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By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Viatris Inc. ("Viatris") submits this petition under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs ("the Commissioner") take the actions set forth below with respect to new drug application ("NDA") 214697 for neffy® or ARS-1, intranasal ("IN") epinephrine, for the emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kilograms. NDA 214697 was submitted in accordance with section 505(b)(2) of the FDCA, and was accepted for filing on October 21, 2022.[1]

On May 11, 2023, FDA's Pulmonary-Allergy Drugs Advisory Committee (the "Advisory Committee") held a meeting to discuss the ARS-1 application, with a particular focus on issues raised by the novel route of administration in treating anaphylaxis in the community setting. In the context of the Advisory Committee, data regarding ARS-1 was publicly presented and the Agency raised for the committee's consideration questions regarding the adequacy of the data presented in support of NDA 214697. Recognizing the lack of clinical data, FDA highlighted the importance of "[a] high level of confidence in both PK [pharmacokinetic] and PD [pharmacodynamic] results and confidence in bridging the PK/PD findings to clinical efficacy in the setting of anaphylaxis . . . to support a favorable benefit-risk assessment."[2] In assessing whether the available data provide the necessary high level of confidence, FDA rightly asked the Advisory Committee if the PK and PD studies are sufficient to conclude that NDA 214697 is safe

[1] *See* Press Release, ARS Pharmaceuticals announces FDA acceptance of NDA for neffy® (epinephrine nasal spray) for the Treatment of Allergic Reactions (type I) including Anaphylaxis (Oct. 21, 2022) (Tab 1).

[2] *See generally* FDA Briefing Document, Pulmonary-Allergy Drug Advisory Committee Meeting (May 11, 2023) at 17 ("FDA Advisory Committee Briefing Document") (Tab 2).

and effective for the proposed use, *i.e.*, emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kilograms.[3]

Mylan Specialty L.P., a Viatris Company, is the application holder for EPIPEN® (epinephrine injection) and EPIPEN Jr® (epinephrine injection) auto-injectors (NDA 019430) ("EpiPen"). We support providing improved access to reliable, safe, and effective treatments for use in an emergency anaphylaxis event, but also recognize the seriousness of unresolved uncertainties regarding the efficacy and safety of a new (and fundamentally different) route of administration and dosage form for treating anaphylaxis with epinephrine. Anaphylaxis is potentially fatal, and can progress from exposure to cardiorespiratory arrest quickly. It is imperative that any treatment for anaphylaxis work quickly and effectively to achieve potentially lifesaving therapeutic effect following administration.

As FDA has recognized, approving an alternative emergency treatment for anaphylaxis such as ARS-1 requires the Agency to have a high degree of confidence in the efficacy and safety of IN epinephrine for such use. Because FDA is necessarily relying on comparative PK and PD data (and not clinical data directly demonstrating safety and effectiveness), those data must report comparisons to the appropriate products and relate to the conditions of use for which the product is proposed. Moreover, the Agency must carefully consider the potential safety and/or effectiveness implications of differences demonstrated by such comparisons. The possible impact of such differences cannot be overstated, because (1) anaphylaxis is life-threatening; (2) the onset of anaphylaxis can be rapid (and can move from exposure to cardiorespiratory arrest in as little as five minutes)[4] and therefore requires quick systemic exposure to epinephrine; and (3) ARS-1 is being proposed for use by patients and caregivers in at-home settings, rather than by healthcare professionals in a medical setting.

Against this background, Viatris previously expressed concerns about certain open issues relating to ARS-1, as shown by the company's recent comment to the Advisory Committee docket.[5] It was Viatris' hope that such issues would be resolved at the Advisory Committee Meeting on May 11, 2023. However, Viatris shares the view of a number of Advisory Committee members that the discussion at that meeting and the evidence presented did not sufficiently address those issues. Having carefully reviewed the Advisory Committee Meeting materials and other publicly available data on ARS-1, Viatris believes the totality of currently available evidence does not yet

[3] *See generally id*. at 17.

[4] Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. CLIN EXP ALLERGY. 2000; 30(8):1144-50 (Tab 3).

[5] *See* Comment from Viatris, Docket No. FDA-2023-N-0984-0606 (May 10, 2023) (Tab 4).

answer several critical questions regarding how ARS-1 will perform in a real-world anaphylaxis event.

Viatris thus files this Citizen Petition now to ensure that there are sufficient data to support a favorable benefit-risk determination with the requisite high degree of confidence for patients requiring emergency treatment for anaphylaxis. As discussed below, additional PK/PD studies that are carefully tailored to reflect real-world conditions of use for ARS-1 could materially reduce residual uncertainties regarding the safety and effectiveness of ARS-1. Accordingly, this petition asks the Agency to consider whether the studies outlined below could provide additional information and data on ARS-1 such that the Agency can make a well-informed benefit-risk determination regarding the use of ARS-1 for anaphylaxis with an appropriate degree of confidence.

The pending ARS-1 application proposes a materially different route of administration than has previously been approved for epinephrine for the emergency treatment of allergic reactions. With that in mind, the benefit-risk determination should be supported by evidence that the proposed product will not result in patient harm because of reduced effectiveness or increased safety risks as compared to available epinephrine products that are used in similar settings to the proposed conditions of use for ARS-1. Those relevant products are epinephrine auto-injectors ("EAIs"). A well-informed benefit-risk determination should also be supported by evidence that the proposed product will have comparable performance to EAIs in a real-world anaphylaxis event, including the implications of symptoms that might complicate intranasal epinephrine uptake. Further, the benefit-risk analysis should incorporate evidence of repeat dosing of ARS-1 under conditions similar to a real-world anaphylaxis event.

The actions Viatris is asking the Agency to take are focused on addressing these critical issues.

ACTIONS REQUESTED

Viatris believes additional PK/PD studies with the below parameters could reduce residual uncertainties regarding the efficacy and safety profile of ARS-1, and minimize unnecessary risks to patients experiencing anaphylaxis. Accordingly we respectfully request that the Commissioner require ARS to take the following actions and submit the resulting data and information to NDA 214697 as necessary steps before the Agency determines whether the NDA meets the requirements for approval:

> Conduct PK/PD studies under normal nasal conditions and nasal allergen challenge ("NAC") conditions that include:
>
> - Bracketing with two EAIs;
> - Single and repeat dose administration; and
> - Subgroup analyses for rhinorrhea.

STATEMENT OF GROUNDS

I. FACTUAL BACKGROUND

A. Anaphylaxis

Anaphylaxis is defined as "a serious allergic reaction that is rapid in onset and may cause death."[6] Anaphylaxis is a complex condition and presenting symptoms can be varied and progression can be unpredictable.[7] Typical symptoms include, but are not limited to, rhinitis (inflammation of the nasal mucosa), rhinorrhea (runny nose), hives, swelling, vomiting, difficulty breathing, and hypotension. Common triggers of anaphylaxis include food, drugs, and Hymenoptera venom, but idiopathic cases have also been described in which no trigger is identified.[8]

The onset of anaphylaxis is extremely rapid, and immediate medical intervention to arrest the reaction is essential. The gold standard in the management of anaphylaxis is epinephrine injection, which has been used for over 100 years in the treatment of anaphylaxis and remains the first-line and only life-saving treatment for anaphylaxis.[9] Rapid and adequate intervention

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[6] Sampson HA *et al*., Second symposium on the definition and management of anaphylaxis: summary report, J ALLERGY CLIN IMMUNOL. 2006; 117:391-97 (Tab 5).

[7] FDA Advisory Committee Briefing Document at 13 (Tab 2).

[8] *Id*.

[9] *Id*.; *see also* Ring J, Klimek L, Worm M. Adrenaline in the Acute Treatment of Anaphylaxis. DTSCH ARZTEBL INT. 2018; 115(31-32):528-34 (Tab 6).

with epinephrine relieves upper airway obstruction, alleviates shock, and can prevent cardiopulmonary arrest.[10] After a patient with a life-threatening allergy has been exposed to a triggering allergen, cardiorespiratory arrest may occur in as little as five minutes, and there may be an extremely short window for effective pharmacological intervention.[11]

Accordingly, international guidelines, supported by multiple peer-reviewed publications, recommend the administration of epinephrine as the first-line treatment of choice for anaphylaxis as soon as possible to "achieve peak plasma and tissue concentrations rapidly."[12] Therefore, rapid achievement of peak plasma and tissue concentrations of epinephrine following identification of anaphylaxis is crucial to successful treatment.

B. FDA-Approved Epinephrine Injections for the Emergency Treatment of Anaphylaxis

Epinephrine has been used for over a century as an emergency treatment for anaphylaxis. All currently FDA-approved epinephrine products for the treatment of anaphylaxis are injection products. These injection products generally come in two forms: (1) auto-injectors (*e.g.*, EpiPen, Auvi-Q, Adrenaclick) and (2) needle-syringe and pre-filled syringe products (*e.g.*, Adrenalin, Symjepi).

