EXHIBIT A

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

NDA 213005

Liquidia Technologies, Inc.
Attention: Jennifer Weidman, Ph.D., RAC
Vice President, Global Regulatory Affairs
419 Davis Dr., Suite 100
Morrisville, NC 27560

Dear Dr. Weidman:

Please refer to your New Drug Application (NDA) 213005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for Yutrepia (treprostinil) inhalation powder.

This letter provides the Agency's analysis regarding the eligibility of NDA 214324 for Tyvaso DPI (treprostinil) inhalation powder, approved on May 23, 2022, held by United Therapeutics Corporation (United Therapeutics), for 3-year exclusivity and the impact of such exclusivity on Liquidia's application. The Agency determined that Tyvaso DPI qualifies for 3-year exclusivity and that the exclusivity for Tyvaso DPI delays the approval of Yutrepia.

In making this decision, the Agency considered communications submitted on behalf of Liquidia, the relevant statutory and regulatory background, precedents, and the administrative record related to the approval of NDA 214324. This decision also was made with input from the Agency's scientific experts and policymakers from the Center for Drug Evaluation and Research (CDER), including scientific experts in the Division of Cardiology and Nephrology (the Division), and CDER's Exclusivity Board, among others, and this letter reflects that input. The background and reasoning for the Agency's decision is set forth below.

I. STATUTORY AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval

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is safe and effective.[1] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling, and that it meets other applicable requirements.[2]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[3] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[4] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[5] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[6]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[7] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the

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[1] See section 505(b)(1)(A) of the FD&C Act.

[2] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[3] Public Law 98-417 (1984).

[4] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent (BE) to the listed drug it references (RLD), that the conditions of use have been previously approved for the RLD, and that it is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[5] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[6] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[7] Section 505(b)(2) of the FD&C Act provides for approval of an application:

source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the applicant owns or to which it has a right of reference, the 505(b)(2) applicant may also rely on, for example, the Agency's findings of safety and/or effectiveness for one or more previously approved drugs.[8]

A 505(b)(2) application can be submitted for a change to a previously approved drug and, in some instances, may describe a drug product with substantial differences from a listed drug.[9] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*[10] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability[11] of the two products, or other appropriate scientific information. FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking

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> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted…

See also 21 CFR 314.3(b) (defining *right of reference or use*).

[8] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

[9] In October 1999, the Agency issued a draft guidance for industry titled *Applications Covered by Section 505(b)(2)* (505(b)(2) Draft Guidance), which states that "[a] 505(b)(2) application may be submitted for an NCE [new chemical entity] when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[10] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the relied-upon FDA-approved drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

[11] *Bioavailability* is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. 21 CFR 314.3(b). 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. See, e.g., FDA's Draft Guidance for Industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (February 2019) (BA NDA/IND Draft Guidance), at 2. When final, this guidance will represent the FDA's current thinking on this topic.

process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[12] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. The 505(b)(2) pathway permits applicants and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the listed drug on which the 505(b)(2) application seeks to rely.[13]

B. 3-Year Exclusivity Under the FD&C Act

An NDA or supplement for a drug containing a previously approved active moiety[14] is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which approved NDAs and supplements are eligible for 3-year exclusivity and which NDAs and ANDAs are barred or blocked from approval until the expiration of that exclusivity.

Relevant here, section 505(c)(3)(E)(iii) of the FD&C Act states:

> *If an application submitted under subsection (b) [of section 505 of the FD&C Act] for a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application approved under subsection (b) [of section 505 of the FD&C Act], is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of section 505 of the FD&C Act] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of section 505 of the FD&C Act] if the investigations described in subsection (b)(1)(A)(i) [of section 505 of the FD&C Act] and relied upon by the applicant for approval of the application were not conducted by or

[12] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[13] 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

[14] FDA regulations define "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 CFR 314.3(b).

> for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[15]

As addressed further below, the first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes the conditions under which certain 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity.

1. Eligibility for 3-Year Exclusivity

Under the eligibility clause in section 505(c)(3)(E)(iii) applications for drugs that are not eligible for 5-year new chemical entity (NCE) exclusivity (because they "include[] an active moiety…that has been approved in another application")[16] are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant.

FDA's regulation on 3-year exclusivity mirrors the statutory framework[17] and defines relevant statutory terms.[18] FDA regulations define the term *clinical investigation* as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."[19] *Bioavailability study* is defined as "a study to determine the bioavailability or the pharmacokinetics of a drug."[20] *New clinical investigation* is defined, in relevant part, as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient

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[15] See section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also section 505(j)(5)(F)(iii), which describes which NDAs are eligible for 3-year exclusivity and which ANDAs are blocked from approval, and 21 CFR 314.108(b)(4).

[16] The longest period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided for a drug "no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) of which has been approved in any other application under [section 505(b)]." FDA has interpreted this exclusivity to generally prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[17] 21 CFR 314.108(b)(4).

[18] 21 CFR 314.108(a).

[19] Id.

[20] Id. *Bioavailability* is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. 21 CFR 314.3(b).

population of a previously approved drug product."[21] The Agency's regulations define the term *essential to approval* to mean, "with regard to an investigation, that there are no other data available that could support approval of the NDA."[22] The term *conducted or sponsored by the applicant* is defined, in relevant part, to mean "that before or during the investigation, the applicant was named in Form FDA 1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation."[23]

2. Scope of 3-Year Exclusivity

Under the Agency's interpretation of the bar clause, a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. The first step of the scope inquiry focuses on the drug with 3-year exclusivity. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause, i.e., "a drug, which includes an active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) that has been approved in another application." Thus, 3-year exclusivity for a drug only bars drugs that contain the same active moiety (or the same combination of active moieties for fixed-combination drugs).

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant, including aspects of the approval that were supported by those new clinical investigations. Under this step of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred. The Agency's interpretation of "conditions of approval," and its approach to assessing whether exclusivity blocks approval of a 505(b)(2) application, are discussed below.

a. Interpretation of "Conditions of Approval"

Although neither the statute nor the regulations define the phrase *conditions of approval* for purposes of determining whether exclusivity blocks approval of a 505(b)(2) application,[24] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[25] addresses the Agency's interpretation. It makes clear FDA's view that conditions of approval for the purposes of 3-year exclusivity means the innovative change for which new clinical investigations are essential to approval:

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[21] 21 CFR 314.108(a).

[22] Id.

[23] Id.

[24] See generally, e.g., section 505 of the FD&C Act, 21 CFR 314.108(a), and 314.108(b)(4)(iv).

[25] See generally, Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989).

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[26]

FDA interprets the scope of exclusivity to be related both to the underlying *new clinical investigations* that were essential to the approval and to aspects of the approval that were supported by those new clinical investigations. Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

Thus, in the case of an application submitted for a drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval.

The Agency's interpretation ties the incentive provided by 3-year exclusivity to the innovative change supported by the new clinical investigations conducted or sponsored by an applicant, reflecting the way in which the statute's *eligibility clause* and *bar clause* operate together. That is, it considers the "conditions of approval" to which exclusivity applies under the bar clause to be determined by the "new clinical investigations (other than bioavailability studies) essential to the approval of the application"[27] that establish the drug product's eligibility for exclusivity. In this way, "[t]he [FD&C Act] sets up 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 exclusivity.'"[28] This interpretation "respects the relationship between [section 505(c)(3)(E)(iii)]'s complementary clauses [and] Congress's intent, and is a first step toward filling the statutory ambiguity [inherent in the phrase 'conditions of approval']."[29] The legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval.[30]

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[26] 1989 Proposed Rule at 28896-97.

[27] Section 505(c)(3)(E)(iii) of the FD&C Act.

[28] See *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 120-21 (D.D.C. 2015).

[29] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 24 (D.D.C. 2019).

[30] See 59 Fed. Reg. 50338, at 50357 (Oct. 3, 1994).

Moreover, we believe that other interpretations of "conditions of approval" would lead to results that are inconsistent with the statute's purpose. For example, *conditions of approval* might be understood to mean all the conditions stated in FDA-approved labeling. That is, the conditions of approval would include *all* the information in approved labeling, so that exclusivity for one product would block a subsequent product's approval only where the labeling is exactly the same. But this interpretation would risk rendering an eligible product's exclusivity meaningless because of the high likelihood that a subsequent product's labeling would differ from the protected product's labeling in at least some ways. If any difference in labeling were sufficient to take a subsequent product outside the scope of a prior approved product's exclusivity, 505(b)(2) applications (which are not subject to a "same labeling" requirement) would almost never be blocked.[31] Interpreted in this manner, section 505(c)(3)(E)(iii), which governs the application of 3-year exclusivity to 505(b)(2) applications, might be considered superfluous because the only products that might be blocked by such narrow exclusivity likely would be ANDAs, which are subject to the exclusivity provision in section 505(j)(5)(F)(iii) of the FD&C Act. It is also significant that section 505(c)(3)(E)(iii) does not refer to approved labeling. Thus, it is reasonable to conclude that the scope of exclusivity is not limited to blocking products only with the same labeling. At the same time, if "conditions of approval" were to mean that any approved uses or characteristics of the product with exclusivity might block approval of a subsequent 505(b)(2) application with the same active moiety if it has any of the same characteristics or uses (even those not associated with new clinical investigations essential to approval), then almost any 505(b)(2) application with the same active moiety would be blocked. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[32] Given that section 505(c)(3)(E)(iii) is silent on

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[31] As the court noted in its decision in *Braeburn Inc. v. FDA*, "[p]rotecting exclusivity rights only if a follow-on product matches every condition listed in the first product's label would curtail exclusivity narrowly to exclude only precisely identical drug products, a result plainly at odds with Congress's goal of incentivizing research with market exclusivity." 389 F. Supp. 3d at 21.

In that case, Braeburn Inc. challenged the Agency's conclusion that 3-year exclusivity recognized for a previously approved monthly injectable buprenorphine product, Sublocade, precluded final approval of Braeburn's monthly buprenorphine product, Brixadi. The court vacated the Agency's exclusivity decision and remanded to the Agency to reconsider whether approval of Braeburn's NDA was blocked by Sublocade's exclusivity and to provide additional explanation for its decision. In a November 7, 2019, letter (referred to here as the "Braeburn Remand Letter") (No. 19-cv-00982-BAH, ECF No. 53 (D.D.C. Nov. 7, 2019)), FDA issued its reconsidered exclusivity analysis, setting forth in additional detail FDA's framework for determining a drug's innovation based on the new clinical investigations essential to its approval and again concluding that Sublocade's exclusivity precluded final approval of Braeburn's monthly buprenorphine product. Braeburn did not further challenge this decision.

[32] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

reliance, a subsequent 505(b)(2) application need not rely upon the drug product with unexpired exclusivity to be considered within the scope of and blocked by that product's exclusivity.[33]

b. Defining the Scope of Exclusivity

The link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a drug product containing the same active moiety or same active moieties as a previously approved drug product, the Agency looks at the innovation represented by the drug product eligible for exclusivity relative to previously approved drug products.[34]

i. Identifying the Innovation Relative to Previously Approved Drug Products

In identifying the innovation, the Agency asks a key question: for what aspects relative to previously approved drug products were the new clinical investigations essential to approval? More specifically, we ask *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?* By framing the inquiry in this way, the Agency seeks to ensure that the incentive provided by exclusivity rewards sponsors for conducting studies that will answer clinical questions relevant to the drug's approval, and not for establishing or confirming what is already known about the drug.

