UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

LIQUIDIA TECHNOLOGIES, INC., *Plaintiff*, v. FOOD AND DRUG ADMIN., *et al.*, *Defendants*, and UNITED THERAPEUTICS CORPORATION, *Intervenor-Defendant.*	Case No. 1:24-cv-02428-TJK

Federal Defendants' Reply in Support of Cross-Motion for Summary Judgment

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INTRODUCTION

As Federal Defendants (collectively, FDA) explained in their opening brief (FDA MSJ, ECF No. 52), the agency reasonably determined that Tyvaso DPI is eligible for 3-year exclusivity and that Yutrepia cannot be approved until that period expires on May 23, 2025. FDA explained that the BREEZE study answered a specific safety question about treprostinil inhalation powder. No other study addressed that question. And without the BREEZE study, FDA would not have had sufficient information to approve Tyvaso DPI. FDA therefore concluded that the BREEZE study meets all the requirements for eligibility. Moreover, because Yutrepia proposes the same innovative change for which the BREEZE study was essential, FDA determined that it falls within the scope of Tyvaso DPI's exclusivity. Liquidia's response (Pl. Opp., ECF No. 63) does nothing to rebut those conclusions.

First, as to eligibility, Liquidia's primary argument is that the BREEZE study is a "bioavailability study" ineligible for exclusivity. Pl. Opp. 5-15. It reaches this conclusion because one of the BREEZE study's secondary endpoints measured pharmacokinetics. But that argument is inconsistent with the position Liquidia advanced before the agency and thus cannot be a basis for setting aside FDA's decision. In any event, Liquidia's interpretation of the statutory phrase "clinical investigations (other than bioavailability studies)" is wrong. That phrase requires examining whether a study has a purpose "other than" measuring bioavailability. As Liquidia concedes, the BREEZE study had non-bioavailability purposes, specifically, to assess safety and tolerability. These other purposes rendered the BREEZE study a "clinical investigation[] (other than [a]

bioavailability stud[y]),” even if it also measured bioavailability. Liquidia fails to explain why a study with a purpose “other than” measuring bioavailability is not “other than a bioavailability study.”

Liquidia also contends that the BREEZE study fails to meet other requirements for eligibility. Specifically, Liquidia argues that the BREEZE study was not a “*new* clinical investigation” because it allegedly duplicated the results of previous studies relied on to support the approval of other drugs. Pl. Opp. 15-19. Relatedly, Liquidia argues that the BREEZE study was not “essential to approval” because, according to Liquidia, FDA relied on those other studies, not BREEZE, to determine Tyvaso DPI’s safety and tolerability. Pl. Opp. 23-31. Liquidia is wrong as to both points. Tyvaso DPI is the inhalation *powder* dosage form of the active moiety treprostinil. None of those other studies involved treprostinil inhalation powder. Thus, those studies alone could not answer the specific safety question FDA had about the inhalation powder dosage form of the active moiety treprostinil. Liquidia points to nothing in the record to show that FDA relied on other studies to address that question.

Liquidia also continues to insist that FDA changed its position on eligibility without explanation. Pl. Opp. 19-23. But as FDA explained, the document that Liquidia paints as the agency’s initial eligibility determination (the Original Exclusivity Summary) was nothing of the sort. Rather, it was merely input provided by one agency component to help inform the Office of Generic Drug Policy’s future eligibility determination. Thus, that document never reflected *the agency’s* decision on eligibility. Liquidia’s response simply ignores this point. Instead, it reasons that the Original

Exclusivity Summary must have been the agency's decisional document based on incorrect inferences drawn from FDA's FOIA response and the title of another document. To the contrary, FDA's eligibility determination was made on August 14, 2024, and FDA's reasoning is reflected in the Exclusivity Memorandum. FDA-000413-52.

Second, as to the scope of exclusivity, Liquidia agrees with FDA that any exclusivity applies to the innovative change for which the BREEZE study was essential. Pl. Opp. 32. Here, FDA determined that the innovative change was the inhalation powder dosage form of treprostinil for chronic use. In response, Liquidia mischaracterizes FDA's decision as extending exclusivity to innovations supported by other studies, including the TRIUMPH I, INCREASE, and Afrezza studies. Pl. Opp. 34. Liquidia is incorrect. Tyvaso DPI's exclusivity does not extend either to the treprostinil inhalation solution studied in TRIUMPH I or INCREASE or to non-treprostinil drugs like Afrezza.