Although FDA has not required sponsors to conduct any clinical trials to support the applications for any epinephrine injection products currently approved for the emergency treatment of

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[10] Simons FER, Anaphylaxis: recent advances in assessment and treatment, J ALLERGY CLIN IMMUNOL. 2009; 124:625-36 (Tab 7).

[11] For example, in a UK registry study of 164 people with fatal anaphylaxis, the median time to cardiorespiratory arrest was five minutes after iatrogenic exposure (*e.g.*, anesthesia or antibiotic), 15 minutes after insect sting, and 30 minutes after food allergen ingestion. *See* Pumphrey RS, Lessons for management of anaphylaxis from a study of fatal reactions (Tab 3).

As another example, a US observational study reporting fatal and near-fatal reactions to food in children and adolescents conducted over a 14-month period identified six fatal and seven near-fatal cases of food-induced anaphylaxis in children and adolescents. All cases had symptoms within 30 minutes of food ingestion. Two of the six who died received epinephrine within the first hour, whereas six of the seven who survived the episode received epinephrine within 30 minutes. Sampson HA, *et al.*, Fatal and near-fatal anaphylactic reactions to food in children and adolescents, N ENGL J MED. 1992; 327:380-84 (Tab 8). Another study documented 25 unselected cases of fatal anaphylaxis in adults between 1989 and 2001. The majority of patients had symptoms within 30 minutes of exposure. The time to death was 0-60 minutes in 13 cases, 1-6 hours in 4 cases, 24-96 hours in 4 cases and unknown in 4 cases. Greenberger PA, *et al.*, Fatal anaphylaxis: postmortem findings and associated comorbid diseases, ANN ALLERGY ASTHMA IMMUNOL 2007; 98:252-57 (Tab 9).

[12] *See* Simons FER, *et al.*, World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis, WORLD ALLERGY ORGAN J. 2011; 4(2):13-37, ("Epinephrine should be injected by the intramuscular route in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected… This achieves peak plasma and tissue concentrations rapidly.") (Tab 10); *see also* Cardona V, *et al.*, World allergy organization anaphylaxis guidance 2020. WORLD ALLERGY ORGAN J. 2020; 13(10):100472 (Tab 11).

anaphylaxis, there is a significant amount of real world data and scientific literature regarding the use of epinephrine injections for anaphylaxis because the use of epinephrine predates even the enactment of the Federal Food, Drug, and Cosmetic Act. In contrast, there are **no** available clinical or real-world data for the use of IN epinephrine for the treatment of anaphylaxis.[13]

1. Epinephrine Auto-Injectors

FDA has approved several EAIs under new drug applications to treat anaphylaxis, including EpiPen, Adrenaclick, and Auvi-Q.[14]

EpiPen (epinephrine auto-injector) is a drug-device combination product that was approved on December 22, 1987, under NDA 19430.[15] EpiPen is intended for immediate administration in patients who are at increased risk of anaphylaxis, as emergency supportive therapy; patients are directed to seek immediate medical or hospital care in conjunction with use of EpiPen.[16] Although no clinical trials were conducted in support of the EpiPen application, over 50 years of clinical data on the use of epinephrine for the treatment of anaphylaxis were available to support a determination regarding the efficacy and safety profile of EpiPen. FDA accordingly approved the EpiPen application on the basis of scientific literature supporting the efficacy and safety of epinephrine injections.

Auvi-Q (epinephrine auto-injector) is an EAI approved on August 10, 2012, for the emergency treatment of allergic reactions (Type I) including anaphylaxis.[17] The Auvi-Q application was approved in accordance with FDCA section 505(b)(2), with EpiPen as the reference product.[18] The sponsor included data from a comparative pharmacokinetics trial between the Auvi-Q auto-

[13] *See* FDA Advisory Committee Briefing Document at 7 ("Since there are no clinical efficacy data for anaphylaxis treatment in the ARS-1 development program, there are several key issues for discussion.") (Tab 2).

[14] *See* EpiPen Approval (NDA 019430), Drugs@FDA (Approval Letter not publicly available), *available at* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019430; Auvi-Q (NDA 201739) Approval Letter (Aug. 10, 2012), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/201739Orig1s000ltr.pdf; Adrenaclick (NDA 020800) Approval Letter (May 30, 2003), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/20800ltr.pdf. Because Adrenaclick was not tested in any part of the ARS-1 development program (as far as we are aware), we focus solely on EpiPen and Auvi-Q EAIs in this petition.

[15] EpiPen (NDA 019430), Drugs@FDA.

[16] EpiPen (NDA 019430) Prescribing Information, Section 1 – Indications and Usage & Section 5 – Warnings and Precautions (Feb. 2023) (Tab 12).

[17] Auvi-Q (NDA 201739) Approval Letter (Aug. 10, 2012).

[18] Auvi-Q (NDA 201739) Medical Review at 1 (Tab 13).

injector and the EpiPen auto-injector that used a scaled bioequivalence approach because of the high intra- and inter-subject variability.[19]

Twinject/Adrenaclick is an EAI approved on May 30, 2003, for the "treatment of severe allergic reactions, including anaphylaxis and anaphylactoid reactions, in response to exposure to bee stings, allergy injections, etc."[20] The application was supported by literature regarding the use of epinephrine for the treatment of anaphylaxis and asthma.[21] No human PK studies or data were submitted in support of the application.[22]

2. Non-EAI Epinephrine Injection Products

Adrenalin (epinephrine injection) is an epinephrine product supplied as single-use vials and administered via needle-syringe.[23] The Adrenalin application was approved in 2012 for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Like Auvi-Q, Adrenalin was approved in accordance with FDCA section 505(b)(2), with EpiPen as the reference product.[24] Importantly, Adrenalin is primarily administered by healthcare providers in hospital settings. The sponsor for Adrenalin did not conduct any clinical pharmacology studies to support the application because of the long documented history of use through intramuscular ("IM") and subcutaneous ("SC") routes of administration for the emergency treatment of anaphylaxis.[25] Unlike EAIs, the FDA-approved labeling for Adrenalin requires clinical monitoring in a medical setting upon and immediately following administration.[26]

Symjepi (epinephrine injection) is a prefilled syringe product.[27] The application for Symjepi was approved in 2017 for the emergency treatment of allergic reactions (Type I) including

[19] *Id*. at 3. The Agency noted this bioequivalence study was not required, as the similarity between EpiPen and Auvi-Q's needle length, gauge, and injection force was sufficient to support approval. *Id*.

[20] Twinject (NDA 20800) Approval Letter, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/20800ltr.pdf.

[21] *See* Twinject (NDA 20800) Medical Review (Tab 14).

[22] *See id*.

[23] Adrenalin (NDA 204200) Prescribing Information, Section 16 – How Supplied/Storage and Handling (Jan. 2023) (Tab 15).

[24] Adrenalin (NDA 204200) Summary Review at 2 (Tab 16).

[25] *Id*. at 5.

[26] *See* Adrenalin (NDA 204200) Prescribing Information, Section 2 – Dosage and Administration (Tab 15); *see also* FDA Advisory Committee Briefing Materials at 17 (Tab 2).

[27] Symjepi (NDA 207534) Summary Review at 1 (Tab 17).

anaphylaxis.[28] Like Auvi-Q and Adrenalin, Symjepi was approved in accordance with FDCA section 505(b)(2), with EpiPen as the reference product.[29] No clinical trials or clinical pharmacology studies were conducted to support the application because of the similarity of the formulation composition and route of administration to the listed drug.[30] Although Symjepi is approved for both community and medical-setting use, community use is very low. EAIs make up the vast majority (~99%) of community use.[31]

C. Mechanism of Action, Pharmacokinetics and Pharmacodynamics of Approved Epinephrine Injection Products

Epinephrine non-selectively activates α- and β- adrenergic receptors that are differentially expressed in various tissues. [32] Although the epinephrine mechanism of action is well-established, available PK data from the ARS-1 development program suggest there is substantial variability in the PK profiles of epinephrine injection products.[33] This variability is due in part to intra- and inter-patient PK variability that is likely inherent to epinephrine, and in part to the limited amount of PK data on approved epinephrine injection products.[34] Although PK data for epinephrine products are relatively sparse, PK data from the Auvi-Q application suggest that the PK profiles for EAIs are relatively similar.[35] This is in contrast to PK profiles across all epinephrine injection products; as shown in studies conducted as part of the ARS-1 development program (discussed below), there appear to be significant differences between the PK profiles for EAIs and needle-syringe products.[36]

The PD effects of epinephrine injection include increases in systolic blood pressure ("SBP"), decreases in diastolic blood pressure ("DBP"), reductions in peripheral resistance, increases in

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[28] Symjepi (NDA 207534) Approval Letter (Jun. 15, 2017), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/207534Orig1s000ltr.pdf.

