CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214697Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA Resubmission
Application Number(s)	214697
Priority or Standard	Standard
Submit Date(s)	April 2, 2024
Received Date(s)	April 2, 2024
PDUFA Goal Date	October 2, 2024
Division/Office	Division of Pulmonology Allergy, and Critical Care/ Office of Immunology and Inflammation
Review Completion Date	August 5, 2024
Established/Proper Name	Epinephrine nasal spray
(Proposed) Trade Name	neffy
Pharmacologic Class	alpha- and beta- adrenergic agonist
Code Name	ARS-1
Applicant	ARS Pharmaceuticals
Dosage Form	Nasal spray
Applicant Proposed Dosing Regimen	2 mg as needed for allergic reactions (Type I) including anaphylaxis. In the absence of clinical improvement or (b) (4) after the initial treatment a second may be administered in the same nostril approximately (b) (4) minutes after the first dose.
Applicant Proposed Indication(s)/Population(s)	For emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater
Recommended Dosing Regimen	2 mg as needed for type I allergic reactions including anaphylaxis. In the absence of clinical improvement or if symptoms worsen after the initial treatment, administer a second dose of neffy in the same nostril with a new nasal spray starting 5 minutes after the first dose.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Ji Hyun LaRose, PharmD
Nonclinical Reviewer	Anup Srivastava, PhD
Nonclinical Team Leader	Carol Galvis, PhD
Office of Clinical Pharmacology Primary Reviewer	Qianni Wu, PharmD
Office of Clinical Pharmacology Master Pharmacokineticist	Yunzhao Ren, MD, PhD
Office of Clinical Pharmacology Division Director	Chandrahas Sahajwalla, PhD
Clinical Reviewer	Jennifer Lan, MD
Clinical Team Leader	Miya Paterniti, MD
Statistical Reviewer and Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Miya Paterniti, MD
Associate Director for Therapeutic Review	Kelly Stone, MD, PhD

Additional Reviewers of Application

OPQ	Drug Substance: Sharon Kelly/ Lawrence Perez Drug Product: Xin Feng/ Craig Bertha Process/Facilities: Quamrul Majumder/Christine Falabella Microbiology: Catherine Gilbert/Yan Zheng Regulatory Buisness Project Manager: Anika Lalmansingh/Emma Gimose Cai Hong/ Nina Ni
PLT	Nyedra Booker/Marcia Williams
OPDP	Quynh-Nhu Capasso/Kyle Snyder
OSE/DMEPA	Matthew Barlow/Oluwamurewa Oguntimein/Jason Flint/Scott Janiczak/ Lisa Wolf Lissa Owens/ Idalia Rychlik Cristina Attinello/Ameet Joshi
CDRH	Gang Peng/Shruti Mistry
Associate Director for Labeling	Jessica Lee

Abbreviations: OPQ, Office of Pharmaceutical Quality; PLT, Patient Labeling Team; OPDP, Office of Prescription Drug Promotion; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; CDRH, Center for Devices and Radiological Health

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Qianni Wu	Office of Translational Sciences (OTS)/ Office of Clinical Pharmacology (OCP)/ Division of Inflammation and Immune Pharmacology (DIIP)	Section: 7, 15.3	**Select one:** _x_ Authored ___ Approved
	Signature: Qianni Wu -S Digitally signed by Qianni Wu -S Date: 2024.08.05 12:10:48 -04'00'			
Clinical Pharmacology Master Pharmacokineticist	Yunzhao Ren	OTS/OCP/DIIP	Section: 7, 15.3	**Select one:** _x_ Authored _x_ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S Date: 2024.08.05 12:19:07 -04'00'			
Clinical Pharmacology Division Director	Chandrahas Sahajwalla	OTS/OCP/DIIP	Section: 7, 15.3	**Select one:** ___ Authored _x_ Approved
	Signature: Chandrahas G. Sahajwalla -S Digitally signed by Chandrahas G. Sahajwalla -S Date: 2024.08.05 13:22:05 -04'00'			
Clinical Reviewer	Jennifer Lan	OND/OII/Division of Pulmonology, Allergy, and Critical Care (DPACC)	Sections: 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15.1, 15.2	**Select one:** _x_ Authored ___ Approved
	Signature: Jennifer P. Lan -S Digitally signed by Jennifer P. Lan -S Date: 2024.08.05 12:02:32 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Miya Paterniti	OND/OII/DPACC	Sections: : 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15.1, 15.2	**Select one:** _x_ Authored _x_ Approved
	Signature: Miya Paterniti -S Digitally signed by Miya Paterniti -S Date: 2024.08.05 13:43:10 -04'00'			
Associate Director for Therapeutic Review (Clinical)	Kelly Stone	OND/OII/DPACC	Sections: all	**Select one:** _x_ Authored _x_ Approved
	Signature: Kelly D. Stone -S Digitally signed by Kelly D. Stone -S Date: 2024.08.05 14:27:51 -04'00'			

Glossary

ABPM	automated blood pressure measuring
AE	adverse event
API	active pharmaceutical ingredients
AR	adverse reaction
CDRH	Center for Devices and Radiological Health
CMC	chemistry, manufacturing, and controls
CR	complete response
DBP	diastolic blood pressure
DDM	n-dodecyl-β-D-maltoside
ECG	electrocardiogram
EMS	emergency medical services
EPC	established pharmacologic class
FDA	Food and Drug Administration
FDRR	formal dispute resolution request
HF	human factor
ICH	International Conference on Harmonisation
IM	intramuscular
IND	Investigational New Drug
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NAC	nasal allergen challenge
NDA	new drug application
NDSRI	nitrosamine drug substance-related impurities
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PADAC	Pulmonary-Allergy Drugs Advisory Committee
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PR	pulse rate
PREA	Pediatric Research Equity Act
PT	preferred term

REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
SAE	serious adverse event
SBP	systolic blood pressure
SOC	standard of care
TEAE	treatment-emergent adverse event
TNSS	Total Nasal Symptom Score

1. Executive Summary

1.1. Product Introduction

ARS Pharmaceuticals (Applicant) provided a resubmission to new drug application (NDA) 214697 for epinephrine nasal spray (ARS-1) for "the emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and pediatric patients who weigh 30 kg or greater." ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection or intravenous infusion.

Epinephrine administered by injection (intramuscular or subcutaneous), or intravenously in monitored settings, is currently the first-line and only life-saving treatment for anaphylaxis. Epinephrine is a direct-acting, nonselective, sympathomimetic, alpha- and beta-adrenergic agonist that, at high plasma and tissue concentrations, can correct the pathophysiologic conditions of anaphylaxis within minutes (Brown et al. 2020) through vasoconstriction, relaxation of smooth muscle, and increased rate and force of cardiac contractions, leading to decreased mucosal edema, bronchodilation, and increased cardiac output.

ARS-1 is a single-dose (2 mg) epinephrine nasal spray that has a (b) (4) (n-dodecyl-β-D-maltoside [DDM]) to enhance absorption of epinephrine. The solution is packaged into a nasal spray device; the device is the same as used for naloxone nasal spray for the treatment of opioid overdose, as well as other approved nasal spray products. The proposed dose is 2 mg administered as one spray (100 µl) into one nostril for children and adults weighing ≥30 kg. The Applicant also proposes that in the absence of clinical improvement or (b) (4) after the initial treatment, a second dose of ARS-1 may be administered with a new nasal spray in the same nostril approximately (b) (4) minutes after the first dose.

For the remainder of this document, we refer to the 2 mg epinephrine nasal spray product as ARS-1, unless otherwise specified. We also refer to ARS-1 given once as one dose and given twice (repeat) (b) (4) minutes apart, as two doses.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action for this resubmission is **Approval** of ARS-1 for "the emergency treatment of type I allergic reactions including anaphylaxis for adults and children who weigh ≥30 kg," based on pharmacokinetic (PK) bracketing of ARS-1 to approved epinephrine injection products, as well as supportive pharmacodynamics (PD) (e.g., systolic blood pressure [SBP] and pulse rate [PR]), in healthy adults and in adults with allergic rhinitis following nasal allergen challenge (NAC)-induced rhinitis. PK/PD of ARS-1 in children ≥30 kg was similar to adults.

To support this indication, for the original NDA, the Applicant conducted three PK/PD trials in adults (EPI 15, EPI 16, and EPI 17) and one trial in pediatric subjects ≥30 kg (EPI 10), using the proposed 2-mg dose, to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway.

- EPI 15 assessed PK/PD in healthy adults following administration of one and two doses of ARS-1, administered 10 minutes apart, compared to Adrenalin and EpiPen.

- EPI 16 assessed PK/PD in subjects with allergic rhinitis following administration of one dose of ARS-1, compared to Adrenalin, under NAC-induced rhinitis conditions; ARS-1 administered under NAC-induced rhinitis conditions was used to assess the effects of acute rhinitis, including congestion and rhinorrhea, on PK/PD.

- EPI 17 assessed PK/PD in healthy adults following self-administration of one dose of ARS-1, compared to EpiPen. ARS-1 was administered by trial staff administration in all other trials.

- EPI 10 assessed PK/PD following administration of one dose of ARS-1 in pediatric subjects ≥30 kg.

Detailed analyses and discussions of these four trials are provided in the review of the original NDA submission, dated September 19, 2023. Overall, the PK/PD results from the adult studies, EPI 15 and EPI 17, and the pediatric trial in children ≥30 kg, EPI 10, provided an adequate scientific bridge to approved epinephrine injection products to demonstrate substantial evidence of effectiveness, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and more than 100 years of clinical use.

The basis for the Complete Response (CR) of the original NDA submission was focused on the results from EPI 16. While the PK/PD results from administration of a single dose under NAC-induced rhinitis conditions in EPI 16 demonstrated adequate PK and PD responses in the first 20 minutes post-dose, epinephrine mean plasma concentration and pulse rate (PR) dropped below those of the epinephrine injection comparator (Adrenalin), starting around 20 minutes post-dose. The lack of sustainability of epinephrine concentrations after 20 minutes, when compared to Adrenalin, raised concern as to the durability of effect in anaphylaxis patients with acute rhinitis. Given the complex interaction between acute rhinitis (i.e., congestion and rhinorrhea) and local pharmacologic effects of epinephrine following the initial administration of ARS-1, there was uncertainty in leveraging the PK/PD results from EPI 15 and EPI 16 to simulate the epinephrine PK/PD profiles following a repeat dose of ARS-1 under acute rhinitis conditions. In addition, since the initial dose of ARS-1 administered under acute rhinitis conditions may impact the PK/PD profile of a subsequent dose administered in the same nostril, due to local pharmacologic effects, it was not clear whether there were significant differences in PK/PD

following administration of the second dose in the same or alternate nostril. As a result, it was determined that additional data from a PK/PD trial(s) assessing PK/PD under NAC-induced rhinitis conditions, following a repeat dose of ARS-1 compared to repeat doses of epinephrine injection product(s), was needed to address the remaining uncertainties, including assessment of PK/PD findings when the second dose is administered in the same and alternate nostrils.

To address the deficiencies in the original NDA submission, the Applicant submitted data from a new clinical pharmacology PK/PD trial (EPI 18) in adults with allergic rhinitis under NAC-induced rhinitis conditions, that includes administration of two doses of ARS-1 compared to two doses of Adrenalin, both administered 10 minutes apart; EPI 18 also assesses PK/PD when the second dose is administered in the same compared to alternate nostril.

Summary of EPI 18 findings:

- Same-nostril administration of two doses of ARS-1 under NAC-induced rhinitis conditions: Similar to the results of EPI 16, the first dose of ARS-1 demonstrated higher mean epinephrine concentrations compared to Adrenalin through 10 minutes. With administration of the second dose of ARS-1 in the same nostril at 10 minutes, the mean epinephrine concentration was higher than that observed with administration of the second dose of Adrenalin for up to 40 minutes (after the first dose) and was similar after 40 minutes. The median PD responses (SBP and PR) following administration of two doses of ARS-1 in the same nostril were generally higher than those observed with two doses of Adrenalin throughout 60 minutes post-dose.
- Alternate-nostril administration of two doses of ARS-1 under NAC-induced rhinitis conditions: Mean epinephrine concentrations following two doses of ARS-1 administered in alternate nostrils in adults with NAC-induced rhinitis were comparable to higher than two doses of Adrenalin within 25 to 30 minutes post-dose, but they became lower after 30 minutes. SBP and PR responses (evaluated as change from baseline, using pre-NAC values as baseline) remained comparable to Adrenalin within the first 40 minutes, but were lower after 40 minutes.

Based on these results:

- EPI 18 addresses the uncertainty from the original NDA submission regarding durability of PK/PD effect of ARS-1 under NAC-induced rhinitis conditions when a second dose is administered. PK/PD findings following two doses of ARS-1, compared to two doses of Adrenalin, demonstrates sustainability and strength of PK and PD for patients who may require a second dose, consistent with proposed conditions of use. This scientific bridge is now established between ARS-1 and the listed product when administered in both healthy subjects and patients with acute rhinitis under NAC-induced rhinitis conditions. As a result, the Applicant can rely on the Agency's finding of effectiveness of two doses of Adrenalin.

- EPI 18 addresses the uncertainty from the original NDA submission regarding whether there are significant differences in PK/PD following administration of a second dose in the same compared to alternate nostril. As a result, ARS-1 will be labeled to be administered in the same nostril in cases where a second dose is required.

Overall, the PK/PD results from the adult studies, EPI 15, EPI 16, EPI 17, and EPI 18, and the pediatric trial in children ≥30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. Based on this scientific bridge, substantial evidence of effectiveness is demonstrated, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and more than 100 years of use. New results from EPI 18 address the uncertainties identified in the original NDA review that led to a CR. As a result, substantial evidence of effectiveness has been demonstrated and the recommended regulatory action is **Approval** of this NDA with an indication "for emergency treatment of type I allergic reactions including anaphylaxis in adult and pediatric patients who weigh 30 kg or greater."

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Epinephrine administered by injection (intramuscular or subcutaneous), or intravenously in a monitored setting, is currently the first-line and only life-saving treatment for anaphylaxis. The use of epinephrine injection for the treatment of anaphylaxis is based on historical and anecdotal use for more than 100 years; adequate and well-controlled clinical trials to demonstrate efficacy of epinephrine injection products have not been conducted. Early administration of epinephrine is recommended, as fatal anaphylaxis is in some cases associated with delayed administration of epinephrine. Barriers to administration of epinephrine for treatment of anaphylaxis are multifactorial, but they include fear of injection. Availability of alternative routes of administration of epinephrine, such as the nasal route, may improve compliance and time to administration for epinephrine, and may, as a result, lead to improved outcomes. ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection or infusion.

To support this submission for ARS-1 "for the emergency treatment of type 1 allergic reactions, including anaphylaxis, in adults and children ≥30 kg," using the 505(b)(2) pathway, the Applicant conducted five pharmacokinetics (PK)/pharmacodynamics (PD) trials to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via PK bracketing. Additional support is provided by hemodynamic PD results, namely systolic blood pressure (SBP) and pulse rate (PR) change from baseline, that are directly relevant to anaphylaxis treatment. No clinical efficacy studies were conducted for ARS-1 administered during anaphylaxis, and no PK/PD studies were conducted in patients undergoing anaphylaxis due to feasibility and interpretability concerns. The ARS-1 development program was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on May 11, 2023. The advisory committee generally supported the use of PK bracketing with supporting PD data in healthy subjects as a basis for approval, without the need for clinical efficacy data. Based on the results from EPI 15, EPI 16, EPI 17, and EPI 10, the advisory committee voted that the benefit-risk assessment of ARS-1 for adults ≥18 years (16 yes, 6 no) was favorable; the committee voted similarly for a favorable benefit-risk assessment of ARS-1 children who weigh ≥30 kg (17 yes, 5 no). An additional PK/PD trial, EPI 18, was conducted after the advisory committee meeting to address residual uncertainties identified by the division.

Four PK/PD trials were conducted in adults (EPI 15, EPI 16, EPI 17, and EPI 18) and one was conducted in pediatric subjects ≥30 kg (EPI 10). Refer to the original NDA Review from September 19, 2023, for detailed discussion of trials EPI 15, EPI 17, and EPI 10 and how they provide an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. However, for EPI 16, where ARS-1 was administered under NAC-induced rhinitis conditions, there was a noticeable decline in ARS-1 PK and PD below Adrenalin at approximately 20 minutes after administration. Both the decline in PK and PR at 20 minutes, compared to epinephrine injection, raised concerns with the durability of the effect in patients with acute allergen-induced rhinitis and whether this would lead to more patients requiring a second dose of ARS-1, or whether patients who require a second dose would be adequately treated with a second dose of ARS-1 in comparison to a second dose of epinephrine injection.

EPI 18, conducted subsequently, addresses the uncertainty seen in EPI 16. EPI 18 demonstrated that after NAC, two doses of ARS-1, administered in the same nostril 10 minutes apart, produced an epinephrine concentration profile higher than two doses of the epinephrine injection comparator, Adrenalin. The median PD responses of two doses of ARS-1 administered in the same nostril after NAC were generally higher than two doses of Adrenalin with NAC throughout 60 minutes post-dose. The results of EPI 18 provided the necessary data to complete the scientific bridge to conclude that ARS-1 is comparable to the listed epinephrine injection products, consistent with the proposed conditions of use.

Assessment of systemic safety of ARS-1 relies primarily on the known safety of the listed epinephrine injection products since epinephrine exposure is comparable. The limited systemic safety adverse event profile of ARS-1 from the PK studies did not identify new safety concerns.

Given the nasal route of administration, local nasal adverse events were of particular interest. Local adverse events observed included throat irritation, intranasal paresthesia, nasal discomfort, rhinorrhea, nasal pruritus, sneezing, and nasal congestion. Although the overall safety database was small, the local adverse event profile of ARS-1 did not raise concerns. As the studies were limited, with the majority of subjects receiving only one dose, the local adverse event profile is not well defined for more frequent use; however, frequent use is expected to be minimal.

The review team's assessment is that there is a favorable benefit-risk assessment, and they recommend Approval of ARS-1 "for emergency treatment of type I allergic reactions including anaphylaxis for adults and children who weigh ≥30 kg." Overall, the five clinical pharmacology studies provide PK/PD results from adults and children ≥30 kg to establish a scientific bridge to approved

epinephrine injection products to rely on FDA's prior findings of safety and effectiveness of EpiPen and Adrenalin, including with repeat dosing and in the setting of acute rhinitis. ARS-1 provides an alternative route for administration of epinephrine in the treatment of anaphylaxis that has the potential to improve compliance and timeliness of treatment of anaphylaxis episodes.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Anaphylaxis is an acute, potentially life-threatening, systemic allergic reaction; approximately 200 deaths occur per year in the United States. • A large population in the United States is at risk of anaphylaxis, primarily due to allergy to foods, drugs, and Hymenoptera venom, among other causes. • Although risk factors for fatal anaphylaxis have been described, it is not possible to identify patients at risk for fatal reactions based solely on these risk factors.	Anaphylaxis is an emergency condition that can occur suddenly and can be rapidly progressive and fatal.
Current Treatment Options	• Epinephrine injection is the first-line and only available life-saving treatment for anaphylaxis. • Adequate and well-controlled clinicals trials to demonstrate efficacy of epinephrine injection products have not been conducted; evidence for efficacy is based on animal models, case series, expert opinion, and more than 100 years of use. • Early administration of epinephrine reduces morbidity and mortality from anaphylaxis. • Approximately 10% of patients require more than one dose of epinephrine injection (Patel et al. 2021).	Epinephrine injection products are safe and effective. Barriers to administration of epinephrine injection for treatment of anaphylaxis include needle phobia. There is an unmet need for alternative routes of administration for epinephrine that may increase use and reduce time to administration.