To determine the clinical questions for which the new clinical investigations were essential to approval, the Agency compares what has been shown in clinical investigations for the product at issue to what was known about previously approved drug products with the same active moiety. The analysis is, by definition, context-specific: a change that may have significance as an innovation in one instance – that is, a change for which studies were needed to demonstrate its safety or efficacy – may not require further studies in another instance, for example, in another therapeutic area. The nature of what aspect(s) of a drug will constitute an innovation must be determined on a case-by-case basis.[35]

Because the Agency evaluates the scope of a drug product's innovation in relation to previously approved drug products, the scope of 3-year exclusivity for a drug product is generally affected by previously approved drug products containing the same active moiety or the same active moieties.

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[33] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F.Supp.3d 104, at 116-120.

[34] A product eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) will, by definition, not be the first approved product containing the active moiety (or active moieties) at issue.

[35] For example, circumstances including the development of new technologies or evolving understanding of a disease area may affect whether an aspect of a drug constitutes an innovation.

In practice, where two drug products that have the same active moiety or same active moieties are sequentially approved, the result is often that the scope of exclusivity of the second drug product is limited – often narrower in scope – relative to any exclusivity recognized for the first drug product. This is because exclusivity is recognized only for new clinical investigations that are "essential to approval," which "means, with regard to an investigation, that there are no other data available that could support approval of the NDA."[36] As explained above, exclusivity does not protect aspects of the drug product for which new clinical investigations were not essential – that is, it does not cover aspects of the product which have already been demonstrated to be safe and effective (or which could be supported without the new clinical investigations).

If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered "essential" to support the same condition of approval for a later-approved drug product containing the same active moiety. Rather, the new clinical investigations would be considered essential only to support conditions of approval for the later-approved drug product that are different from the conditions of approval of the earlier-approved drug product. Thus, because 3-year exclusivity generally covers only the innovative differences from a previously approved product, as a practical matter each later-approved product typically will have a narrower scope of exclusivity than the product(s) approved previously.

Under FDA's interpretation, the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety or active moieties. A drug product may, however, qualify for exclusivity for an aspect that differs from the earlier-approved drug product, thus providing a continued exclusivity incentive – albeit one that is typically narrower in effect – for manufacturers to conduct new clinical investigations of previously approved drugs. In this way, the Agency's interpretation encourages both further innovation and expansion of what is known about a drug.

ii. Characteristics that Further Define Scope of Exclusivity

Because the 3-year exclusivity provisions of the Hatch-Waxman Amendments entail a balance between innovation and competition, the Agency considers whether certain characteristics of the eligible product, supported by new clinical investigations essential to the product's approval, may further define the scope of its innovation (i.e., the scope of its exclusivity).

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[36] 21 CFR 314.108(a). See 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("The phrase 'essential to the approval' suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement…'[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.'" (internal citations omitted)); 1989 Proposed Rule at 28900 ("In addition, there must not be an already approved drug product for which the applicant could submit an ANDA or 505(b)(2) application…A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.").

This assessment requires the Agency to make a fact-specific determination. The Agency does this by determining whether the relevant characteristics of the drug studied are clinically meaningful (for example, as opposed to merely reflecting the conditions under which the study was conducted). In making this assessment, the Agency may consider a characteristic to be *clinically meaningful* for purposes of 3-year exclusivity if, for example, it significantly changes the population or use for which the drug is appropriate with respect to previously approved drugs with the same active moiety, or would otherwise be expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient.

This assessment is made by FDA's medical and scientific staff based on FDA's understanding of the drug product, the indication or condition the drug is intended to treat, the clinical context of its use, its mechanism of action, and other relevant factors. The scope of an exclusivity-eligible product's innovation is generally cabined by characteristics that affect these clinically meaningful dimensions. Specific characteristics of a product could define the scope of its exclusivity where, for example, FDA determines that these characteristics, which are reflected in the details of the new clinical investigations essential to approval, are clinically meaningful.

Importantly, however, a particular clinical investigation may be more limited in scope or more specific than the conclusions (and thus the scope of exclusivity) that can be drawn from it. As a result, a drug studied in very specific conditions might be approved with a broader indication and not limited to those conditions under which it happened to be studied.[37] The scope of a product's innovation similarly might not be defined by specific characteristics of its clinical studies where such characteristics are not clinically meaningful. Thus, FDA interprets the conditions of approval to which exclusivity applies to be the product's innovation for which new clinical investigations were essential, defined by clinically meaningful characteristics of the product supported by the new clinical investigations essential to its approval.

II. FACTUAL BACKGROUND

A. Tyvaso DPI

NDA 214324 for Tyvaso DPI (treprostinil) inhalation powder, held by United Therapeutics, was approved on May 23, 2022. Treprostinil is a prostacyclin analogue, and its major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Inhaled treprostinil therapy provides selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects compared to other routes of administration.[38]

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[37] See, e.g., FDA Guidance for Industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (July 2018) (hereafter, Indications and Usage Draft Guidance), at 3 ("In some cases, FDA's expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication that is broader or narrower in scope than the precise population studied.").

[38] NDA 214324, Cross-Discipline Team Leader Review (October 14, 2021) (CDTL Review) at 2.

Tyvaso DPI is a drug-device combination product comprising plastic cartridges containing treprostinil dry powder for oral inhalation. It is approved for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability.
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

Tyvaso DPI is provided in single-dose cartridges that are available in 4 strengths: 16 mcg, 32 mcg, 48 mcg, and 64 mcg. The labeling states: "Tyvaso DPI therapy should begin with one 16 mcg cartridge per treatment session, 4 times daily." Regarding maintenance, the labeling states: "increase dosage by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals. The target maintenance dosage is usually 48 mcg to 64 mcg per session. If adverse effects preclude titration, continue Tyvaso DPI at the highest tolerated dose."[39]

NDA 214324 was submitted as a 505(b)(1) NDA that cross-referenced the following NDAs, also held by United Therapeutics:

- NDA 021272 for Remodulin (treprostinil) injection for subcutaneous or intravenous administration
- NDA 022387 for Tyvaso (treprostinil) inhalation solution for oral inhalation use
- NDA 203496 for Orenitram (treprostinil) extended-release tablets for oral administration

Tyvaso DPI contains the same active moiety, treprostinil, as Tyvaso, but provides for a change in dosage form from a solution for oral inhalation to a dry powder for oral inhalation.

To support approval of Tyvaso DPI, United Therapeutics relied on safety and efficacy data submitted in the Tyvaso NDA and provided relative bioavailability data to justify extrapolation of the previously submitted data to Tyvaso DPI.[40] 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.[41]

Study LRX-TRIUMPH 001 (TRIUMPH I) *Double Blind Placebo Controlled Clinical Investigation into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension*

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[39] Tyvaso DPI labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214324s000lbl.pdf), Section 2.2.

[40] The approach is similar to one that might be used by a 505(b)(2) applicant, as described in Section I.A.2, but United Therapeutics owns all of the data necessary for approval and therefore the data themselves were relied on.

[41] NDA 214324, Clinical Review (September 23, 2021) (Clinical Review) at 12.

The TRIUMPH I study was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of 235 patients with PAH. The study population included 235 clinically stable subjects with PAH (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least 3 months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. The primary efficacy endpoint of the trial was the change in 6-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3 to 5 hours after bosentan or 0.5 to 2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.[42]

Study RIN-PH-201 (INCREASE) *A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease*

The INCREASE study was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. The mean baseline 6MWD was 260 meters. Patients in the INCREASE study were randomized (1:1) to either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of patients randomized to Tyvaso titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to Tyvaso reaching a dose of 12 breaths, 4 times daily during the study. The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ($p=0.004$) using Hodges Lehmann estimate. The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose.[43]

In addition to this cross-referenced data, United Therapeutics submitted data to NDA 214324 from investigations that involved use of Tyvaso DPI, described below.

Study MKC-475-001 *A Phase 1, Single-center, Open-label, Dose-Rising Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Treprostinil Inhalation Powder (TrIP) in Healthy Normal Volunteers*

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[42] Tyvaso labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022387s020lbl.pdf), Section 14.1. See also Tyvaso DPI labeling, Section 14.1.

[43] Tyvaso labeling, Section 14.3. See also Tyvaso DPI labeling, Section 14.3.

MKC-475-001 was a standard phase 1, single-dose, open-label, dose-escalation study of Tyvaso DPI in healthy normal volunteers. Thirty-six subjects were enrolled in 6 cohorts of 6 subjects each. Single doses starting at 30 mcg and increasing to 180 mcg (30 mcg, 60 mcg, 90 mcg, 120 mcg, 150 mcg, and 180 mcg) were administered to healthy normal volunteers, and the pharmacokinetics of the drug product were characterized. Safety assessments included incidence and severity of reported adverse events, as well as changes from screening in vital signs, clinical laboratory tests, electrocardiograms (ECGs), and physical examinations. The PK profile was assessed at the different dose levels, along with C_{max}, time of maximum concentration (T_{max}), terminal elimination half-life ($t_{½}$), and area under the curve from time 0 to 480 minutes (AUC_{0-480}).[44]

Each subject received one dose of Tyvaso DPI by oral inhalation during the treatment period; no control groups were enrolled. The safety and tolerability of the drug was evaluated based on all available data in each sequential cohort prior to each dose cohort escalation. Subject safety data, including adverse events, from each dose group were assessed to determine whether the study should proceed to the next (ascending) dose level. Blood samples were obtained before study drug administration and at selected times through 480 minutes (8 hours) after study drug administration; 13 PK blood samples were collected from each subject. Plasma PK samples were analyzed for treprostinil, and PK parameters were calculated using noncompartmental methods.[45] Based on subject safety data (onset of respiratory symptoms), dose escalation was stopped at 180 mcg.[46]

Study TIP-PH-101 (BREEZE) *An Open-label, Clinical Study to Evaluate the Safety and Tolerability of Treprostinil Inhalation Powder (TreT) in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso*

The BREEZE study was a phase 1b open-label, single-sequence study enrolling 51 subjects with WHO Group 1 PAH on a stable regimen of Tyvaso who were then switched to a corresponding dose of Tyvaso DPI. The primary endpoint was safety and tolerability, and the secondary endpoints were PK assessments after administration of each treatment, 6-minute walk distance (6MWD), PAH-Symptoms and Impact (PAH-SYMPACT) Questionnaire, and Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD).

At baseline, subjects stabilized on Tyvaso (6 to 12 breaths, 4 times daily) took a dose of Tyvaso in the clinic and underwent safety assessments (including incidence and severity of reported adverse events, vital signs, clinical laboratory tests, electrocardiograms, and physical examinations), PK assessments (at 5, 10, 15, 30, 45, 90, 120, 180, 240, and 300 minutes after administration), and a 6MWD; subjects were also given the PAH-SYMPACT Questionnaire. Following the assessments, subjects switched from Tyvaso to the corresponding dose of Tyvaso

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[44] IND 134582, Clinical Study Report, MKC-475-001 at 17-18.