[29] Symjepi (NDA 207534) Summary Review at 1 (Tab 17).

[30] *Id*. at 3.

[31] Data on file with Viatris.

[32] FDA Advisory Committee Briefing Document at 15. *See also* EpiPen (NDA 019430) Prescribing Information, Section 12.1 – Mechanism of Action (Tab 12).

[33] *See, e.g.*, FDA Advisory Committee Briefing Document at 9 ("The PK data generated from the ARS-1 development program demonstrates that there is substantial variability in PK profiles with epinephrine injection products, despite being administered via the same route.") (Tab 2).

[34] *Id*. at 15.

[35] *See* Auvi-Q (NDA 201739) Clinical Pharmacology Review at 3 (Tab 18).

[36] *See* FDA Advisory Committee Briefing Document at 26 ("The cross-product PK comparison of epinephrine injection products generally demonstrated earlier T_{max}, higher C_{max}, and greater early partial AUCs for epinephrine following EpiPen IM injection compared to Adrenalin (needle-syringe) IM injection.") (Tab 2).

heart rate ("HR"), increases in skeletal muscle blood flow, and decreases in cutaneous and renal blood flow in humans.[37] These effects are concentration-dependent, but the exact therapeutic threshold concentration of epinephrine is unknown.[38]

D. NDA 214697 (ARS-1) Application and Development

ARS-1 is an intranasal epinephrine product proposed for the emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kg. The product is a solution packaged in a nasal spray delivery device intended to be administered as one spray of 100 µL, followed by another spray if symptoms continue to progress 10 minutes after administration.[39] It is intended to be self-administered or administered by a caregiver.[40]

The NDA for ARS-1 is supported only by PK/PD and human factors studies. Clinical studies were not feasible, given ethical concerns with conducting studies in patients with anaphylaxis. The sponsor instead proposed to bridge to a listed epinephrine drug, Adrenalin, by showing PK/PD similarity.[41] The sponsor and FDA agreed on a clinical pharmacology program that included the following studies:[42]

PK/PD/Safety Trial	Purpose
Dose ranging (EPI 11b)	Determine an appropriate ARS-1 dose compared to EpiPen 0.3 mg (autoinjector) and Symjepi 0.3 mg (prefilled syringe) based on PK similarity.
PK matching (EPI 15)	Bracket the single-dose PK profile of ARS-1 with EpiPen 0.3 mg and Adrenalin 0.3 mg (needle-syringe) with support of comparable safety and PD profiles.
Second dose (EPI 15)	Assess the PK/PD and safety of two doses of ARS-1 compared to two doses of EpiPen 0.3 mg.
Nasal allergen challenge (EPI 16)	Assess the effect of nasal congestion on the PK/PD and safety of single-dose ARS-1 compared to Adrenalin 0.3 mg and 0.5 mg.
Self-administration (EPI 17)	Assess if self-administration of a single-dose of ARS-1 changes the PK/PD and safety compared to Adrenalin (staff-administered).
Pediatric PK (EPI 10)	Assess the PK/PD and safety of various single-doses of ARS-1 in pediatric allergy subjects 4 to < 17 years of age and ≥ 15 kg.

[37] *Id.* at 15.

[38] *Id*. at 17. For purposes of the ARS-1 review and comparison to other epinephrine products, FDA set "arbitrary" threshold concentrations of epinephrine at 100 and 200 pg/mL. *Id*. at 16.

[39] *Id.* at 7.

[40] *Id.* at 54, 61.

[41] *Id.* at 22.

[42] *Id.* at 18. The development program for ARS-1 included additional studies that used doses other than the proposed 2 mg. These studies, as well as EPI 10 in pediatric subjects, are not relevant to the issues raised in this petition and are therefore omitted from the discussion.

1. EPI 11b

Study EPI 11b was a single-dose crossover study in healthy subjects that assessed different doses and formulations of ARS-1.[43] The study compared healthy subjects that were administered various doses and formulations of ARS-1 to subjects administered Symjepi or EpiPen 0.3 mg.[44] EPI 11b is the only study in the entire ARS-1 development program that compared ARS-1 2 mg to an epinephrine product other than Adrenalin or EpiPen.[45]

In analyzing the results of EPI 11b, FDA noted "markedly different PK profiles for the two epinephrine injection product comparators approved for community use (EpiPen and Symjepi)."[46] Of note, the C_{max} and $pAUC_{0\text{-}10mins}$ parameters for EpiPen are significantly higher, and T_{max} substantially lower, compared to all other comparators.[47] For ARS-1, the epinephrine mean concentration was higher than EpiPen after approximately 15 min and Symjepi after approximately 10 min, but lower for the first 10 minutes.

2. EPI 15

EPI 15 was a two-part, six treatment, six-period, single and repeat dose, partial crossover study.[48] In the first part, the sponsor used a bracketing approach to assess the comparability of the PK profiles of EpiPen, Adrenalin, and ARS-1 after a single dose in healthy adults (*i.e.*, normal nasal conditions).[49] Each subject was given a single dose of ARS-1 in the left naris, and a single dose of EpiPen and Adrenalin in the left and right thighs, respectively, with a washout period of 24 hours between each.[50]

FDA concluded that the "PK profile following a single dose of ARS-1 is reasonably bracketed by Adrenalin 0.3 mg and EpiPen 0.3 mg IM injection starting 10 min postdose; however, plasma epinephrine concentration in the first 10 min postdose are lower than both epinephrine injection comparators (Figure 1), likely due to an initial slower absorption rate."[51] Similarly, SBP and pulse

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[43] *Id.* at 25.

[44] *Id*.

[45] *Id.* at 23-24.

[46] *Id.* at 25.

[47] *Id.* (Figure 3).

[48] *Id.* at 27.

[49] *Id.* at 27 (describing the comparative bioavailability evaluation) and 44 (describing the bracketing approach).

[50] *Id.* at 27.

[51] *Id.* at 10 (internal parenthetical omitted).

rate ("PR") were bracketed by the two comparators, but only for the initial 10 minutes.[52] Starting at 10 minutes postdose, the SBP and PR responses for ARS-1 were higher than Adrenalin and EpiPen, despite the lower PK of ARS-1 compared to EpiPen during the same timeframe.[53] In Part 2 of EPI 15, subjects were given a second dose 10 minutes after the initial dose.[54] The results showed that the ARS-1 epinephrine concentrations were lower than EpiPen epinephrine concentrations for the first 20 minutes, followed by a similar profile to EpiPen after 20 minutes, suggesting a slower initial absorption rate of ARS-1 compared to EpiPen.[55] SBP and PR for ARS-1 mirrored the response seen in Part 1 following a single dose, with ARS-1 displaying higher responses for both PD measurements "despite the comparable $AUC_{0\text{-}60min}$ values between treatments."[56] As in Part 1, the DBP profile for ARS-1 in Part 2 of EPI 15 was "more stable" compared to EpiPen.[57]

3. EPI 16

EPI 16 assessed the plasma concentration-time profile and PD effects of Adrenalin and ARS-1 under nasal allergen challenge conditions.[58] The study was a four-treatment, partially randomized, crossover study in adults with allergic rhinitis.[59] Subjects were administered ARS-1, then Adrenalin, followed by Adrenalin, and ARS-1 again—each followed by a 12-day washout period.[60] ARS-1 with nasal challenge appeared to have both a faster initial absorption and a faster decline than Adrenalin, "resulting in a lack of PK sustainability starting about 10 min postdose compared to ARS-1 PK under normal nasal conditions and 20 min postdose compared to epinephrine injection."[61]

PD responses mirrored PK profiles. ARS-1 with nasal challenge showed higher SBP and HR effects initially, "which soon declined and become lower compared to normal nasal conditions after around 15 min postdose."[62] The HR effects of ARS-1 experienced a quick decline between 5 and

[52] *Id.* at 31.

[53] *Id.* at 31-32.

[54] *Id.* at 27.

[55] *Id.* at 11.

[56] *Id.* at 35-36.

[57] *Id.* at 36.

[58] *Id*.

[59] *Id*.

[60] *Id.*

[61] *Id.* at 11(internal parenthetical omitted).

[62] *Id.* at 38.