	• Administration of epinephrine injection products is frequently delayed or avoided, increasing the risk of morbidity and mortality.	
Benefit	• Clinical efficacy trials were not conducted due to feasibility and interpretability concerns. • PK/PD studies in healthy adults and children and in adults with NAC-induced rhinitis establish a scientific bridge to approved epinephrine injection products (EpiPen and Adrenalin). <u>Healthy adults:</u> – The PK profile of a single dose of ARS-1 is bracketed by Adrenalin and EpiPen 60 minutes post administration. – The PK profile of two doses of ARS-1 was similar to that of two doses of EpiPen, with both administered 10 minutes apart. – ARS-1 PD (SBP and PR) findings were generally higher compared to EpiPen and Adrenalin, providing supportive data. <u>Adults with NAC-induced rhinitis:</u> – With administration of a single-dose, there was a lack of sustainable PK and PR response 20 minutes post-dose that raised concerns regarding the durability of effect of ARS-1.	Efficacy of ARS-1 in healthy adults is established through PK bracketing to Adrenalin and EpiPen, with reliance on the Agency's prior finding of safety and effectiveness of both listed products. Efficacy of ARS-1 in subjects with NAC-induced acute rhinitis in adults is established through PK matching to Adrenalin following single- and repeat-dose, with reliance on the Agency's prior finding of safety and effectiveness of the listed product. Hemodynamic PD markers relevant to anaphylaxis provide additional support in the absence of clinical trial data. It is unclear whether the drop in PK under NAC-induced rhinitis conditions will result in greater need for repeat dosing of ARS-1; however, results with repeat dosing support efficacy.

	– With administration of repeat doses, when given in the same nostril, PK/PD responses were higher when compared to repeat-dosing of Adrenalin. – With administration of repeat doses, when given in the alternate nostril, PK/PD responses were not sustained above repeat-doses of Adrenalin starting 30 minutes after administration of the second dose.	
Risk and Risk Management	• Systemic safety relies on the known safety profile of epinephrine injection products, as the PK of ARS-1 is comparable to the listed epinephrine injection products. • Systemic adverse events observed with ARS-1 include headache, feeling jittery, tremor, dizziness, nausea, vomiting, paresthesia, and fatigue. With repeat-dose ARS-1, systemic adverse events occurred more frequently, likely due to the higher systemic dose. • Local adverse events observed in the ARS-1 development program included throat irritation, intranasal paresthesia, nasal discomfort, rhinorrhea, nasal pruritus, sneezing, and nasal congestion. The majority of adverse events were reported as mild. Local safety with administration of multiple doses of ARS-1 was limited. • A carryover effect was observed in the ARS-1 development program, with increased absorption of ARS-1 during a 2-week window following ARS-1 administration. Administration of	One- and two-dose PK studies did not raise safety concerns beyond the established systemic safety of epinephrine injection products. The majority of local adverse events were mild. Repeat-dosing within the carryover window is not expected to occur frequently, given that epinephrine is an emergency treatment medication. As clinical trials in patients with anaphylaxis were not conducted, a registry-based clinical trial in patients with anaphylaxis will be conducted to assess the efficacy and safety of ARS-1 as a postmarketing commitment.

[redacted]	ARS-1, or other nasal products, during this 2-week period may result in higher PK results.	

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

See original NDA Review from September 19, 2023, for details.

2.2. Summary of Presubmission/Submission Regulatory Activity

Refer to the original NDA Review from September 19, 2023, for regulatory history during the IND stage.

The Applicant submitted their original NDA on August 19, 2022. Major amendments were received on May 30, 2023 and June 5, 2023, with additional CMC and device data. A CR action was taken on September 19, 2023, due to the following deficiencies:

1. Clinical/Clinical Pharmacology: EPI 16, which assessed one dose of ARS-1 administered to adults with NAC-induced rhinitis, compared to one dose of an epinephrine injection comparator (Adrenalin), raised concern regarding the durability of ARS-1's effect in patients with NAC-induced rhinitis. There was also uncertainty with the PK/PD effects when two doses of ARS-1 were administered in the same or alternate nostril. To address these concerns, the Applicant was to provide PK/PD data assessing two doses of ARS-1 compared to two doses of epinephrine injection product(s) under NAC-induced rhinitis conditions, including an assessment of PK/PD findings when the second dose of ARS-1 is administered in the same or alternate nostril.
2. Product Quality: As outlined in the FDA guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023),[1] applicants are required to ascertain the presence of nitrosamine drug substance-related impurities (NDSRIs) in their drug products. The NDA did not include data or information, such as a risk assessment, and/or confirmatory testing data as needed, demonstrating that they ascertained the presence of NDSRIs in their drug product, including specifically (b) (4)

[1] NDSRI guidance refers to a 3-step mitigation strategy described in FDA's guidance for industry, *Control of Nitrosamine Impurities in Human Drugs* (February 2021).

Type A Meeting

A Type A Meeting was held on October 24, 2023. During the meeting, the Division reiterated the need for a trial comparing two doses of ARS-1 in adults under NAC-induced rhinitis conditions to two doses of epinephrine injection product to address the deficiency outlined in the CR letter, in addition to the NDSRI data. Clarification was provided regarding data submission for the resubmission.

Formal Dispute

On November 27, 2023, the Applicant submitted a formal dispute resolution request (FDRR) regarding the CR Letter that was issued by the Division. In the FDRR, the Applicant relayed they disagreed with the Agency's requirement to conduct an additional PK/PD trial assessing two doses of ARS-1 and two doses of epinephrine injection product(s) in patients with NAC-induced rhinitis trial to support efficacy and safety, as a condition of approval. The Applicant also disagreed with the need for NDSRI data as a condition of approval. Dr. Nikolay Nikolov, Acting Director, Office of Immunology and Inflammation, acknowledged the public health importance of a needle-free epinephrine product, but agreed with the issues raised by the Division in the CR Letter and that a reasonable path forward was laid out to address the deficiencies. Therefore, the formal dispute request was denied. See Dispute Appeal Denied letter dated February 2, 2024, for further details.

3. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Office of Scientific Investigations (OSI)

As EPI 18 is conducted in the same facility as the trials from the original review, this resubmission did not require further Office of Study Integrity and Surveillance (OSIS) inspections.

3.2. Product Quality

The original application received a CR in part due to the absence of information regarding the potential nitrosamine impurities, as outlined in the FDA guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023). This deficiency was outlined in the CR Letter. To address the deficiency, the Applicant was required to complete the following: (1) conduct risk assessments for nitrosamines in active pharmaceutical ingredients (APIs) and drug products; (2) conduct confirmatory testing if risks are identified; and (3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in APIs and drug products in approved and pending NDAs and ANDAs. Review of the submitted information demonstrated sufficient information and the CMC/Quality team recommends approval of ARS-1. See review dated April 19, 2024, from Craig Bertha for further details.

3.3. Clinical Microbiology

None for the resubmission.

3.4. Devices and Companion Diagnostic Issues

For the resubmission, the Applicant submitted additional irritation testing for the (b) (4) device that had not been completed with the first submission. The (b) (4) device irritation testing was not needed for approvability. An adequate irritation assessment was completed, and the Center for Devices and Radiological Health (CDRH) reviewer concludes that the device constituent parts of the combination product are approvable. See review dated June 12, 2024, from Gang Peng.

4. Nonclinical Pharmacology/Toxicology

No additional nonclinical studies were submitted in the resubmission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

See original NDA Review from September 19, 2023, table 3. In addition to the trials listed in the original review, EPI 18 described below is considered a pivotal trial in support of safety and effectiveness.

Table 1. EPI 18 Trial Design

Trial Name	Trial Design	Objective of the Trial	Test Product	Number of Subjects	Population
EPI 18 Nasal allergen challenge with two-dose administration	Phase 1, five period, five treatments, two dose*, cross over trial	Assess the comparative bioavailability of epinephrine after two doses of 2 mg ARS-1 and two doses of 0.3 mg epinephrine IM in subjects with seasonal allergic rhinitis after nasal allergen challenge	2 mg ARS-1 x2 0.3 mg epinephrine IM x2 0.3 mg epinephrine IM x2 after nasal allergen challenge **2 mg ARS-1 x2 after nasal allergen challenge	46 subjects	Adults with seasonal allergic rhinitis

* The two doses were administered 10 minutes apart.
** Dosed either in the same nostril or alternate nostril
Abbreviations: IM, intramuscular.

5.2. Review Strategy

No clinical efficacy studies were conducted for this NDA. This resubmission review will focus on the additional PK/PD trial, EPI 18. The original NDA reviewed PK/PD trials EPI 15, EPI 16, EPI 17, and EPI 10 and conclusions from those trials along with EPI 18 support the efficacy and safety of ARS-1 for the proposed indication. The review of EPI 18 will include a brief description of the clinical pharmacology protocol in Section 6, followed by the clinical pharmacology results in Section 7. Additional information on the trial design and clinical pharmacology results are also provided in the Appendix (15.3). The review of safety includes the entire safety database for EPI 15, EPI 16, EPI 17, and EPI 18, as discussed in Section 8.

6. Additional Pivotal Trial Protocol

6.1. Review of Relevant Individual Trials Used to Support Efficacy

6.1.1. EPI 18: A Five-Treatment, Five-Period, Randomized, Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Repeat Administration of ARS-1 and Intramuscular Epinephrine Injection in Type I Allergy Patients with Seasonal Rhinitis

Administrative Information

Trial Dates: October 9, 2023 to December 12, 2023

Trial Sites:

Novum Pharmaceutical Research Services
3760 Pecos McLeod
Las Vegas, NV 89121

Trial Report Date: March 26, 2024

Trial Design

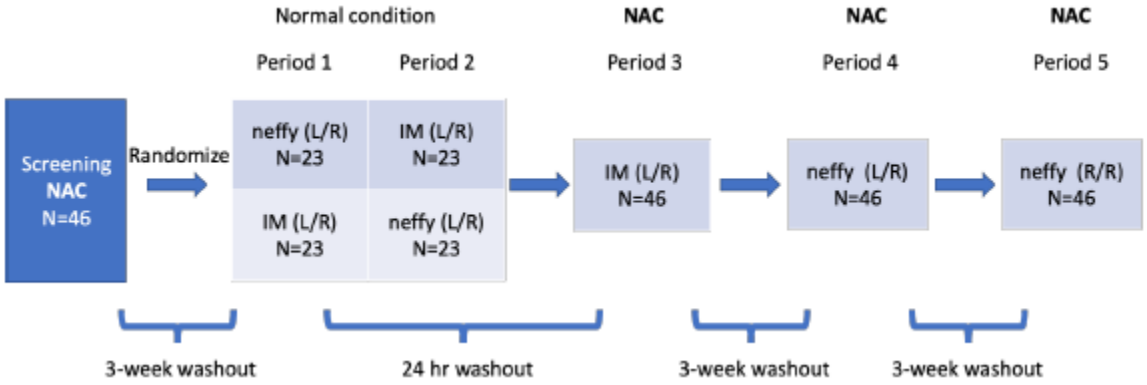
This is a phase 1, five period, randomized, cross-over trial that consisted of a screening period and an open-label treatment period (Figure 1). The trial enrolled adults between 18 and 64 years old with a body weight ≤50 kg and body mass index between 18 and 35 kg/m^2. Subjects had to have a history of seasonal allergic rhinitis demonstrated with a positive skin prick (skin prick wheal ≥3 mm over negative control) and/or intradermal test to allergen(s) within 12 months of enrollment. Subjects had to have a Total Nasal Symptom Score (TNSS) of ≥5 out of 12 and a congestion score of ≥2 out of 3 with NAC at screening. In treatment periods under normal nasal condition, subjects had to have a nasal congestion score of 0 to 1 at screening and prior to dosing.

Subjects with history of nasal conditions that could interfere with nasal spray administration were excluded. At screening subjects could not have hypertension and subjects with a history of clinically significant cardiovascular disease were also excluded.

The bioavailability of two doses of ARS-1 (given 10 minutes apart) with and without NAC-induced rhinitis was assessed and compared to two doses of 0.3 mg intramuscular (IM)

injection administered 10 minutes apart with a standard needle and syringe. There was at least three-weeks between any adjacent ARS-1 treatment periods.

Figure 1. EPI 18 Trial Schematic



Source: EPI 18 Protocol
Abbreviations: IM, intramuscular epinephrine injection; L, left; NAC, nasal allergen challenge; R, right.

Screening:

Subjects had an assessment for response to their previously diagnosed target antigen (standardized HollisterStier allergen solutions) based on TNSS in advance of study treatment. An initial nasal wash with saline and phenol was used to exclude subjects with nonspecific hyperresponsiveness. Subjects reporting a TNSS response greater than 2 from the diluent dose were excluded. Allergen concentration was prepared from stock solutions (HollisterStier) in serial dilutions, using a diluent solution of saline and phenol, from 1:128 to 1:2; each concentration a 4-fold dilution of the previous. Subjects were challenged in both nostrils with escalating (4-fold) increments of allergen at 15 min (±5 min) intervals until a positive reaction (i.e., TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3) was reached. If the subject reached the highest concentration of 1:2 without qualifying, the subject was excluded.

The qualifying concentration was used to determine the cumulative dilution for Treatment Periods 3, 4, and 5. Subjects who met criteria by TNSS score at screening had the following higher dilutions used for Treatment Periods 3-5, noted as “cumulative dilution,” to ensure adequate induction of nasal symptoms (Table 2).

Table 2. EPI 18 Allergen Challenge Concentration Determination

Dilution Concentration Established at Screening	Cumulative Dilution Concentration for Periods 3-5
1:128	1:25.6
1:32	1:6.1
1:8	1:6.1
1:2	1:1.5

Source: EPI 18 Protocol

Open-Label Treatment

Forty-three subjects were enrolled in Treatment Periods 1-5. In Treatment Periods 1-2, each subject was randomized to receive one of the following treatments and then crossed over to the other product:

- Two doses of ARS-1 in the right and left nostril administered 10 minutes apart
- Two doses of epinephrine IM 0.3 mg in the right and left anterolateral thigh administered 10 minutes apart

In Treatment Periods 3-5, each subject received each of the following doses after induction of NAC-induced rhinitis:

1. Two doses of epinephrine IM 0.3 mg in the right and left anterolateral thigh administered 10 minutes apart
2. Two doses of ARS-1 in the left and right nostril administered 10 minutes apart
3. Two doses of ARS-1 in the right and right nostril administered 10 minutes apart

If there was excessive nasal drip after the NAC, the nose was wiped before administering study drugs. Each dose was separated by a 24-hour washout period for Treatment Periods 1-3 and by 3 weeks for Treatment Periods 3-5.

Trial Endpoints

See Section 8 for PK and PD endpoints.

Statistical Analysis Plan

Not applicable

Protocol Amendments

Two protocol amendments (September 19, 2023 and October 25, 2023) were made in response to FDA Information Requests asking for clarification of the protocol. The amendment contained minor modifications to clarify procedures and PK/PD parameters.

6.1.2. Trial Results

Compliance with Good Clinical Practices

The Investigators agreed to conduct the trial in compliance with the trial protocol, with the ICH guidance for industry *E6(R2) Good Clinical Practice* (March 2018), and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 15.2 of this review for additional details.

Patient Disposition

A total of 43 subjects were enrolled, with 41 subjects completing the trial. Two subjects withdrew prematurely and did not receive all doses, but were included in both the safety and PK analysis populations. The reasons for withdrawal were as follows:

- Subject (b) (6) withdrew as the subject had high blood pressure prior to dosing.
- Subject (b) (6) did not show up for dosing Periods 4 and 5.

Two subjects did not receive all doses, but continued in the trial, as follows:

- Subjects (b) (6) skipped Period 4 dosing.
- Subject (b) (6) did not receive the second dose in Period 2 due to low blood pressure, nausea, and diaphoresis. They did not receive a dose in Period 3 for reasons unknown.

Protocol Violations/Deviations

During the trial, there were 219 protocol deviations. The deviations included PK sampling being conducted outside the specified window, TNSS not assessed or delayed assessment, and vital signs collected outside of the collection window.

Table of Demographic Characteristics

Table 3 displays the demographics of the participants enrolled in EPI 18. Since the trial used a crossover design, the majority of subjects in each treatment arm (N) were the same participant

(see Patient Disposition above regarding patient withdrawals). The participants in the trial were roughly evenly distributed by gender (female 56%, male 44%), predominantly African American (42%) and White (37%), with an average weight of 77 kg.

Table 3. Demographics, Trial EPI 18

Characteristic	ARS-1 2 mg x2 (R/L) N=43	ARS-1 2 mg x2 (R/L) with NAC N=40	ARS-1 2 mg x2 (R/R) with NAC N=41	IM 0.3 mg x2 (R/L) N=42	IM 0.3 mg x2 (R/L) with NAC N=42
Age (years)					
Mean (SD)	43 (11)	43 (10)	42 (10)	42 (10)	43 (11)
Median (min, max)	43 (24, 63)	43 (28, 63)	42 (24, 63)	43 (24, 63)	44 (24, 63)
Sex, n (%)					
Female	24 (56)	24 (60)	24 (59)	24 (57)	23 (55)
Male	19 (44)	16 (40)	17 (42)	18 (43)	19 (45)
Race, n (%)					
American Indian or Alaska Native	3 (7)	2 (5)	3 (7)	3 (7)	3 (7)
Asian	6 (14)	5 (13)	5 (12)	6 (14)	6 (14)
Black or African American	18 (42)	18 (45)	18 (44)	18 (43)	18 (43)
White	16 (37)	15 (38)	15 (37)	15 (36)	15 (36)
Ethnicity, n (%)					
Hispanic or Latino	6 (14)	5 (13)	6 (15)	6 (14)	6 (14)
Not Hispanic or Latino	37 (86)	35 (88)	35 (85)	36 (86)	36 (86)
Weight (kg)					
Mean (SD)	77 (15)	77 (15)	77 (16)	77 (16)	77 (15)
Median (min, max)	77 (52, 108)	77 (52, 108)	80 (52, 108)	77 (52, 108)	78 (52, 108)
Height (cm)					
Mean (SD)	169 (9)	169 (9)	169 (9)	169 (9)	169 (9)
Median (min, max)	168 (147, 188)	168 (147, 188)	168 (147, 188)	168 (147, 188)	169 (147, 188)

Source: OCS Analysis Studio, Custom Table Tool.
Abbreviations: NAC, nasal allergen challenge; IM, intramuscular Adrenalin epinephrine; N, number of subjects per treatment arm.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No concomitant medications were permitted during the trial, with the exception of hormonal contraceptives or medications necessary to manage chronic conditions that could not have been discontinued in the opinion of the principal investigator and were approved by the Medical Monitor as unlikely to have resulted in an impact on PK and safety. Only two subjects used concomitant medications during the trial (hydrocortisone ointment for skin irritation).

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

7. Clinical Pharmacology

7.1. Executive Summary

ARS Pharmaceuticals developed an epinephrine nasal spray (ARS-1) to seek approval for the emergency treatment of allergic reactions (Type I) including anaphylaxis in adult and pediatric patients who weigh 30 kg or greater. The proposed dosing regimen is one dose (2 mg) into one nostril. In the absence of clinical improvement or (b) (4) after initial treatment, a second dose of ARS-1 may be administered with a new nasal spray in the same nostril approximately (b) (4) minutes after the first dose.