Beyond exaggerating the scope of exclusivity FDA identified, Liquidia repeats arguments it previously made about various FDA precedents. Pl. Opp. 36-42. But a simple review of those precedents shows that they do not stand for the broad propositions Liquidia cites them for. Rather, they establish that determining the innovation for which a clinical investigation was essential is a fact-intensive inquiry. That FDA's fact-intensive inquiry here led to a conclusion that Liquidia dislikes is no basis on which to set aside FDA's reasoned determination.

The Court should therefore grant FDA's cross-motion for summary judgment.

ARGUMENT

I. Tyvaso DPI Is Eligible For 3-Year Exclusivity

Under the 3-year exclusivity provision, Tyvaso DPI is eligible for exclusivity if the BREEZE study is (1) a "clinical investigation[] (other than [a] bioavailability stud[y])" that was (2) "new," (3) "essential to the approval" of Tyvaso DPI, and (4) conducted or sponsored by the applicant. 21 U.S.C. § 355(c)(3)(E)(iii). There is no dispute that the BREEZE study meets the last requirement. And, as FDA reasonably explained, the BREEZE study also meets the other three requirements. Liquidia fails to show otherwise.

A. The BREEZE study is a "clinical investigation (other than a bioavailability study)"

Liquidia contends that the BREEZE study is ineligible for exclusivity because one of its secondary endpoints measured pharmacokinetics.[1] Pl. Opp. 5-15. That argument fails for two reasons. First, it is inconsistent with the position that Liquidia took before the agency, and it thus cannot be a basis for setting aside FDA's decision. FDA MSJ 16-17. And second, on the merits, the BREEZE study was a clinical investigation "*other than* a bioavailability study" because it had purposes other than measuring bioavailability: it also assessed safety and tolerability. FDA MSJ 18-20.

1. Despite its protestations (Pl. Opp. 8-9), there is no serious doubt that the argument Liquidia now makes is inconsistent with what it argued to the agency. In its

[1] FDA defines "bioavailability study" to mean "a study to determine the bioavailability or the pharmacokinetics of a drug." *See* 21 C.F.R. § 314.108(a).

July 2021 letter, Liquidia focused exclusively on primary endpoints, not secondary endpoints. It argued for classifying the BREEZE study and another study (the "pivotal [pharmacokinetics] study") based on their primary, and not secondary, endpoints or objectives. FDA-000010 (arguing that "secondary endpoints" were treated as "irrelevant" under an agency precedent). Specifically, Liquidia argued that this *other* study failed to qualify for exclusivity because *it* was a bioavailability study based on its "primary objective." FDA-000008. By contrast, Liquidia contended that the BREEZE study did not qualify for exclusivity because, based on its "primary endpoint," it was a "general safety study." *Id.* Liquidia did *not* contend, however, that the BREEZE study was a bioavailability study. Accordingly, FDA noted in its Exclusivity Decision that "Liquidia [did] not contest that the BREEZE study was a new clinical investigation (other than a bioavailability study)." FDA-000436; *see also Veloxis Pharm., Inc. v. FDA*, 109 F. Supp. 3d 104, 123-24 (D.D.C. 2015) (plaintiff waived its challenge to whether a study was a "new clinical investigation" because it failed to "give FDA an opportunity to consider the merits of its arguments"), cited in UTC Mem. 21. Now, however, Liquidia urges the Court to find the BREEZE study an ineligible "bioavailability study" based on its secondary pharmacokinetics endpoint.

Liquidia claims that it "repeatedly raised" its argument that the BREEZE study is ineligible for exclusivity because it is a bioavailability study. Pl. Opp. 8-9. But it plucks statements from its July 2021 letter out of context. Taken together, those statements show only that Liquidia argued that (1) the BREEZE study failed to qualify for exclusivity, (2) a bioavailability study is not eligible for exclusivity, and (3)

pharmacokinetics was a secondary endpoint of the BREEZE study. Liquidia points to no statement from its letters articulating its present position: that the BREEZE study's secondary pharmacokinetics endpoint made it a "bioavailability study."[2]