15 minutes postdose, [63] dropping below the effects for Adrenalin at 5 minutes postdose.[64] From these data, FDA concluded:

> The lack of epinephrine PK/PD sustainability under nasal allergen challenge conditions raises concerns for durability of effect, and the need for a repeat dose, in patients with anaphylaxis who experience nasal edema. Since repeat dose studies have not been performed under nasal allergen challenge conditions, and proposed labeling includes repeating a dose if symptoms persist, there is residual uncertainty in the PK/PD response following a repeat dose. Additional data may be needed to assess this decrease in exposure; options include a repeat dose nasal allergen challenge PK/PD study and/or exploration of a higher dose.[65]

4. EPI 17

EPI 17 was a two-period, two-treatment, randomized, crossover study in adults with Type I allergies.[66] Unlike the other studies discussed, EPI 17 involved self-administration, rather than administration by study staff. The study did not include a staff-administered arm, so the Agency used a cross-study comparison to determine the effects of self-administration.[67] FDA's analysis led the Agency to conclude that, although self-administration resulted in a "generally higher" PK profile, it nevertheless showed a similar pattern.[68]

II. LEGAL AND REGULATORY BACKGROUND

A. Demonstration of Safety and Effectiveness

To approve an NDA, FDA must consider the benefits and risks of the drug in a systematic manner[69] to determine that the drug product is safe and effective for its intended use.[70] The

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[63] *Id.* at 12.

[64] *Id.* at 38.

[65] *Id.* at 12.

[66] *Id.* at 24.

[67] *Id.* at 41.

[68] *Id.*

[69] Specifically, under FDCA section 505(d), FDA must "implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks [and] a consistent and systematic approach to the discussion and regulatory decision making." 21 USC 355(d).

[70] *Id*.; 21 CFR 314.105(c). To demonstrate that a product is effective, a sponsor must provide "substantial evidence" that the drug will have the effect it purports or is represented to have under the conditions described in the proposed labeling. 21 USC 355(d)(5). The "substantial evidence" standard refers to both the quality and the

benefit-risk assessment takes into account "the extensive evidence of safety and effectiveness submitted by a sponsor in an NDA . . . the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh the risks."[71]

B. 505(b)(2) Approval Pathway

In accordance with FDCA section 505(b)(2), a sponsor may submit an NDA that relies in whole or in part on data developed by someone other than the applicant and for which the applicant does not have a right of reference.[72] Such reliance is permitted "only to the extent that the proposed product in the 505(b)(2) application shares characteristics (active ingredient, dosage form, strength, route of administration, indications, and conditions of use) in common with the listed drug."[73] To the extent the proposed product and listed drug differ, the sponsor must provide bridging data to address the implications of such differences.[74]

For a 505(b)(2) application relying on bioavailability studies as the scientific bridge to the reference product, reliance on FDA's previous findings of safety and effectiveness are relevant only to the extent the products are the same.[75] A sponsor seeking to rely on a listed drug with different conditions of use must bridge the gap created by the difference with adequate data.[76]

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quantity of the evidence that the drug will have benefit. *See* FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1999). To determine whether a drug product is safe, FDA must determine whether the product is safe for use under the conditions described in the proposed labeling. 21 USC 355(d)(4).

[71] FDA, Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products at 3 (Sep. 2021) (Tab 19).

[72] 21 USC 355(b)(2); *see* FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2) at 7-9 (Oct. 1999) (Tab 20). A "listed drug" is a new drug product that has been approved under section 505(c) of the FDCA for safety and effectiveness or under section 505(j) of the FDCA, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the FDCA, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" ("Orange Book") as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the NDA or ANDA for that drug product. 21 CFR 314.3(b) (defining "listed drug").

[73] FDA Response to TorPharm, Inc., Docket No. FDA-2003-P-0274-0015, at 14 (Oct. 13, 2003) (internal citations omitted) (Tab 21).

[74] *Id*. ("The safety and effectiveness of any differences between the listed drug and the drug proposed in the 505(b)(2) application must be supported by additional data, including clinical or animal data, as appropriate[.]").

[75] *Id*.

[76] *Id*.

III. DISCUSSION

Viatris supports providing improved access to safe and effective treatment options for anaphylaxis. With decades of experience and knowledge related to epinephrine and anaphylaxis, we understand the importance and urgency of providing reliable, safe, and effective treatments for use in an emergency anaphylaxis event. We agree with FDA's expressed view:

> Based on the severity of the indication and the availability of approved safe and effective products, we need to have confidence that efficacy and safety of epinephrine administered by this novel route of administration have been established; residual uncertainties should be minimized. A high level of confidence in both PK and PD results and confidence in bridging the PK/PD findings to clinical efficacy in the setting of anaphylaxis are expected to support a favorable benefit-risk assessment.[77]

To that end, we also acknowledge the publicly available data ARS has generated to date regarding the pharmacokinetic profile and pharmacodynamic effects of ARS-1. Having carefully reviewed these data, the Advisory Committee materials more broadly, and the meeting recording, Viatris believes the totality of currently available evidence leaves open several critical questions regarding how ARS-1 will perform in a real-world anaphylaxis event. We recognize the ethical challenges of conducting clinical trials in this indication, but believe there are additional PK/PD studies that could resolve residual uncertainties regarding the safety and effectiveness of ARS-1.

Specifically, the ARS-1 development program attempts to answer key questions regarding the safety and effectiveness of this new route of administration for epinephrine, but does so in a piecemeal fashion. The program relies on cross-study comparisons of individual ARS-1 studies that each provide only a portion of the evidence needed to make an informed determination regarding the potential benefits and risks of ARS-1, rather than conducting carefully-tailored studies that closely mimic real-world conditions of use for ARS-1. For example, the development program includes a PK/PD bracketing study with two comparators, and a nasal congestion model study, but does not include a study with both components, *i.e.*, a nasal congestion model study that brackets ARS-1 between two appropriate comparators to show comparable PK/PD profiles in patients with symptoms known to be experienced during anaphylaxis. This, along with other shortfalls of the studies conducted by the sponsor, leaves residual uncertainties regarding how ARS-1 will perform when administered under real-world conditions.

In light of the seriousness of the indication and availability of alternative treatments, Viatris believes additional data regarding the PK profile and PD effects of single and repeat doses of ARS-

[77] FDA Advisory Committee Briefing Document at 8 (Tab 2).

1 in normal nasal conditions and in a nasal congestion model, as compared to and bracketed by EAIs, would provide an appropriate level of confidence regarding the product's safety and effectiveness.

A. PK/PD Studies Should be Conducted Under Both Normal Nasal Conditions and Nasal Allergen Conditions to Better Understand Use During Anaphylaxis.

Histamine-mediated vasodilation and increased vascular permeability of the nasal mucosa during anaphylaxis may affect the local absorption of epinephrine.[78] Indeed, nasal mucosal symptoms such as rhinitis are common early signs of anaphylaxis,[79] including nasal congestion (*i.e.*, irritation and swelling inside the nose) and rhinorrhea (*i.e.*, runny nose).[80] Given the novel intranasal route of administration, understanding the impact of such nasal symptoms is particularly relevant for evaluating the safety and effectiveness of ARS-1. A comprehensive understanding of the effects of such symptoms, and the lack of such symptoms (*i.e.*, normal nasal conditions) for individuals that do not experience rhinitis during an anaphylaxis event, on epinephrine uptake, absorption kinetics, and metabolism are critical to any benefit/risk determination about the use of ARS-1 for the emergency treatment of anaphylaxis.

Animal models demonstrate that vasodilation during an allergic reaction can significantly alter the pharmacokinetics of drugs administered via the intranasal route.[81] Specifically, animal nasal allergen models had a significantly lower T_{max} versus the normal nasal condition group, although

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[78] *See* White MV, The role of histamine in allergic diseases. J ALLERGY CLIN IMMUNOL. 1990; 86(4 Pt 2):599-605 (Tab 22); *see also* FDA Advisory Committee Briefing Document at 11 ("Under nasal allergen challenge conditions, the ARS-1 epinephrine plasma concentration-time profile was characterized with an initial faster absorption, followed by a faster decline, resulting in a lack of PK sustainability starting about 10 min postdose compared to ARS-1 PK under normal nasal conditions.") (Tab 2).

[79] FDA Advisory Committee Briefing Document at 36 (nasal mucosal symptoms experience by as many as 2-11% of anaphylaxis patients) (citing Brown, AF, D McKinnon, and K Chu, Emergency department anaphylaxis: A review of 142 patients in a single year, J ALLERGY CLIN IMMUNOL. 2001; 108(5):861-66 (Tab 23); Braganza, SC, JP Acworth, DR McKinnon, JE Peake, and AF Brown, Paediatric emergency department anaphylaxis: different patterns from adults, ARCH DIS CHILD. 2006; 91(2):159-63 (Tab 24); Gonzalez-Estrada A, *et al.*, Epidemiology of anaphylaxis at a tertiary care center: A report of 730 cases, ANN ALLERGY ASTHMA IMMUNOL, 2017; 118(1):80-85) (Tab 25)). Statistics reported from literature are limited because they are based on retrospective case study reviews. The true incidence of mucosal involvement, particularly nasal mucosal involvement, is unclear.