In this NDA resubmission, the Applicant submitted a new clinical pharmacology trial, EPI 18, to evaluate the systemic exposure of epinephrine following two doses of ARS-1 under NAC-induced rhinitis conditions compared to two doses of IM epinephrine injection (needle and syringe product, Adrenalin, NDA 204200). The purpose of this trial was to address the Complete Response clinical/clinical pharmacology deficiency from the original NDA. The submitted data for EPI 16, the NAC trial, raised concern regarding the durability of the drug's effect under NAC-induced rhinitis conditions and the strength of PK/PD for patients who may require two doses, consistent with proposed conditions of use. In addition, since the initial dose of ARS-1 administered under acute rhinitis conditions may impact the PK/PD profile of a subsequent dose administered in the same nostril, due to local pharmacologic effects, it was not clear whether there were significant differences in PK/PD following administration of the second dose in the same or alternate nostril. To address this concern, a two-dose trial in subjects with NAC-induced rhinitis that compares the PK/PD findings of two doses of ARS-1 administered in the same and alternate nostril to two doses of a listed epinephrine injection product was required.

In addition, new PK and PD data from 5 additional pediatric subjects who weigh 30 kg or greater and received a single dose of ARS-1 (2 mg) was submitted under IND 139091 on January 24, 2024. The PK/PD data from these 5 additional pediatric subjects was not included in this review since, as concluded from the original review, the PK/PD results from the original 16 pediatric subjects who weighed 30 kg or greater and received a single dose of ARS-1 (2 mg) were acceptable to support the extrapolation of efficacy from adults. Of note, the safety data from the 5 new subjects were reviewed in the original NDA review.

The key clinical pharmacology review question for EPI 18 focuses on the PK and PD comparison between two doses of ARS-1 administered in the same or alternate nostril 10 minutes apart and two doses of Adrenalin with or without NAC-induced rhinitis administered 10 minutes apart. Overall, EPI 18 addresses the clinical/clinical pharmacology deficiencies outlined in the CR Letter. EPI 18 demonstrated sustained PK and PD profiles with two doses of ARS-1 administered

in the same nostril 10 minutes apart after NAC when compared to two doses of epinephrine injection (Adrenalin).

7.1.1. Recommendation

The Office of Clinical Pharmacology has reviewed the information contained in the resubmission of NDA 214697 (EPI 18) and concluded that plasma epinephrine concentrations following two doses of ARS-1 administered in the same nostril 10 minutes apart are higher than or comparable to two doses of IM epinephrine (Adrenalin) administered 10 minutes apart with and without NAC within 60 minutes post-dose. In addition, a similar trend of PD (SBP and PR) comparison results was also observed. Therefore, a scientific bridge has been established between ARS-1 administered under the NAC-induced rhinitis state and the listed product, Adrenalin, such that the Applicant can rely on the Agency's finding of effectiveness of two doses of Adrenalin.

Based on the results of EPI 18, ARS-1 will be labeled to be given in the same nostril if a second dose is required. If a patient accidentally administers the second dose of ARS-1 in the alternate nostril, the risk of lack of efficacy is low given that the NAC-induced rhinitis state is a worst-case scenario model and, the PK of two doses given in the alternate nostril in the non-congested state (i.e., without NAC) maintained sufficient PK comparable to epinephrine injection. Therefore, in real-world settings, the PK/PD following two doses of ARS-1 in the alternate nostril is likely somewhere in between normal nasal conditions and that of the NAC-induced rhinitis scenario. The PD of two doses of ARS-1 tracked with the PK curves, being higher in those given in the same nostril when compared to alternate nostrils.

From a safety perspective, EPI 18 also demonstrated that the overall epinephrine systemic exposure within 60 minutes following two doses of ARS-1 administered in the same nostril with NAC was similar to that of two doses of ARS-1 into alternate nostrils under normal nasal conditions. Since the overall epinephrine systemic exposure within 60 minutes between two doses of ARS-1 into the same or alternate nostril were comparable to two doses of EpiPen under normal nasal conditions, as demonstrated by EPI 15 (refer to the original NDA review dated September 19, 2023), a scientific bridge has been established between ARS-1 administered under the NAC-induced rhinitis state and the listed product, EpiPen, such that the Applicant can rely on the Agency's findings of safety of two doses of EpiPen.

Overall, the Clinical Pharmacology Review Team supports the approval of ARS-1 in the emergency treatment of allergic reaction (Type I) including anaphylaxis in adult and pediatric patients who weigh 30 kg or greater.

7.2. Summary of Clinical Pharmacology Assessment

7.2.1. Pharmacology and Clinical Pharmacokinetics

General Dosing

The Applicant proposes ARS-1 as a single nasal administration into one nostril for emergency treatment of allergic reactions (Type I), including anaphylaxis, in adults and pediatric patients who weigh 30 kg or greater. In the absence of clinical improvement or (b) (4) (b) (4) after the initial treatment, a second dose of ARS-1 may be administered with a new nasal spray in the same nostril approximately (b) (4) minutes after the first dose.

The efficacy of the proposed dosing regimen is supported by establishment of a bridge to the listed epinephrine injection products Adrenalin (NDA 204200) and EpiPen (NDA 019430) via PK and PD comparisons in healthy adults and pediatric subjects who weigh 30 kg or greater. This resubmission review discusses the results of EPI 18. Other studies were reviewed with the original NDA submission (See Multidisciplinary Review dated September 19, 2023 for details). Safety is reviewed in Section 8.2.

The Applicant proposed in their labeling that in the absence of clinical improvement or if symptoms return after one dose of ARS-1, a second dose of ARS-1 may be administered with a new device in the same nostril approximately (b) (4) minutes after the first dose. The proposed dosing strategy of administering the second dose of ARS-1 in the same nostril is supported by the results of EPI 18 which demonstrated higher or comparable PK and PD profiles between two doses of ARS-1 in the same nostril in subjects with NAC-induced rhinitis and two doses of Adrenalin injection in subjects with and without NAC-induced rhinitis. However, as some patients may have symptoms prior to (b) (4) minutes post first dose, we recommend a shorter 5-minute interval between the first and second dosing in the labeling to allow flexibility for the second dosing and to ensure that patients do not delay treatment. Refer to Section 11. A shorter interval (5 minutes) than what was studied in EPI 18 is less likely to affect the magnitude of C_{max} and AUC significantly compared to a longer interval (10 minutes) but may result in an earlier T_{max}, as ARS-1 following nasal administration demonstrated a slow absorption with a T_{max} of single-dose ARS-1 around 30 minutes.

Therapeutic Individualization

No dose adjustment was proposed for renal or hepatic impairment, elderly, or various body weights in adults.

Pediatric subjects weighing 30 kg or greater who received ARS-1 (2 mg) demonstrated similar epinephrine exposure to healthy adults who received the same dose.

See original NDA review dated September 19, 2023 for details.

Outstanding Issues

None

7.3. Comprehensive Clinical Pharmacology Review

7.3.1. General Pharmacology and Pharmacokinetic Characteristics

See original NDA review dated September 19, 2023 regarding PK and PD parameters following ARS-1 in healthy adults (one and two doses; EPI 15), adults with NAC-induced rhinitis (one dose; EPI 16), impact of self-administration in healthy adults (one dose; EPI 17) and pediatric subjects who weigh 30 kg or greater (one dose; EPI 10).

7.3.2. Clinical Pharmacology Questions

How was epinephrine plasma concentration data handled during the review?

All plasma concentrations of epinephrine time profiles in this review are presented with geometric mean values to reduce the influence of extreme outliers. The plasma concentrations that were below limit of quantification (BLQ) at predose and post-dose were imputed as one-half of the lower limit of quantification (LLOQ/2=5.5 pg/mL for EPI 18).

The post-dose epinephrine concentrations were not adjusted by baseline values, as the mean baseline epinephrine plasma concentrations were less than 10 percent of the mean C_{max} in most subjects, and baseline uncorrected values are expected to be more clinically relevant. See Section 15.3 for details regarding epinephrine baseline concentrations.

Did the PK and PD following two doses of ARS-1 administered 10 minutes apart in adults with NAC-induced rhinitis show improved durability during the first 60 minutes post-dose?

In the original review dated September 19, 2023, results from EPI 16 showed that the PK profile of one dose of ARS-1 under NAC-induced rhinitis conditions demonstrated a relatively more rapid absorption phase during the first 10 minutes followed by a relatively less sustained phase in which epinephrine concentration became lower than that of single-dose Adrenalin around 20 minutes. The PR response (change from baseline) was initially higher than that of Adrenalin within 5 minutes post-dose but became lower afterwards. The less sustained epinephrine plasma concentrations and lower PR response raised concerns regarding durability of effect in patients with allergen-induced acute rhinitis, as similar nasal conditions can occur in patients with anaphylaxis.

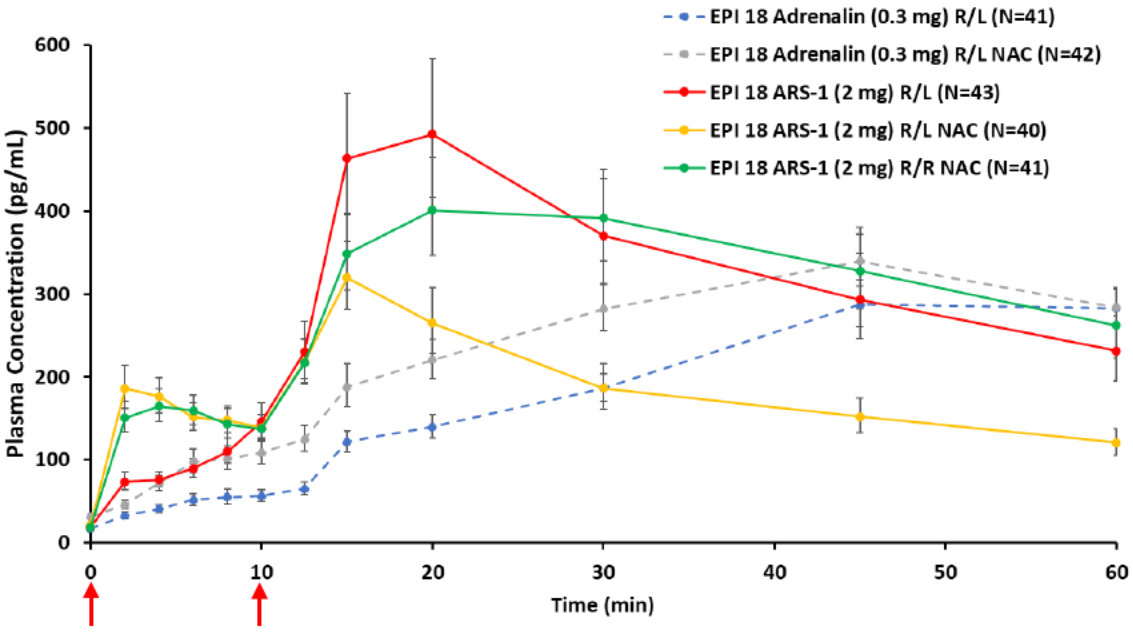
As approximately 10 percent of patients require a second dose of epinephrine to treat anaphylaxis, there remained uncertainty regarding the PK and PD profiles following a second dose of ARS-1 in patients with allergen-induced acute rhinitis, as there was no data available in

the initial submission. EPI 18, included in the resubmission, provided PK and PD data following two doses of ARS-1 in patients with NAC-induced rhinitis administered in the same or alternate nostril in comparison to two doses of epinephrine injection product (Adrenalin) to help address this uncertainty.

PK Comparison Results for EPI 18

In EPI 18, within 60 minutes after the first dose, the geometric mean epinephrine plasma concentration-time profile of two doses of ARS-1 administered 10 minutes apart in the same nostril under NAC-induced rhinitis conditions was higher than that of two IM doses of Adrenalin (0.3 mg) administered 10 minutes apart, with and without NAC, up to 40 minutes post-dose. After 40 minutes, the epinephrine profiles of ARS-1 and Adrenalin were comparable. The geometric mean epinephrine concentration following two doses of ARS-1 given in the alternate nostril in adults with NAC-induced rhinitis were comparable to higher than two doses of Adrenalin within 25 to 30 minutes post-dose, but fell lower than Adrenalin afterwards. The PK comparison results are shown in Figure 2 and Table 4.

Figure 2. Epinephrine Geometric Mean (CV%) Plasma Concentration-Time Profile (60 Minutes After First Dose) for EPI 18



Source: Reviewer's analysis based on adpc.xpt dataset.
Red arrows indicate the time of dose administration.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: CV, coefficient of variation; L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right.

Table 4. Bioequivalence Assessment for PK Parameters in EPI 18

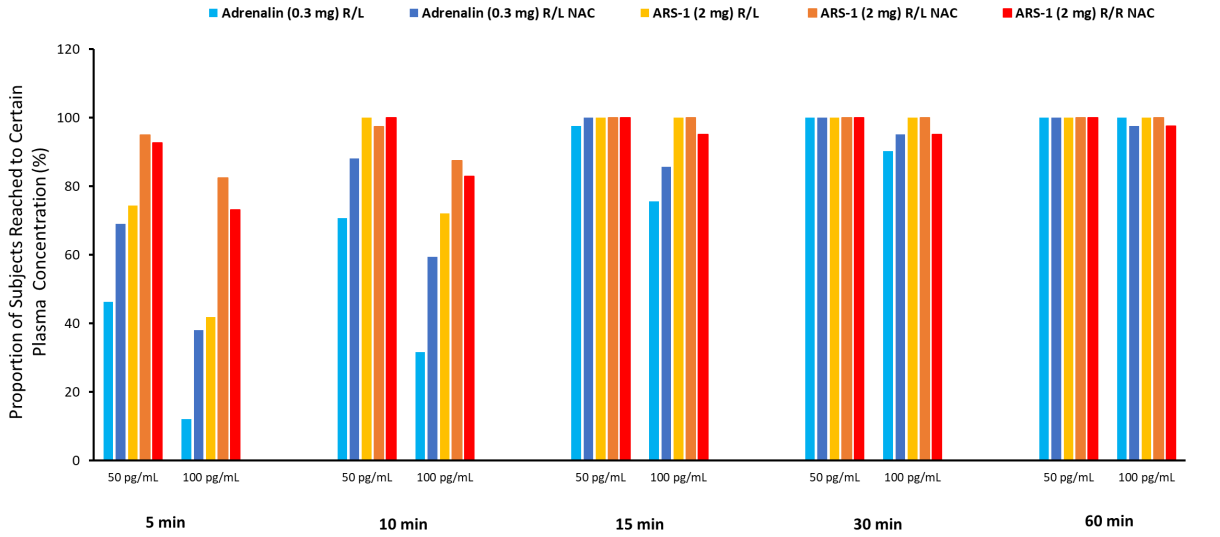
	Geometric Mean Ratio (Test vs. Reference) % (90% CI)			
Parameter	**Test: Two Doses ARS-1 (2 mg) (R/L) with NAC vs. Reference: Two Doses Adrenalin (0.3 mg) (R/L) with NAC**	**Test: Two Doses ARS-1 (2 mg) (R/R) with NAC vs. Reference: Two Doses Adrenalin (0.3 mg) (R/L) with NAC**	**Test: Two Doses ARS-1 (2 mg) (R/L) without NAC vs. Reference: Two Doses Adrenalin (0.3 mg) (R/L) without NAC**	**Test: Two Doses ARS-1 (2 mg) (R/R) with NAC vs. Reference: Two Doses ARS-1 (2 mg) (R/L) without NAC**
C_{max}	101.74 (80.44, 128.69)	142.28 (112.68, 179.67)	191.87 (152.19, 241.91)	90.15 (71.50, 113.65)
$AUC_{0\text{-}10\ min}$	181.93 (150.06, 220.57)	174.33 (143.99, 211.05)	205.81 (170.24, 248.81)	151.73 (125.51, 183.44)
$AUC_{0\text{-}20\ min}$	167.83 (137.30, 205.15)	185.49 (151.97, 226.39)	332.47 (272.78, 405.21)	94.03 (77.15, 114.60)
$AUC_{0\text{-}30\ min}$	132.68 (107.60, 163.60)	180.26 (146.41, 221.94)	303.42 (246.80, 373.01)	95.57 (77.74, 117.50)
$AUC_{0\text{-}60\ min}$	78.98 (63.44, 98.33)	133.70 (107.56, 166.17)	168.75 (135.97, 209.43)	102.31 (82.44, 126.97)

Source: Reviewer's analysis based on adpc.xpt dataset.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: AUC, area under curve; CI, confidence interval; Cmax, maximum concentration; CV, coefficient of variation; L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; PK, pharmacokinetic; R, right.

The geometric mean epinephrine systemic exposure within 60 minutes following two doses of ARS-1 administered into the same nostril with NAC was overall similar to that of two nasal doses of ARS-1 administered into the alternate nostril under normal nasal conditions (Figure 2 and Table 4).

The proportion of subjects reaching ≥50 and ≥100 pg/mL also showed that more subjects following two doses of ARS-1 compared to Adrenalin achieved these concentrations 10 minutes after the first dose (Figure 3).

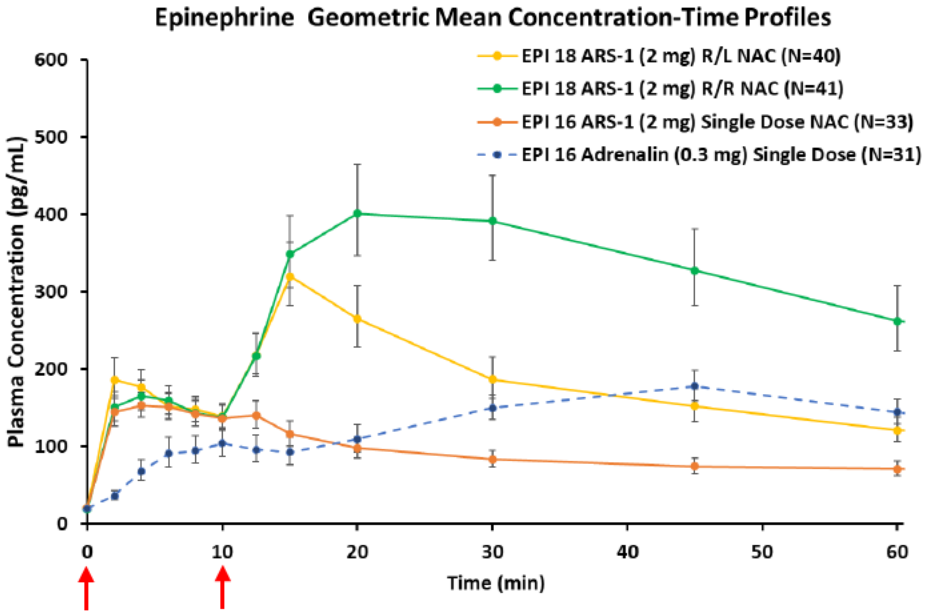
Figure 3. Proportion of Subjects With Plasma Epinephrine Concentrations ≥50 or ≥100 pg/mL Over Time in First 60 Minutes After First Dose Following Two Doses of ARS-1 or Adrenalin With or Without NAC in EPI 18



Source: Reviewer's analysis based on adpc.xpt dataset.
Note: Doses were administered at time 0 and 10 minutes.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: IM, intramuscular (Adrenalin); L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right.

A cross-study comparison between one dose of ARS-1 with NAC or one dose of Adrenalin (EPI 16) and two doses of ARS-1 administered into the same or alternate nostril with NAC (EPI 18) showed that the second dose of ARS-1 resulted in a much higher second epinephrine concentration peak accompanied by robust PK sustainability after 10 minutes following the first dose. In addition, a more sustained PK profile was achieved with two doses of ARS-1 administered in the same nostril with NAC compared to two doses administered in alternate nostrils, as shown in Figure 2 and Figure 4.