[45] Id.

[46] IND 134582, Clinical Study Report, MKC-475-001 at 57.

DPI and took their first dose of Tyvaso DPI in the clinic. Following 3 weeks of treatment with Tyvaso DPI (corresponding dose 4 times daily), subjects returned to the clinic and received a single dose of Tyvaso DPI and underwent safety assessments (including incidence and severity of reported adverse events, changes from screening in vital signs, clinical laboratory tests, electrocardiograms, and physical examinations), PK assessments (at 5, 10, 15, 30, 45, 90, 120, 180, 240, and 300 minutes), and 6MWD; subjects were also given the PAH-SYMPACT Questionnaire and PQ-ITD.

After the week 3 visit, subjects were offered the opportunity to participate in the optional extension phase (OEP) of the study. Subjects who elected to discontinue Tyvaso DPI at the end of the treatment phase could resume Tyvaso therapy and were required to return to the clinic 2 weeks later for an end-of-study visit. Subjects who elected to enter the OEP remained on Tyvaso DPI and attended follow-up study visits every 8 weeks. Dosing titration was allowed in the OEP of the study.

The applicant pre-specified PK analyses for plasma concentrations of treprostinil above the lower limit of quantitation to be used to calculate area under the curve from time 0 to 300 minutes (AUC_{0-300}) and maximal drug concentration (C_{max}) for each treatment.[47] Adverse events were tabulated. No formal statistical analysis plan was formulated for the secondary endpoints, and 6MWD and PAH-SYMPACT Questionnaire scores were summarized with descriptive statistics.[48]

As described in the Clinical Review, PK testing demonstrated similar AUCs for all doses between Tyvaso and Tyvaso DPI, although the C_{max} for the Tyvaso DPI formulation was greater than 120% of the Tyvaso liquid formulation for all doses.[49] The Clinical Review further explained that the BREEZE study provided limited safety data, but that the results did not show a substantial increase in adverse events associated with the transition from Tyvaso to Tyvaso DPI over 3 weeks or longer, despite a higher exposure to treprostinil from the Tyvaso DPI formulation.[50] No new risks associated with treprostinil formulated as an inhaled powder (Tyvaso DPI) were identified in the BREEZE study.[51] There were no deaths during the 3-week treatment or OEP, and the most common adverse events were headache (8 headaches occurred in 8 patients (17.6%)), cough (13 episodes of cough occurred in 13 patients (25.5%)), and shortness of breath (3 episodes of shortness of breath occurred in 3 patients (5.9%)).[52] No bronchospastic

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[47] NDA 214324, Clinical Review at 20.

[48] NDA 214324, Clinical Review at 20.

[49] NDA 214324, Clinical Review at 28

[50] NDA 214324, Clinical Review at 32. The CDTL Review (at 4) also notes, “The safety data (though limited) from the single and multiple dose studies did not indicate any notable difference in respiratory adverse events (AEs) between proposed treprostinil inhalation powder and Tyvaso.”

[51] NDA 214324, Clinical Review at 13.

[52] NDA 214324, Clinical Review at 32-33.

adverse events were identified during the 3-week treatment or OEP, and the prevalence of adverse events was similar to that observed with Tyvaso inhalation solution.[53]

Similarly, the results of the BREEZE study did not show clinical worsening based on the 6MWD and symptom burden as measured by the PAH-SYMPACT Questionnaire.[54] The median change in 6MWD from baseline to 3-weeks following transition from Tyvaso to Tyvaso DPI was an increase in 8 meters, with an interquartile range of 47.3 meters, and a maximal decrease of 46 meters and maximal increase of 110 meters.[55] The PAH-SYMPACT patient reported outcomes measure for PAH can help quantify the symptom burden and health-related quality of life for patients with PAH. Detectable improvements in symptoms on a population level have been associated with a decrease in the cardiopulmonary symptom score of 0.32 points, whereas symptomatic worsening has been associated with an increase in the cardiopulmonary symptom score of 0.08 points.[56] In the BREEZE study, after 3 weeks, the median overall population change in the patient-reported outcome measure PAH-SYMPACT was 0 (interquartile range -0.17 to 0.17).[57]

The results of the BREEZE study are described in Section 6.1 of Tyvaso DPI's approved labeling as follows:

> In a 3-week, open-label, single-sequence, safety and tolerability study (BREEZE) conducted in 51 patients on stable doses of Tyvaso Inhalation Solution who switched to a corresponding dose of Tyvaso DPI, the most commonly reported adverse events on Tyvaso DPI during the 3-week treatment phase included cough, headache, dyspnea, and nausea. Patient 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. Table 1 lists the adverse events that occurred at a rate of at least 4%.

[53] NDA 214324, Clinical Review at 32

[54] Id.

[55] NDA 214324, Clinical Review at 28. The Clinical Review also provides the results by dose group.

[56] NDA 214324, Clinical Review at 30.

[57] Id. The Clinical Review also provides the results by dose group.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving Tyvaso Inhalation Solution and More Frequent[a] than Placebo in TRIUMPH I

Adverse Event	Treatment n (%)	
	Tyvaso Inhalation Solution n=115	Placebo n=120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

[a] More than 3% greater than placebo

The safety of Tyvaso DPI was also studied in an extension phase of the study in which 49 patients were dosed for a duration of 43 patient-years. Fifty-nine percent (59%) of patients achieved a dose of 64 mcg, 4 times daily or higher. The adverse events during this long-term, extension phase were similar to those observed in the 3-week treatment phase.

Study TIP-PH-102 *A 6-Period Crossover Study Comparing Systemic Exposure of 3 Doses of Treprostinil Inhalation Powder and 3 Doses of Tyvaso in Healthy Normal Volunteers*

TIP-PH-102, the pivotal relative bioavailability study (bridging study), was a randomized, 6-treatment, 6-period, 6-sequence crossover study comparing systemic exposure of 3 dose levels of Tyvaso DPI (16, 48, 64 mcg) and 3 dose levels of Tyvaso (18, 54, 72 mcg) in healthy volunteers. The study evaluated the systemic exposure and PK of treprostinil administered as treprostinil inhalation powder (Tyvaso DPI) and treprostinil inhalation solution (Tyvaso).[58]

The study included a screening phase and a treatment phase with 6 treatment periods. Subjects were randomly assigned to 1 of 6 treatment sequences to receive 3 doses each of Tyvaso DPI and Tyvaso. A total of 36 healthy male and female subjects were included. Each subject received a single dose of drug per treatment period followed by a washout period of either 24 or 48 hours (approximately) prior to the next dose. During the study, subjects underwent PK and safety assessments. PK samples were collected up to 5 hours post-dose. Safety assessments included adverse events, vital signs, clinical laboratory tests, 12-lead ECGs, and physical examinations.[59]

[58] NDA 214324, OCP Review at 5.

[59] Id.

The applicant conducted noncompartmental analysis and reported the corresponding PK parameters, including $AUC_{0\text{-}5hr}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, and $t_{1/2}$ for each tested dose level of Tyvaso DPI and Tyvaso. Bioequivalence analyses were used to compare the exposure of Tyvaso DPI and Tyvaso for each tested dose level, using $AUC_{0\text{-}5hr}$ and C_{max} as the primary PK parameters. The applicant reported that for $AUC_{0\text{-}5hr}$, the geometric least squares mean (GLSM) ratios for the low-, mid-, and high-dose comparisons were 115% (90% confidence interval (CI): 104.59, 127.42), 101% (90% CI: 91.63, 111.65), and 91.5% (90% CI: 83.16, 100.78), respectively. C_{max} values of treprostinil for Tyvaso DPI were higher than for Tyvaso across matched-dose comparisons. The GLSM ratios of C_{max} for the low-, mid-, and high-dose comparisons were 130% (90% CI: 115.55, 145.95), 139% (90% CI: 124.13, 156.73), and 124% (90% CI: 110.56, 139.61), respectively.[60]

The study findings for treprostinil were reanalyzed and confirmed by the Office of Clinical Pharmacology (OCP) Reviewer using Statistical Analysis System (SAS®) (version 9.4), where $AUC_{0\text{-}inf}$ was also included for comparison. The C_{max} for Tyvaso DPI was higher than for Tyvaso across the studied dose levels. C_{max} of treprostinil for Tyvaso DPI and Tyvaso were attained with a median T_{max} of 0.17 – 0.25 hour (ranged from 0.08 to 0.52 hour). The $AUC_{0\text{-}inf}$ of Tyvaso DPI and Tyvaso were similar at mid- and high- dose levels, whereas the $AUC_{0\text{-}inf}$ ratio for the low-dose level was 17% higher for Tyvaso DPI.[61]

The incidences of the observed respiratory adverse events (AEs) (respiratory, thoracic, and mediastinal disorders) from Study TIP-PH-102 were similar between Tyvaso DPI and Tyvaso at each dose level after single-dose administration.[62]

B. Yutrepia

Liquidia submitted NDA 213005 for Yutrepia on January 24, 2020, pursuant to section 505(b)(2) of the FD&C Act. NDA 213005 relies on the findings of safety and effectiveness for the listed drug Tyvaso (NDA 022387). Yutrepia is a proposed treprostinil inhalation powder, where the powder is contained in capsules that are intended to be used with the supplied inhaler. Four strengths are proposed for Yutrepia: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg. The proposed labeling states: “In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily.”

Liquidia initially proposed the use of Yutrepia “for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability.” The NDA received a complete response letter on November 24, 2020, for manufacturing and device-related deficiencies. Liquidia resubmitted its application for Yutrepia on May 7, 2021. The resubmission was deemed a Class II resubmission and received a tentative approval on November 4, 2021.

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[60] Id.

[61] NDA 214324, OCP Review at 6.

[62] NDA 214324, OCP Review at 8.

Liquidia resubmitted its application for a second time on July 24, 2023, and included in its resubmission an amendment to add the following indication to align with the labeling of Tyvaso: "treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability." The July 24, 2023, amendment was classified as a Class II resubmission with a PDUFA goal date of January 24, 2024.

C. Liquidia's Submissions to the Board Regarding 3-Year Exclusivity

On behalf of Liquidia, two letters were submitted to the CDER Exclusivity Board (Board) on July 15, 2021, and July 25, 2022, regarding 3-year exclusivity for Tyvaso DPI.[63] In its letters to the Board, Liquidia argues that 3-year exclusivity should not be recognized for Tyvaso DPI and, if it is recognized, that the scope of 3-year exclusivity should be limited and should not block approval of Yutrepia.

III. DISCUSSION

This section applies the 3-year exclusivity framework (described in Section I.B) to analyze whether Tyvaso DPI qualifies for 3-year exclusivity and whether any exclusivity recognized for Tyvaso DPI under section 505(c)(3)(E)(iii) of the FD&C Act delays approval of Yutrepia.

