to any study of "novel indications or patient populations for which the drug product may be used," *Braeburn*, 389 F. Supp. 3d at 22–23, FDA further ran afoul of the FDCA.

Tellingly, in defending the scope of Tyvaso DPI's exclusivity encompassing ***all*** patient populations and indications, including PH-ILD, not once does FDA cite FDA's letter to UTC dated February 15, 2022. FDA-000915–918 (NDA 214324 Information Request). In that letter, FDA stressed that BREEZE had narrowly "enrolled patients with PAH WHO Group 1 but not PH-ILD WHO Group 3, and patients with FEV1 <60% predicted were excluded." FDA-000916. Given BREEZE's narrow patient population, FDA's letter expressed "concerns" that BREEZE could not justify "extrapolation of pulmonary safety (e.g., bronchospasm risk) for Tyvaso DPI from the PAH WHO Group 1 population to the PH-ILD WHO Group 3 population." *Id.*

And crucially, when FDA issued the Exclusivity Decision two years later granting NCI exclusivity to Tyvaso DPI covering de novo and stable-switching PH-ILD patients, FDA failed to even acknowledge—much less address—FDA's articulated concerns regarding BREEZE's wholesale exclusion of PH-ILD WHO Group 3 patients. *See* FDA-000460-497. FDA's failure to explain this critical issue at the heart of the NCI exclusivity it awarded is the very definition of arbitrary and capricious. *See Encino Motorcars*, 579 U.S. at 221; *Int'l Union*, 358 F.3d at 45.

It is uncontested that BREEZE's eligibility criteria failed to "closely mirror the target population" of treatment naïve PAH patients or PH-ILD patients (whether de novo or switching). FDA-000932. Indeed, the indication "PH-ILD" does not even appear once in BREEZE, and BREEZE never once explains "the basis for generalization [of Tyvaso DPI] . . . to the [PH-ILD] patient population." FDA-000931. BREEZE rendered no "innovations" for PH-ILD patients, such that any exclusivity awarded by FDA on the basis of BREEZE could not cover that distinct indication. The only grounds for FDA's finding that Tyvaso DPI can treat PH-ILD patients is its NDA's cross-reference to INCREASE—which is neither a new clinical investigation, nor part of BREEZE. 21 U.S.C. § 355(c)(3)(E)(iii) (excluding previously-submitted studies from qualifying a drug for NCI exclusivity); 21 C.F.R. § 314.108(a) (same); UTC Answer ¶ 68 (conceding that Tyvaso Inhalation Solution already received exclusivity for INCREASE's prior innovations, which "expired in March 2024"). In short, FDA's view is that rightly awarded exclusivity covering PH-ILD patients impermissibly grafts INCREASE's prior innovations onto BREEZE's limited findings, in stark violation of the FDCA and FDA regulations.

2. FDA Contravened Its Precedent by Granting NCI Exclusivity Beyond the BREEZE's Limited Scope.

Had FDA followed its prior precedents, FDA would have limited the scope of exclusivity to the patient population, the indication, and the formulation of Tyvaso DPI that BREEZE studied.

Those precedents firmly demonstrate that the scope of NCI exclusivity must be narrowly tailored based on the innovative findings in the new clinical investigations, which for BREEZE would at most cover short-term use of a combined FDKP-treprostinil dry powder by stable PAH patients transitioning from Tyvaso Inhalation Solution.

Here, however, FDA upended its prior exclusivity precedents by awarding NCI exclusivity to Tyvaso DPI for *all* indications (even those not studied), for *chronic use* (even though BREEZE was indisputably a short-term study); and for *any* dry powder inhalation form of treprostinil (even though the FDKP excipient accounts for virtually the entirety of Tyvaso DPI's formulation). *See Bonumose, Inc. v. FDA*, 2024 WL 3967258, at *11 (D.D.C. Aug. 28, 2024) (finding agency action arbitrary when it "fail[ed] to come to grips with conflicting precedent"); *Braeburn*, 389 F. Supp. 3d at 27–28 ("[T]he alleged inconsistency is that the FDA failed to limit the scope of Sublocade's innovation by the patient population on which the drug product was tested, as was done elsewhere. Braeburn is right as to each inconsistency, each of which is, in fact, a symptom of the FDA's unreasonable statutory interpretation discussed in the prior section.").