Notwithstanding this inconsistency, Liquidia asserts that its previous position is no obstacle to judicial review. Pl. Opp. 7-8. But as FDA explained in its opening brief, the effect of Liquidia's apparent concession before the agency should be the same as if Liquidia were asking a court of appeals to review a point it conceded in the lower courts. The D.C. Circuit has frequently observed that this Court must review an agency decision as though it were an "appellate tribunal" reviewing a lower court decision. *Hill Dermaceuticals, Inc. v. FDA*, 709 F.3d 44, 46 n.1 (D.C. Cir. 2013) (*per curiam*); *see also Marshall Cnty. Health Care Auth. v. Shalala*, 988 F.2d 1221, 1225 (D.C. Cir. 1993) (explaining that "when it reviews agency action," a "district court sits as an appellate tribunal"). One of the most familiar principles of appellate review is that a litigant may not seek reversal on the basis of an alleged error that the litigant itself conceded. *See, e.g.*, *Archdiocese of Wash. v. Wash. Metro. Area Trans. Auth.*, 897 F.3d 314, 322 (D.C. Cir. 2018).

[2] Liquidia points out (Pl. Opp. 8-9) that it argued that "a bioavailability study cannot be used to confer 'new clinical investigation' exclusivity on a new drug product." FDA-000008. It fails to mention, however, that this statement appears in a section of the letter addressing the *other* study discussed in its letter, not the BREEZE study. Indeed, the very next sentence states, "In this case, *the pivotal PK study* [i.e., the *other* study] unquestionably is a bioavailability study." FDA-000008 (emphasis added). It is telling that Liquidia's letter made no similar statement about the BREEZE study.

Tellingly, Liquidia cites *no* case permitting it to take back its concession before the agency. It suggests (Pl. Opp. 7) that holding it to its previous position would somehow run afoul of *Loper Bright Enterprises v. Raimondo*, 144 S. Ct. 2244 (2024), which held that "courts, not agencies, will decide 'all relevant questions of law' arising on review of agency action," *id.* at 2261 (quoting 5 U.S.C. § 706). But that principle does not mean that a plaintiff who concedes a point before the agency can then take back that concession in court. Liquidia calls this an abdication of the "judicial function." Pl. Opp. 7. It is not, for the same reasons that a court of appeals does not abdicate its function by declining to review a matter conceded in the lower court.

Finally, Liquidia argues that it is not always necessary for a party to raise an issue before the agency if the agency nonetheless considered the issue. Pl. Opp. 8 (citing *Wash. Ass'n for Television & Child. v. FCC*, 712 F.2d 677, 681 (D.C. Cir. 1983)); *cf.* 21 C.F.R. § 10.45(f) (forbidding an "interested person" seeking review of FDA action from "rely[ing] upon information or views not included in the administrative record"). But FDA did not consider the specific bioavailability argument Liquidia now raises. Moreover, Liquidia did not merely *fail to raise* its bioavailability argument. Rather, as explained above *supra* pp. 4-5, it advanced a position *inconsistent* with that argument.

2. In any event, FDA's interpretation and application of the phrase "clinical investigation (other than a bioavailability study)" was correct. The BREEZE study was a study in humans and had a purpose of assessing safety and tolerability. *See* FDA MSJ 18-19; *see also* Pl. Opp. 5-6 (acknowledging that the BREEZE study encompassed

endpoints that included "safety and tolerability"). It was therefore a clinical investigation "other than a bioavailability study."

While insisting that the statute's language must control—which FDA does not dispute—Liquidia pays little attention to the relevant statutory phrase: "clinical investigations (other than bioavailability studies)." Contrary to Liquidia's assumption, this phrase does not exclude a study merely because one of its purposes is to study bioavailability. Rather, it encompasses human studies, including those that measure bioavailability, so long as they are also something "*other than* bioavailability studies." Thus, if a study has a purpose *other than* measuring bioavailability, the fact that it *also* measures bioavailability is not enough to defeat its eligibility for exclusivity.

Rather than deal squarely with the language of the statute, Liquidia offers a plethora of invalid, non-textual arguments.

First, Liquidia contends that FDA's interpretation would make all human studies eligible for exclusivity because they necessarily include safety data. Pl. Opp. 9. Not so. To be sure, by regulation, all human studies must collect data on adverse events. *See, e.g.*, 21 C.F.R. §§ 312.32, 312.64(b), 320.31(d)(3). But FDA does not regard such routine, legally mandated data collection as a *purpose* of a study. Indeed, Liquidia does not point to any instance where FDA has determined this type of routine data collection rendered a study eligible for exclusivity. And in this case, the record is clear that a purpose of the

BREEZE study was to assess safety and tolerability.[3] Moreover, "clinical investigations (other than bioavailability studies)" are ineligible for 3-year exclusivity unless they are also (1) new, (2) essential to approval, and (3) conducted or sponsored by the applicant.