[80] White MV, The role of histamine in allergic diseases. J ALLERGY CLIN IMMUNOL. 1990; 86(4 Pt 2):599-605 (Tab 22); *see also, e.g.*, AAAAI, Tools for the Public: Anaphylaxis, Symptoms of Anaphylaxis (Tab 26); Harvard Medical School, Harvard Health Publishing, Anaphylaxis: An overwhelming allergic reaction (2009) (Tab 27). *See also* Bayat R and Borici-Mazi R, A case of anaphylaxis to peppermint, ALLERGY ASTHMA CLIN IMMUNOL. 2014; 10(1):6 (Tab 28); and Soller L *et al.*, First reported case in Canada of anaphylaxis to lupine in a child with peanut allergy, ALLERGY ASTHMA CLIN IMMUNOL. 2018; 14:64 (Tab 29).

[81] *See* Tuttle R, *et al.*, Intranasal epinephrine effects on epinephrine pharmacokinetics and heart rate in a nasal congestion canine model. RESPIR RES. 2020; 21(1):78 ("Histamine release and vasodilation during an allergic reaction can alter the pharmacokinetics of drugs administered via the intranasal (IN) route.") (Tab 30).

C_{max} and $AUC_{0\text{-}90}$ were relatively similar.[82] Following epinephrine administration, the nasal allergen model group in the animal model showed rapidly increased heart rate at 5 minutes, compared to a delayed increase in heart rate occurring 30-60 minutes after administration in the control group.[83] These results suggest that vasodilation caused by an allergic reaction may lead to more rapid absorption of intranasally-administered epinephrine.

Recognizing the unique uncertainties related to an intranasal form of epinephrine for the treatment of anaphylaxis, FDA asked ARS to conduct a PK/PD study for ARS-1 in a nasal allergen challenge ("NAC") model (*i.e.*, patients with allergic rhinitis).[84] ARS conducted study EPI 16 to evaluate the comparative bioavailability of ARS-1, both with and without induced allergic rhinitis by NAC, relative to Epinephrine 0.3 mg IM (Adrenalin).[85] According to ARS, EPI 16 was an "experimental study" with no pre-specified criteria for success.[86] ARS-1 was administered immediately after NAC induction when symptoms of congestion and rhinorrhea were greatest.[87] To be dosed with ARS-1 in the EPI 16 study, subjects had to have a Total Nasal Symptom Score (TNSS) of $\geq$ 5 out of 12 and a congestion score of $\geq$ 2 out of 3 for at least one allergen during the screening challenge.[88] Thirty of the 34 subjects reported positive symptoms of rhinorrhea after NAC induction and before dosing of ARS-1.[89]

PK results from EPI 16 demonstrate that, relative to normal nasal conditions, NAC conditions resulted in a more rapid (reduced T_{max}) absorption of epinephrine from ARS-1 (7 min in NAC model versus 20 min in normal nasal state), as well as more rapid clearance (lower C_{max} and overall $AUC_{0\text{-}t}$). As shown below in Figure 11, this may be due to more rapid nasal fluid flow causing increased clearance of the drug from the nasal mucosa (see Section II below).[90] These results demonstrate a clear difference between the PK profile of ARS-1 under normal nasal and

[82] *See id*.

[83] *See id*.

[84] FDA Advisory Committee Briefing Document at 10 (Tab 2).

[85] ARS Briefing Document, Pulmonary-Allergy Drug Advisory Committee Meeting at 28-29 (May 11, 2023) ("ARS Advisory Committee Briefing Document") (Tab 31).

[86] FDA, May 11, 2023 Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) at 2:20:35 to 2:20:53, YOUTUBE, *available at* https://www.youtube.com/watch?v=IoMiKoY4rso ("ARS-1 Advisory Committee Recording").

[87] ARS Advisory Committee Briefing Document at 28 (Tab 31).

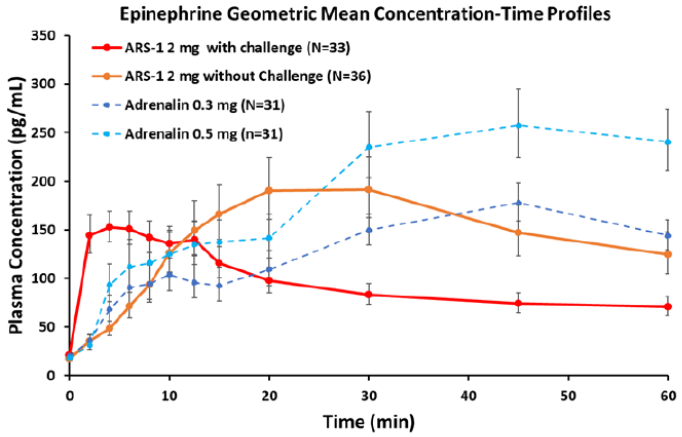
[88] *Id*. at 28-29.

[89] *Id*.

[90] FDA Advisory Committee Briefing Document at 37 (Tab 2).

nasal allergen conditions, confirming the importance of understanding intranasal epinephrine uptake and absorption under both conditions to assess the safety and efficacy profile of ARS-1.[91]

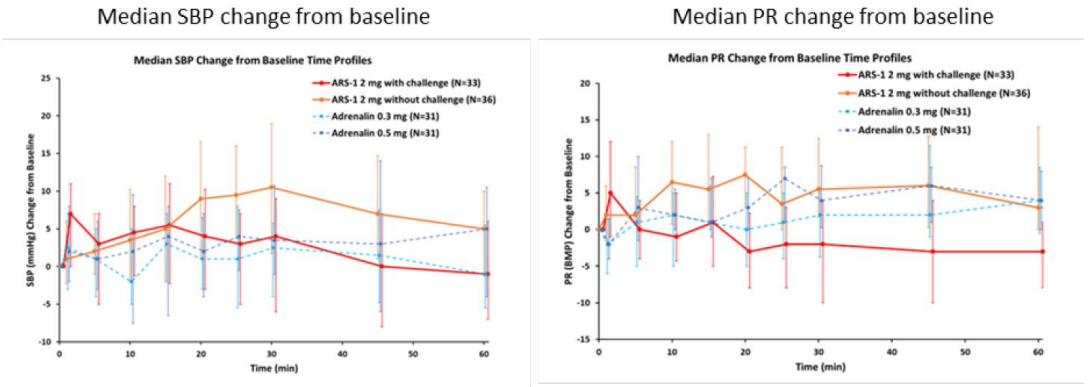
Figure 11. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 16.

As reflected in Figure 12, results from EPI 16 suggest nasal conditions may also have an impact on the PD and clinical effects of epinephrine in ARS-1.[92] Changes in SBP and PR effects are significantly lower for ARS-1 under NAC conditions than under normal nasal conditions. Indeed, changes in PR from baseline for ARS-1 under NAC conditions are negative at most timepoints after five minutes.

Figure 12. Median PD Responses (SBP and PR Changes From Baseline) in Subjects With Allergic Rhinitis



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Study EPI 16.
Subjects who were included in the PK analysis were included in the PD analysis.
Error bars represent 25% and 75% percentile of the PD values.
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; PR, pulse rate; SBP, systolic blood pressure

Taken together, the discrepancies between both PK profiles and PD effects for ARS-1 across different nasal conditions highlight the importance of having a robust understanding of the

[91] *Id*. at 38-39 (Section 3.1.2.3.3 – Nasal Congestion and its Effect on PK/PD).

[92] *Id*. at 38.

effects of NAC on ARS-1 administration. Data from study designs that do not include both normal nasal condition and NAC condition arms (such as EPI 11b and EPI 15, both of which evaluated ARS-1 only under normal nasal conditions) provide important information regarding ARS-1, but such studies leave open key uncertainties regarding the potential real-world performance of ARS-1 across individuals experiencing a range of vasodilatory effects in the nasal mucosa during anaphylaxis. Any PK/PD studies forming the basis of a benefit/risk determination for the ARS-1 application should include not only an arm with patients under normal nasal conditions, but also an arm with patients under NAC conditions.[93]

B. Subgroup Analysis by Degree of Rhinorrhea Could Reduce Residual Uncertainties Regarding the Effect of Rhinorrhea on PK and PD for ARS-1.

In addition to nasal congestion symptoms, individuals experiencing an anaphylaxis event may also experience rhinorrhea, *i.e.*, runny nose. Rhinorrhea is particularly relevant in evaluating intranasally administered epinephrine because it may prevent or reduce uptake of epinephrine administration (*i.e.*, fluid from rhinorrhea symptoms will clear epinephrine from the nasal cavity). The mean PK profile of intranasally-administered epinephrine from EPI 16 generally suggests this effect, as the rapid absorption of epinephrine in the first 10 minutes (thought to be from vasodilation) is followed by rapid clearance and a steep drop in epinephrine plasma concentration levels after 10 minutes as compared to both Adrenalin and ARS-1 without nasal challenge. This drop in epinephrine levels is also reflected in the decline in PD responses. Changes in PR were inferior to Adrenalin, and the mean PR change for ARS-1 with nasal challenge went below baseline values by 20 minutes. That is, both the PK and PD results under NAC conditions suggest that rhinorrhea washes off the drug in the nasal cavity. It is also possible that in cases of no or mild rhinorrhea, there may be a depot effect in the nasal mucosa causing sustained absorption and hence sustained PK and PD response in later timepoints.