First, FDA failed to limit NCI exclusivity for Tyvaso DPI to the conditions of approval supported by BREEZE, as it did in the MorphaBond exclusivity memo. There, FDA correctly determined that "the scope of MorphaBond exclusivity is limited to the condition of approval supported by Study M-ARER-002: ***labeling*** describing the expected reduction of abuse of a single-entity [extended-release tablet] morphine by the intranasal route of administration due to physicochemical properties." FDA-001199 (emphasis added). Because the innovation presented and studied in M-ARER-002 was a reduced risk of drug abuse only through the intranasal route, FDA expressly rejected a "broad[] scope" of exclusivity for MorphaBond that would apply to "abuse deterrence generally" of opioid drugs as "inconsistent with the scope of [the underlying]

[s]tudy." FDA-001200. FDA recognized that the study, rather than addressing abuse deterrence of opioids generally, was "***intended only*** to measure the ability to deter abuse of ***single-entity ER morphine*** via the intranasal route due to the drug's physicochemical properties." *Id.* (emphasis added). Thus, the grant of NCI exclusivity to MorphaBond did not bar FDA approval of other morphine drugs, other morphine drugs with non-intranasal abuse deterrence properties, or other morphine drugs with extended-release tablets. *Id*. The correct approach that FDA took in Morphabond demonstrates that FDA knows how to correctly limit the NCI exclusivity to the specific innovations (i.e., the specific "pie pieces" in Figure 1 above) that were studied by a new clinical investigation.

Contrary to MorphaBond, FDA adopted a sweeping scope of NCI exclusivity for Tyvaso DPI that includes all the prior innovations of TRIUMPH and INCREASE—for which FDA already granted exclusivity periods that have now expired. FDA has done so despite its own position that later-in-time NCI exclusivity periods should be "narrower in scope—relative to any exclusivity recognized for the first drug product." FDA-000469. And FDA has done so despite the fact that BREEZE was intended only to address FDA's interest in Tyvaso DPI's treprostinil/FDKP dry inhalation powder, not treprostinil dry inhalation powder generally. FDA-000691 (noting that sponsor would "conduct an open-label, uncontrolled study to evaluate the short-term (~2 to 3 weeks) safety and tolerability ***of your product*** following repeat doses in PAH patients"); FDA-000690 (noting FDA's concerns with Tyvaso DPI's combined "treprostinil/FDKP dry inhalation powder" and questioning whether "FDKP particles . . . may impact inhalation toxicity").

FDA tries to recharacterize the MorphaBond exclusivity memo as a "highly fact-bound" decision, FDA Br. 28, and asserts that "it does not follow . . . that *no* study can *ever* support *any* conclusion beyond the precise conditions of the study." FDA Br. 29. But this assertion is belied

the administrative record. FDA could only extrapolate the results of BREEZE by relying on the findings of TRIUMPH, INCREASE, TIP-PH-102 and MKC-475-001—all ineligible studies that already shown the safety and efficacy of inhaled treprostinil for treatment naïve PAH and PH-ILD patients. Had FDA followed its approach in the MorphaBond exclusivity summary and carefully examined the data before it, it would not have granted NCI exclusivity to Tyvaso DPI that extends to the "chronic use" of every dry inhalation powder form of treprostinil.

Second, FDA failed to the limit scope of NCI exclusivity to the product's specific formulation, drug release profile, and/or excipient, despite FDA's Dyanavel XR precedent to that effect. There, FDA limited the scope of exclusivity for Dyanavel XR, an amphetamine product, to the unique formulation and associated drug release profile, and concluded the drug did not block approval of Adzenys ER, another amphetamine drug. FDA-001204 (finding that the "exclusivity-protected condition of approval for which new clinical investigations were essential to approval" was a specific "formulation," and Adzenys was not blocked as "[it] comprises a different formulation that results in a drug release profile different from that of Dyanavel XR and Mydayis"). FDA's sole response to the Dyanavel precedent is its bare assertion that "the 'scope of exclusivity is, by definition, context-specific.'" FDA Br. 30 (quoting FDA-000446).

But based on the record here, FDA should have followed its analysis in Dynavel XR and award exclusivity based on, at most, Tyvaso DPI's formulation—particularly because FDA focused on the specific formulation "of your product" Tyvaso DPI during its review of the Tyvaso DPI. [redacted] FDA-000150 ("Tyvaso DPI incorporate[d] the dry powder formulation technology and . . . inhalation device technology used in . . . Afrezza® (insulin human)

Inhalation Powder product, which was approved by the FDA in 2014.").

For FDA to claim that Tyvaso DPI blocks all dry powder formulations of treprostinil is to ignore FDA's own review of the drug, which focused heavily on the safety of the FDKP excipient, which was already used in the dry inhalation powder drug Afrezza. FDA-000909 ("the safety of the excipient fumaryl diketopiperazine (FDKP) is supported by a comprehensive battery of safety pharmacology and toxicology studies conducted for Afrezza"); *see also* FDA-000881–882. In fact, across the Clinical and CDTL Reviews for Tyvaso DPI, FDA mentions Afrezza ***20*** times and FDA mentions FDKP ***31*** times, either by name or as the relevant "excipient." FDA-000869–906; FDA-000907–912. FDA only concluded that Tyvaso DPI was safe because it included a lower dosage of FDKP than Afrezza. FDA-000881–882; FDA-000910. Nowhere did FDA cite any concerns related to dry powder treprostinil generally; rather, the agency raised concerns about the ***particular formulation*** of Tyvaso DPI's FDKP/treprostinil dry inhalation powder. Thus, if FDA had taken the same approach here as it did with Dyanavel XR, then FDA would have limited the scope of NCI exclusivity to Tyvaso DPI's particular dry inhalation powder form of treprostinil using the FDKP excipient, which would not block Yutrepia.