Second, Liquidia faults FDA for not "explain[ing] how, under [FDA's] interpretation, it lawfully selected BREEZE rather than" two other studies "for [3-year] exclusivity when all three of those studies expressly studied pharmacokinetics, safety, and tolerability as separate endpoints." Pl. Opp. 9; *see also* Pl. Opp. 14-15. But an explanation was not needed because FDA concluded, based on the BREEZE study, that Tyyaso DPI was eligible for exclusivity and that that exclusivity blocked approval of Yutrepia. *See* FDA-000436 n.86.

Third, Liquidia dismisses as "nonsensical" FDA's concern that Liquidia's own interpretation would invite sponsors to study pharmacokinetics in separate studies. Pl. Opp. 10. It is not. Liquidia's interpretation would mean sponsors could obtain 3-year exclusivity based only on studies that do not measure bioavailability at all. That would incentivize sponsors *not* to measure bioavailability in any study that might otherwise qualify for exclusivity. Rather than attempt to explain how its interpretation would *not* lead to additional, unnecessary human research, Liquidia merely asserts that "[s]ponsors will still design studies to generate data to support NDA approval." Pl. Opp. 11. That misses the point that Liquidia's interpretation (unlike FDA's) would give

[3] A study's purpose or purposes may be identified by examining, among other things, its endpoints, its design, and/or its role in the evidentiary package. FDA did not specifically explain how it determines the purposes of a study in its decision because Liquidia itself did not raise before the agency the arguments it now advances.

sponsors an incentive to unnecessarily segregate bioavailability assessments from other studies supporting approval in their own drug development.

Finally, Liquidia argues that FDA did not state in its Exclusivity Decision that a study's proper classification "turns on whether the study characterized its bioavailability or pharmacokinetic endpoints as 'primary' or 'secondary.'" Pl. Opp. 13. True. Nor does FDA take that position now. Rather, FDA's position is that purposes other than bioavailability can render a study "other than a bioavailability study." Whether those purposes are characterized as primary or secondary is not determinative. In this case, a purpose of the BREEZE study was to assess safety and tolerability, and its primary endpoints reflected this purpose.[4]

B. The BREEZE study was a "new clinical investigation"

To qualify for 3-year exclusivity, a "clinical investigation (other than a bioavailability study)" must also be "new." 21 U.S.C. § 355(c)(3)(E)(iii). FDA determined that the BREEZE study was a "new" clinical investigation because (1) its results had not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication, or safety for a new patient population; and (2) it did not duplicate the results of another investigation that was

[4] Ironically, the position Liquidia accuses FDA of advocating now echoes one Liquidia appeared to advance before the agency. FDA-000010 (urging FDA to follow a precedent that Liquidia characterized as "focus[ing] on the primary endpoint" and treating secondary endpoints as "irrelevant"). While FDA agrees that the BREEZE study's secondary bioavailability endpoint does not in itself render the study ineligible for exclusivity, it does not take the position that secondary endpoints are categorically irrelevant.

relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. FDA-000432 (citing 21 C.F.R. § 314.108(a)); *see* FDA MSJ 10. That determination was reasonable and, given FDA's expertise in evaluating scientific studies, entitled to deference. *See Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836, 840 (D.C. Cir. 2024) (court "must be careful not to unduly second-guess an agency's scientific judgments") (citation omitted); *Alpharma, Inc. v. Leavitt*, 460 F.3d 1, 9 (D.C. Cir. 2006) ("Such a judgment as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merits deference from us.") (cleaned up); *Jazz Pharm., Inc. v. Becerra, et al.*, Civ. A. No. 23-1819, ECF No. 104 (D.D.C. Oct. 30, 2024) ("Fundamentally, these are challenges to an area of special expertise of the FDA. When FDA makes scientific judgments, the court owes the agency the most deferential review.") (cleaned up).[5]

Liquidia contends that the BREEZE study was not "new" because it "merely confirmed what FDA already knew about inhaled treprostinil" and "duplicated the results" of the TRIUMPH I, INCREASE, and Afrezza studies. Pl. Opp. 15-18. But none of these studies involved treprostinil inhalation powder. That difference was crucial

[5] Despite its extensive reliance on *Loper Bright*, Liquidia does not identify any contested statutory interpretation question regarding the meaning of "new," "essential to approval," or "conditions of approval." Rather, Liquidia simply challenges the adequacy of FDA's reasoning in its application of each requirement. Such challenges are reviewed under the deferential "arbitrary and capricious" standard. *See Van Hollen, Jr. v. FEC*, 811 F.3d 486, 496 n.5 (D.C. Cir. 2016); *Arent v. Shalala*, 70 F.3d 610, 616 (D.C. Cir. 1995).

because FDA's specific safety question—and the specific purpose for which it considered the BREEZE study essential—related to the attributes of the inhalation powder dosage form for the active moiety treprostinil. *See, e.g.*, FDA-000435, 691, 881, 921.