Different individuals experience different grades of rhinorrhea during an allergic reaction. It is not clear how the PK and PD results for individuals experiencing no or mild rhinorrhea differ from individuals experiencing severe rhinorrhea, and whether individuals experiencing either extreme have significantly skewed the mean PK and PD results for the NAC model. The sponsor partially analyzed differences in degrees of rhinorrhea; however, this analysis appears incomplete.[94] Although the sponsor's Advisory Committee briefing materials indicate that some analyses were performed to understand the differential impact of various grades of rhinorrhea on C_{max} (which demonstrate a moderate impact), an analysis should be done for all relevant PK parameters (T_{max}, pAUC) and for PD effects. The impact of rhinorrhea on overall absorption in the first 20-30

[93] *See also* discussion of appropriate comparators in Section III.D below.

[94] *See generally* discussion of EPI 16 study in ARS Advisory Committee Briefing Document at 53 (Tab 31).

minutes is expected to be more pronounced than its moderate impact observed for C_{max}. Based on the degree of rhinorrhea, there is a possibility of failing to maintain adequate PK and PD response in the initial 30 minutes, raising potential efficacy and safety issues that merit additional consideration and should be taken into account as part of benefit/risk analysis.

Also, it is not possible to know whether any particular individual will experience rhinorrhea with anaphylaxis, or to what extent. This raises the importance of gaining a better understanding of the effects of rhinorrhea on different groups of individuals, and how that may affect treatment decisions after initial administration (*e.g.*, with a repeat dose of intranasal epinephrine or with a second dose of epinephrine by a different route of administration). Data from study designs that do not include rhinorrhea subgroup analyses provide only some of the evidence necessary to evaluate the efficacy and safety of ARS-1 for anaphylaxis. Such studies leave open key uncertainties regarding the potential real-world performance of ARS-1 across individuals experiencing a range of vasodilatory effects in the nasal mucosa during anaphylaxis. Any studies forming the basis of a benefit/risk determination for the ARS-1 application should include subgroup analyses based on degrees of rhinorrhea for the NAC arm.

C. PK/PD Studies Should Include Repeat Dose Comparisons in a Nasal Congestion Model to Adequately Account for the Potential Need for Additional Doses.

Understanding the effects of repeat administration of intranasally administered epinephrine is critical to evaluating the potential benefits and risks of ARS-1, because the proposed labeling (as with other, approved epinephrine products) includes instructions for administering a second dose if symptoms persist.[95] Members of the Advisory Committee noted several times that their standard instruction to patients for approved epinephrine products is to administer a second dose if an inadequate effect is observed several minutes after the first dose. To that end, the sponsor conducted a repeat-dose study for ARS-1 in its EPI 15 study under normal nasal conditions. PK/PD results from EPI 15 suggest that repeat dosing of ARS-1 under normal nasal conditions has a dose proportional increase in bioavailability.

However, there are no data on the effects of repeat dosing of ARS-1 under NAC conditions. As discussed above, the vasodilation and rhinorrhea experienced under NAC conditions may significantly alter the PK profile and PD effects of intranasally administered epinephrine. Reducing uncertainties regarding repeat dosing of ARS-1 under NAC conditions would most likely mimic use of ARS-1 in a real-world setting. The currently available evidence does not answer outstanding questions regarding, among other things, whether the vasoconstrictive effects of the first dose of epinephrine under NAC will counteract the vasodilatory effects of anaphylaxis in a way or to an extent that reduces the effectiveness of the repeat dose under NAC. Currently

[95] FDA Advisory Committee Briefing Document at 12 (Tab 2).

available data also do not indicate if individuals that experience only mild rhinorrhea will experience a depot effect with a repeat dose, or if the second dose washes off immediately in patients having significant rhinorrhea in the background of vasoconstriction from the first dose compromising bioavailability for the second dose. Nor do we know, based on currently available evidence, if the PK and PD results for repeat doses of ARS-1 will be comparable to repeat doses of EAIs.

The Agency has said the lack of repeat-dose data for ARS-1 in a NAC model is a serious "residual uncertainty," and indicated that "[a]dditional data may be needed to assess this decrease in exposure."[96] With that in mind, data of repeat dosing in a NAC model (with varying grades of rhinorrhea) is necessary to be able to make judgments regarding the safety and effectiveness of ARS-1. Study designs using the NAC model but failing to incorporate repeat-dose administration (*e.g.*, EPI 16), or testing repeat-dose administration but not under NAC conditions (*e.g.*, EPI 15), leave open key uncertainties regarding the potential real-world performance of ARS-1 across individuals that may require a second dose of ARS-1 or other epinephrine product. Repeat-dose data for ARS-1 in an NAC model would address these uncertainties.

D. PK/PD Studies Should be Bracketed by EAIs, Because They are the Most Appropriate Comparators to ARS-1.

As discussed during the Advisory Committee, the kinetics of EAIs are markedly different from needle-syringe injections of epinephrine such as Adrenalin. EAIs have a pressure head, *i.e.*, a spring in the EAI that induces a propulsive force when injected, and are likely injected much deeper than needle-syringe dosage forms,[97] such that when epinephrine is injected via EAI, the epinephrine diffuses into the tissue rather than having a reservoir effect like a needle-syringe injection.[98] These differences result in EAIs' having different PK profiles compared to needle-syringe epinephrine products such as Adrenalin.

Notwithstanding these differences, FDA and ARS agreed upon the use of two epinephrine products, Adrenalin (also referred to as IM epinephrine or needle-syringe epinephrine) and EpiPen (an EAI), as the comparators used for the bracketing study in the ARS-1 development program.

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[96] *Id*. at 11.

[97] Worm M, *et al*., Epinephrine delivery via EpiPen® Auto-Injector or manual syringe across participants with a wide range of skin-to-muscle distances. CLIN TRANSL ALLERGY. 2020; 10:21 (Tab 32).

[98] *See id*. ("[T]he spring-loaded mechanism of EpiPen may enable the propulsion of epinephrine beyond the SC fat layer or promote greater contact between the injectate and the vascular bed, resulting in greater dispersion and systemic uptake of epinephrine."); *see also* ARS-1 Advisory Committee Recording at 2:55:48-2:56:22 (comment from Dr. Nelson).

FDA explained the rationale for this choice as follows:

> Since both products are approved for the treatment of anaphylaxis and there is no reported difference in efficacy, the Agency considered that bracketing the ARS-1 PK profile by PK profiles of two different epinephrine injection products with different delivery systems (i.e., autoinjector versus needle-syringe) would be a reasonable approach to establish a scientific and regulatory bridge between ARS-1 and approved epinephrine injection products. Moreover, although EpiPen demonstrates higher intra-product PK variability, EpiPen is widely prescribed for community use and is therefore considered a clinically relevant comparison.[99]

FDA's comment recognizes EpiPen is a "clinically relevant comparison" because – like ARS-1 and unlike needle-syringe epinephrine – it is "widely prescribed for community use." Recognizing this, several Advisory Committee members expressed the view that EAIs would have been better comparators for ARS-1 PK/PD studies than Adrenalin,[100] as the use of Adrenalin in many of the ARS-1 studies makes it challenging (at best) to rely on the PK/PD data to reach conclusions about the safety and effectiveness of ARS-1. Accordingly, developing data that minimize residual uncertainties requires bracketing the ARS-1 data by two different EAIs, not an EAI and a needle-syringe.

1. EAIs Have Different PK/PD Profiles Than Needle-Syringe Products, Which Limits the Interpretability of the Bracketing Study.

PK data on epinephrine products suggest there is substantial variability in the PK profiles of epinephrine injection products.[101] This variability is due in part to intra- and inter-patient PK variability that is likely inherent to epinephrine, and in part to the limited amount of PK data on approved epinephrine injection products.[102] Because of the paucity of available epinephrine PK data, both FDA and the sponsor rely to some degree on cross-study PK comparisons for different epinephrine products.[103] However, it is well established that post-hoc, cross-trial comparisons like those outlined in some of the Advisory Committee materials have inherent limitations, and meaningful conclusions are difficult to draw from such comparisons. This is due at least in part

[99] FDA Advisory Committee Briefing Document at 26 (Tab 2).

[100] *See, e.g.*, ARS-1 Advisory Committee Recording at 2:30:00-2:30:54 (Comment from Dr. Kelso).

[101] FDA Advisory Committee Briefing Document at 9 (Tab 2).