Figure 4. Cross-Study Comparison of One Dose of ARS-1 With NAC (EPI 16) and Two Doses ARS-1 With NAC (EPI 18)

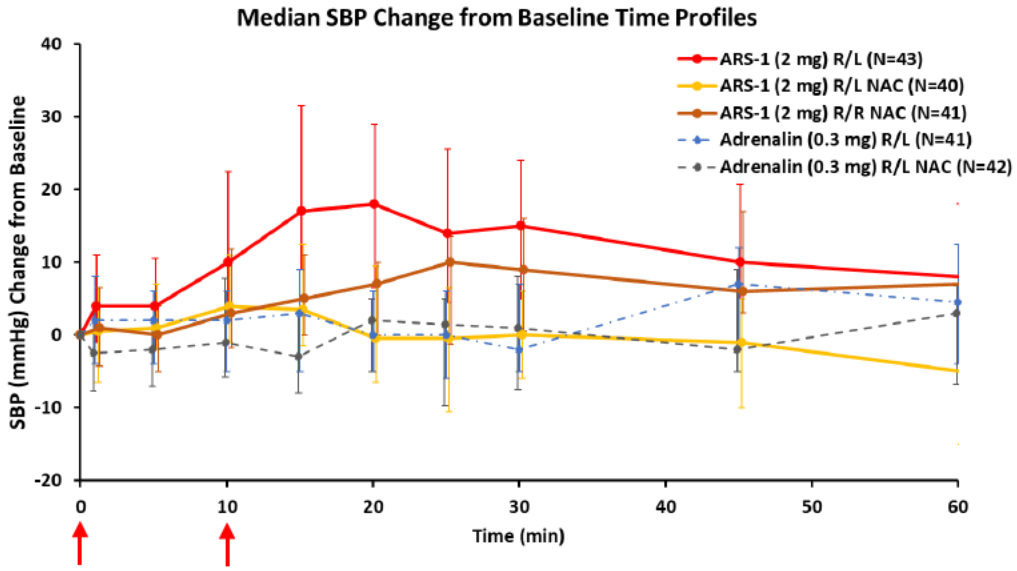


Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18 and EPI 16.
Red arrows indicated the administration time of the two doses in EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right; SD, single dose.

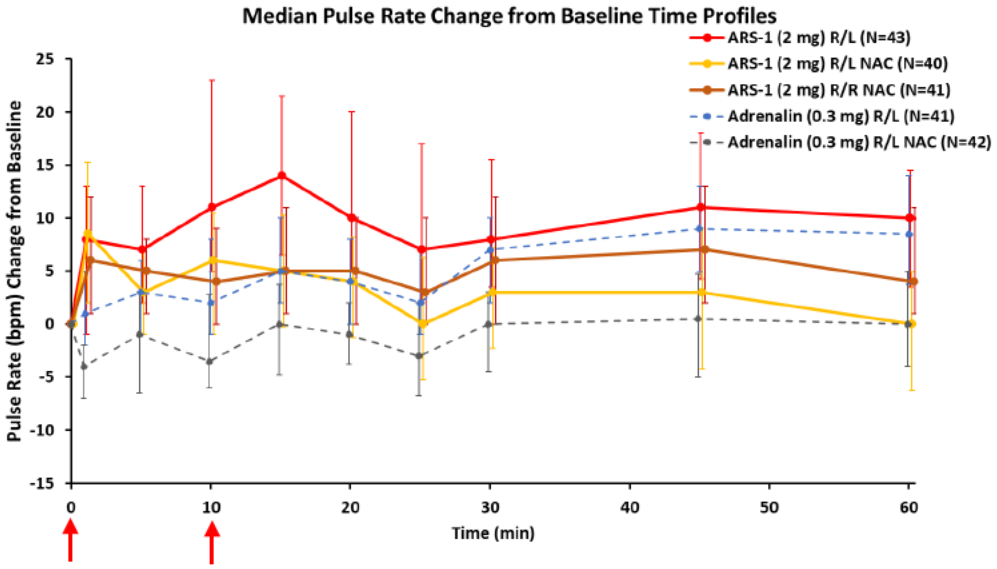
PD Comparison Results for EPI 18

The median SBP and PR responses (i.e., change from baseline; post-NAC baseline were used to assess change for NAC treatment periods) for two doses of ARS-1 into the same nostril with NAC were higher than or comparable to those of Adrenalin with or without NAC during the first 60 minutes after the first dose, as shown in Figure 5. By comparing the SBP and PR response profiles following two doses of Adrenalin IM injection with and without NAC, it appears that NAC slightly increased SBP and PR baseline levels (i.e., higher post-NAC baseline value compared to pre-NAC baseline value), which may explain a relatively lower response for Adrenalin with NAC compared to without NAC when a post-NAC baseline was used (see next Clinical Pharmacology Question – "How did NAC affect the plasma epinephrine concentrations and PD responses?" for more details). In addition, if using a pre-NAC baseline to evaluate the change in all NAC treatment periods, the PD (SBP and PR) responses of two doses of ARS-1 into the same nostril with NAC were generally higher than those of two doses of Adrenalin with and without NAC. See Section 15.3 for details.

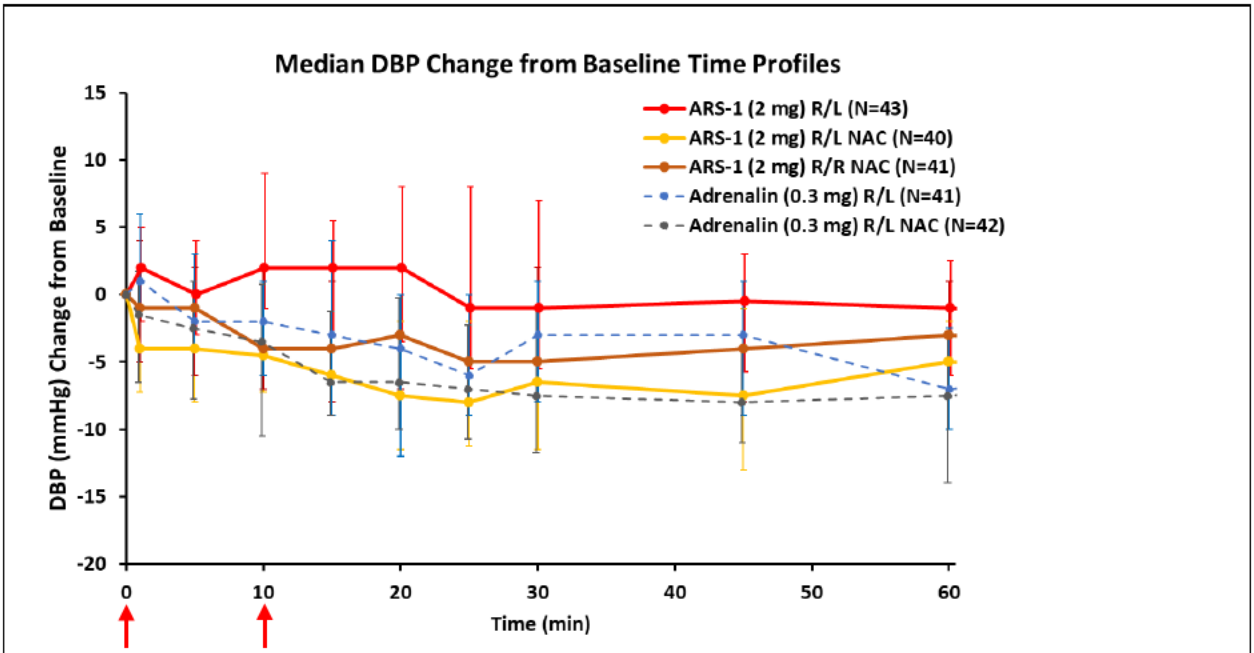
Figure 5. Median PD (SBP, PR and DBP) Change From Baseline Following Two Doses of ARS-1 or Adrenalin With or Without NAC (Using Average Post-NAC Baseline to Calculate the Change in NAC Treatment Periods) in EPI 18



A. Median Change of SBP From Baseline



B. Median Change of PR From Baseline



C. Median Change of DBP From Baseline

Source: Reviewer's analysis based on adxd.xpt dataset.
Error bar represents 25% and 75% percentile of PD values.
Red arrows indicate the timing of dosing.
Note: Average Post-NAC PD baseline values for each individual was calculated by taking the mean of -10 and -5 min values.
Abbreviations: DBP, diastolic blood pressure; IM, Adrenalin (intramuscular, needle-syringe); L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; PD, pharmacodynamic; PR, pulse rate; R, right; SBP, systolic blood pressure; SD, single dose.

When using a post-NAC baseline, the median SBP response for two doses of ARS-1 into alternate nostrils with NAC were higher or comparable to that of two doses of Adrenalin with NAC within the first 65 minutes, except for the last time point (i.e., 60 minutes), while the median PR responses for two doses of ARS-1 administered into alternate nostrils with NAC were generally comparable or higher than those of two doses of Adrenalin administered with NAC (Figure 5). When using a pre-NAC baseline, the median SBP and PR responses for two doses of ARS-1 administered into alternate nostrils with NAC were higher or comparable to those of two-doses of Adrenalin with NAC during the first 40 minutes, and then became slightly lower afterwards. See Section 15.3.1.1 for more details.

The median diastolic blood pressure (DBP) response for two doses of ARS-1 administered into the same or alternate nostril with NAC was similar to that of two doses of Adrenalin with or without NAC, which showed a trend of decline from baseline when using a post-NAC baseline (Figure 5). When using a pre-NAC baseline, the median DBP became relatively consistent at around pre-NAC baseline level for two doses of ARS-1 administered into the same or alternate nostrils with NAC. Their median DBP responses were higher than those of two doses of

Adrenalin with or without NAC and similar to those of two doses of ARS-1 without NAC. See Section 15.3.1.1 for more details.

The summary of maximum SBP and PR responses (using post-NAC baseline to calculate change in NAC treatment periods) for each treatment is shown in Table 5. The time to reach maximum PD effect was earlier with two doses of ARS-1 into the same nostril with NAC compared to two doses of Adrenalin with NAC. A similar trend was observed when a pre-NAC baseline was used. See Section 15.3 for details.

Table 5. Maximum SBP and PR Response Following Two Doses of ARS-1 or Adrenalin With or Without NAC (Using Average Post-NAC Baseline to Calculate the Change in NAC Treatment Periods) in EPI 18

Parameter	Two Doses of Adrenalin (0.3 mg) R/L Without NAC N=41	Two Doses of ARS-1 (2 mg) R/L Without NAC N=43	Two Doses of Adrenalin (0.3 mg) R/L With NAC N=42	Two Doses of ARS-1 (2 mg) R/L With NAC N=40	Two Doses of ARS-1 (2 mg) R/R With NAC N=41
Maximum SBP response over 60 minutes					
Mean (SD) (mmHg)	15.20 (7.98)	29.40 (15.73)	12.05 (7.61)	14.70 (10.18)	18.90 (11.23)
Median (range) (mmHg)	16 (0, 39)	28 (2, 71)	13.5 (0, 31)	13.50 (0, 35)	19 (0, 46)
Median Tmax (range) (min)	45 (0, 240)	20 (1, 120)	30 (0, 240)	15 (0, 180)	25 (0, 120)
Maximum PR response over 60 minutes					
Mean (SD) (BPM)	14.56 (9.06)	23.88 (11.56)	8.52 (6.19)	15.8 (9.29)	17 (10.24)
Median (range) (BPM)	13 (2, 53)	23 (6, 57)	8 (0, 27)	15.5 (0, 36)	16 (0, 47)
Median Tmax (range) (min)	45 (1, 240)	15 (1, 180)	22.5 (0, 240)	7.5 (0, 240)	15 (0, 240)

Source: Reviewer's analysis based on adxd.xpt dataset.
Average Post-NAC PD baseline values for each individual was calculated by taking the mean of -10 and -5 min values.
Abbreviations: BPM, beats per minute; DBP, diastolic blood pressure; L, left; NAC, nasal allergen challenge; PR, pulse rate; R, right; SBP, systolic blood pressure; T_{max}, peak effect time.

Conclusion

- The geometric mean epinephrine plasma concentration-time profile of two doses of ARS-1 administered 10 minutes apart into the same nostril in subjects with NAC-induced rhinitis was higher than that of two IM doses of Adrenalin (0.3 mg), administered 10 minutes apart, with and without NAC up to 40 minutes and became similar afterwards.
- The geometric mean epinephrine plasma concentration following two doses of ARS-1 given in alternate nostrils in adults with NAC-induced rhinitis was comparable to higher than two doses of Adrenalin within 25 to 30 minutes after the first dose, but it fell lower than Adrenalin afterwards.
- A cross-study comparison demonstrated robust epinephrine PK sustainability following two nasal doses of ARS-1 administered 10 minutes apart into the same nostril or

alternate nostrils in adults with NAC-induced rhinitis compared to a single dose of ARS-1 in adults with NAC-induced rhinitis and a single dose of Adrenalin in healthy adults.

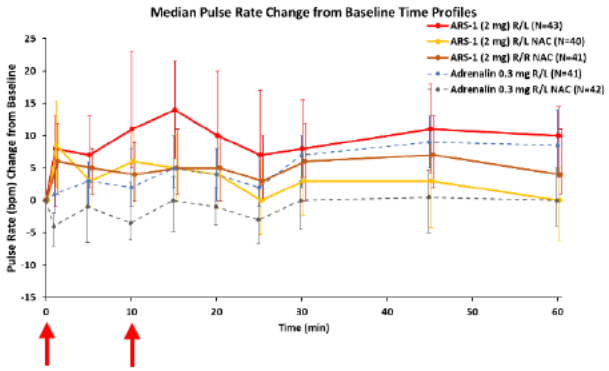
- The median SBP and PR responses (i.e., change from baseline, post-NAC baseline were used to assess change for NAC treatment periods) of two doses of ARS-1 into the same or alternate nostril with NAC were generally higher or comparable to those of two doses of Adrenalin with NAC during the first 60 minutes after the first dose, except the lower SBP following ARS-1 into the alternate nostril at 60 minutes after the first dose.

How did NAC affect the plasma epinephrine concentrations and PD responses?

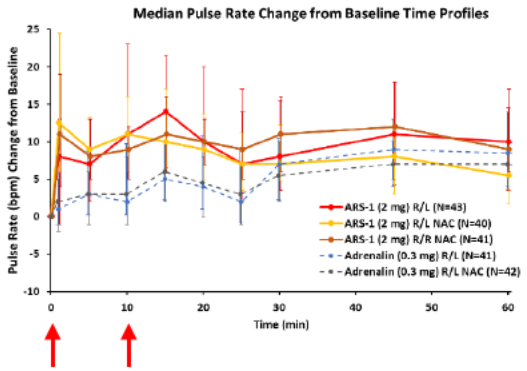
In the NAC treatment periods of EPI 18, pre-dose plasma epinephrine concentrations were assessed prior to NAC administration (i.e., −45 and −30 minutes before epinephrine administration) and with NAC administration (i.e., −10 and −5 minutes before epinephrine administration). A slight increase of mean endogenous epinephrine concentrations after NAC (around 2 to 10 pg/mL) was observed for both ARS-1 and Adrenalin treatment periods. See Section 15.3 for details. The slight increase in endogenous epinephrine concentration did not impact the comparison of PK profiles using the baseline-uncorrected values, as the baseline remained lower than 10 percent of C_{max} in most subjects.

An increase in median SBP (2 to 3.5 mmHg) and PR (4 to 6.5 beats per minute) was observed after NAC. Therefore, the different baseline (i.e., by using pre-NAC or post-NAC values) of SBP and PR values will change the overall mean/median post-dose PD response values calculated as change from baseline. This difference was especially noted for PR response. A lower PR response was observed for two doses of IM Adrenalin with NAC when using post-NAC baseline when compared to two doses of IM Adrenalin without NAC (Figure 6). However, the difference in PR response between Adrenalin with and without NAC was diminished when a pre-NAC baseline was used (Figure 6). A similar trend of NAC effect on comparison of PR responses between two doses of ARS-1 with and without NAC was also observed (Figure 6).

Figure 6. Median PR Response Using Post-NAC vs. Pre-NAC Baseline for NAC Treatment Periods in EPI 18



A. Median PR Change from Baseline (Use Post-NAC Baseline for NAC treatment periods)



B. Median PR Change from Baseline (Use Pre-NAC Baseline for NAC treatment periods)

Source: Reviewer's analysis based on adxd.xpt dataset.
Error bar represents 25% and 75% percentile of PD values.
Red arrows indicate the timing of dosing.
Note: Average Post-NAC PD baseline values for each individual was calculated by taking the mean of -10 and -5 min values.
Abbreviations: L, left; NAC, nasal allergen challenge; PR, pulse rate; R, right.

Regardless of what baseline was used, two doses of ARS-1 into the same nostril with NAC produced greater SBP and PR responses than those of two doses of Adrenalin with NAC. See Section 15.3 for details.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No food-drug interactions are expected with the proposed product, as ARS-1 is administered nasally.

As nasal epinephrine may result in nasal mucosa change, an increase in the absorption of other nasal products is likely when co-administered with ARS-1. The effect of altered nasal mucosa on the increase of epinephrine absorption (i.e., carryover effect) in the same nostril was observed in some early clinical PK studies in ARS-1 program. This carryover effect appears to peak around 2 days post-dose. This effect was minimized after spacing two doses of ARS-1 by 12 days in the same nostril. See Multidisciplinary Review dated September 19, 2023, regarding the carryover effect assessment. Labeling will reflect the potential increase in risk of adverse reactions associated with use of nasal products, including use of ARS-1, due to increased systemic absorption when used (b) (4) with ARS-1 within 2 weeks.

8. Clinical and Evaluation

8.1.1. Assessment of Efficacy for EPI 18

Refer to section 9 of the original NDA review for a detailed discussion of efficacy across EPI 15, EPI 16, EPI 17, and EPI 10. Overall, the PK/PD results from the adult studies, EPI 15 and EPI 17, and the pediatric trial in children <18 years of age and ≥30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products in healthy adults to demonstrate substantial evidence of effectiveness. The PK/PD results in adults ≥18 years of age with allergic rhinitis (EPI 16) under NAC conditions demonstrated adequate PK and PD responses in the first 20 minutes post-dose; however, the lack of sustainability of epinephrine concentrations for ARS-1 after 20 minutes when compared to Adrenalin raised uncertainty regarding the durability of effect in patients with acute allergen-induced rhinitis, and repeat dosing was not studied under NAC conditions to demonstrate durability of effect in patients who may require a second dose of ARS-1, consistent with proposed labeling. The results from EPI 18 included with this resubmission addressed this uncertainty, demonstrating that PK and PD following a second dose of ARS-1, administered 10 min after the first dose, was comparable to two doses of epinephrine injection given 10 minutes apart under NAC-induced rhinitis. Therefore, with the addition of EPI 18, the application adequately demonstrates substantial evidence of effectiveness for ARS-1 in the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and pediatric patients who weigh ≥30 kg.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of ARS-1 primarily relies on the determination of safety of approved epinephrine injection products, as systemic epinephrine exposure with ARS-1 is comparable to approved products. Systemic adverse reactions reported for epinephrine injection products from observational trials and case reports include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.[2] Local adverse events (AEs) from nasal administration rely only on the data presented from the ARS-1 development program.

The safety review for the original NDA review consisted of pooling AE data from the adult pivotal trials: EPI 15, EPI 16, and EPI 17. This safety review assesses the safety profile of the new

[2] See the EpiPen label, available at: https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=7560c201-9246-487c-a13b-6295db04274a&type=pdf.

trial, EPI 18, and the safety pool from the original NDA review, with the addition of the new trial EPI 18. In the original NDA review, AEs for one and two doses of ARS-1 were pooled, as the safety profiles for one and two doses were similar. This safety review evaluates one and two doses separately, as dose-dependent AEs were noted with the addition of EPI 18, which assessed two doses. The safety profile for one dose of ARS-1 is unchanged from the original review, as no new data was submitted for one dose of ARS-1. Safety of ARS-1 in pediatric subjects ≥30 kg relies on EPI 10, the pediatric trial, which was reviewed in the original NDA review. Pediatric safety is not discussed as no new data were submitted with this resubmission.