FDA's further assertion that it "defies logic" how "the scope of Tyvaso DPI's exclusivity should be limited to an 'innovation' supported by a different drug," FDA Br. 29, is ***exactly*** Liquidia's point. FDA should not be rewarding Tyvaso DPI NCI exclusivity based on an innovation not studied in BREEZE. The innovation of dry powder and FDKP was ***not*** an innovation of Tyvaso DPI. Thus, even if BREEZE could be considered eligible for NCI exclusivity, the scope of NCI exclusivity it supports must be limited to its particular combined FDKP-treprostinil formulation—***not*** all dry inhalation powder formulations. And, accordingly, because Yutrepia does not share this "condition of approval," the NCI exclusivity awarded to

Tyvaso DPI for BREEZE should not block Yutrepia from full approval.

Third, FDA failed to limit the scope of NCI exclusivity to the patient populations studied by BREEZE, as it had in *Veloxis*. In the Astagraf XL exclusivity summary, FDA determined that two new clinical studies made a drug eligible for NCI exclusivity ***only*** insofar as 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." *Veloxis*, 109 F. Supp. 3d at 111 (brackets in original). Although FDA had approved the drug "for the prophylaxis of organ rejection in patients receiving *de novo* kidney transplant," FDA-001136, ***FDA did not grant NCI exclusivity identical to the approved indication***. Instead, FDA limited the scope of exclusivity because "the new clinical investigations . . . for which Astagraf XL received exclusivity ***did not*** also demonstrate the safety and effectiveness of the Astagraf XL once-daily, ER dosage form for every use (or even just for conversion use), but rather ***only*** for *de novo* use in kidney transplant patients." FDA-001165 (emphasis added). Thus, FDA found that "the scope of 3-year exclusivity for Astagraf XL **does *not* extend** to a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for converting kidney transplant patients who are stable on IR tacrolimus." FDA-001166.

Applying FDA's approach to NCI exclusivity in Astagraf XL, FDA should have limited NCI exclusivity here to the specific PAH patient population that BREEZE studied. As discussed, BREEZE studied only PAH patients who were already taking stable doses of Tyvaso Inhalation Solution and who then switched to Tyvaso DPI. FDA-000762. By design, BREEZE excluded patients "diagnosed with PH for reasons other than WHO Group 1." FDA-000778. BREEZE "enrolled patients with PAH WHO Group 1 but not PH-ILD WHO Group 3, and patients with FEV1 <60% predicted were excluded." FDA-000916. In light of BREEZE's limited design,

FDA raised concerns with UTC that BREEZE's stable-switching PAH patient population could not justify "extrapolation of pulmonary safety (e.g., bronchospasm risk) for Tyvaso DPI from the PAH WHO Group 1 population to the PH-ILD WHO Group 3 population." FDA-000916. There is no response from UTC to this question in the administrative record.

Had FDA approached NCI exclusivity consistent with the Astagraf XL, FDA would have at most awarded exclusivity to Tyvaso DPI for only the limited treprostinil stable PAH patient population that BREEZE studied. FDA's contrary determination in the Exclusivity Decision was premised on little more than FDA's bare assertion that "BREEZE . . . supported the approval of Tyvaso DPI for use in a broader patient population than that included in the study (PAH patients switching from a stable dose of Tyvaso inhalation solution)." FDA-000448. FDA provided no explanation for this assertion, making it impossible to understand how FDA concluded that BREEZE could support use in a broader patient population despite the fundamental limitations in the study's scope and despite FDA's prior precedents. *See Patterson v. Comm'r of Soc. Sec. Admin.*, 846 F.3d 656, 663 (4th Cir. 2017) (failure to "[s]how [its] work" was arbitrary and capricious); *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. Nat'l Transp. Safety Bd.*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009) ("Reasoned decision-making . . . necessarily requires the agency to acknowledge and provide an adequate explanation for its departure from established precedent.").