Applying this framework, the Agency determined that Tyvaso DPI qualifies for 3-year exclusivity because the application includes a new clinical investigation (other than a bioavailability study) that was essential to approval and conducted or sponsored by the applicant – the BREEZE study. The Agency further determined that the 3-year exclusivity for Tyvaso DPI delays the approval of Yutrepia because the conditions of approval proposed in the Yutrepia application are within the scope of Tyvaso DPI's exclusivity.

A. Eligibility of Tyvaso DPI for 3-Year Exclusivity

For the Tyvaso DPI NDA to qualify for 3-year exclusivity, it must include at least one new clinical investigation (other than a bioavailability study) that was essential to approval of the NDA and conducted or sponsored by or on behalf of the applicant, United Therapeutics. As explained below, Study TIP-PH-101 (BREEZE) meets these criteria, and therefore, Tyvaso DPI qualifies for 3-year exclusivity.

1. New Clinical Investigation (Other Than a Bioavailability Study)

The BREEZE study is considered a clinical investigation because, consistent with 21 CFR

[63] Letter from Scott Lassman, Lassman Law + Policy, to Jay Sitlani, J.D., CDER Exclusivity Board, FDA, re: Request to Deny or Limit Three-Year Exclusivity for Tyvaso DPI ™ (July 15, 2021) (2021 Letter); Letter from Scott Lassman, Lassman Law + Policy, to Jay Sitlani, J.D., CDER Exclusivity Board, FDA, re: Supplement to July 15, 2021, Request to Deny or Limit Three-Year Exclusivity for Tyvaso DPI™ (July 25, 2022) (2022 Letter).

314.108(a), it was an experiment in which a drug was administered or dispensed to, or used on, human subjects. As described above, the BREEZE study involved the administration and use on 51 PAH patients of Tyvaso and Tyvaso DPI. It also is considered an investigation *other than a bioavailability study*. As noted above, the primary endpoint was safety and tolerability, and the secondary endpoints included 6MWD, PAH-SYMPACT Questionnaire, and PQ-ITD. Although the study also assessed pharmacokinetics after administration of each dose as a secondary endpoint, the BREEZE study is not considered to be solely a bioavailability study because it specifically evaluated the safety and tolerability of Tyvaso DPI and additionally provided limited efficacy data.

The BREEZE study further qualifies as a *new* clinical investigation, because FDA has not relied on its results to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population, and its results did not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.[64]

For the reasons explained above, the BREEZE study is a new clinical investigation (other than a bioavailability study).

2. Essential to Approval

As noted in Section I.B, the phrase essential to approval means "with regard to an investigation, that there are no other data available that could support approval of the NDA."[65] To meet this standard, FDA generally examines whether a clinical investigation is "vital" to the approval of the application or supplement, such that the investigation was part of the finding of safety and effectiveness.[66] "That is, without these new clinical studies, FDA would not have sufficient information to conclude that the drug product…for which the applicant is seeking approval is safe and effective."[67] FDA does not consider an investigation to be essential to approval just because the applicant conducted and submitted the investigation in its application for Agency review.[68] The assessment of whether a clinical investigation is essential to approval is made at or

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[64] See 21 CFR 314.108(a).

[65] Id.

[66] See final rule, "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions," 59 FR 50338 at 50357 (October 3, 1994) (1994 Final Rule).

[67] 1989 Proposed Rule at 28900. See also 21 CFR 314.50(j)(4)(ii) (requiring, to support a claim of 3-year exclusivity, submission of"[a] list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the NDA, and an explanation as to why the studies or reports are insufficient.").

[68] See 1994 Final Rule at 50357.

after the time of approval, based on information available at the time of approval.[69]

The BREEZE study provided information that was essential to the approval of Tyvaso DPI and not available from any other source. The study addressed an important safety question, specifically the tolerability[70] of the inhalation powder dosage form of treprostinil. While FDA had previously approved treprostinil for use by oral inhalation (Tyvaso), Tyvaso DPI represented a novel dosage form of treprostinil for use by oral inhalation, i.e., inhalation powder. Treprostinil is known to present tolerability challenges, including when administered by oral inhalation.[71] Notably, in the TRIUMPH I study conducted with Tyvaso, 54% of patients had cough, 41% headache, 25% throat irritation or pharyngeal pain, and 19% nausea.[72] The Division was concerned that the inhalation powder dosage form could present new or worse tolerability issues than those observed with Tyvaso and other approved treprostinil products. For example, in theory, an inhalation powder might present a risk of getting stuck in the throat or might cause a sensation of something stuck in the throat. For these reasons, the Division did not believe relying on single-dose experience in healthy subjects (as provided by Studies MKC-475-001 and TIP-PH-102) was adequate to assess safety and tolerability of the new inhalation powder for chronic use, regardless of whether the product was found to provide similar bioavailability to the approved Tyvaso inhalation solution. While the BREEZE study was limited in size and provided short follow-up, it provided vital data on safety and tolerability beyond single-dose use in patients to support the finding of safety for the inhalation powder dosage form of treprostinil.[73]

The need for such data to support approval is reflected in FDA's recommendations during the development phase for Tyvaso DPI. At a Type B Pre-IND meeting held on June 28, 2017, the Division discussed with the sponsor[74] the proposed development plan for Tyvaso DPI. The sponsor noted its plan to conduct a single ascending dose study (SAD) and assess relative bioavailability between the proposed inhalation powder and Tyvaso. The sponsor asked: "If the pharmacokinetics are comparable and Tmax for Treprostinil Inhalation Powder is comparable to

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[69] See 1994 Final Rule at 50359.

[70] "The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and hematology), vital signs, clinical adverse events (diseases, signs and symptoms), and other special safety tests (e.g., electrocardiograms, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject." FDA Guidance for Industry *E9 Statistical Principles for Clinical Trials* (September 1998) at 43.

[71] See Tyvaso labeling, Section 6.1. See also Orenitram labeling, Section 6.1 (stating "Orenitram patients in Study 1 (N=151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients in Study 1 experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). Study 4 enrolled a total of 690 patients, 346 received Orenitram and 344 received placebo. Overall, 19% of patients discontinued treatment in Study 4 due to an adverse event (compared to 4% of patients receiving placebo).").

[72] See Tyvaso labeling, Section 6.1

[73] See NDA 214324, Clinical Review at 13.

[74] As described in Section III.A.3, the original sponsor of IND 134582 was MannKind Corporation; the IND was transferred to United Therapeutics on October 19, 2018.

or faster than the comparator [Tyvaso], is this sufficient for approval of Treprostinil Inhalation Powder for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability?" In response, the Division agreed with the proposal to conduct a SAD study and assess relative bioavailability, but recommended that the sponsor additionally conduct "an open-label, uncontrolled study to evaluate the short-term (~2 to 3 weeks) safety and tolerability of [the] product following repeat doses in PAH patients." The Division advised: "In this study, you can enroll patients stabilized on Tyvaso and switch them to your product using the relative bioavailability estimate that you obtain from the healthy volunteer study. Pharmacokinetics of treprostinil can be compared prior to and after switching to ensure that the patients were transitioned to an appropriate dose of your product."[75] Consistent with the Division's recommendation, the sponsor conducted the BREEZE study to assess the safety and tolerability of its proposed inhalation powder following multiple doses in PAH patients. The "data [from the BREEZE study] allow[ed] for adequate characterization of the safety profile and support[ed] a positive benefit risk profile consistent with approval."[76]

As described in the Clinical Review for NDA 214324, evidence for the safety and effectiveness of treprostinil when administered by oral inhalation comes from the TRIUMPH I and INCREASE studies conducted with Tyvaso inhalation solution.[77,78] Meanwhile, the safety and tolerability of treprostinil inhalation powder was assessed for the first time in the BREEZE study.[79] The Clinical Review states:[80]

> Pharmacokinetic testing demonstrated similar AUCs for all doses between the treprostinil inhaled liquid formulation and powder formulation, although the Cmax for the inhaled powder formulation was greater than 120% of the liquid formulation for all doses. However, in the BREEZE study there was no clinically significant change in 6-minute walk test distance, patient-reported outcome assessment, or increase in adverse events associated with the transition from treprostinil inhaled liquid to treprostinil inhaled powder. Two patients (3.9%) withdrew from the 3-week study due to treatment-related adverse events of dyspnea and globus pharyngus, and 3 additional patients (4.1%) withdrew in the open-label optional extension phase due to treatment-related adverse events of dyspnea and chest pain. Otherwise, the prevalence of adverse events was similar to those reported in the TRIUMPH I study of the treprostinil inhaled liquid formulation, with the most common being cough and headache.

The BREEZE study thus provided essential data on "[p]atient tolerability [with multiple-dose

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[75] IND 134582, Type B Pre-IND Meeting Minutes (July 28, 2017) at 6.

[76] NDA 214324, Clinical/Decisional Memo (May 23, 2022) at 3.

[77] As noted in Section II, the results of the TRIUMPH I and INCREASE studies were extrapolated to Tyvaso DPI through the relative bioavailability study (Study TIP-PH-102).

[78] NDA 214324, Clinical Review at 10.

[79] Id.

[80] Id. See also NDA 214324, Clinical Review at 32.

use], as assessed by incidence of new adverse events following transition to Tyvaso DPI."[81] As reflected in the labeling, this "was consistent with the expected known safety profile of Tyvaso Inhalation Solution" and enabled the Division to conclude that the benefit/risk profile of the new dosage form was acceptable.[82]

This role for the BREEZE study is also addressed in the Cross-Discipline Team Leader (CDTL) Review and the Division Director's Divisional Memorandum. The CDTL Review states: "The safety data (though limited) from the single and multiple dose studies did not indicate any notable difference in respiratory adverse events (AEs) between proposed treprostinil inhalation powder and TYVASO®."[83] The Division Director's Divisional Memorandum states: "Safety of Tyvaso DPI is supported by a 51-subject, 3-week study with an open-label extension. The safety profile in this study is indistinguishable from that for the inhaled liquid – a mix of vasodilatory and airway irritation effects."[84]

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. As captured in the NDA reviews and memoranda, the BREEZE study provided essential information on the safety and tolerability of the new dosage form that supported a positive benefit/risk profile consistent with approval. Accordingly, the BREEZE study answered an important safety question about Tyvaso DPI, specifically, the tolerability of the new inhalation powder dosage form for chronic use. Therefore, the BREEZE study was essential to approval.

3. Conducted or Sponsored by the Applicant

United Therapeutics is identified on the Form FDA-1571 dated October 19, 2018, as the sponsor of IND 134582, the IND under which the BREEZE study was conducted.[85] Thus, the BREEZE study was conducted or sponsored by United Therapeutics within the meaning of 21 CFR 314.108(a).

In sum, the BREEZE study submitted to support approval of Tyvaso DPI was a new clinical investigation (other than a bioavailability study) that was essential to approval and conducted for sponsored by the applicant. Thus, the Agency determined that Tyvaso DPI qualifies for 3-year exclusivity.

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[81] See Tyvaso DPI labeling, Section 6.1.

[82] Id.

[83] NDA 214324, CDTL Review at 4.

[84] NDA 214324, Division of Cardiology and Nephrology Divisional Memorandum (October 14, 2021) (Divisional Memorandum).