The approach to the safety analysis is the same as the original NDA review. N is reported as the number of subjects (per each treatment received) and not number of exposures.

8.2.2. Review of the Safety Database

Overall Exposure

Of the four pivotal adult trials (EPI 15, EPI 16, EPI 17, and EPI 18), 180 subjects with 175 unique subjects received at least one dose of ARS-1. As the trials employed a crossover design, subjects may have received more than one dose of ARS-1. There were 572 total exposures to ARS-1 (where one exposure = one spray of ARS-1). There were 119 subjects who received more than one dose (N=38 for two exposures, N=4 for three exposures, N=2 for four exposures, N=30 for five exposures, and N=45 for six exposures). The 119 subjects were derived from assessing how many doses each individual actually received. Review of the data provided by the Applicant shows the same number of overall exposures.

Adequacy of the Safety Database

Overall, the safety database was adequate to inform the local safety of ARS-1. The systemic safety of ARS-1 relies on the known safety profile of epinephrine injection products due to comparable PK.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocols. AEs were captured from signing of informed consent through the end of the trial. Treatment-emergent AEs (TEAEs) were events that were not present at baseline, or if present at baseline, worsened in severity. For the trials, increases in blood pressure or PR were not considered an AE, unless such event required treatment, due to the known mechanism of action of epinephrine. AEs were coded using the MedDRA dictionary Version 16.1 or later. The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. Of note, a

reporting bias towards nasal pain, irritation, and discomfort was noted as these symptoms were solicited, but injection site discomfort was not solicited.

8.2.4. Safety Results

Demographics

The demographics of the entire safety population is highlighted in Table 6. The mean age of the trial participants was approximately 40 years; the population was predominantly male (44 to 71% depending on treatment arm). In terms of race, the largest populations represented were White (37 to 48%) and African American (23 to 42%).

Each individual trial employed a cross-over design resulting in balanced demographics between arms. For the pooled safety population, as each included different treatment arms, there were some differences in demographic characteristics across treatment arms; however, the pooled safety analysis (see Table 7) combined epinephrine injection treatment arms, therefore the imbalances noted in the table below did not directly impact the safety conclusions for the pooled safety analysis.

Table 6. Safety Database Demographics (EPI 15, EPI 16, EPI 17, and EPI 18)

Characteristic	ARS-1 2 mg N=134	Two Doses of ARS-1 2 mg* N=85	Adrenalin 0.3 mg N=134	Adrenalin 0.5 mg N=35	Two Doses of Adrenalin 0.3 mg* N=43	EpiPen 0.3 mg N=55	Two Doses of EpiPen 0.3 mg* N=42
Age (years)							
Mean (SD)	40 (9)	41 (10)	40 (9)	38 (8)	43 (11)	41 (10)	40 (9)
Median (min, max)	40 (20, 54)	39 (24, 63)	40 (20, 54)	38 (20, 52)	43 (24, 63)	43 (22, 54)	39 (25, 54)
Sex, n (%)							
Female	52 (39)	36 (42)	53 (40)	16 (46)	24 (56)	18 (33)	12 (29)
Male	82 (61)	49 (58)	81 (60)	19 (54)	19 (44)	37 (67)	30 (71)
Race, n (%)							
American Indian or Alaska Native	3 (2)	3 (4)	3 (2)	0	3 (7)	0	0
Asian	18 (13)	10 (12)	17 (13)	8 (23)	6 (14)	4 (7)	4 (10)
Black or African American	40 (30)	33 (39)	41 (31)	8 (23)	18 (42)	16 (29)	15 (36)
Native Hawaiian or other Pacific Islander	2 (2)	0	2 (2)	1 (3)	0	0	0
Other	10 (8)	3 (4)	10 (8)	3 (9)	0	3 (6)	3 (7)
White	61 (46)	36 (42)	61 (46)	15 (43)	16 (37)	32 (58)	20 (48)
Ethnicity, n (%)							
Hispanic or Latino	39 (29)	21 (25)	40 (30)	5 (14)	6 (14)	24 (44)	15 (36)
Not Hispanic or Latino	95 (71)	64 (75)	94 (70)	30 (86)	37 (86)	31 (56)	27 (64)

Source: OCS Analysis Studio, Custom Table Tool.
* Each dose was administered 10 minutes apart.
Abbreviations: SD, standard deviation.

Deaths

No deaths were reported across the four adult trials (EPI 15, EPI 16, EPI 17, and EPI 18).

Serious Adverse Events

No SAEs were reported across the four adult trials (EPI 15, EPI 16, EPI 17, and EPI 18).

Dropouts and/or Discontinuations Due to Adverse Effects

In the original NDA submission with pooled trials EPI 15, EPI 16, and EPI 17, three subjects discontinued (two subjects in the epinephrine injection 0.3-mg arm and one subject in the 2-mg ARS-1 arm). Two subjects discontinued due to syncope after administration of IM epinephrine. The one subject who discontinued after ARS-1 withdrew after developing syncope with the initiation of blood sampling that occurred shortly after ARS-1 administration. There were no discontinuations due to AEs in EPI 18.

As noted in the clinical pharmacology review (Section 7), Subject (b) (6) was noted to have discontinued as his pre-dose blood pressure was too high for dosing and, therefore, was discontinued without dosing. From the protocol, increases in blood pressure or heart rate were not considered an AE, unless such event required treatment, due to the known mechanism of action of epinephrine.

Treatment-Emergent Adverse Events and Adverse Reactions

The Common AEs with an incidence ≥2% in any arm for the pooled safety population (EPI 15, EPI 16, EPI 17, and EPI 18), following one and two doses of ARS-1 compared with one and two doses of epinephrine injection, are provided in Table 7.

The safety profile for one dose of ARS-1 is unchanged from the original review, as no new data was submitted for one dose of ARS-1. The safety profile of ARS-1 given as two doses was not highlighted in the original NDA review, as the incidence rate was not different from one dose. However, with the inclusion of the additional 43 subjects who received two doses enrolled in EPI 18, a change in AE incidence rate is seen between one dose and two dose exposure. Common AEs occurring in more than one subject (≥2%) following one or two doses of ARS-1: throat irritation, intranasal paresthesia, headache, nasal discomfort, feeling jittery, paresthesia, fatigue, tremor, rhinorrhea, nasal pruritus, sneezing, abdominal pain, gingival pain, hypoesthesia oral, nasal congestion, dizziness, nausea, and vomiting. Intranasal paresthesia, paresthesia, and fatigue were added based on AEs seen in the pediatric population (see original NDA review).

Following two doses of ARS-1, the incidence of local AEs (throat irritation, rhinorrhea, nasal pruritus, sneezing, gingival pain, hypoesthesia oral, and nasal congestion) increased along with new reports of systemic AEs, such as tremor and feeling jittery. The systemic adverse event profile of two doses (feeling jittery, tremors) have been reported with epinephrine injection.

Despite increase in incidences, AEs following two doses of ARS-1 were mild in severity. Interestingly, the incidence of AEs in the epinephrine injection treatment arms were low, although the incidence was slightly higher in the two-dose epinephrine injection treatment arm. As the Applicant specifically checked for local symptoms during their safety monitoring and not for injection site symptoms, this may have skewed adverse event reporting.

Table 7. Common Adverse Events Occurring ≥2% in Any Treatment Arm for One Dose vs. Two Doses of ARS-1 or Epinephrine Injection, Trial EPI 15, EPI 16, EPI 17, and EPI 18

Body System or Organ Class Preferred Term	ARS-1 2.0 mg N=134 n (%)	Two Doses of ARS-1 2.0 mg* N=85 n (%)	Epinephrine Injection *** 0.3 mg N=189 n (%)	Two Doses of Epinephrine Injection *** 0.3 mg N=85 n (%)
Respiratory, thoracic, and mediastinal disorders				
Throat irritation	2 (2)	16 (19)	0 (0)	5 (6)
Nasal discomfort	13 (10)	11 (13)	0 (0)	4 (5)
Rhinorrhea	4 (3)	6 (7)	0 (0)	0 (0)
Nasal pruritus	0 (0)	3 (4)	0 (0)	1 (1)
Sneezing	0 (0)	3 (4)	0 (0)	0 (0)
Nasal Congestion	0 (0)	2 (2)	0 (0)	0 (0)
Nervous system disorders				
Headache	8 (6)	15 (18)	4 (2)	4 (5)
Tremor	0 (0)	7 (8)	0 (0)	1 (1)
Dizziness	4 (3)	2 (2)	2 (1)	1 (1)
General disorders				
Feeling jittery	1 (1)	9 (11)	0 (0)	5 (6)
Gastrointestinal disorders				
Abdominal pain	1 (1)	3 (4)	0 (0)	0 (0)
Gingival pain	0 (0)	3 (4)	0 (0)	0 (0)
Hypoesthesia oral	0 (0)	3 (4)	0 (0)	0 (0)
Nausea	4 (3)	2 (2)	4 (2)	1 (1)
Vomiting	3 (2)	2 (2)	2 (1)	0 (0)
Injection site pain**	0 (0)	0 (0)	1 (1)	5 (6)

Source: FDA Clinical Reviewer, OCS Studio Analysis
*Two doses were administered 10 minutes apart
**injection site pain includes the PT terms injection site pain and discomfort
***Epinephrine injection includes EpiPen and Adrenalin. Epinephrine injection was administered intramuscularly.

Although EPI 18 on its own does not change the benefit/risk or affect labeling, when reviewing EPI 18, there was an increase in local safety AEs with two doses of ARS-1 when administered without NAC in comparison to two doses with NAC (Table 8). When two doses of ARS-1 were given without NAC, there was an increase in AEs such as throat irritation, nasal discomfort, rhinorrhea, nasal pruritis and sneezing. This may be due to the vasodilatory state caused by the NAC which leads to higher absorption of ARS-1, reducing the amount of ARS-1 solution left in the nasal cavity. Review of AEs for EPI 16 with one dose of ARS-1 under NAC did not show this difference, possibly due to the increased volume of two doses (200 mL) versus one dose (100 mL). Overall, EPI 18 demonstrated that the local AEs were not related to NAC.

Table 8. Summary of Local TEAEs by SOC and PT, Trial EPI 18

System Organ Class Preferred Term	Two Doses of ARS-1 2 mg* (R/L) N=43 n (%)	Two Doses of ARS-1 2 mg* (R/L) with NAC N=40 n (%)	Two Doses of ARS-1 2 mg* (R/R) with NAC N=41 n (%)	Two doses of Adrenalin IM 0.3 mg* (R/L) N=42 n (%)	Two Doses of Adrenalin IM 0.3 mg* (R/L) with NAC N=42 n (%)
Any AE	31 (72)	16 (40)	15 (37)	19 (45)	9 (21)
Respiratory, thoracic and mediastinal disorders	29 (67)	6 (15)	6 (15)	7 (17)	3 (7)
Throat irritation	14 (33)	1 (3)	1 (2)	3 (7)	2 (5)
Nasal discomfort	9 (21)	5 (13)	4 (10)	4 (10)	0 (0)
Rhinorrhea	4 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal pruritus	3 (7)	0 (0)	0 (0)	1 (2)	0 (0)
Nasal congestion	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Sneezing	2 (5)	0 (0)	0 (0)	1 (2)	0 (0)
Dry throat	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Increased upper airway secretion	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Pharyngeal hypoesthesia	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)
Pharyngeal paresthesia	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)

Source: FDA Clinical Reviewer, OCS Studio Analysis
* Each dose administered 10 minutes apart
Abbreviations: AE, adverse event; IM, intramuscular; TEAE, treatment-emergent adverse event; SOC, standard of care; PT, preferred term; NAC, nasal allergen challenge; R, right; L, left.

There continues to be no safety concerns and no notable PD-related (elevated blood pressure or PR) AEs. Nasal examinations were performed for all trials, and local AEs were mild.

There are limited safety data for repeat use, especially for more than two doses. In EPI 18, all but three subjects (n=40) underwent six exposures of ARS-1 (one exposure defined as one dose of ARS-1) over a 6-week period. Review of the AE profile at the 5th and 6th exposure (the last treatment arm, ARS-1 R/R nostril administration), did not show an increase or change in the incidence of AEs compared to previous treatment arms (exposures 1-4) (Table 8). Furthermore, as this product is intended for acute use, frequent and/or long-term use is unlikely.

Laboratory Findings

Routine clinical laboratory values were only obtained at screening/baseline for this trial.

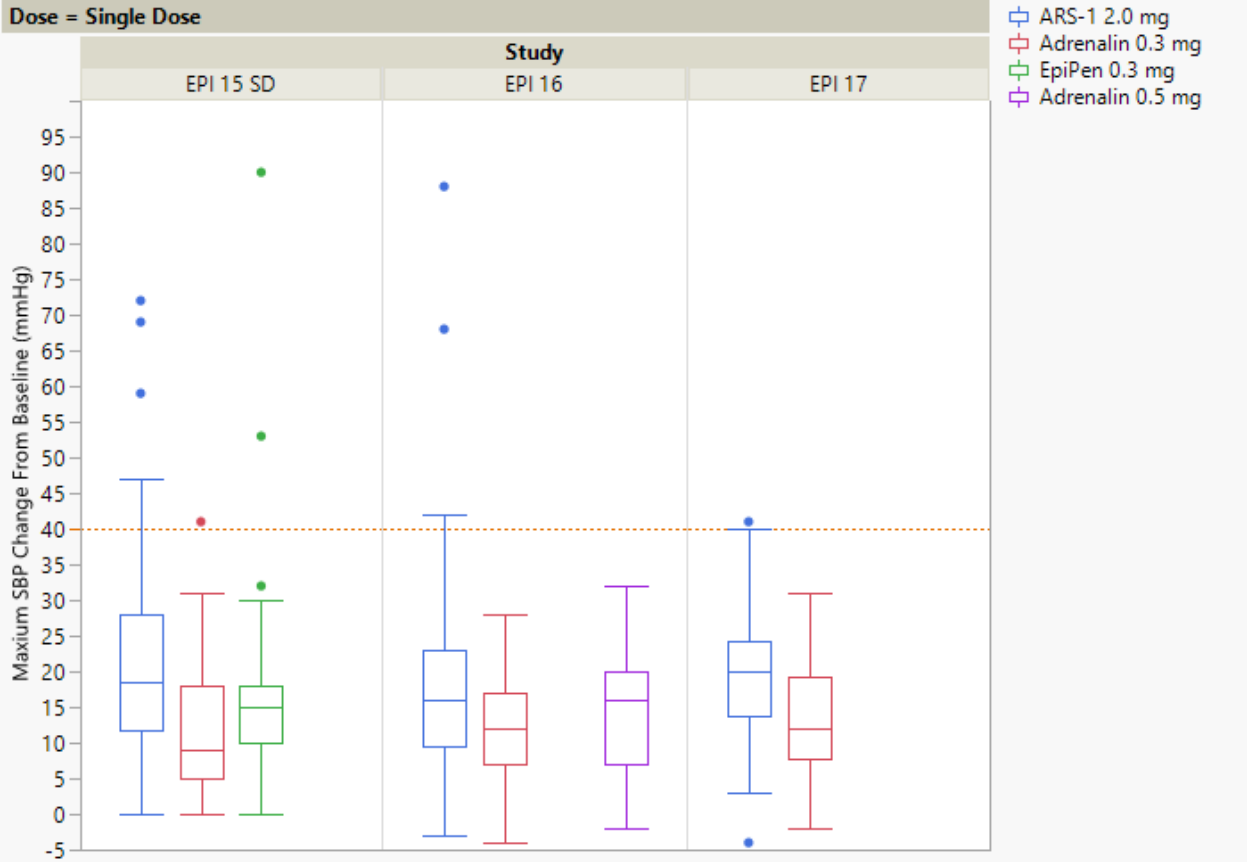
Vital Signs

Given the known mechanism of action of epinephrine, SBP, PR, and DBP were reviewed primarily as an efficacy assessment (Section 8). Although an increase in blood pressure is a desired effect of epinephrine, an extreme rise in SBP may be a safety concern (i.e., hypertensive crisis). From a safety standpoint, "blood pressure increased" and "heart rate increased" were not considered an AE in the ARS-1 program, unless such event required treatment, due to the

known mechanism of action of epinephrine. No AEs were reported for "blood pressure increase" or "heart rate increased." No associated AEs were reported for subjects with maximum SBP ≥40 mmHg change from baseline.

Taking a more granular approach, review of the PD data assessing the distribution of maximum SBP change from baseline in 60 minutes post-dose of ARS-1 in comparison with epinephrine injection was done to assess whether the outlier distribution of maximum SBP change from baseline was different between epinephrine drug products and potentially a safety concern for ARS-1 (Figure 7 and Figure 8).

Figure 7. Distribution of Maximum SBP Change From Baseline in 60 Minutes Post One Dose of ARS-1 in Comparison With One Dose of Adrenalin and EpiPen (EPI 15, EPI 16, and EPI 17)



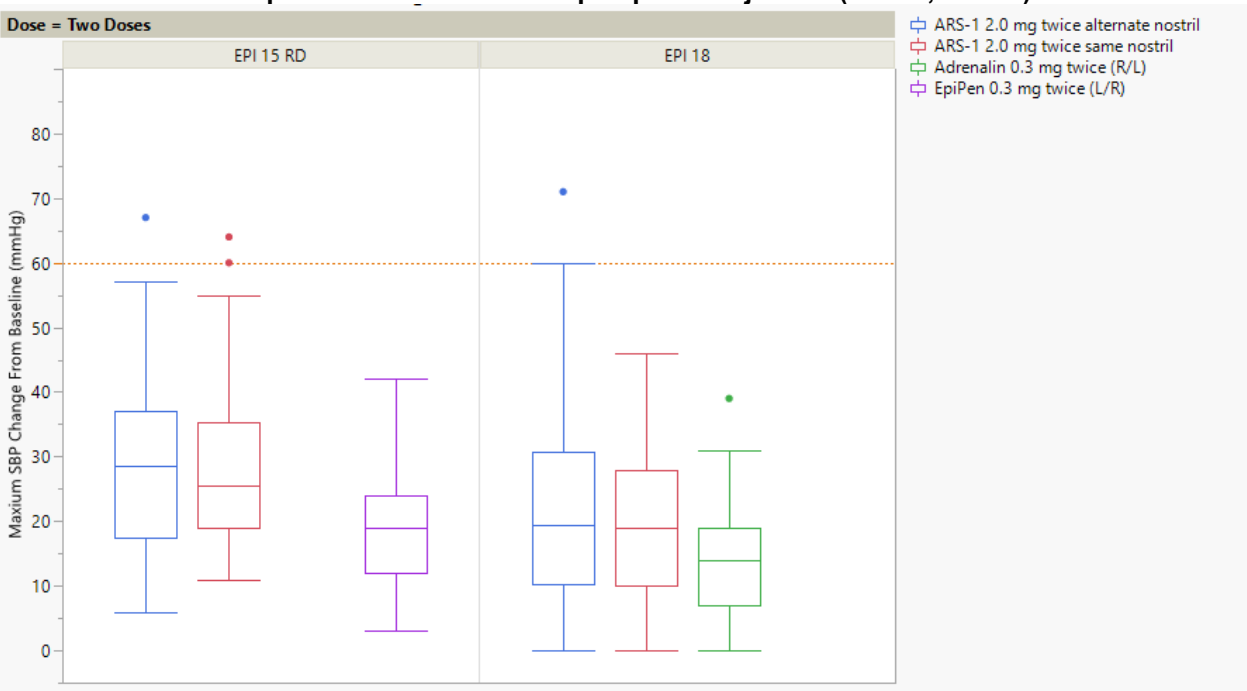
Source: Clinical Pharmacology Reviewer's analysis based on adxd.xpt for EPI 15, 16, and 17.
Abbreviations: SBP, systolic blood pressure; SD, single dose.