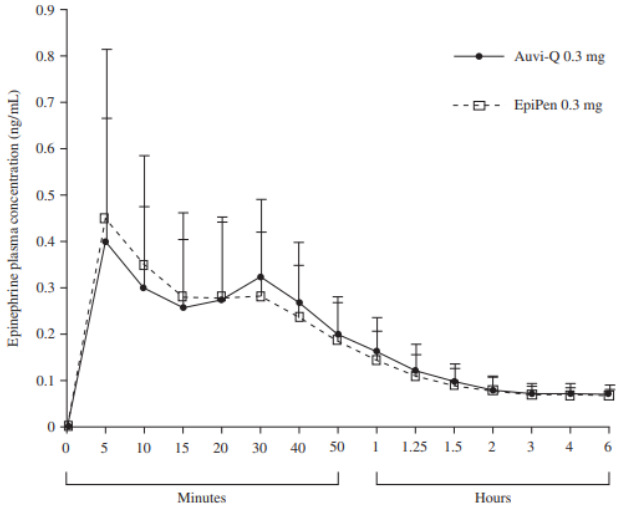
[102] *Id*. at 9, 15.

[103] For example, several slides in FDA's presentation to the Advisory Committee showed the PK profiles of EpiPen and Symjepi. However, all charts presented on slides 45-48 note that the profiles shown are "cross-study comparisons" that are using data across the various studies conducted during the ARS-1 development program.

to differences in study designs, which confound "apples-to-apples" comparisons and may lead to flawed conclusions.[104]

Although PK data for epinephrine products are relatively sparse, there are some reliable PK data suggesting that the PK profiles for EAIs are relatively similar compared to PK profiles across all epinephrine injection products, particularly with respect to T_{max} and C_{max}. Specifically, Auvi-Q (epinephrine) is an EAI approved under the 505(b)(2) pathway relying on FDA's findings of safety and efficacy for EpiPen. The Clinical Pharmacology Review of Auvi-Q explains the primary PK parameter (C_{max} and AUC_{0-t}) for the comparison of Auvi-Q and EpiPen "met the equivalence criteria[.]"[105]

The plasma concentration time-profiles of Auvi-Q and EpiPen presented in the review documents for Auvi-Q are shown below:[106]



[104] Sullivan KM and Keyes-Elstein L, Cross-trial comparisons in reviews: proceed with caution. NAT REV RHEUM 2020; 16:663-64 ("[F]ailure to recognize inherent differences across studies or apply proper statistical principles could yield flawed conclusions") (Tab 33).

[105] *See* Auvi-Q (NDA 201739) Clinical Pharmacology Review at 3 (Tab 18).

[106] Adapted from *id*. at 8.

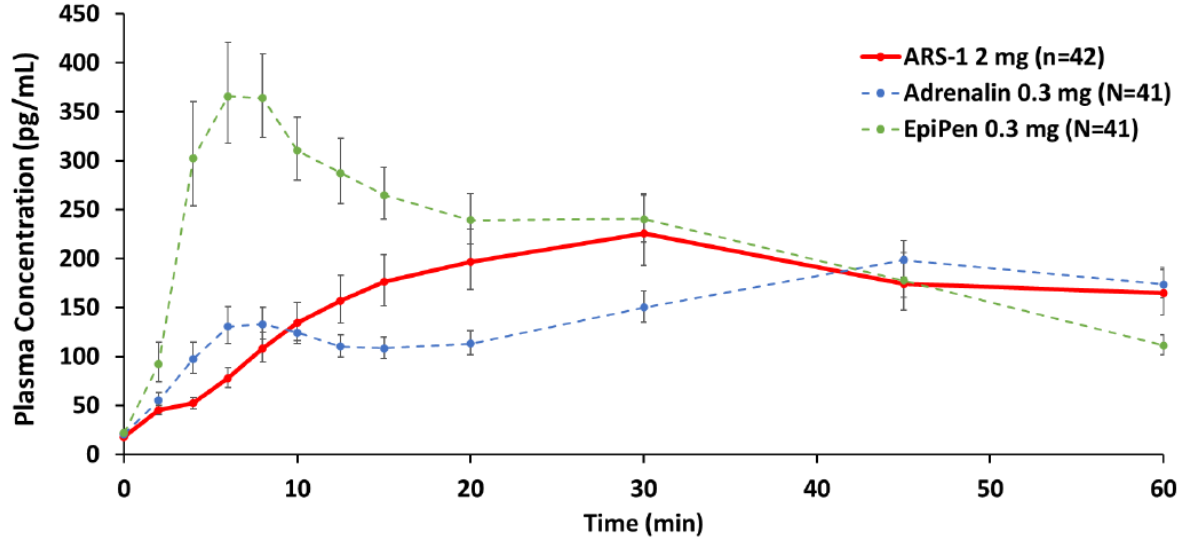
In contrast, there are significant differences between the profiles for EpiPen and Adrenalin, as shown in EPI 15.[107] Below are the PK parameters and concentration-time profiles for Adrenalin and EpiPen collected for EPI 15:[108]

Table 7. PK Parameters Following a Single Dose of ARS-1 vs. a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects

	Geometric Mean (CV%)			
Parameter	**ARS-1 (N=42)**	**Adrenalin 0.3 mg IM (N=41)[b]**	**EpiPen 0.3 mg IM (N=41)[b]**	**Bracketed (Y/N)**
C_{max} (pg/mL)	341(114)	286 (63)	618 (79)	Y
T_{max} (min)[a]	30	45	6	---
$AUC_{0\text{-}10min}$ (pg·min/mL)	**712 (93)**	**937 (108)**	**2979 (98)**	**N (lower than both)**
$AUC_{0\text{-}20min}$ (pg·min/mL)	2596 (102)	2141 (80)	6007 (77)	Y
$AUC_{0\text{-}30min}$ (pg·min/mL)	4901 (109)	3570 (72)	8759 (67)	Y
$AUC_{0\text{-}60min}$ (pg·min/mL)	10925 (116)	9377 (59)	14772 (56)	Y

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 15.

Figure 5. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profile Following a Single Dose of ARS-1 vs. a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI15.

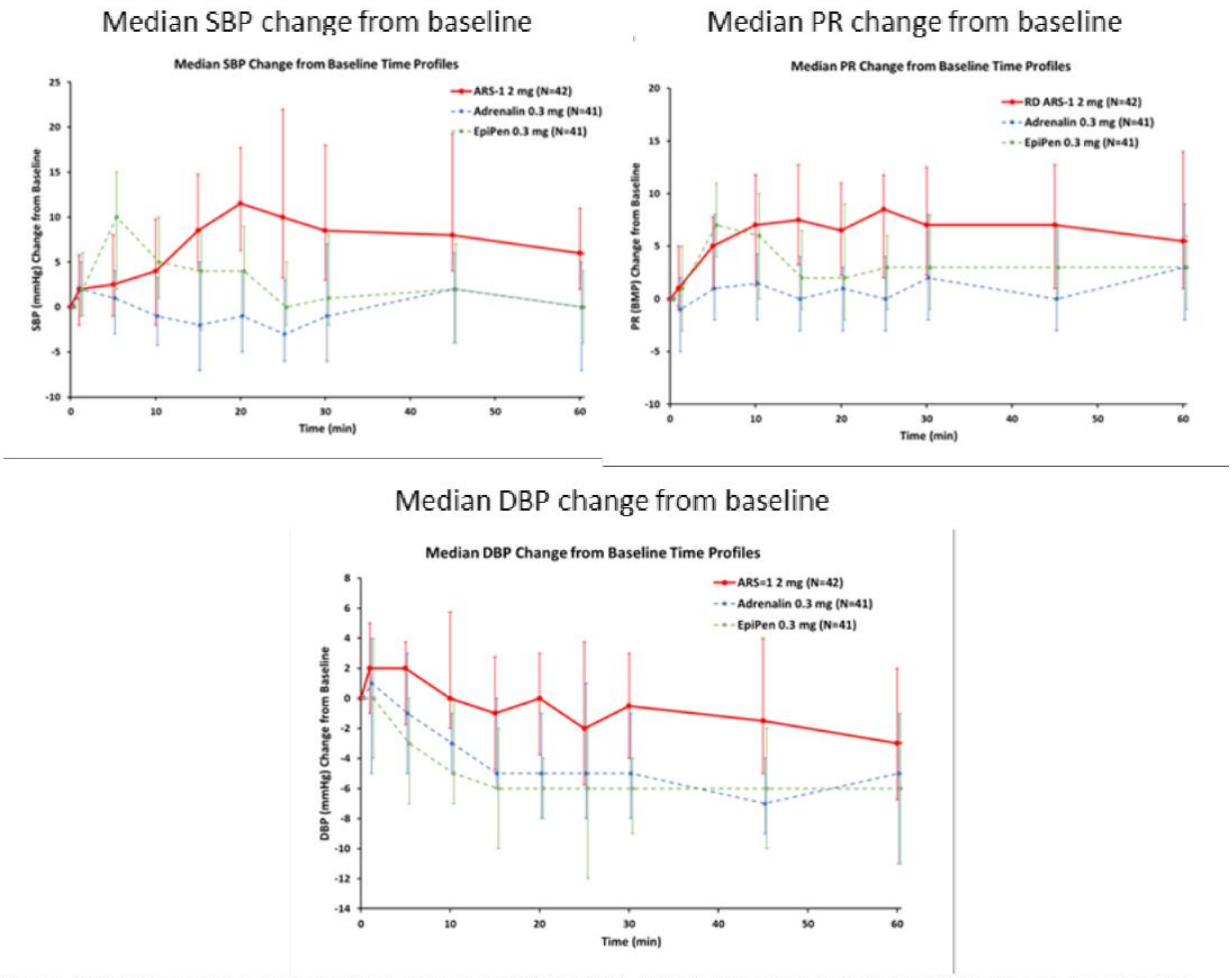
Although the ultimate significance of the differences between EpiPen and Adrenalin on crucial PK parameters (*e.g.*, C_{max}, T_{max}, pAUC measurements) are not fully known, these discrepancies cannot be ignored, especially because of the differences in administration settings for both products (see discussion below).