[85] MannKind, the original sponsor of IND 134582, transferred the IND to the current NDA-holder, United Therapeutics, on October 19, 2018. The BREEZE study was then initiated on September 17, 2019. IND 134582, Clinical Study Report, TIP-PH-101 at 1.

4. Liquidia's Arguments Regarding Eligibility of Tyvaso DPI for 3-Year Exclusivity

In its July 15, 2021, and July 25, 2022, letters to the Board, Liquidia argues that Tyvaso DPI should not qualify for 3-year exclusivity. Liquidia does not contest that the BREEZE study was a new clinical investigation (other than a bioavailability study) or that it was conducted or sponsored by the applicant. Liquidia argues that the BREEZE study fails to qualify Tyvaso DPI for 3-year exclusivity (1) because it was a general safety study that did not expand the use of the drug or allow it to be used in a new patient population and (2) because it was not essential to approval of Tyvaso DPI.[86] We disagree.

a. The BREEZE study expanded use by assessing tolerability for a new dosage form.

Liquidia first argues that the BREEZE study "does not qualify for three-year exclusivity because it is merely a general safety study."[87] It contends that the BREEZE study cannot be the basis for 3-year exclusivity because it "provides only modest supporting information for the general safety of Tyvaso DPI for the same use and patient population as Tyvaso Inhalation Solution."[88] Liquidia notes in support of its argument the absence of a formal statistical analysis plan to evaluate any safety or effectiveness endpoints, and contends that the secondary efficacy endpoints "do[] not change this analysis [that the BREEZE study is a general safety study]."[89]

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[86] In its July 15, 2021, submission, Liquidia also argues that the pivotal pharmacokinetics study (Study TIP-PH-102) is a bioavailability study that "cannot be used to support three-year exclusivity for Tyvaso DPI." It is not necessary to address those arguments here. 2021 Letter at 8.

[87] 2021 Letter at 8 (citing 54 Fed. Reg. 28872, 28899); see also 2021 Letter at 9 (citing 21 CFR 314.108(a)), 2022 Letter at 3-5. Relying in large part on the preamble to the 1989 proposed rule on ANDAs, Liquidia contends that it is "FDA's longstanding position that general safety studies that neither permit broader use of a drug nor establish safety of a drug for a new patient population do not qualify for exclusivity." 2021 Letter at 8 (citing 54 Fed. Reg. 28872, 28899). Liquidia also states that this interpretation is incorporated into the regulatory definition of "new clinical investigation" to mean, in relevant part, "an investigation in humans the results of which have not been relied on by FDA to demonstrate…*safety for a new patient population*...." and cites legislative history as well as FDA decisions it states applies the policy. 2021 Letter at 9 (citing Buprenorphine Exclusivity Letter, p. 5, n. 15 (Feb. 28, 2019) and 2022 Letter at 4 (citing 21 CFR 314.108(a)). We need not address this particular claim by Liquidia, however, because even assuming a general safety study that neither permits broader use of a drug nor establishes its safety for a new patient population does not qualify for exclusivity under the definitions in FDA's regulations, the BREEZE study is not such a general safety study. As explained in the text, the BREEZE study specifically evaluated the tolerability in patients of multiple doses of treprostinil in an inhalation powder dosage form and permitted broader use of treprostinil through the approval of this new dosage form.

[88] 2021 Letter at 10; see also 2022 Letter at 3 (citing Tyvaso DPI Prescribing Information §1.1 (5/2022)). Liquidia further notes in the 2022 Letter that Tyvaso DPI is approved for use in the same patient population as Tyvaso Inhalation Solution, patients suffering from PAH, and "may be safe and appropriate for use in *an even more limited patient population* than Tyvaso Inhalation Solution because of its relatively low [maximum tolerated dose] and associated dosing limitations, which will prevent its use in patients with severe, progressive, or late-stage PAH who need or are taking high doses of inhaled tresprostinil." 2022 Letter at 3-4. For the reasons discussed in Section III.B.3.d below, however, we disagree with Liquidia's contentions that use of Tyvaso DPI is limited in such patients.

[89] 2021 Letter at 10.

Liquidia is incorrect in its assertions. First, the BREEZE study permitted broader use of treprostinil, as it was essential to the approval of treprostinil in a new dosage form, i.e., inhalation powder. Prior to approval of Tyvaso DPI, treprostinil was available in other dosage forms and for use by other routes of administration, including as a solution for oral inhalation (Tyvaso). While the bioavailability and safety profile of the inhalation solution (Tyvaso) and inhalation powder (Tyvaso DPI) are similar (as established by the relative bioavailability and BREEZE studies), they differ in dosage form and certain features of use. For example, the Tyvaso inhalation solution is used with a pump that is too large to fit in a pocket, must be charged, and must be prepared for use and cleaned each day.[90] The Tyvaso DPI inhaler, on the other hand, is pocket-sized, requires no power, and is disposed of in household trash after seven days of use.[91] Here, Tyvaso DPI represented an additional treatment option for patients, thus permitting broader use of the drug.

Moreover, the BREEZE study assessed a specific safety question, the tolerability of multiple doses daily over multiple weeks of treprostinil in the new inhalation powder dosage form to support approval for chronic use.[92] As explained above, treprostinil, including when administered by oral inhalation, is known to present tolerability issues.[93] Tolerability often determines dosing for an individual patient.[94] In addition, the Division was concerned that the new dosage form, inhalation powder, could present tolerability issues different from, and/or in addition to, those observed with the inhalation solution and other approved treprostinil products.[95]

The BREEZE study investigated this specific question of tolerability of the new inhalation powder dosage form. The BREEZE study followed patients, who switched from Tyvaso to Tyvaso DPI, as they took four doses a day over a 3-week period and then through an optional extension phase. Indeed, it was the only study in the Tyvaso DPI NDA that provided data on the multiple-dose use of Tyvaso DPI, and as described above, these data were necessary to support

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[90] See Tyvaso labeling, Section 2.2.

[91] See Tyvaso DPI labeling, Section 2.1.

[92] Specifically, as described above in Section II.A, the BREEZE study assessed 51 patients administered doses of Tyvaso DPI based on their Tyvaso inhalation solution dose, four times daily for three weeks, with a primary endpoint of safety and tolerability. See NDA 214324, Clinical Review at 18.

[93] See Tyvaso labeling, Section 6.1; see also Orenitram labeling, Section 6.1.

[94] See NDA 214324, Divisional Memorandum (noting "treprostinil's dose is limited by tolerability"). See also NDA 214324, Clinical Review at 8 (noting for treprostinil inhaled solution (Tyvaso), "If 3 breaths are not tolerated the dose can be reduced to 1 or 2 breaths" and that "The dosage should be increased every 1-2 weeks by 3 additional breaths to a target maintenance dose of 9-12 breaths (54-72 mcg) per treatment session, if tolerated.") and Tyvaso DPI labeling, Section 2.2 (stating, "If adverse effects preclude titration, continue Tyvaso DPI at the highest tolerated dose.").

[95] For example, an inhalation powder, in theory, might present a risk of getting stuck in the throat or might cause a sensation of something stuck in the throat.

the finding of safety for the inhalation powder dosage form of treprostinil for chronic use.[96] As such, Liquidia's argument that the BREEZE study was a "general safety" study that did not permit broader use of treprostinil is incorrect. The BREEZE study provided information that was specific to this dosage form for chronic use and was essential to approval of the new dosage form.

b. The BREEZE study was essential to approval.

Second and relatedly, Liquidia argues that the BREEZE study was not essential to approval, because it was "an uncontrolled, general safety study [that] provides only supportive information for the application."[97] It asserts that "[g]eneral safety studies typically are considered by FDA to be merely 'supportive.'"[98] Additionally, Liquidia contends that the BREEZE study was merely supportive, because "it is an uncontrolled, Phase 1b study that enrolled only 51 PAH patients (per ClinicalTrials.gov)" with a primary objective of "obtain[ing] *general information* about the safety and tolerability of Tyvaso DPI, not to expand the safe use of Treprostinil into new patient populations" and that the efficacy measures were "secondary endpoints…intended to provide only *supportive* efficacy information."[99] Liquidia asserts that the BREEZE study was not designed to establish the safety and effectiveness of Tyvaso DPI, and that United Therapeutics relied on the TRIUMPH I study for the primary safety and effectiveness data to support approval of Tyvaso DPI and thus that the TRIUMPH I study is the only study essential to approval of Tyvaso DPI.[100] Finally,[101] Liquidia selects statements from the Tyvaso DPI reviews and labeling, which it contends support its arguments that the BREEZE study was merely supportive.[102]

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[96] The other design features of the BREEZE study raised by Liquidia do not negate this. See, e.g., 2021 Letter at 10 (noting that the BREEZE Study was an uncontrolled, Phase I study in a small number of patients, already on a stable dose of Tyvaso Inhalation Solution), 2022 Letter at 6 (noting that "The safety data was 'limited' because of the significant limitations with the BREEZE study itself, which was an uncontrolled, open-label, Phase 1b study that enrolled a small number of patients (*i.e.*, 51) and had no SAP for any of its endpoints except PK"). As discussed above, notwithstanding these various design features of the study, the Division found that the BREEZE study provided vital data to address a specific safety question.

[97] 2021 Letter at 10; 2022 Letter at 5-6.

[98] 2021 Letter at 11.

[99] Id.

[100] 2021 Letter at 12; 2022 Letter at 2.

[101] Liquidia also contends that the BREEZE study was not essential for demonstrating the safety of the excipient fumaryl diketopiperazine (FDKP). It is unnecessary to address these arguments in this context as the BREEZE study was essential to approval of Tyvaso DPI based on other grounds discussed herein. As discussed in Section III.B.3.a below, the safety of FDKP is not the basis for FDA's determination that the BREEZE study was essential.

[102] Liquidia selects several pieces out of the Tyvaso DPI approval record that it asserts support its argument that the BREEZE study was not vital, but merely supportive of approval:

- FDA agreement in a pre-NDA Meeting that Bioresearch Monitoring (BIMO) would not be needed because "none of these studies [submitted with the application, including the BREEZE study,] are major, pivotal

Liquidia's arguments, however, misunderstand the nature of the BREEZE study and its role in the data package for the approval of the Tyvaso DPI inhalation powder dosage form. As noted above, the BREEZE study was not a general safety study that did not expand use or enable a new patient population to use the drug. It addressed a specific safety question, the tolerability of an active moiety (treprostinil) in a new inhalation powder dosage form; it was a vital piece of the data package for the approval of treprostinil in this new dosage form. Accordingly, Liquidia's arguments that general safety studies are merely supportive and thus not essential to approval are not relevant here.

The BREEZE study was not "merely supportive;" it was, in fact, needed for approval. As explained in Section III.A.2, the Division specifically recommended that the sponsor conduct a short-term safety and tolerability study, in addition to the planned dose-escalation and relative bioavailability studies,[103] as the Division was concerned that the single-dose studies in healthy subjects would not be adequate to assess tolerability of the new inhalation powder for chronic use, even if the product were found to provide similar bioavailability to the approved Tyvaso inhalation solution. The BREEZE study provided this vital information for approval for chronic use of the tolerability of treprostinil in this new dosage form following multiple-dose use in patients. The results of the study provided assurance that there was no significant change in safety or tolerability with the new inhalation powder dosage form as compared to approved inhalation solution (Tyvaso). Such information was not available from any other source, and it was an essential part of determining that Tyvaso DPI met the approval standard and that a positive benefit/risk profile existed.