Following one dose of ARS-1 administration in Studies EPI 15, EPI 16, and EPI 17, the median value of maximum SBP following ARS-1 was slightly higher than Adrenalin and EpiPen. However, the maximum SBP response values for outliers were comparable between ARS-1 and EpiPen.

Following two doses of ARS-1 administration in EPI 15 and EPI 18, the median value of maximum SBP following ARS-1 was slightly higher than Adrenalin and EpiPen. However, the

maximum SBP values of outliers following two doses of ARS-1 were not numerically higher than the maximum SBP value following one dose of ARS-1.

Figure 8. Distribution of Maximum SBP Change From Baseline to 60 Minutes Post-Dose in Two Doses of ARS-1 Compared to Two Doses of Epinephrine Injection (EPI 15, EPI 18)



Source: Clinical Pharmacology Reviewer's analysis based on adxd.xpt for EPI 15 and EPI 18.
Abbreviations: L, left; RD, repeat dose; R, right; SBP, systolic blood pressure.

As seen in the data above, although the median maximum change in SBP is slightly higher than epinephrine injection for both one and two doses, the outlier data is not higher following ARS-1 when compared to EpiPen and therefore does not increase the risk for ARS-1 of blood pressure AEs compared to epinephrine injection.

See Pharmacodynamic analysis discussed in Section 8 and the original NDA submission review for further details regarding PR and DBP discussion.

Electrocardiograms (ECGs)

ECGs were only obtained at screening/baseline for this trial.

8.2.5. Safety in the Postmarket Setting

See original NDA review.

8.2.6. Integrated Assessment of Safety

The safety review of ARS-1 primarily relies on the determination of systemic safety of epinephrine injection listed products, as ARS-1 epinephrine exposure is comparable to approved epinephrine injection products. Support for local safety of ARS-1 relies on EPI 15, EPI 16, EPI 17, and EPI 18.

In this resubmission, safety data were submitted from the new trial, EPI 18, to provide additional safety support for two doses of ARS-1. The common AEs (≥3%) for one dose of ARS-1 are unchanged with this resubmission and include nasal discomfort (10%), headache (6%), nausea (3%) and dizziness (3%). The safety profile for two doses of ARS-1 is notable for increased incidence of headache (18%) and nasal discomfort (13%). Other local and systemic AEs also increased in incidence compared to one dose (range for all AEs listed below: 0 to 3%), including throat irritation (19%), rhinorrhea (7%), nasal pruritus (4%), sneezing (4%), nasal congestion (2%), tremor (8%), feeling jittery (11%), abdominal pain (4%), gingival pain (4%), and hypoesthesia oral (4%). Although several of the AEs from two-dose administration were obtained in subjects who underwent NAC, the incidence of local AEs was higher in patients without NAC compared to with NAC, demonstrating that the local AEs were not related to the NAC.

The safety database is adequate to support the use of one and two doses of ARS-1 based on the 175 unique subjects, 572 total doses, and 119 subjects who received more than one dose. The safety profile from more repetitive or frequent use is not well defined; however, as this is an acute use product, frequent use is unlikely. The use of more than two doses is also expected to be low.

8.3. Conclusions and Recommendations

To support this submission for ARS-1 “for the emergency treatment of type 1 allergic reactions, including anaphylaxis, in adults and pediatric patients who weigh 30 kg or greater,” using the 505(b)(2) pathway, the Applicant conducted five PK/PD trials to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via PK bracketing. Additional support is provided by hemodynamic PD results, namely systolic blood pressure (SBP) and pulse rate (PR) change from baseline, that are directly relevant to anaphylaxis treatment. No clinical efficacy studies were conducted for ARS-1 administered during anaphylaxis, and no PK/PD studies were conducted in patients undergoing anaphylaxis due to feasibility and interpretability concerns.

Overall, the PK/PD results from the adult studies, EPI 15, EPI 16, EPI 17, and EPI 18, and the pediatric trial in children ≥30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. Based on this scientific bridge, substantial evidence of effectiveness is demonstrated, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and more than 100 years of use.

ARS-1 systemic safety relies on the safety of epinephrine injection products as epinephrine exposure with ARS-1 is matched to approved epinephrine injection products. The limited systemic safety adverse event profile of ARS-1 from the PK studies did not identify new safety concerns. Local safety was assessed in the ARS-1 development program. The most common local adverse events included throat irritation, intranasal paresthesia, nasal discomfort, rhinorrhea, nasal pruritus, sneezing, and nasal congestion.

The review team's assessment is that there is a favorable benefit-risk assessment, and they recommend **Approval** of ARS-1 "for emergency treatment of type I allergic reactions including anaphylaxis for adults and pediatric patients who weigh 30 kg or greater." ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection or infusion. ARS-1 provides an alternative route for administration of epinephrine in the treatment of anaphylaxis that has the potential to improve compliance and timeliness of treatment of anaphylaxis episodes.

9. Advisory Committee Meeting and Other External Consultations

See original NDA Review from September 19, 2023, for details regarding the Pulmonary-Allergy Drugs Advisory Committee (PADAC) that was held on May 11, 2023. The review team did not identify any additional issues that would benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

As noted in the original NDA Review from September 19, 2023, this 505(b)(2) NDA submission triggers the Pediatric Research Equity Act (PREA) since ARS-1 is a new route of administration for epinephrine. The Applicant requested a partial waiver for children <4 years of age and <15 kg in this NDA submission as studies are impossible or highly impracticable in subjects <4 years of age given that the device is not fit-for-purpose for children <4 years of age, the immaturity of their nasal physiology precluding efficient absorption of drug, and that there is less assurance that a proper dose will be administered due to patient noncompliance at this age. The Division agrees that pediatric studies can be waived in this age group as studies are impossible or highly impracticable given that the device is not-fit-for-purpose for children <4 years of age.

We are deferring submission of pediatric studies for pediatric patients ≥4 years of age and between 15 to <30 kg as the product is ready for approval in adults and pediatric patients (b) (4) years of age and ≥30 kg. PREA will be fulfilled with the planned submission of the pediatric data from the completed pediatric trial, EPI 10, in children ≥4 years of age and ≥15 kg. The results from EPI 10 that support approval of ARS-1 pediatric patients ≥30 kg are based on an interim analysis of EPI 10 for that patient population.

The following PREA Postmarketing Requirement (PMR) will be issued upon approval. The Applicant has provided the listed timeline to fulfill this PREA PMR.

> *Conduct a single-dose, pharmacokinetic and pharmacodynamics study of ARS-1 in pediatric patients ≥4 years of age and between 15 to <30 kg with Type I allergies that require prescription of an epinephrine product.*
>
> (b) (4)
>
> *Final Report Submission: November 2024*

The clinical study report for the completed EPI 10 trial was submitted to IND 139091 on January 24, 2034. However, the PREA requirement is not considered fully submitted (labeled as Final Report Submission above) until the applicant submits the pediatric supplement, which is planned for November 2024.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	Neffy is an alpha and beta-adrenergic receptor agonist indicated for emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater. *Although it is unusual to modify the word 'treatment' in the indication statement, the team included 'emergency' as a modifier for treatment so that neffy is not used for allergic reactions that do not require epinephrine.* *'Type I' was removed from parentheses and incorporated into the indication statement because the term 'type I' is an essential part of the indicated condition.* (b) (4) *was removed as part of the Established Pharmacologic Class (EPC) for epinephrine consistent with the FDA EPC text phrase which does not include* (b) (4) (b) (4)
2 DOSAGE AND ADMINISTRATION	The recommended dosage of neffy is one spray (2 mg of epinephrine) administered into one nostril. In the absence of clinical improvement or if symptoms worsen after the initial treatment, a second dose of neffy may be administered in the same nostril with a new nasal spray starting 5 minutes after the first dose. • Advise patients when to seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event further treatment is required. • It is recommended that patients are prescribed and have immediate access to two neffy nasal sprays at all times. *Administration of the repeat or second dose of neffy in the same nostril as the first dose is supported by the EPI 18 trial provided in the resubmission, dated April 2, 2024.*

	Furthermore, the administration of the second dose is recommended starting 5 minutes after the first dose, rather than the 10 minutes that was studied in the clinical pharmacology studies, so that the patient does not delay additional treatment should symptoms not improve or worsen after the first dose. *Language to 'advise patients when to seek emergency medical assistance for anaphylactic episode and in the event further treatment is required' was modified from current epinephrine injection product instructions for patients to seek medical care following administration of epinephrine. The rationale for this modification is discussed in more detail following this table. In general, the recommendation to seek emergency treatment in current epinephrine injection product labeling may be a barrier to use of epinephrine for some patients. In addition, the COVID-19 pandemic prompted the allergy community to re-evaluate the recommendations to seek emergency treatment for anaphylaxis, given the risks of infection and strain on the health care system. Instead of an indiscriminate recommendation to advise all patients to seek emergency treatment, shared decision-making was promoted to identify patients who can safely administer epinephrine at home and those patients who should initiate treatment and seek emergency assistance. The modified language in the neffy label reflects this shared decision-making approach.*
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	A new subsection, 5.1 'Potential Altered Absorption of neffy in Patients with Underlying Structural or Anatomical Nasal Conditions,' was added to highlight the potential for altered absorption of neffy in patients with underlying structural or anatomical nasal conditions; neffy was not evaluated in subjects with underlying structural and anatomical nasal conditions, such as nasal polyps or following (b) (4) surgery, and (b) (4)

6 ADVERSE REACTIONS	This section is formatted by headings that convey adverse reactions (Ars) from four clinical pharmacology studies and Ars from post-approval of epinephrine products. Most common adverse reactions for one or two dose(s) of neffy in adults are provided in a table. Separate from the adverse reactions observed from adults, adverse reactions in pediatric subjects are provided in this section with a concise summary of the AR data from the PK/PD trial in pediatric subjects. The Applicant included a compilation of ARs from epinephrine products, which was organized and formatted as AR from post-approval use of epinephrine products.
7 DRUG INTERACTIONS	This section consists of class labeling, with the addition of a subsection, 7.1 'Potential Increased Exposure of Nasal Spray Drugs' to address drug interactions unique to nasal administration of epinephrine. A carryover effect was observed in the ARS-1 development program, demonstrating that neffy may alter the nasal mucosa up to 2 weeks after administration, increasing absorption of nasal products, including use of neffy, and hence, increasing adverse reactions associated with the products.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	This section for Pregnancy and Lactation Labeling Rule (PLLR) is consistent with the Reference Listed Drug (RLD). The Pediatric Use subsection includes the pediatric use statement and support from clinical pharmacology studies in adults, PK/PD of neffy in epinephrine injection products, and clinical pharmacology data with neffy in pediatric subjects.
10 OVERDOSAGE	Aligned with RLD.
12 CLINICAL PHARMACOLOGY	**12.1 Mechanism of Action:** consistent with class labeling

	12.2 Pharmacodynamics Includes description of the clinical pharmacology studies conducted for neffy that compared the PK and PD (i.e., SBP and PR) following administration of neffy and epinephrine injection. **12.3 Pharmacokinetics** Provides PK assessment, the geometric mean plasma epinephrine concentration, from the clinical pharmacology studies (Study 1 (EPI 15), 2 (EPI 17), 3 (EPI 16), 4 (EPI 18), and 5 (EPI 10)).
13 NONCLINICAL TOXICOLOGY	Aligned with RLD.
14 CLINICAL STUDIES	This section is omitted from the PI because clinical efficacy studies were not conducted for neffy.
17 PATIENT COUNSELING INFORMATION	Administration instructions to convey to patients are included. Risks associated with certain coexisting conditions to convey to patients are included. Removed (b) (4) from this section because Section 17 should not include (b) (4)
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Sections 3, 11, 16 are presented consistent with OPQ information and best labeling practice.

Additional Discussion of Section 2 Dosage and Administration

Advise patients when to seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event further treatment is required.

With this application, labeling recommendations regarding seeking emergency medical assistance were modified. Labeling of epinephrine injection products that are approved for community treatment of anaphylaxis includes the following warning and precautions statement: 'in conjunction with use, patients should seek immediate medical or hospital care.' This recommendation is long-standing based on concerns of persistent, refractory, or biphasic anaphylaxis despite epinephrine treatment (Dribin et al. 2020). Close observation in an acute medical care setting following epinephrine administration is intended to monitor for progressive anaphylaxis that may require treatment escalation and to observe for biphasic reactions.

The need for all patients treated with epinephrine in the community to seek emergency medical care, however, is unclear. Most anaphylaxis episodes respond/resolve to one (90%) or two (>95%) doses of epinephrine (Patel et al. 2021). Fatal anaphylaxis is very rare (approximately 0.002 deaths/million person years) (Pühringer et al. 2023), with lower rates reported in food allergy (Umasunthar et al. 2013). In addition, biphasic reactions are rare (~5%), rarely lethal, and may be delayed beyond the usual timeframe for observation in an emergency department (Lee et al. 2015; Kim et al. 2019). The requirement to activate EMS after administration of epinephrine is identified as a barrier to prompt administration of epinephrine for some patients.

In 2020, the COVID-19 pandemic prompted careful benefit-risk assessments for when emergency medical services (EMS) should be activated following epinephrine use based on increased infection risks; shared decision-making was promoted to identify patients who could manage anaphylaxis safely at home (Casale et al. 2020). Recent recommendations have extended home management for some patients, using a risk-stratified approach, advising patients when EMS should be activated following epinephrine administration (Casale et al. 2022; Golden et al. 2024). As a result, home management may be recommended, for example, when two doses of epinephrine are available, patients/caregivers have a clear understanding of anaphylaxis symptoms and treatment with epinephrine, EMS is readily available if symptoms persist or progress, and the patient is around other people who can provide assistance, if needed. Some patients with certain risk factors may be advised to seek emergency medical assistance immediately after administering epinephrine, regardless of response.

Based on these factors, to promote a shared decision-making approach and to eliminate potential barriers to prompt treatment of anaphylaxis, neffy labeling includes, 'Advise patients when to seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event further treatment is required.' The nasal route of administration may lead to earlier and more frequent treatment of anaphylaxis, including with milder symptoms. This change in labeling aligns with the goals for effective treatment of anaphylaxis.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13. Postmarketing Requirements and Commitment

Postmarketing Requirement (PMR)

PMR 4671-1: Conduct a single-dose, pharmacokinetic and pharmacodynamics study of ARS-1 in pediatric patients ≥4 years of age and between 15 to <30 kg with Type I allergies that require prescription of an epinephrine product.

(b) (4)

Final Report Submission: November 2024

Postmarketing Commitment (PMC)

PMC 4671-2: Conduct a registry-based study in high volume oral food challenge and allergen immunotherapy clinics in which subjects would use either ARS-1 or an epinephrine injection product for treatment of anaphylaxis. Collect initial symptoms along with clinical outcome data comparing ARS-1 to epinephrine injection, including time to symptom resolution, adverse events, and whether a repeat dose is needed.

Draft Protocol Submission: 12/2024
Final Protocol Submission: 02/2025
Study Completion: 02/2026
Final Report Submission: 06/2026

14. Associate Director for Therapeutic Review (Clinical) Comments

These comments provide a brief summary of the ARS-1 development program and new data included in this resubmission. Refer to the Division Director and Associate Director for Therapeutic Review Comments from the original Multidisciplinary Review, dated September 19, 2023, for additional details of the ARS-1 development program.

ARS Pharmaceuticals submitted a 505 (b)(2) NDA, 214697, on August 19, 2022, for epinephrine nasal spray (ARS-1) for the proposed indication of emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥30 kg. Major amendments were received on May 30, 2023 and June 5, 2023, with additional CMC and device data. A CR action was taken on September 19, 2023, due to the following deficiencies:

1) Clinical/Clinical Pharmacology: EPI 16, which assessed one dose of ARS-1 administered to adults with NAC-induced rhinitis, compared to one dose of an epinephrine injection comparator (Adrenalin), raised concern regarding the durability of ARS-1's effect in patients with NAC-induced rhinitis. There was also uncertainty with the PK/PD effects when two doses of ARS-1 were administered in the same or alternate nostril given the local pharmacologic effects of epinephrine on the nasal mucosa. To address these concerns, the Applicant was to provide PK/PD data assessing two doses of ARS-1 compared to two doses of epinephrine injection product(s) under NAC-induced rhinitis conditions, including an assessment of PK/PD findings when the second dose of ARS-1 is administered in the same or alternate nostril.
2) Product Quality: As outlined in the FDA guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023),[3] applicants are required to ascertain the presence of nitrosamine drug substance-related impurities (NDSRIs) in their drug products. The NDA did not include data or information, such as a risk assessment, and/or confirmatory testing data as needed, demonstrating that they ascertained the presence of NDSRIs in their drug product, including specifically (b) (4)

Following issuance of the CR letter, the Applicant requested, and was granted, a Type A Meeting. The meeting was held on October 24, 2023. At the meeting, the Division reiterated the need for a trial comparing two doses of ARS-1 in adults under NAC-induced rhinitis conditions to two doses of epinephrine injection product to address the deficiency outlined in the CR letter, in addition to the NDSRI data. Clarification was provided regarding data submission requirements for the resubmission.

[3] NDSRI guidance refers to a 3-step mitigation strategy described in FDA's guidance for industry, *Control of Nitrosamine Impurities in Human Drugs* (February 2021).

On November 27, 2023, the Applicant submitted a FDRR regarding the CR letter. In the FDRR, the Applicant relayed they disagreed with the Agency's requirement to conduct an additional PK/PD trial assessing two doses of ARS-1 and two doses of epinephrine injection product(s) in patients with NAC-induced rhinitis trial to support efficacy and safety, as a condition of approval, as well as the need for NDSRI data as a condition of approval. The Acting Director of the Office of Immunology and Inflammation, Dr. Nikolay Nikolov, acknowledged the public health importance of a needle-free epinephrine product, but agreed with the issues raised by the Division in the CR Letter and that a reasonable path forward was laid out to address the deficiencies. Therefore, the formal dispute request was denied.

The Applicant provided a resubmission to NDA 214697 on April 2, 2024, for epinephrine nasal spray (ARS-1) for "the emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and pediatric patients who weigh 30 kg or greater." The resubmission includes data from a new PK/PD trial, EPI 18, designed to address the clinical/clinical pharmacology deficiencies identified in the original submission. It also includes data to address the product quality deficiency and includes the method, method validation, and confirmatory data needed to assess NDSRIs in ARS-1, particularly (b) (4)

EPI 18

To address the clinical/clinical pharmacology deficiency outlined in the CR letter the Applicant included with this resubmission data from a new clinical pharmacology PK/PD trial, EPI 18, in adults with allergic rhinitis under NAC-induced rhinitis conditions, that includes administration of two doses of ARS-1 compared to two doses of Adrenalin, both administered 10 minutes apart; EPI 18 also assesses PK/PD when the second dose is administered in the same compared to alternate nostril. Similar to the results of EPI 16, the first dose of ARS-1 demonstrated higher mean epinephrine concentrations than the Adrenalin comparator through 10 minutes. With administration of the second dose in the same nostril at 10 minutes, the mean epinephrine concentrations were higher than observed with administration of the second dose of Adrenalin for up to 40 minutes (after the first dose) and was similar after 40 minutes. The median hemodynamic PD responses (SBP and PR) following administration of two doses of ARS-1 in the same nostril were generally higher than those observed with two doses of Adrenalin throughout 60 minutes post-dose. Overall, these results are reassuring that, under acute allergic rhinitis conditions, epinephrine concentrations and hemodynamic PD responses are maintained for at least 60 minutes at a level comparable to those observed for a listed epinephrine injection product. This finding adequately addresses the concern with the early drop in epinephrine concentration and PR observed in EPI 16, and it emphasizes the need for two neffy devices to be available at all times, as reflected in labeling. With administration of the second dose in the alternate nostril, epinephrine concentrations were comparable to higher than observed following the second dose of the Adrenalin comparator for the first 30 minutes, then dropped below epinephrine concentrations observed for Adrenalin. A similar drop in hemodynamic PD markers was observed after 40 minutes. The differential results likely reflect local pharmacologic effects of epinephrine and their favorable impact on absorption of the

second dose administered in the same nostril. As a result of this finding of differential PK/PD results, labeling clearly specifies that a second dose of neffy, when indicated, should be administered in the same nostril for optimal effect.