Contrary to Liquidia's misunderstanding, the fact that FDA relied on data from the TRIUMPH I, INCREASE, and Afrezza studies does not mean that the BREEZE study merely "duplicated" their results. While FDA relied on these other studies to support a finding of safety for Tyvaso DPI, it did not rely on them to answer the specific question it had about the tolerability of multiple-dose use of the inhalation powder dosage form of treprostinil. As the Exclusivity Memorandum explains, the "results of the [BREEZE] study 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)." *See, e.g.*, FDA-000439.[6] And providing assurance that was needed to address a safety and tolerability question is not "duplicating" another study's result.

Liquidia also argues that, under what it calls FDA's "longstanding policy," Pl. MSJ 27-29 (citing 54 Fed. Reg. 28872, 28899 (July 10, 1989)), the BREEZE study did not qualify for exclusivity because it did not involve a "new patient population" for

[6] Liquidia triumphantly touts the statement in the Original Exclusivity Summary that the "safety and tolerability [i.e., BREEZE] study" provided "confirmatory efficacy information only." Putting aside the fact that the Original Exclusivity Summary was not a decision by the agency, *see infra* pp. 16-19, this statement is irrelevant on its face. FDA has not claimed that the BREEZE study was essential to answering any question relating to *efficacy*.

treprostinil. Pl. Opp. 18. Even assuming Liquidia is right about that policy, the alleged policy contemplates the recognition of exclusivity for a study that permits "broader use of the drug." 54 Fed. Reg. at 28899. FDA found that the BREEZE study permitted a broader use of treprostinil by giving patients a treprostinil option in a new dosage form, which had not previously been shown to be well-tolerated and safe. FDA MSJ 22 (citing FDA-000436 n.87; FDA-000437). Rather than rebut that point, Liquidia simply restates its view that the BREEZE study "***did not*** study an expanded patient population." Pl. Opp. 18. But it provides no explanation for its assumption that only an "expanded patient population" can permit broader use of a drug.

C. The BREEZE study was "essential to approval"

To qualify for 3-year exclusivity, a "clinical investigation (other than a bioavailability study)" must also be "essential to approval." 21 U.S.C. § 355(c)(3)(E)(iii). FDA determined the BREEZE study was "essential to approval" because it addressed a "specific safety question" that was not addressed by any other study: "the tolerability of multiple doses daily over multiple weeks of treprostinil in the new inhalation powder dosage form to support approval for chronic use." FDA-000437; *see* FDA MSJ 23-25. Without the BREEZE study, FDA would not have had sufficient information to approve Tyvaso DPI. FDA-000439 (explaining that the BREEZE study "was, in fact, needed for approval"). That determination, too, falls squarely within the scope of deference the APA affords FDA's scientific evaluation of studies. *See Alpharma*, 460 F.3d at 9.

Liquidia contends that the BREEZE study was not "essential to approval" of Tyvaso DPI because the TRIUMPH I, INCREASE, and Afrezza studies provided FDA

with the data it needed to determine the safety and tolerability of treprostinil inhalation powder. Pl. Opp. 23-28. But the fact that the BREEZE study identified no new risks associated with the inhalation powder dosage form and showed a prevalence of adverse events similar to Tyvaso does not make it any less essential to approval. To the contrary, the study was needed "precisely to assess whether the new dosage form presented any such new or greater safety and tolerability risks . . ." FDA-000440. And FDA made clear that "the other available data, including from the TRIUMPH I, INCREASE, and relative bioavailability studies, were not enough on their own to support approval." *Id*.