The statements Liquidia plucks from the record are not inconsistent with this determination of essentialness. Liquidia asserts that many of these statements reflect certain limitations of the BREEZE study. However, 3-year exclusivity is not reserved for innovations supported by "major, pivotal trials."[104] The BREEZE study was sufficient in size and duration to allow

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studies…" (2022 Letter at 5 (citing FDA, Written Responses for Pre-NDA Meeting (IND 134582), p.2 (Nov. 19, 2020) (Exhibit 7)).

- NDA 214324, Clinical Review statement that "TIP-PH-101 (BREEZE) provides limited safety data…" (2022 Letter at 5-6 (citing Clinical Review, p. 32 and Cross-Discipline Team Leader Review, p. 4)), that "[t]he prevalence of adverse events in the BREEZE study…was similar to those reported in the TRIUMPH I study…" (2022 Letter at 6 (citing Clinical Review, p. 14)), and that "the BREEZE study identified '[n]o new risks associated with Treprostinil formulated as an inhaled powder (TYVASO DPI™)…'".
- NDA 214324, OCP Review reference to "limited safety data from single and multiple dose studies" (2022 Letter at 6 (citing RPM Review, p. 5)).
- NDA 214324, Divisional Memorandum noting that "Treprostinil is approved in an inhaled liquid formulation…, *so little beyond demonstrating bioavailability was necessary for Tyvaso DPI.*" (2022 Letter at 3 (citing Norman Stockbridge, M.D., Ph.D., Divisional Memorandum, p. 1 (Oct. 14, 2021 (emphasis added) (Exhibit 4)).

[103] See IND 134582, Type B Pre-IND Meeting Minutes (July 28, 2017) at 6.

[104] For example, FDA recognized 3-year exclusivity for MorphaBond (morphine sulfate) extended-release tablets (NDA 206544) based on a human abuse liability study (Study M-ARER-002), which assessed the drug's abuse

appropriate characterization of safety and tolerability. The BREEZE study did not need to be a "major, pivotal trial" to provide vital information on patient safety and tolerability for this drug product and to serve as the basis for 3-year exclusivity. In the preamble to the 1989 Proposed Rule, the Agency specifically noted that the 3-year exclusivity provision "could be interpreted to confer exclusivity only for innovations requiring adequate and well-controlled trials in human subjects that meet the substantial evidence requirement for approval."[105] FDA, however, declined to adopt that interpretation and stated: "The agency's interpretation of this exclusivity provision…is ordinarily to require only one clinical study and that it be of the type necessary to support approval of the proposed change."[106] That the BREEZE study identified "[n]o new risks associated with treprostinil formulated as an inhaled powder" and showed a similar prevalence of adverse events relative to Tyvaso inhalation solution does not make it any less essential to approval.[107] The BREEZE study was needed precisely to assess whether the new dosage form presented any such new or greater safety and tolerability risks relative to previously approved treprostinil products. Additionally, the statement cited by Liquidia from the Divisional Memorandum, in fact, confirms that the other available data, including from the TRIUMPH I, INCREASE, and relative bioavailability studies, were not enough on their own to support approval; as specifically noted, "little" more – i.e., something more – was needed.

Notwithstanding Liquidia's assertions, the BREEZE study was a new clinical investigation (other than a bioavailability study) that was essential to approval of Tyvaso DPI and conducted or sponsored by United Therapeutics, and thus Tyvaso DPI is eligible for 3-year exclusivity.

B. Scope of 3-Year Exclusivity for Tyvaso DPI

Having determined that Tyvaso DPI qualifies for 3-year exclusivity based on the BREEZE study, we next address the scope of that exclusivity and its impact on the approval of Yutrepia.

As explained in Section I.B.2, FDA's determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) of the FD&C Act involves two steps. The first step of the scope inquiry focuses on the drug with 3-year exclusivity. Tyvaso DPI and Yutrepia are both single-entity drugs that contain the same active moiety, treprostinil.[108] Because both Tyvaso DPI and

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potential by the intranasal route of administration. Study M-ARER-002 involved 25 non-dependent recreational opioid users with a history of intranasal drug abuse in a randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study to determine the relative bioavailability and abuse potential of crushed intranasal MorphaBond 60 mg tablets compared with crushed intranasal morphine sulfate extended-release 60 mg tablets and intact orally administered MorphaBond 60 mg tablets. See NDA 206544, Exclusivity Summary (October 2, 2015) at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206544Orig1s000Admincorres.pdf; see also CDER Exclusivity Board Memorandum on MorphaBond (November 16, 2016) at https://www.fda.gov/media/103075/download.

[105] 1989 Proposed Rule at 28899.

[106] Id.

[107] See 2022 Letter at 6 (citing Clinical Review at 13-14).

[108] Treprostinil is also the active ingredient in both Tyvaso DPI and Yutrepia.

Yutrepia have the same active moiety, the 3-year exclusivity for Tyvaso DPI may bar the approval of Yutrepia.

We therefore address the second step of the scope inquiry, which examines the new clinical investigations essential to approval to determine the "conditions of approval" for which certain subsequent applications are blocked during the exclusivity period. As noted above in Section I.B.2.a, although the FD&C Act and implementing regulations do not define "conditions of approval," when one or more drugs with the same active moiety have been previously approved, the Agency interprets the scope of 3-year exclusivity to cover the innovation in the application for which the underlying new clinical investigations were essential to the approval as compared to previously approved drug products containing the same active moiety.

Accordingly, to determine the scope of exclusivity for Tyvaso DPI, the Agency determined the innovation(s) for which the new clinical investigation, the BREEZE study, was essential to Tyvaso DPI's approval, and for which 3-year exclusivity attaches. This innovation is assessed relative to previously approved drug products containing the same active moiety. Specifically, the Agency asks what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use the new clinical investigation essential to approval answered for the first time. The Agency also considered whether particular characteristics of Tyvaso DPI, supported by the new clinical investigation essential to its approval, are clinically meaningful such that they may further define the scope of its innovation. If a later 505(b)(2) NDA is seeking the exclusivity-protected conditions of approval of Tyvaso DPI, it will be blocked from approval even if the two products differ in other ways.

1. Innovation for Which the New Clinical Investigation Was Essential

Prior to Tyvaso DPI's approval, treprostinil had been approved as the active moiety in three NDAs (all owned by United Therapeutics):

- NDA 021272 for Remodulin (treprostinil) injection, for subcutaneous or intravenous administration, for (1) treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise and (2) in patients with PAH requiring transition from epoprostenol, to diminish the rate of clinical deterioration.
- NDA 022387 for Tyvaso (treprostinil) inhalation solution, for oral inhalation use, for treatment of (1) pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and (2) pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.
- NDA 203496 for Orenitram (treprostinil) extended-release tablets, for oral administration, for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to increase exercise capacity.

Thus, treprostinil had previously been approved for the route of administration and indications proposed for Tyvaso DPI, use by oral inhalation for treatment of PAH to improve exercise ability and PH-ILD to improve exercise ability. A new clinical investigation was not needed to answer,

for the first time, questions about the efficacy or safety of treprostinil for this route of administration or these indications.

However, prior to Tyvaso DPI, FDA had not approved treprostinil as a *powder* for oral inhalation, and a new clinical investigation was needed to answer questions specific to this new dosage form. As described in more detail above in Section III.A.2, the Division was concerned about potential safety and tolerability issues with the novel inhalation powder dosage form of treprostinil, particularly given the known tolerability challenges with inhalational treprostinil generally. The Division did not believe relying on single-dose experience in healthy subjects was adequate to assess tolerability of the new inhalation powder for chronic use, even if the product were found to provide similar bioavailability to the approved Tyvaso inhalation solution. Thus, the BREEZE study was needed to assess the safety and tolerability of the new dosage form for chronic use. The data from the BREEZE study showing 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" were essential to the Agency's safety findings in approving Tyvaso DPI as the first approved treprostinil inhalation powder.[109]

Accordingly, based on a review of the relevant data and information, and in consultation with the Division, the Agency determined that the BREEZE study answered for the first time whether the active moiety treprostinil administered as an inhalation powder is safe and tolerable for chronic use. In other words, the 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.[110]

2. Characteristics Relevant to Tyvaso DPI's Innovation

Under the 3-year exclusivity framework described in Section I.B.2.b, the Agency also considered whether certain specific characteristics of Tyvaso DPI supported by the new clinical investigation essential to its approval may further define the scope of Tyvaso DPI's innovation. In general, the purpose of this step is to determine whether the innovation represented by a product's approval should only block a subsequent product that includes specific characteristics of the product with exclusivity.[111]

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[109] See Tyvaso DPI labeling, Section 6.1.

[110] For purposes of this analysis and as described further in footnote 111, it is not necessary to address whether the exclusivity-protected condition of approval is limited by the approved indications. It is sufficient to note that the approved indications are for chronic use of the drug, and as described above, the BREEZE study provided vital information to support such chronic use of the inhalation powder dosage form of treprostinil.

[111] We note that every approved drug product can be viewed as having numerous characteristics and the Agency need not look at every characteristic in the abstract to determine whether a subsequent application is blocked. To the extent a potentially blocking and a potentially blocked product share characteristics that have the potential to further narrow the scope of exclusivity, we need not analyze their effect on the scope of exclusivity because the second product would be blocked by exclusivity for Tyvaso DPI regardless of which of those characteristics were part of the exclusivity's scope. For example, in addition to sharing the inhalation powder dosage form, Tyvaso DPI and

The scope of a product's exclusivity is determined relative to previously approved products, not relative to products that are subsequently approved. As a result, this step of the exclusivity analysis focuses on characteristics of the exclusivity-protected product for which the scope of exclusivity is being assessed, to determine which, if any, such characteristics further define (limit or narrow) the innovation of the exclusivity-protected product assessed in the preceding steps. It does not entail a comparison of differences between the exclusivity-protected product and subsequent products to determine whether those differences are clinically meaningful.[112] Indeed, as explained above, where a subsequent 505(b)(2) application is seeking approval for the exclusivity-protected conditions of approval of the earlier-approved product, it may be blocked even if it differs from the earlier product in other ways.

As described in detail in Section III.B.3.c and d below, Liquidia argues that two characteristics of Tyvaso DPI – (1) the inclusion of the excipient fumaryl diketopiperazine (FDKP) in the product's formulation, and (2) the product's labeled dosing – are "clinically meaningful" and thus further define the scope of any exclusivity for Tyvaso DPI. The Agency evaluated these specific characteristics of Tyvaso DPI and concluded that they are not characteristics that further define or limit the scope of Tyvaso DPI's exclusivity. As explained below, these characteristics neither constrain the population for which use of Tyvaso DPI is appropriate, nor are they expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient. Therefore, neither the inclusion of FDKP nor the labeled dosing limits the innovation represented by Tyvaso DPI, i.e., the inhalation powder dosage form of treprostinil for chronic use.