Product Quality

As detailed in the Office of Pharmaceutical Quality Assessment II, Division of Product Quality Assessment VII chemistry reviewer's memorandum, dated April 19, 2024, 'the Applicant has gone beyond the requirements of the CR deficiency and has also submitted the method, method validation, and confirmatory data. As such, no further action is needed in regard to the NDSRI issue.' Therefore, the product quality deficiency has been adequately addressed and the CMC/Quality team recommends approval of ARS-1.

Human Factors

The Applicant submitted a new post-validation human factor (HF) study with this resubmission, conducted to evaluate the proposed labeling instruction update specifying that a second dose be administered in the same nostril as the first dose. Based on their review of the HF study, the Division of Medication Error Prevention and Analysis 1 found that the revised labeling supports safe and effective use of the proposed product.

Labeling

Proposed labeling was reviewed by the review team and labeling consultants. Following several Information Requests from the Applicant, final labeling was agreed upon between FDA and the Applicant.

As discussed in detail in Section 11 Labeling Recommendations, labeling of epinephrine injection products that are approved for community treatment of anaphylaxis includes the following warning and precautions statement: 'in conjunction with use, patients should seek immediate medical or hospital care.' The requirement to activate EMS after administration of epinephrine is identified as a barrier to prompt administration of epinephrine for some patients. As a result, this language was modified to, 'advise patients when to seek emergency medical assistance for anaphylactic episode and in the event further treatment is required.' The rationale for this modification is discussed in detail in Section 11. During the COVID-19 pandemic, the allergy community re-evaluated the recommendations to seek emergency treatment for anaphylaxis, given the risks of infection and strain on the health care system. Instead of an indiscriminate recommendation to advise all patients to seek emergency treatment, shared decision-making was promoted to identify patients who can safely administer epinephrine at home and those patients who should initiate treatment and seek emergency assistance. The modified language in the neffy label reflects this shared decision-making approach.

Postmarketing Requirement/Commitment

A PMR was issued for this application (PMR 4671-1), under the Pediatric Research Equity Act, to conduct a single-dose, pharmacokinetic and pharmacodynamics study of ARS-1 in pediatric patients ≥4 years of age and between 15 to <30 kg with Type I allergies that require prescription of an epinephrine product. The study is complete and final report submission is expected November 2024.

Since clinical efficacy was not assessed in the setting of anaphylaxis, a PMC was issued (PMC 4671-2) to conduct a registry-based study in high volume oral food challenge and allergen immunotherapy clinics in which subjects would use either ARS-1 or an epinephrine injection product for treatment of anaphylaxis. The Applicant is expected to collect initial symptoms along with clinical outcome data, comparing ARS-1 to epinephrine injection, including time to symptom resolution, adverse events, and whether a repeat dose is needed. The draft protocol submission is expected in December 2024; the final protocol submission is expected in February 2025; study completion is expected in February 2026; and the final report submission is expected in June 2026.

Benefit/Risk Assessment and Recommendation

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs rapidly, generally minutes after contact with an allergen to which an individual is sensitized. Up to 5% of the U.S. population has experienced an anaphylactic reaction. Although fatal anaphylaxis is rare, with an estimated 200 deaths per year in the United States, a significant number of people are at risk for anaphylaxis, such as those with allergy to food, Hymenoptera venom, and drugs, among others. Fatal anaphylaxis usually occurs within 60 minutes of exposure to an allergenic substance, and most frequently within 5 to 35 minutes of exposure. Factors associated with fatal anaphylaxis from food allergy registries include age (adolescents and young adults), history of peanut allergy, comorbid asthma, and delayed administration of epinephrine. For drug and Hymenoptera venom allergy, risk factors for fatal anaphylaxis include increased age and cardiovascular comorbidities. Notably, the severity of past anaphylaxis episodes is not sufficient to predict the severity of future reactions.

For patients with Type 1 allergy at risk for anaphylaxis, such as children and adults with food allergy, standard of care includes allergen avoidance and treatment with an epinephrine injection product if anaphylaxis occurs. Epinephrine injection is the first-line and only lifesaving treatment for anaphylaxis. Although early administration of epinephrine is recommended, epinephrine administration is frequently avoided or delayed, including due to needle phobia. In addition, epinephrine is often under-prescribed in patients at risk for anaphylaxis. As discussed by the Applicant in their original NDA submission, by patients and caregivers at a Patient-Focused Drug Development session with the Agency on September 9, 2021, and by PADAC members and in public testimony at the May 11, 2023, PADAC meeting, availability of alternative routes of administration of epinephrine, such as by the nasal route, may improve

the compliance and time to administration for epinephrine. ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection or intravenous infusion.

To support this submission for ARS-1 "for the emergency treatment of type 1 allergic reactions, including anaphylaxis, in adults and pediatric patients who weigh 30 kg or greater," using the 505(b)(2) pathway, the Applicant conducted five PK/PD trials to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via PK bracketing. Additional support is provided by hemodynamic PD results, namely systolic blood pressure (SBP) and pulse rate (PR) change from baseline, that are directly relevant to anaphylaxis treatment. No clinical efficacy studies were conducted for ARS-1 administered during anaphylaxis, and no PK/PD studies were conducted in patients undergoing anaphylaxis due to feasibility and interpretability concerns.

Overall, the PK/PD results from the adult trials, EPI 15, EPI 16, EPI 17, and EPI 18, and the pediatric trial in children ≥30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. Based on this scientific bridge, substantial evidence of effectiveness is demonstrated, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and more than 100 years of use.

ARS-1 systemic safety relies on the safety of epinephrine injection products as epinephrine exposure with ARS-1 is matched to approved epinephrine injection products. The limited systemic safety adverse event profile of ARS-1 from the PK studies did not identify new safety concerns. Local safety was assessed in the ARS-1 development program. The most common local adverse events included throat irritation, intranasal paresthesia, nasal discomfort, rhinorrhea, nasal pruritus, sneezing, and nasal congestion.

I agree with the review team's assessment that there is a favorable benefit-risk assessment, and their recommendation for **Approval** of ARS-1 "for emergency treatment of type I allergic reactions including anaphylaxis for adults and pediatric patients who weigh 30 kg or greater." ARS-1 provides an alternative route for administration of epinephrine in the treatment of anaphylaxis that has the potential to improve compliance and timeliness of treatment of anaphylaxis episodes, and may reasonably be expected to translate into improved outcomes.

15. Appendices

15.1. References

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ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

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Umasunthar, T, J Leonardi-Bee, M Hodes, PJ Turner, C Gore, P Habibi, JO Warner, and RJ Boyle, 2013, Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis, Clin Exp Allergy, 43(12):1333-1341.

15.2. Financial Disclosure

Covered Clinical Trial (Name and/or Number): EPI 18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (technical documents supporting OCP recommendations)

15.3.1. Individual Trial Review

15.3.1.1. Trial EPI 18

Trial Type:

Phase 1 repeat-dose trial in subjects with allergic rhinitis

Trial Date: October 9, 2023 to December 12, 2023

Formulation:

- ARS-1 2 mg (Lot: 230211)
- Adrenalin 1 mg/1 mL single-dose vial (Lot: 64103)

Title: A Five-Treatment, Five-Period, Randomized, Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Repeat Administration of ARS-1 and Intramuscular Epinephrine Injection in Type I Allergy Patients with Seasonal Rhinitis (EPI 18)

Objective:

The primary objectives of the trial were as follows:

- To evaluate the comparative PK of two doses of ARS-1 with Adrenalin IM 0.3 mg under NAC-induced rhinitis conditions compared to two-dose administration under normal conditions.
- To evaluate the comparative PD of two doses of ARS-1 with Adrenalin IM 0.3 mg based on SBP, DBP, and PR using an automated blood pressure measuring (ABPM) device under allergic rhinitis conditions compared to two-dose administration under normal conditions.

Trial Design and Method: See Section 6

Protocol Deviation:

See Applicant's EPI 18 Clinical Study Report, table 19 dated April 2, 2024. There were a total of 219 protocol deviations. Most were PK or PD samples collected outside of the specified window or not collected due to difficult venipuncture. The deviation of sample collection from nominal time ranged from several seconds to 7 minutes. As the PK and PD samples were collected

following an intensive sampling schedule (every 2 to 15 minutes with allowed window between ±1 to ±2 minutes during the first hour), the reported deviation is less likely to impact the PK and PD analyses.

Demographics:

A total of 43 subjects were enrolled. Four subjects did not complete the trial, as shown in Table 9. Two subjects withdrew prematurely and did not participate in Treatment Periods 4 and 5. Two subjects skipped one or two treatment periods during the trial. Therefore, these subjects did not have PK/PD data for these periods.

Table 9. Subjects Who Did Not Complete the Trial in EPI 18

Subject ID	Treatment Periods With No Dose or Incomplete Dose
(b) (6)	Period 2, 4, 5 (early withdrew due to AE)
	Period 4, 5 (early withdrew due to no-show)
	Period 4
	Period 2*, 3

Source: reviewer's generated table based on EPI 18 CSR.
* Subject received one dose during period 2 but was not given second dose due to AE.
Abbreviations: AE, adverse event.

The baseline demographics for subjects who participated in the trial are summarized in Table 10.

Table 10. Baseline Demographics of Subjects in EPI 18

Characteristic	EPI 18 N=43
Body weight, kg	
Mean (SD)	76.8 (15.4)
Median (range)	76.7 (51.7, 107.5)
Age, years	
Mean (SD)	42.8 (10.56)
Median (range)	43 (24, 63)

Source: reviewer's analysis based on adsl.xpt for EPI 18.
Abbreviations: kg, kilograms; SD, standard deviation.

PK Endpoints:

Periods 1 and 2 (normal nasal conditions)

Blood samples were obtained pre-dose (at −30 and −15 minutes) after at least 20 minutes in a relaxed sitting position with back supported, legs uncrossed, and upper arm bare (slight recline for comfort was permitted), and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, and 240 minutes after dosing. Actual blood collection times were permitted to vary as follows: ±10 minutes for the −45 to −15-minute samples, ±1 minute for the −10 to 20-minute samples, ±2 minutes for the 30 to 90-minute samples, and ±5 minutes for the 120 to 240-minute samples.

Periods 3 to 5 (NAC)

Blood samples were obtained pre-NAC (at −45 and −30 minutes) after at least 20 minutes in a relaxed sitting position with back supported, legs uncrossed, and upper arm bare (slight recline for comfort was permitted), after NAC/predose (at −10 and −5 minutes), and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, and 240 minutes after dosing. Actual blood collection times were permitted to vary as follows: ±10 minutes for the −45 to −15-minute samples, ±1 minute for the −10 to 20-minute samples, ±2 minutes for the 30 to 90-minute samples, and ±5 minutes for the 120 to 240-minute samples.

PD Endpoints:

Screening

Evaluation of allergy symptoms Day −60 to Day −21 to determine allergen type that induces adequate nasal edema and congestion (TNSS score of ≥5 out of 12 and a congestion score of ≥2 out of 3) by NAC. Subjects testing with an initial nasal wash with saline and phenol reporting a TNSS score greater than 2 were excluded.

Periods 1 and 2 (normal nasal conditions)

BP and PR using ABPM device were evaluated while the subject remained sitting relaxed with back supported, legs uncrossed, and upper arm bare (slight recline for comfort was permitted). BP and PR were taken at pre-dose (at −30 and −15 minutes [±5 min]), and at 1 (+1 min), 5 (±2 min), 10 (±2 min), 15 (±2 min), 20 (±2 min) 25 (±2 min), 30 (±2 min), 45 (±5 min), 60 (±5 min), 90 (±5 min) and 120 (±5 min) minutes after dosing.

TNSS assessment was evaluated at pre-dose (−15 minutes).

Periods 3 to 5 (NAC)

BP and PR were also assessed in sitting positions. BP and PR were taken pre-NAC at −45 (±10 min) and −30 (±10 min) minutes, after NAC/predose at −10 (±3 min) and −5 (±3 min) minutes, and at 1 (+1 min), 5 (±2 min), 10 (±2 min), 15 (±2 min), 20 (±2 min) 25 (±2 min), 30 (±2 min), 45 (±5 min), 60 (±5 min), 90 (±5 min) and 120 (±5 min) minutes after dosing.

TNSS assessment was evaluated at −30 (±5 min) minutes (15 minutes before NAC) and at 0 (+2 min), 15 (±2 min), 30 (±5 min), 45 (±5 min), 60 (±5 min), 120 (±10 min), 180 (±15 min), and 240 (±30 min) minutes after dosing.

Positive reaction to NAC (i.e., TNSS score ≥5 out of 12 and a congestion score of ≥2 out of 3) was not re-confirmed after NAC during Treatment Periods 3 to 5. However, the allergen solution concentrations used in Treatment Periods 3 to 5 were 5-fold higher than established concentrations during screening visit. See Section 6 for details.

Results:

PK

The baseline epinephrine concentrations prior to dosing in each treatment are shown in Table 11 for normal nasal conditions treatment periods (1 and 2) and Table 12 for NAC treatment periods (3 to 5). In general, the post-NAC epinephrine plasma concentrations were numerically higher than pre-NAC epinephrine plasma concentration in Periods 3 to 5. Depending on different time points and periods, the numerical differences of geometric mean values ranged from approximately 2 to 10 pg/mL. The pre-dose PK profiles by treatment are displayed in Figure 9.

Table 11. Baseline (Pre-Dose) Epinephrine Plasma Concentrations in Normal Nasal Conditions Treatment Periods (1 and 2) in EPI 18

	Treatment Period 1 N=43				Treatment Period 2 N=41			
Variable	Two Doses Neffy 2 mg (R/L) N=21		Two Doses Adrenalin 0.3 mg (R/L) N=22		Two Doses Neffy 2 mg (R/L) N=22		Two Doses Adrenalin 0.3 mg (R/L) N=19	
Time	-30 min	-15 min	-30 min	-15 min	-30 min	-15 min	-30 min	-15 min
Geometric mean concentration (CV%) (ng/ml)	13.87 (100.46)	15.85 (78.78)	17.21 (111.52)	16.96 (91.24)	22.62 (85.19)	21.21 (79.45)	14.50 (97.66)	18.46 (99.85)
Median concentration (range) (ng/ml)	17.68 (5.50, 74.56)	18.53 (5.50, 51.02)	17.46 (5.50, 159.7)	16.28 (5.50, 76.76)	25.54 (5.50, 99.97)	22.35 (5.50, 82.35)	15.26 (5.50, 55.00)	15.85 (5.50, 84.61)

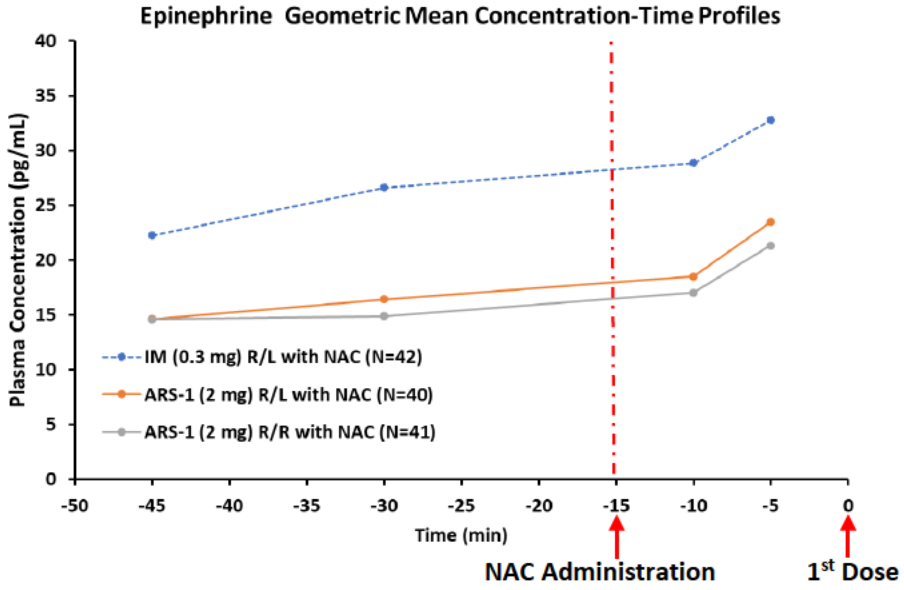
Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: CV, coefficient of variation; L, left; LLOQ, lower limit of quantification; R, right.

Table 12. Baseline (Pre-Dose) Epinephrine Plasma Concentrations in NAC Treatment Periods (3 to 5) in EPI 18

	Before NAC Baseline		After NAC Baseline	
Variable	-45 min N=42	-30 min N=42	-10 min N=41	-5 min N=42
Treatment Period 3: Two Doses Adrenalin (0.3) mg (R/L) with NAC				
Geometric mean concentration (CV%) (ng/mL)	22.24 (83.06)	26.60 (79.72)	28.85 (69.15)	32.75 (78.70)
Median concentration (range) (ng/mL)	20.26 (5.50, 110.30)	27.65 (5.50, 114.69)	29.83 (5.50, 126.10)	31.99 (5.50, 203.84)
Treatment Period 4: Two Doses ARS-1 (2 mg) (R/L) with NAC				
Geometric mean concentration (CV%) (ng/mL)	14.62 (102.62)	16.42 (96.18)	18.51 (86.83)	23.47 (61.82)
Median concentration (range) (ng/mL)	14.46 (5.50, 117.65)	14.48 (5.50, 126.73)	18.30 (5.50, 77.94)	24.71 (5.50, 121.74)
Treatment Period 5: Two Doses ARS-1 (2 mg) (R/R) with NAC				
Geometric mean concentration (CV%) (ng/mL)	14.58 (100.95)	14.88 (96.55)	17.02 (85.09)	21.33 (85.33)
Median concentration (range) (ng/mL)	16.28 (5.50, 96.53)	15.83 (5.50, 140.62)	15.49 (5.50, 118.76)	19.22 (5.50, 89.22)

Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: CV, coefficient of variation; L, left; LLOQ, limit of quantification; NAC, nasal allergen challenge, R, right.