Failing to grasp this point, Liquidia contends that FDA erroneously found that the BREEZE study was eligible for exclusivity merely "because it was part of the clinical package that supported Tyvaso DPI's approval." Pl. Opp. 25. But, in fact, FDA found that the BREEZE study was itself *necessary* for approval because it answered an important safety question addressed by no other study. FDA-000437-38 ("[The BREEZE study] was the only study in the Tyvaso DPI NDA that provided data on the multiple dose-use of Tyvaso DPI, and . . . these data were necessary to support the finding of safety for the inhalation powder dosage form of treprostinil for chronic use."); FDA-000435 ("Without the BREEZE study, the Division would not have had sufficient information regarding the safety and tolerability of multiple doses of the new dosage form of treprostinil to support approval.").

Contrary to Liquidia's accusation, FDA did not "fabricat[e]" this safety concern.[7] Pl. Opp. 28. The 2017 meeting minutes demonstrate that FDA requested the BREEZE study to address "safety and tolerability" following repeat doses—something that would have been unnecessary if FDA thought that the other planned studies of Tyvaso DPI would be sufficient to support approval. FDA examined the BREEZE study to determine whether it showed "new risks associated with treprostinil formulated as an inhaled powder." FDA-000881. And when FDA approved Tyvaso DPI, it stated that the BREEZE study permitted the agency to adequately characterize Tyvaso DPI's safety profile. FDA-000434 (citing FDA-000921).[8]

Finally, Liquidia repeats its arguments that the BREEZE study could not have been essential to establish safety and tolerability for chronic use because of the length of the study. Pl. Opp. 30. Liquidia's narrow focus on the length of the BREEZE study is misplaced. FDA had recommended a study to evaluate short-term safety and tolerability of Tyvaso DPI *following repeat doses*, as these data were expected to provide sufficient data on safety and tolerability to support approval for the same chronic-use indications as Tyvaso, *i.e.*, the PAH and PH-ILD indications. Indeed, because PAH and

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[7] FDA and Liquidia agree that the BREEZE study was not essential to establish the safety of the excipient FDKP. FDA MSJ 22 n.11; Pl. Opp. 18, 26. Liquidia's extended discussion relating to FDKP (Pl. Opp.17-18, 19, 26-27) is therefore irrelevant.

[8] Liquidia disbelieves FDA's explanation because (it claims) the BREEZE study "did not collect any data" on whether its subjects experienced choking sensations. Pl. Opp. 29. But this is incorrect. The study reported that two patients withdrew from the study due to treatment-related adverse events, including one experiencing "sensation of a foreign body" in the throat. FDA-000827; FDA-000434 (citing FDA-000900); *see also* UTC Mem. 34 ("The fact that a particular adverse event never manifested for most study participants does not suggest that BREEZE failed to study the risk.").

PH-ILD are chronic conditions, it would not have made sense for FDA to request the BREEZE study if it did not believe such data could support approval of the product for chronic use. Moreover, as Tyvaso DPI's labeling makes clear, FDA considered both short-term and long-term data from the BREEZE study in approving Tyvaso DPI. FDA-000623; *see also* FDA-000439-40 ("The BREEZE study was sufficient in size and duration to allow appropriate characterization of safety and tolerability.").

D. FDA did not change its position on eligibility

As FDA explained in its opening brief (FDA MSJ 14-16), it did not change its position on whether Tyvaso DPI was eligible for 3-year exclusivity. The Original Exclusivity Summary that Liquidia touts was not a decision by the agency but simply the initial assessment of the Clinical Division. However, the FDA component charged with making FDA's eligibility determination is not the Clinical Division, but the Office of Generic Drug Policy. FDA MSJ 15. In reaching its decision, the Office of Generic Drug Policy adopted the recommendation of the Exclusivity Board that exclusivity be recognized for Tyvaso DPI. FDA MSJ 10.[9]

Undeterred, Liquidia continues to repeat its mantra that the Original Exclusivity Summary represented *the agency's* initial decision. Pl. Opp. 19-22. It simply ignores the point that the component that completed the Original Exclusivity Summary (the Clinical Division) is not the component that makes the agency's decision on eligibility

[9] In any event, the Clinical Division consulted with the Exclusivity Board and ultimately completed a superseding assessment expressing agreement with the rationale adopted by the agency. FDA MSJ 10, 15-16.

for exclusivity (the Office of Generic Drug Policy). *See* FDA MSJ 14-16. Instead, it grasps at straws.