3. Liquidia's Arguments Regarding the Scope of 3-Year Exclusivity for Tyvaso DPI

In its July 15, 2021, and July 25, 2022, letters to the Board, Liquidia argues that, if FDA were to recognize 3-year exclusivity for Tyvaso DPI, the scope of that exclusivity should be limited to: (1) Tyvaso DPI's unique formulation containing FDKP, (2) the patient population enrolled in the BREEZE study (i.e., PAH patients switching from a stable dose of Tyvaso inhalation solution),

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Yutrepia have the same indications and route of administration, and they are intended to be titrated to clinical effect. Therefore, the Agency need not, for purposes of the analysis in this memorandum, determine which of these other characteristics further define the scope of exclusivity. If any one or more of these characteristics were determined to be "clinically meaningful" to further limit the scope of Tyvaso DPI's innovation as described in section III.B.1 above, Yutrepia would still be seeking approval of the protected conditions of approval, and its approval would still be delayed by Tyvaso DPI's exclusivity. However, because Liquidia specifically argues that the inclusion of a particular excipient and the labeled dosing further narrow the scope of exclusivity for Tyvaso DPI, this letter discusses those characteristics below. For the reasons explained in the text below, we reject Liquidia's arguments that these characteristics of Tyvaso DPI narrow the scope of its exclusivity.

[112] See Braeburn Remand Letter at 25. The Agency's assessment in this part of the exclusivity analysis focuses on whether characteristics of the exclusivity-protected product further define the scope of innovation, not whether differences between these products are themselves meaningful.

and/or (3) an inhaled treprostinil product with a maximum tolerated dose (MTD) of 150 mcg.[113] We disagree.

a. The unique clinical question answered by the BREEZE study was not limited to Tyvaso DPI's formulation containing FDKP.

Liquidia argues first that "the only innovative change represented by Tyvaso DPI compared to previously approved treprostinil products is its unique formulation containing FDKP."[114] However, this is incorrect – as discussed above, the innovative change represented by Tyvaso DPI is the new dosage form, inhalation powder, for the active moiety treprostinil. Indeed, Liquidia acknowledges that Tyvaso DPI was "the first treprostinil product approved with a dry powder dosage form" but contends that this new dosage form cannot be the relevant innovation because new clinical investigations were not essential to its approval.[115] On the contrary, as explained above, the BREEZE study was needed precisely to assess the safety and tolerability of the inhalation powder dosage form.

Liquidia asserts that FDA could have approved a treprostinil inhalation powder by relying on the prior clinical studies for Tyvaso inhalation solution because these studies established that treprostinil administered via oral inhalation is safe and effective for the treatment of PAH and PH-ILD patients, and therefore that any treprostinil formulation administered via oral inhalation with comparable drug exposure to Tyvaso inhalation solution would also be safe and effective.[116] However, this assertion assumes that a relative bioavailability study was all that was needed to support approval of Tyvaso DPI. It was not. As explained above, the Division recommended that the sponsor conduct a safety and tolerability study "[i]n addition to…[a] relative bioavailability assessment," because a relative bioavailability study alone would not have been sufficient to support approval.[117]Although the clinical studies supporting the approval of Tyvaso inhalation solution established the safety and effectiveness of treprostinil inhalation solution administered via oral inhalation, they neither assessed nor demonstrated the safety and effectiveness of treprostinil inhalation powder. The Division was concerned that the powder dosage form could present new or worse tolerability issues than those observed with treprostinil inhalation solution, particularly given known tolerability challenges with treprostinil, including when administered by oral inhalation.[118] The Division did not believe relying on single-dose experience in healthy subjects (as provided by Studies MKC-475-001 and TIP-PH-102) was adequate to assess safety and tolerability of the new inhalation powder for chronic use. An additional study, the BREEZE study, was therefore needed to assess the safety and tolerability of treprostinil inhalation powder for multiple-dose use for the first time.

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[113] See 2021 Letter at 12-18; 2022 Letter at 7-9.

[114] See 2021 Letter at 13.

[115] Id.

[116] Id.

[117] See IND 134582, Type B Pre-IND Meeting Minutes (July 28, 2017) at 6.

[118] See Orenitram labeling, Section 6.1; see also Tyvaso labeling, Section 6.1.

Liquidia specifically argues that to the extent the BREEZE study was needed to support approval of Tyvaso DPI, it could only have been needed to assess the safety of FDKP, a novel excipient for an inhaled treprostinil product.[119] FDKP had been previously approved in an inhaled insulin product, Afrezza, the labeling for which contains a boxed warning regarding the risk of acute bronchospasm in patients with chronic lung disease.[120] On July 8, 2021, a citizen petition was submitted on behalf of Liquidia asserting a number of arguments about the potential risks related to the inclusion of FDKP in Tyvaso DPI's formulation and requesting, among other things, that FDA require Tyvaso DPI to be contraindicated in patients with chronic lung disease such as asthma and chronic obstructive pulmonary disease (COPD).[121] On May 23, 2022, the same date FDA approved NDA 214324 for Tyvaso DPI, FDA denied the citizen petition.[122]

In the petition response, FDA disagreed with the petition's assertions about the risks, in particular the risk of acute bronchospasm, associated with FDKP. At the outset, FDA noted "the speculative nature of FDKP's potential role in causing acute bronchospasm in Afrezza patients with chronic lung disease."[123] FDA explained that data do not establish that FDKP causes the risk of acute bronchospasm or other respiratory risks in patients with chronic lung disease, and specifically that "there are no data, including data from the Afrezza program, that definitively support that FDKP is causal in inducing respiratory adverse reactions."[124] Accordingly, FDA disagreed with the petition's assertion that it was "very likely" that Tyvaso DPI may cause acute bronchospasm in patients with chronic lung disease because it contains the excipient FDKP.[125]

For these reasons, the BREEZE study was not needed to assess the safety of FDKP in Tyvaso DPI's formulation. Liquidia agrees that "the BREEZE study was not 'essential' for demonstrating the safety of the excipient [FDKP]."[126] Liquidia argues in the alternative, however, that to the extent the BREEZE study was necessary to assess a specific safety issue, it was the safety of FDKP and FDKP's potential contribution to the risk of bronchospasm.[127] In support of this argument, Liquidia notes that FDA requested information from United

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[119] See 2021 Letter at 14.

[120] See Afrezza labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022472s023lbl.pdf).

[121] Lassman Law+Policy Citizen Petition, FDA-2021-P-0714 (July 8, 2021) (Liquidia Petition).

[122] Letter from Patrizia Cavazzoni, M.D., Director, CDER, FDA to Scott Lassman, Lassman Law+Policy, FDA-2021-P-0714 (May 23, 2022) (Liquidia Petition Response).

[123] Liquidia Petition Response at 8.

[124] Liquidia Petition Response at 8-9.

[125] See Liquidia Petition Response at 9. The petition response additionally explained that any potential pulmonary risks were adequately characterized by the available data and appropriately addressed and mitigated through Tyvaso DPI's approved labeling, and it rejected the petition's requests that a contraindication, boxed warning, and risk evaluation and mitigation strategy (REMS) be included in the labeling. See Liquidia Petition Response at 15.

[126] See 2022 Letter at 6.

[127] See 2022 Letter at 7.

Therapeutics on how data from the BREEZE study supported the pulmonary safety of Tyvaso DPI and also cites the clinical review's discussion of FDKP in relation to the BREEZE Study.[128] These actions by FDA do not establish that the BREEZE study was essential to assess the safety of FDKP. Rather, they reflect FDA's consideration of the arguments raised by Liquidia in its citizen petition. FDA gave United Therapeutics an opportunity to provide its view on how the data from the BREEZE study supported safety of Tyvaso DPI; documented the Agency's thinking regarding FDKP and the BREEZE study in the reviews for Tyvaso DPI; and explained in the petition response that the available data, including data from the BREEZE study, were sufficient to evaluate potential pulmonary risks associated with Tyvaso DPI, including the risk of acute bronchospasm.[129] That FDA appropriately considered and responded to the arguments in the citizen petition does not transform the purpose and function of the BREEZE study in FDA's approval decision or the innovation the BREEZE study supported. As explained above, the BREEZE study was recommended by the Division and conducted by United Therapeutics to assess, for the first time, the safety and tolerability of multiple doses of treprostinil inhalation powder to support approval for chronic use.

Finally, Liquidia cites certain prior decisions by the Agency to assert that the scope of any 3-year exclusivity for Tyvaso DPI should be limited. Specifically, Liquidia points to FDA's determination regarding 3-year exclusivity for Dyanavel XR as an example that "FDA has determined that the scope of exclusivity does not protect a new dosage form but rather is limited to a product's specific formulation [and] drug release profile."[130] In that instance, the Board indeed determined that the innovation protected by Dyanavel XR's exclusivity was its "formulation and associated drug release profile."[131] As explained in Section I.B.2.b.1 above, however, the analysis of the scope of exclusivity is, by definition, context-specific: a change that may have significance as an innovation in one instance – that is, a change for which studies were needed to demonstrate its safety or efficacy – may not require further studies in another instance, for example, in another therapeutic area. And the nature of what aspect(s) of a drug will constitute an innovation must be determined on a case-by-case basis. With Dyanavel XR, a new clinical investigation was not needed to assess the safety and tolerability of its extended-release oral suspension dosage form. What was needed, given the close relationship between plasma concentration and clinical effect for the drug amphetamine, and what the relevant clinical investigation essential to approval provided, was a demonstration that the product's formulation and associated release profile provided clinical efficacy throughout the day.[132] Here, as explained, the BREEZE study answered for the first time whether the active moiety treprostinil

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[128] See 2022 Letter at 7.

[129] See NDA 214324, Information Request (February 15, 2022); NDA 214324, Clinical Review at 10-11, 13-14; Liquidia Petition Response at 9-12.

[130] See 2021 Letter at 13.

[131] See CDER Exclusivity Board Memorandum on Adzenys ER (September 15, 2017) (Adzenys Exclusivity Memo) at 8.

[132] Id.

administered as an inhalation powder is safe and tolerable for chronic use. Thus, the inhalation powder dosage form for chronic use is Tyvaso DPI's innovation.

Liquidia cites a different prior decision to assert that the scope of exclusivity may be limited to a formulation containing an excipient posing safety concerns.[133] But again, the scope inquiry is context- and fact-specific. Here, the Division did not view the inclusion of FDKP in the Tyvaso DPI formulation as posing a significant safety risk,[134] nor did it request the BREEZE study for the purpose of addressing such a risk. The Division's recommendation during development of Tyvaso DPI was for the sponsor to conduct a safety and tolerability study of its product following repeat doses in PAH patients. This was needed because the tolerability of multiple-dose use of a treprostinil inhalation powder had never before been evaluated and would not be evaluated in a single-dose dose-escalation or relative bioavailability study. In this case, therefore, the innovation is the new dosage form for chronic use and is not limited to the inclusion of FDKP in the product's formulation.

b. The unique clinical question answered by the BREEZE study was not limited to PAH patients switching from a stable dose of Tyvaso inhalation solution.