FDA now argues that FDA refused to extend Astagraf XL's exclusivity to an indication for which Astagraf was not approved. FDA Br. 28 (citing FDA-000448). FDA reasons that because it approved Tyvaso DPI for the PH-ILD indication, it can disregard the specific patient

population studied in the sole supposed new clinical investigation submitted in the NDA. *Id.* This reasoning, like much FDA's defense of the Exclusivity Decision, is unavailing. It also appears nowhere in the Decision. *See DHS*, 591 U.S. at 21 ("It is a 'foundational principle of administrative law' that judicial review of agency action is limited to 'the grounds that the agency invoked when it took the action.'") (citation omitted).

Even entertaining FDA's argument further, it is an unpersuasive defense of FDA's failure to apply the approach to exclusivity that FDA took with Astagraf XL. FDA effectively seeks to rewrite its analysis in the Astagraf XL exclusivity decision—excising only the parts of the decision that are fatal to its exclusivity analysis for Tyvaso DPI—solely for the purpose of defending its flawed exclusivity analysis for Tyvaso DPI. This *post hoc* rationalization of FDA's approach to exclusivity in a prior FDA precedent not only concedes FDA's failure to follow the relevant analysis in the Astagraf XL exclusivity decision, but it also provides no basis to uphold the Exclusivity Decision. *See Am. Fed'n of Gov't Emps., AFL-CIO, Local 1929 v. Fed. Lab. Rels. Auth.*, 961 F.3d 452, 457 (D.C. Cir. 2020) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored.") (cleaned up).

II. SUMMARY JUDGMENT SHOULD BE PROMPTLY GRANTED FOR LIQUIDIA, OR ALTERNATIVELY, THE COURT SHOULD ISSUE A PRELIMINARY INJUNCTION.

Although the preliminary injunction factors favor Liquidia, FDA objects to an award of an injunctive relief for Liquidia on the ground that the "purpose" of injunctive relief "is merely to preserve the relative positions of the parties until a trial on the merits can be held." *Starbucks Corp. v. McKinney*, 144 S. Ct. 1570, 1576 (2024) (citation omitted). This argument is misguided. Granting preliminary relief would not "obliterate the 'relative position of the parties,'" as FDA alleges, FDA Br. 33, but merely restore the parties to the position they were in before FDA issued

its erroneous Exclusivity Determination in August 2024, when FDA's May 2022 Original Exclusivity Summary had been operative. At that time, there was ***no*** recognized exclusivity for Tyvaso DPI and thus no basis to block full approval for Yutrepia, which meets all safety and efficacy requirements. It is FDA's unlawful Exclusivity Decision that upended that status quo—and injunctive relief here would restore the balance Congress intended between innovation and competition, allowing patients access to a safe and effective alternative to Tyvaso DPI.

Beyond preliminary relief, this Court should set aside the Decision as unlawful and prohibit FDA from recognizing NCI exclusivity for Tyvaso DPI because the Decision exceeds FDA's statutory authority under the FDCA and is contrary to FDA regulations. The Court should also order injunctive relief to effectuate that order. As FDA itself acknowledges, "[i]njunctive relief is typically appropriate when there is ***only one rational course*** for the agency to follow upon remand." *Am. Hosp. Ass'n v. Azar*, 385 F. Supp. 3d 1, 11 (D.D.C. 2019) (cleaned up); FDA Br. 31. Because there is only one rational course based on the law here, the Court should remand with instructions to FDA to grant full approval for Yutrepia. *See Teva Pharms. USA, Inc. v. FDA*, 1999 WL 1042743, at *7 (D.D.C. Aug. 19, 1999) (plaintiff was "entitled to immediate final effective approval" for its drug application); *see also Torpharm, Inc. v. Shalala*, 1997 WL 33472411, at *1, *3-5 (D.D.C. Sept. 15, 1997) (requiring FDA to approve NDA after concluding FDA had incorrectly applied FDCA provisions at issue).

Alternatively, if the Court sets aside the Exclusivity Decision finding that it is arbitrary and capricious, then the proper course is to remand to FDA to reconsider its arbitrary and capricious findings. *See Advocs. for Highway & Auto Safety v. Fed. Motor Carrier Safety Admin.*, 429 F.3d 1136, 1151 (D.C. Cir. 2005) ("[U]nsupported agency action normally warrants vacatur."). Should

the Court remand the matter to FDA, Liquidia respectfully requests that the Court require FDA to render a decision within 14 days of this Court's order to avoid further delay. Liquidia Br. 45.

CONCLUSION

For the foregoing reasons, Liquidia requests that the Court grant summary judgment for Liquidia and deny FDA's Cross-Motion. Liquidia further requests that the Court set aside the Exclusivity Decision or, alternatively, limit the Exclusivity Decision to the stable-switching PAH patient population. Liquidia further requests that the Court order FDA to issue a final decision approving Yutrepia within 14 days of the Court's order granting summary judgment for Liquidia.

Dated: October 30, 2024

Respectfully submitted,

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