First, Liquidia wrongly contends that the Original Exclusivity Summary *must* have been the agency's decision because FDA would otherwise have claimed deliberative process privilege over it in responding to a FOIA request. Pl. Opp. 21-22. Even assuming the question of deliberative process privilege could bear on whether the Original Exclusivity Summary was an agency decision, the government does not always claim every privilege available to it. *Trump v. Thompson*, 573 F. Supp. 3d 1, 16 (D.D.C. 2021) (noting that "history is replete with examples" of voluntary waivers of executive privilege, including deliberative process privilege). That FDA did not claim the deliberative process privilege here does not transform the Original Exclusivity Summary into something it is not.[10]

Second, Liquidia's parsing of the title of the "Superseding Exclusivity Summary" is unpersuasive. Liquidia suggests that one document cannot "supersede" another unless the first document was an agency decision. Pl. Opp. 22. But the word "supersede" implies nothing about the nature of the document superseded. It simply means "to cause to be set aside," "to force out of use as inferior," "to take the place or position of," or "to displace in favor of another." "Supersede," Merriam-Webster, https://perma.cc/8FA3-4PE2. Here, the Clinical Division displaced—that is,

[10] Similarly, Liquidia argues that the cover letter provided by FDA's information disclosure office in response to the FOIA request somehow dictates whether the Original Exclusivity Summary was an agency decision. Pl. Opp. 22. But the language it cites from that letter was lifted Liquidia's FOIA request.

superseded—its original nonbinding assessment with a new nonbinding assessment. Neither of them was an agency decision.[11]

Third, Liquidia cites no authority for its argument that FDA was required "to account for and persuasively distinguish" a document that was never the agency's decision. Pl. Opp. 22-23. Because the Original Exclusivity Summary was not a decision by FDA (initial or otherwise), FDA was not required to proceed as though it were changing positions on eligibility.[12]

Fourth, unable to muster anything substantive, Liquidia resorts to an obvious strawman. It finds it "simply not credible" that FDA "required an additional two years after approving Tyvaso DPI to decide" whether it was eligible for exclusivity. Pl. Opp. 23. But FDA did not make such an assertion. Rather, FDA did not make a decision on Tyvaso DPI's eligibility for 3-year exclusivity until 2024, when the agency needed to determine whether any such exclusivity would block approval of Yutrepia.

Finally, even if FDA erred in not specifically acknowledging and addressing the Original Exclusivity Summary, that error would be harmless. *See* 5 U.S.C. § 706(2) ("due account shall be taken of the rule of prejudicial error"). The Original Exclusivity Summary is a checklist, in which Clinical Division staff checked the box "NO" in response to a question about whether the Tyvaso DPI application contained reports of

[11] In a similar vein, Liquidia contends that the word "original" indicates that the "Original Exclusivity Summary" was the agency's decision on eligibility. Pl. Opp. 22. But it is obvious that something can be "original" without being an agency decision.
[12] In any event, the Superseding Exclusivity Summary, which the Clinical Division completed prior to the agency's final determination that Tyvaso DPI was eligible for exclusivity, *does* acknowledge the Original Exclusivity Summary. FDA-000498.

clinical investigations. The Exclusivity Memorandum fully explains why FDA determined that the correct answer to that question was not "no." It is unclear what more Liquidia thinks should be added: it identifies nothing in the Original Exclusivity Summary not addressed by the Exclusivity Memorandum.

II. Yutrepia Is Within The Scope Of Tyvaso DPI's Exclusivity

As FDA explained in its Exclusivity Decision and its opening brief, Tyvaso DPI's exclusivity blocks approval of Yutrepia. FDA MSJ 27-30. The scope of exclusivity is defined by the "conditions of approval" supported by the BREEZE study, which the parties agree means the innovative change for which the BREEZE study was essential. FDA MSJ 27; Pl. Opp. 32. Here, FDA reasonably determined that the innovative change was the inhalation powder dosage form of the active moiety treprostinil for chronic use. FDA-000447.

Liquidia attacks this conclusion through a game of divide-and-conquer. It points out that Tyvaso DPI is not the first approved inhalation powder or the first approved inhaled treprostinil product. Pl. Opp. 33. From there, it insinuates that being the first approved treprostinil inhalation powder is not an innovative change. *See* Pl. Opp. 33. That is illogical. To identify a drug product's innovation in determining the scope of exclusivity, the agency asks "what unique clinical question(s) about the safety and/or efficacy *of the active moiety* for the relevant use do the new clinical investigations essential to approval answer for the first time?" FDA-000421; FDA-000441 (emphasis added). *Insulin* inhalation powder is a different innovation than treprostinil inhalation powder. Likewise, treprostinil inhalation *solution* is a different innovation than

treprostinil inhalation *powder*. In light of FDA's specific concern about the safety and tolerability of the inhalation powder dosage form of treprostinil, it was entirely reasonable for FDA to define the relevant innovative change as treprostinil inhalation powder for chronic use.