In its July 15, 2021, letter to the Board, Liquidia argues that the scope of any exclusivity should be limited to PAH patients switching from a stable dose of Tyvaso inhalation solution because the BREEZE study was designed and conducted only in such "stable, switch patients."[135]

As noted in Section I.B.2.b.iii above, a particular clinical investigation may be more limited in scope or more specific than the conclusions (and thus the scope of exclusivity) that can be drawn from it. As a result, a drug studied in very specific conditions might be approved with a broader indication and not limited to those conditions under which it happened to be studied. Liquidia correctly notes that, in the BREEZE study, Tyvaso DPI was studied in PAH patients switching from a stable dose of Tyvaso inhalation solution. However, the conclusion supported by the BREEZE study that treprostinil inhalation powder is safe for chronic use is not limited to those "stable, switch patients." Based on data from the BREEZE study (and not merely the data that supported the approval of Tyvaso inhalation solution, as Liquidia contends),[136] FDA approved Tyvaso DPI, the first approved treprostinil inhalation powder, for treatment of both PAH and PH-ILD patients who are new to treprostinil inhalation treatment and such patients who transition from Tyvaso inhalation solution.[137] Accordingly, the scope of 3-year exclusivity for

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[133] See 2021 Letter at 14.

[134] See NDA 214324, Divisional Memorandum; see also Liquidia Petition Response at 8-9.

[135] See 2021 Letter at 15. We note that Liquidia does not re-assert this argument in its July 25, 2022, letter, which post-dated the approval of Tyvaso DPI.

[136] See 2021 Letter at 15-16.

[137] See Tyvaso DPI labeling, Sections 1 and 2.

Tyvaso DPI is not limited to the "stable, switch patients" in whom it was studied in the BREEZE study.

In support of its argument that the scope of exclusivity should be limited to such "stable, switch patients," Liquidia cites FDA's prior determination that the scope of 3-year exclusivity for Astagraf XL extended only to de novo use in kidney transplant patients and did not cover conversion of stable kidney transplant patients from immediate-release tacrolimus (i.e., conversion use).[138] In that case, the new clinical investigations that served as the basis for 3-year exclusivity demonstrated the safety and effectiveness of Astagraf XL only for de novo use in kidney transplant patients, and Astagraf XL was approved only for use in de novo patients.[139] Those investigations did not demonstrate the safety and effectiveness of Astagraf XL for use in conversion patients, and the sponsor "did not conduct those clinical investigations that would have been necessary to support that use."[140] Therefore, the scope of exclusivity did not extend to conversion use. Here, by contrast, the BREEZE study 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). Although the population studied was limited, the approval it supported was not; it supported approval in both PAH and PH-ILD patients who are new to treprostinil inhalation treatment and such patients who transition from Tyvaso inhalation solution, and thus the scope of exclusivity is not limited to "stable, switch patients" in whom it was studied.

c. Tyvaso DPI's formulation containing FDKP is not a characteristic that further defines the scope of its innovation.

In its July 15, 2021, letter, Liquidia asserts that the inclusion of FDKP in Tyvaso DPI's formulation is a "clinically meaningful" characteristic that should limit the scope of any 3-year exclusivity for Tyvaso DPI.[141] Specifically, Liquidia argues that this characteristic is "clinically meaningful" because it is likely to limit or prevent the use of Tyvaso DPI in patients with chronic lung disease and in this way affect whether the product is appropriate for a particular

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[138] See 2021 Letter at 15 (citing See NDA 206406, Advice Letter on Exclusivity for Astagraf XL (January 12, 2015) (Astagraf XL Exclusivity Letter) at 39-42).

[139] See Astagraf XL Exclusivity Letter at 12, 39-41. Liquidia asserts that "[Astagraf XL's] approved indication for prophylaxis of organ rejection was worded broadly to apply to *any* kidney transplant patient." See 2021 Letter at 15. However, as articulated in the exclusivity determination relied on by Liquidia, FDA intended that the approved indication encompass only de novo use in kidney transplant patients. See, e.g., Astagraf XL Exclusivity Letter at 12 ("This information was not intended to and does not imply approval of Astagraf XL for the conversion use. The text of the Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling not only is silent on the conversion use but also is specific to *de novo* use in kidney transplant patients.").

[140] See Astagraf XL Exclusivity Letter at 40-41. As noted in the context of the Astagraf XL exclusivity determination, because de novo patients and conversion patients are considered two distinct populations, the Agency generally expects adequate and well-controlled clinical studies to support the safe and effective (and approved) use in each respective population. See Astagraf XL Exclusivity Letter at 41 n.187.

[141] See 2021 Letter at 16-17. We note that Liquidia does not re-assert this argument in its July 25, 2022, letter, which post-dated the denial of Liquidia's citizen petition and the approval of Tyvaso DPI.

patient or class of patients.[142] However, this argument rests on the premise, asserted in Liquidia's July 8, 2021, citizen petition, that Tyvaso DPI should be contraindicated in patients with chronic lung disease because FDKP is associated with an acute risk of bronchospasm.[143] As explained in its response denying the citizen petition, FDA disagreed with this premise, and, as approved, Tyvaso DPI is not contraindicated in patients with chronic lung disease.[144] Because the inclusion of FDKP in Tyvaso DPI does not significantly change the population or use for which Tyvaso DPI is appropriate with respect to previously approved drugs with the same active moiety, nor is it otherwise expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient, FDKP is not a clinically meaningful characteristic of Tyvaso DPI that further defines or limits the scope of its innovation.

d. A maximum tolerated dose of 150 mcg is not a characteristic that further defines the scope of Tyvaso DPI's innovation.

In its letters to the Board, Liquidia asserts that Tyvaso DPI's "apparent [maximum tolerated dose (MTD)] of 150 mcg" is a "clinically meaningful" characteristic that should limit the scope of any 3-year exclusivity for Tyvaso DPI, "because it precludes the use of Tyvaso DPI in patients who could benefit from higher inhaled doses of treprostinil for disease control, particularly patients with more severe, later-stage PAH."[145]

Liquidia is mistaken in its assertion that Tyvaso DPI has a maximum dose of 150 mcg. Tyvaso DPI's approved labeling does not provide a maximum dose. Liquidia notes that the target maintenance dose is "usually 48 to 64 mcg per session." Liquidia also stresses that "there are no instructions for transitioning patients taking doses of Tyvaso Inhalation Solution that are higher than 11 to 12 breaths per session (66 to 72 mcg of treprostinil)," citing a table in the labeling that provides information for each of Tyvaso DPI's four cartridge strengths on the number of breaths of Tyvaso inhalation solution that give similar exposure.[146] But neither the "usual[]" target

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[142] See 2021 Letter at 16.

[143] See 2021 Letter at 17.

[144] See Liquidia Petition Response at 8-9, 13-14; Tyvaso DPI labeling. Section 5.4 of Tyvaso DPI's approved labeling contains the following warning: "Like other inhaled prostaglandins, Tyvaso DPI may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso DPI." However, this warning is not unique to Tyvaso DPI and is also present in the approved labeling for Tyvaso inhalation solution, which does not contain FDKP. See Tyvaso labeling, Section 5.4.

[145] See 2021 Letter at 16-18; 2022 Letter at 8-9.

[146] See 2022 Letter at 8; Tyvaso DPI labeling, Section 2.2. Liquidia asserts that Yutrepia's tentatively approved labeling (Section 2.1, which includes a dosing conversion table similar to that in Tyvaso DPI's labeling) provides instructions for transitioning patients taking 18 or more breaths per session of Tyvaso inhalation solution. See 2022 Letter at 8; NDA 213005, Tentative Approval (November 4, 2021) (TA). But the dosing conversion tables in Tyvaso DPI's labeling and Yutrepia's tentatively approved labeling do not indicate maximum dosing recommendations. Nor do the tables mean that patients taking more than 12 breaths per session of Tyvaso inhalation solution cannot be

maintenance dose nor the table relied on by Liquidia provide a maximum dose of 150 mcg or otherwise.[147] The labeling expressly contemplates doses above 64 mcg per session, stating, "If the prescribed dose is higher than 64 mcg per treatment session, more than 1 cartridge will be needed per session."[148] The labeling also instructs that, "[i]f adverse effects preclude titration, continue Tyvaso DPI at the highest tolerated dose," without specifying a maximum dose.[149] The number of breaths of Tyvaso inhalation solution provided in the table merely corresponds to the available cartridge strengths of Tyvaso DPI and provides information on the comparability of exposure for patients transitioning from Tyvaso inhalation solution. For patients with a "prescribed dose [that] is higher than 64 mcg per treatment session," as contemplated by the labeling, the table can still be used to calculate the cartridge strengths of Tyvaso DPI and number of breaths of Tyvaso inhalation solution (above 11 to 12 breaths per session) that provide similar exposure.

In sum, Tyvaso DPI's approved labeling does not contain the "dosing limitations" that Liquidia claims it contains and allows for use by patients requiring higher doses of inhaled treprostinil, including those with severe or later-stage disease. Accordingly, there is no maximum dose or dosing limitation for Tyvaso DPI that further defines or limits the scope of its innovation.

C. Effect of Tyvaso DPI on Approval of Yutrepia

As explained above, the Agency determined that the innovation represented by Tyvaso DPI's approval – and thus its exclusivity-protected condition of approval for which the new clinical investigation was essential – is the inhalation powder dosage form of the active moiety treprostinil for chronic use. Yutrepia is a proposed treprostinil inhalation powder for chronic use. Because Liquidia is seeking approval of Yutrepia for Tyvaso DPI's exclusivity-protected condition of approval, the approval is delayed until the expiration of Tyvaso DPI's 3-year exclusivity.

IV. CONCLUSION

For the reasons described above, the Agency determined that Tyvaso DPI qualifies for 3-year exclusivity and that the exclusivity-protected condition of approval is the inhalation powder dosage form of the active moiety treprostinil for chronic use. The Agency finds that Liquidia is

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transitioned to Tyvaso DPI. As discussed in the text, doses of Tyvaso DPI higher than those listed in the table may be prescribed, and the table can be used to calculate the cartridge strengths of Tyvaso DPI and number of breaths of Tyvaso inhalation solution (above 11 to 12 breaths per session) that provide similar exposure.

[147] Liquidia asserts that the claimed "labeling limitation" "may be based on an earlier dose escalation study of Tyvaso DPI (MKC-475-001), which found an MTD of 150 mcg." See 2022 Letter at 8-9 & n.19. As noted in the text, however, a dosing limitation is not included in Tyvaso DPI's approved labeling, and a provider may choose to prescribe doses up to and above 150 mcg for a particular patient, as tolerated.

[148] See Tyvaso DPI labeling, Section 2.1.

[149] See Tyvaso DPI labeling, Section 2.2.

seeking approval of Yutrepia (treprostinil) inhalation powder intended for chronic use for this exclusivity-protected condition of approval, and thus Yutrepia's approval is delayed until expiration of Tyvaso DPI's exclusivity on May 23, 2025.

We are happy to discuss any clarifying questions you may have about this matter. Please contact Brian Cooney, Regulatory Health Project Manager, at (301)796-0886, if it would be helpful to discuss.

Sincerely,

Norman Stockbridge, M.D., Ph.D.
Acting Deputy Director
Division of Cardiology and Nephrology
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/s/

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