[107] FDA Advisory Committee Briefing Document at 27-29 (Tab 2).

[108] *Id*. at 28-29.

Similarly, there are substantial differences between PD results for Adrenalin and EpiPen. On crucial PD parameters such as change in SBP and HR, EpiPen had increased PD effects compared to Adrenalin. The relevant PD time profiles seen in EPI 15 are shown below:[109]

Figure 7. Median PD Responses (SBP, PR, and DBP Change from Baseline) Following a Single Dose of ARS-1, Adrenalin 0.3 mg, or EpiPen 0.3 mg in Healthy Subjects



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Study EPI 15. Subjects who were included in the PK analysis were included in the PD analysis.

These data, especially when combined with the differences between the two products in the setting in which the drug is used (*i.e.*, administration by healthcare professionals in a medical setting vs. by patients or caregivers who are not medical professionals in a community setting), make bracketing ARS-1 on PK/PD parameters with a non-EAI such as Adrenalin less relevant to the question of safety and efficacy of ARS-1.

[109] *Id*. at 31.

As the Agency noted in the Advisory Committee briefing materials, a favorable benefit/risk assessment of ARS-1 requires "a high level of confidence in both PK and PD results and confidence in bridging PK/PD findings to clinical efficacy in the setting of anaphylaxis."[110] However, there are substantial differences on key PK/PD parameters between the comparators used to bracket ARS-1 that seriously limit the interpretability of the PK/PD data supporting the ARS-1 application. The existing bracketing study using Adrenalin and EpiPen as comparators provides only one datapoint (*i.e.*, EpiPen) that matches the setting in which ARS-1 will be used—leaving important questions about the expected performance for the proposed product. Additional data, in the form of PK/PD bracketing studies using two appropriate comparators (*i.e.*, two EAIs[111]), would reduce residual uncertainties regarding the interpretability and clinical meaningfulness of PK/PD data for ARS-1.

2. EAIs Match the Proposed Conditions of Use for ARS-1: Patient Self-Administration or Caregiver Administration in a Community Setting.

The proposed use of ARS-1 will be in settings substantially similar, if not identical, to EAIs – that is, in at-home settings and either self-administered or administered by a caregiver who is not a healthcare professional to pediatric patients or potentially patients unable to self-administer (*e.g.*, when unresponsive, including in the supine position). The data submitted in support of approval must therefore show ARS-1 to be safe and effective in this setting. Because of the lack of appropriate comparators, the data currently before FDA do not meet that standard. Adrenalin was the sole comparator in EPI 16 and EPI 17, which assessed comparative PK/PD in subjects with a history of seasonal allergic rhinitis and subjects with Type I allergies, respectively. Neither EpiPen nor any other EAI was used as a comparator in these studies.[112]

Because only one EAI was used in the bracketing study (EPI 15), and no EAI was used in PK/PD studies conducted under NAC conditions (EPI 16 and EPI 17), key questions remain regarding (1) whether a bracketing study using two products with different conditions of use is sufficient to justify reliance on FDA's previous findings of safety and effectiveness for epinephrine administered in a non-medical setting, and (2) whether ARS-1 would show comparative bioavailability and PD effects when administered in community settings with patients with anaphylaxis. PK/PD bracketing studies that utilize two EAIs as the comparators will provide more interpretable data about ARS-1 under the proposed conditions of use.

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[110] *Id*. at 45.

[111] Although Symjepi, which is not an EAI, is approved for community use, it is not an appropriate comparator for this purpose because it is very rarely used in community settings (<1%). Data on file with Viatris.

[112] FDA Advisory Committee Briefing Document at 24 (Tab 2).

Epinephrine is used as a life-saving intervention during anaphylaxis, a condition that can be fatal if not treated quickly and effectively. Because ARS-1 will be administered in the community by patients and caregivers, the Agency should have before it all relevant information bearing on the product's safety and effectiveness that is reasonably possible to develop or gather. For example, the sponsor of Narcan nasal spray conducted PK/PD studies in patients in the supine position, with patients remaining in such position for a period of time following administration.[113] Consideration should be given to a similar approach that mimics conditions of use for ARS-1, including caregiver administration with supine patients, to assess whether the PK/PD of ARS-1 is affected when patients are supine and unresponsive due to anaphylaxis, which would provide additional important information related to the safety and efficacy of ARS-1.

Additionally, a product used in emergencies outside of a medical setting may be a patient's only form of treatment until medical assistance can be obtained. Given the rapid onset of anaphylaxis and the limited timeframe to administer treatment (*i.e.*, < 30 minutes),[114] the outcome for patients is almost entirely dependent on ensuring the treatment works effectively under the proposed conditions of use.

More than 99% of the epinephrine used in unsupervised medical settings in the US is in the form of EAIs.[115] Adrenalin, on the other hand, is primarily used for the emergency treatment of allergic reactions *by medical providers in a hospital setting*. The publicly available documents from FDA's review and approval of the Adrenalin NDA specifically refer to the medical setting in which Adrenalin is expected to be administered, and show that the Agency factored that condition of use into the risk/benefit analysis in approving the product. [116]

Administration in a medical setting differs in important ways from at-home administration by patients or caregivers, primarily because the former offers substantially greater ability to mitigate certain risks, monitor symptoms, and avoid medication error. For example, physicians in a medical setting can monitor and increase dose as needed, and may have access to additional medications or treatments, increasing the likelihood of successful reversal of anaphylaxis or mitigation of any adverse events. Conversely, as acknowledged in the Adrenalin review

[113] Narcan (NDA 208411) Cross-Discipline Team Leader Review at 8, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000CrossR.pdf.

[114] *Id*. at 27.

[115] Data on file with Viatris.

[116] *See e.g.*, Adrenalin (NDA 204200) Cross Discipline Team Leader Review at 7 (Tab 34). Specifically, FDA states "the clinical review team finds the safety and efficacy of the final labeled dosing of Adrenalin through the intramuscular and subcutaneous routes ***acceptable in a medical setting***." The review also states that "[t]he difference between the two indications is that EpiPen is intended for home (patient/caregiver) use, while Adrenalin is intended for use by a medical practitioner." *Id*. at 2.

documents, approved EAIs have a lower dose than Adrenalin as the "products are intended for self or caregiver administration prior to the patient arriving in a medical facility."[117] Patients or caregivers administering EAIs at home are likely reliant on the EAI as the sole method of treatment until follow-up treatment in a medical facility can be sought, and likely are not able to correct dosage or access other treatments.

The differences in conditions of use reduce the relevance of data derived from studies in which the bracketing includes a product that is almost always used by healthcare professionals in a medical setting. Comparing ARS-1 to two products approved under vastly different conditions of use provides insufficient certainty about the clinical benefit and safety of ARS-1 when self-administered or when administered by a caregiver in a community setting where patients may be unresponsive or in the supine position. It is crucial that a product intended for administration in this setting for this condition be supported by adequate scientific data showing comparability to products administered in the same setting. In the absence of clinical efficacy data (which cannot ethically be developed), conducting PK/PD bracketing studies for ARS-1 with two EAI comparators would materially reduce uncertainties about the performance of ARS-1 in a real-world event of anaphylaxis.

IV. CONCLUSION

For the reasons addressed above, Viatris respectfully requests that FDA grant the actions requested in this citizen petition.

[117] *See id*.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 9, 2023. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None (however, as a Viatris Inc. employee, I receive compensation). I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

* * *

Respectfully submitted,

Roisin Wallace

Roisin Wallace
Head of Global Regulatory Affairs

Enclosures