To bolster its argument, Liquidia provides a pie chart (Pl. Opp. 34) purporting to depict the "Data Supporting Approval of the Tyvaso DPI NDA" as six slices of a pie: the BREEZE study; the TRIUMPH I study (of Tyvaso); the INCREASE study (of Tyvaso); the studies submitted to the Afrezza NDA; Study TIP-PH-102 (of Tyvaso DPI); and Study MKC-475-001 (of Tyvaso DPI). Pl. Opp. 34. Liquidia then claims that FDA's scope determination "encompass[es] the whole pie." *Id.*

This is simply wrong. FDA determined that Tyvaso DPI's exclusivity extends only to treprostinil inhalation powder. It does not extend to the treprostinil inhalation solution studied in TRIUMPH I or INCREASE. Nor does it extend to inhalation powders that do not contain treprostinil, such as Afrezza. Nor does Liquidia show how FDA's determination swallows any "slice of the pie" allegedly belonging to Study TIP-PH-102 or Study MKC-475-001.[13] In short, Liquidia's graphic represents nothing but its own exaggeration of what FDA determined.

Attempting to find some basis in the administrative record for further limiting the scope of Tyvaso DPI's exclusivity, Liquidia points to FDA's February 2022 information

[13] Nor, contrary to Liquidia's assertion, did FDA determine that the scope of exclusivity for Tyvaso DPI covers "*all* indications." *See* Pl. Opp. 37. FDA expressly did not decide whether the scope of exclusivity covers indications other than the approved PAH and PH-ILD indications. *See* FDA-000442 n.110.

request to UTC. Pl. Opp. 35-36 But far from supporting Liquidia's position, that request refutes Liquidia's notion that FDA ignored the question whether the BREEZE study data supported the approval of Tyvaso DPI for patients with PH-ILD. In that request, FDA specifically asked UTC to justify extrapolation of the BREEZE study data to patients with PH-ILD. FDA-000916. That FDA approved Tyvaso DPI for both the PAH and PH-ILD indications shows that FDA was satisfied with the submitted data and UTC's response. *See, e.g.*, FDA-000592 ("FDA has determined that the safety data in BREEZE supports the safety of Tyvaso DPI in patients with PH-ILD (WHO Group 3) and that no further data collection is needed to characterize potential pulmonary risks within this population."). Liquidia faults FDA for not addressing the concerns expressed in the information request in its Exclusivity Decision. But by then, FDA had already approved Tyvaso DPI for the PH-ILD indication. FDA's Exclusivity Decision was then predicated on the "conditions of approval" that the agency had determined were supported by the BREEZE study.

Liquidia's discussion of FDA precedent (Pl. Opp. 36-43) adds little beyond what FDA already addressed in its opening brief. Liquidia continues to cite narrow fact-bound determinations to argue for broad rules governing the scope of exclusivity. But in each precedent Liquidia cites, the scope of exclusivity was determined by the particular facts of the studies and drugs at issue. FDA MSJ 28-30; *see also* UTC Mem. 38-39 (noting that the Braeburn precedent declined to limit the scope of exclusivity to the precise patient population studied); FDA-000120 (concluding, based on facts of that case, "that the population studied in Sublocade's trials does not constrain the scope of

its innovation"). [14] None of those precedents is relevant to determining what innovative change the BREEZE study was essential to support.

CONCLUSION

For the foregoing reasons, and those stated in FDA's opening brief, the Court should grant FDA's cross-motion for summary judgment.

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Respectfully submitted,

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[14] As FDA previously explained, in the Veloxis precedent, FDA concluded that exclusivity did not extend to an indication for which Astagraf XL was not approved. FDA MSJ 28. It therefore provides no support for Liquidia's argument that Tyvaso DPI's exclusivity cannot extend to one of its approved indications. Liquidia's bald assertion (Pl. Opp. 43) that this reasoning appears nowhere in the Exclusivity Memorandum is flatly incorrect. *See* FDA-000448 (noting that Astagraf XL "was approved only for use in de novo patients").

CERTIFICATE OF SERVICE

I hereby certify that this document, filed through the CM/ECF system, will be sent via electronic mail through that system to all counsel of record.

November 25, 2024

/s/ Noah T. Katzen
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