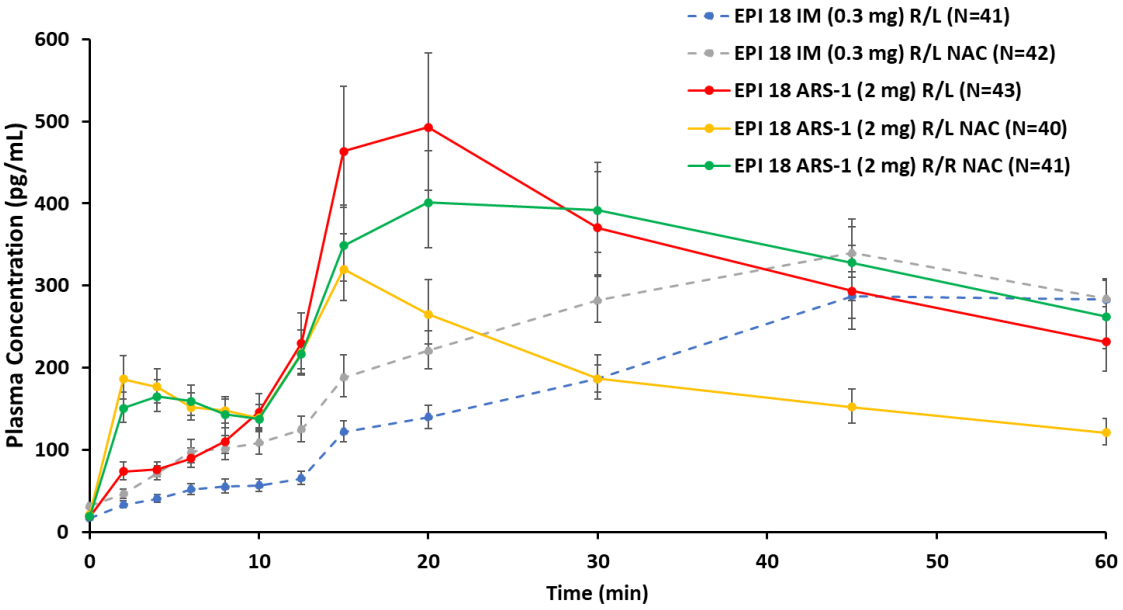
Figure 9. Pre-Dose Plasma Epinephrine Geometric Mean Concentration-Time Profiles Before and After NAC Induction (At -15 Min) In Treatment Periods 3 to 5 In EPI 18



Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Abbreviations: IM, intramuscular (Adrenalin); L, left; NAC, nasal allergen challenge; R, right.

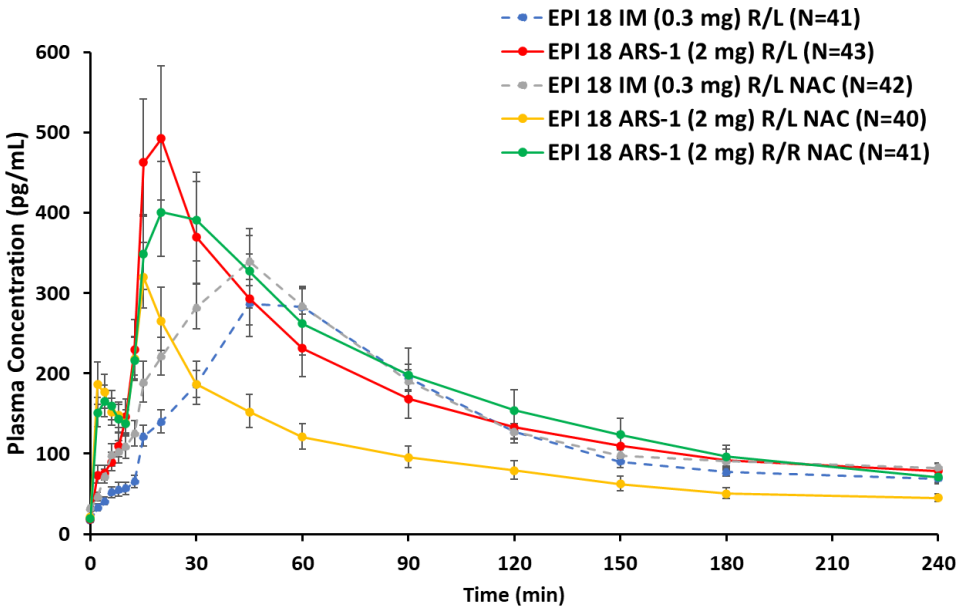
The geometric mean baseline-uncorrected epinephrine concentrations-time profiles are shown in Figure 10 (within 60 minutes post-first dose) and Figure 11 (all timepoints). The PK parameters are shown in Table 13 and bioequivalence analysis is shown in Table 14.

Figure 10. Epinephrine Geometric Mean (CV%) Plasma Concentration-Time Profile (60 Minutes Post-First Dose) for EPI 18



Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: CV, coefficient of variation; IM, intramuscular (Adrenalin); L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right.

Figure 11. Epinephrine Geometric Mean (CV%) Plasma Concentration-Time Profile (240 Minutes Post-First Dose) for EPI 18



Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: CV, coefficient of variation; IM, intramuscular (Adrenalin); L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right.

Table 13. Epinephrine Geometric Mean (CV%) PK Parameters Following Two Dose of ARS-1 or Adrenalin With or Without NAC in EPI 18

PK Parameters	ARS-1 (2 mg) (R/L) Without NAC N=43	Adrenalin (0.3 mg) (R/L) Without NAC N=41	Adrenalin (0.3 mg) (R/L) With NAC N=42	ARS-1 (2 mg) (R/L) With NAC N=40	ARS-1 (2 mg) (R/R) With NAC N=41
C_{max} (pg/mL)	701.53 (123.42)	364.83 (58.04)	445.06 (50.87)	454.87 (85.26)	632.56 (100.44)
T_{max} (min)*	20 (4, 180)	60 (8, 120)	45 (6, 150)	15 (2, 150)	20 (2, 150)
$AUC_{0\text{-}10\ min}$ (pg*min/mL)	968.87 (83.46)	467.39 (86.83)	840.75 (89.51)	1581.88 (73.67)	1473.01 (75.56)
$AUC_{0\text{-}20\ min}$ (pg*min/mL)	5287.15 (98.67)	1592.01 (67.37)	2691.52 (82.06)	4556.76 (73.11)	4960.16 (75.47)
$AUC_{0\text{-}30\ min}$ (pg*min/mL)	10022.07 (111.68)	3298.49 (61.11)	5334.52 (71.19)	7119.65 (80.34)	9546.71 (80.35)
$AUC_{0\text{-}60\ min}$ (pg*min/mL)	19955.05 (124.38)	11786.51 (51.58)	15316.17 (56.68)	12160.75 (84.81)	20427.16 (93.42)

Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
* Median (range)
Note: Concentrations lower than lower limit of quantification (LLOQ) were imputed as LLOQ/2. L=left; R=right; NAC=nasal allergen challenge
Abbreviations: AUC, area under curve; Cmax, maximum concentration; CV, coefficient of variation; NAC, nasal allergen challenge; PK, pharmacokinetic; Tmax, time of maximum concentration.

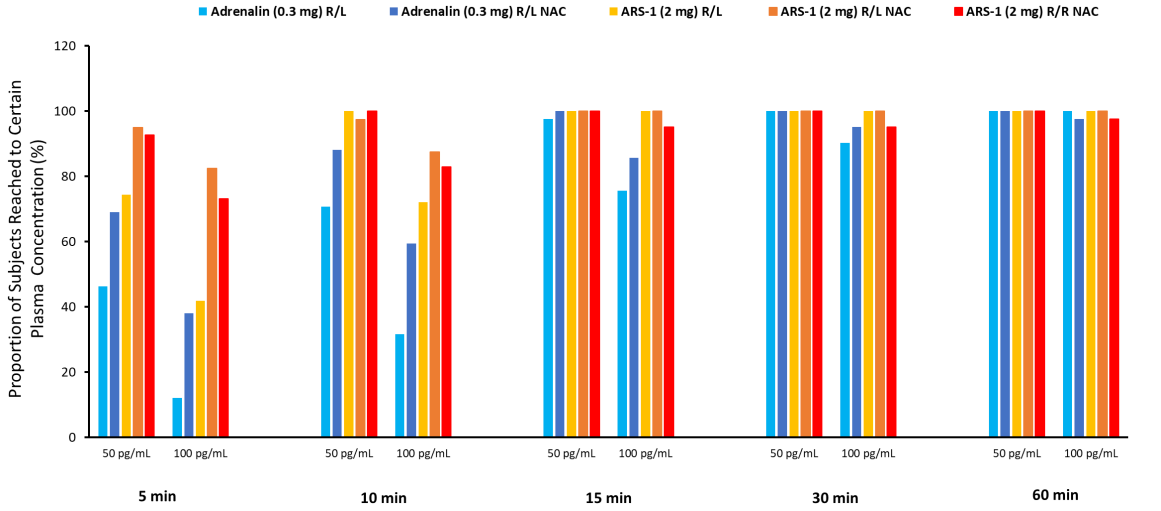
Table 14. Bioequivalence Assessment for PK Parameters Between Two Doses of ARS-1 (2 mg) in Same or Alternate Nostril vs. Two Doses of Adrenalin (3 mg) Under Same Nasal Conditions in EPI 18

	Geometric Mean Ratio (%) (90% CI)			
PK Parameters	**Test: ARS-1 (2 mg) (R/L) With NAC vs. Reference: Adrenalin (0.3 mg) (R/L) with NAC**	**Test: ARS-1 (2 mg) (R/R) With NAC vs. Reference: Adrenalin (0.3 mg) (R/L) with NAC**	**Test: ARS-1 (2 mg) (R/L) Without NAC vs. Reference: Adrenalin (0.3 mg) (R/L) Without NAC**	**Test: ARS-1 (2 mg) (R/R) With NAC vs. Reference: ARS-1 (2 mg) (R/L) without NAC**
C_{max}	101.74 (80.44, 128.69)	142.28 (112.68, 179.67)	191.87 (152.19, 241.91)	90.15 (71.50, 113.65)
$AUC_{0\text{-}10\ min}$	181.93 (150.06, 220.57)	174.33 (143.99, 211.05)	205.81 (170.24, 248.81)	151.73 (125.51, 183.44)
$AUC_{0\text{-}20\ min}$	167.83 (137.30, 205.15)	185.49 (151.97, 226.39)	332.47 (272.78, 405.21)	94.03 (77.15, 114.60)
$AUC_{0\text{-}30\ min}$	132.68 (107.60, 163.60)	180.26 (146.41, 221.94)	303.42 (246.80, 373.01)	95.57 (77.74, 117.50)
$AUC_{0\text{-}60\ min}$	78.98 (63.44, 98.33)	133.70 (107.56, 166.17)	168.75 (135.97, 209.43)	102.31 (82.44, 126.97)

Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18.
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: AUC, area under curve; CI, confidence interval; Cmax, maximum concentration; L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; PK, pharmacokinetic; R, right.

When comparing the PK profile following two-dose IM epinephrine spaced by 10 minutes with and without NAC in EPI 18, the PK profile with NAC was noticeably higher than that without NAC despite that a cross-over design and same batch of IM product were used. The cause of this difference is unknown but likely due to the PK variability of epinephrine injection products as discussed in the original review.

Figure 12. Proportion of Subjects With Plasma Epinephrine Concentrations ≥50 or ≥100 pg/mL Over Time in First 60 Minutes Post-First Dose in EPI 18

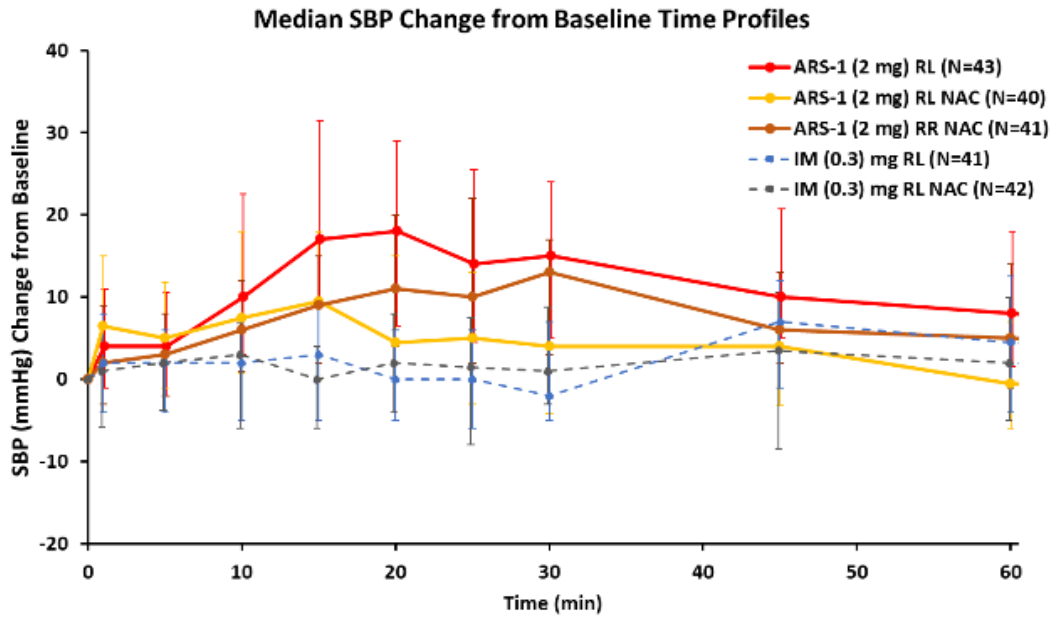


Source: Reviewer's analysis based on adpc.xpt dataset for EPI 18
Note: Concentrations lower than LLOQ were imputed as LLOQ/2.
Abbreviations: L, left; LLOQ, lower limit of quantification; NAC, nasal allergen challenge; R, right.

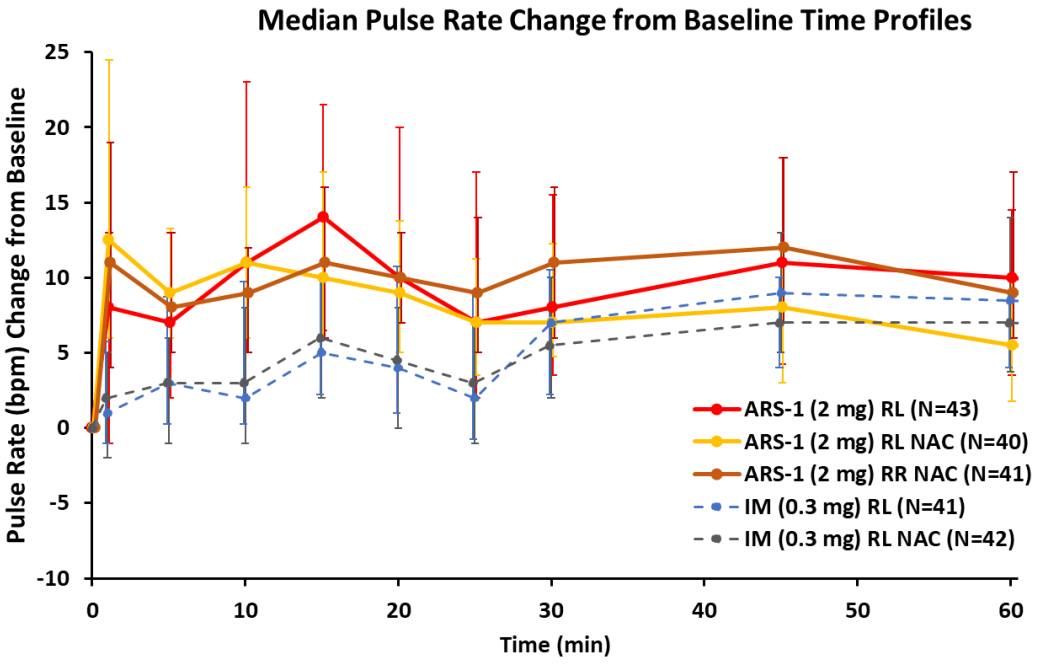
PD

In Treatment Periods 3 to 5 (i.e., NAC treatment periods), both pre-NAC (−45 min and −30 min) and post-NAC (−10 min and −5 min) baseline SBP, DBP, and PR were assessed prior to ARS-1 administration. The median PD responses (change of SBP, DBP, and PR from baseline) profiles over 60 minutes following the first dose are shown in Figure 13 (using average pre-NAC baseline for NAC treatment periods) and Figure 14 using average post-NAC baseline for NAC treatment periods).

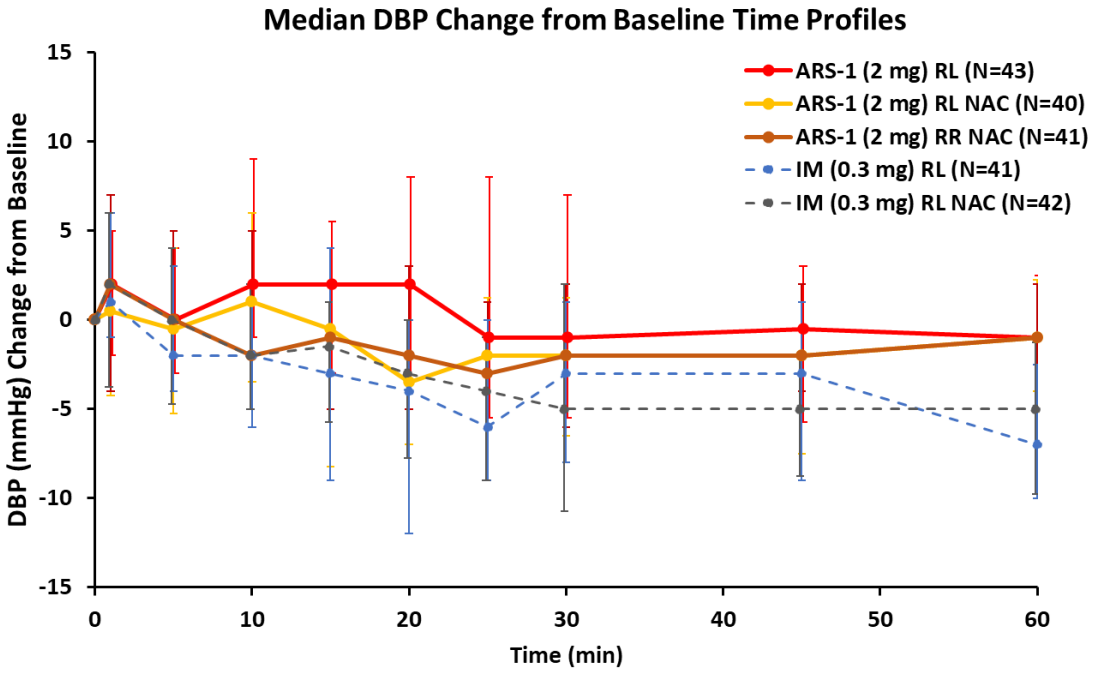
Figure 13. Median PD (SBP, PR, and DBP) Change From Baseline in EPI 18 (Using Average Pre-NAC Baseline to Calculate Change in NAC Treatment Periods)



A. Median Change of SBP From Baseline



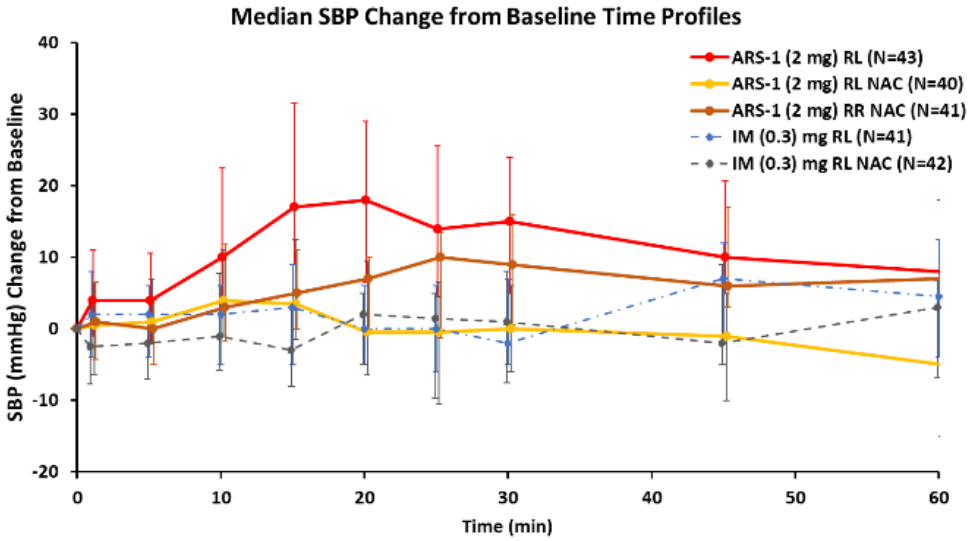
B. Median Change of PR From Baseline



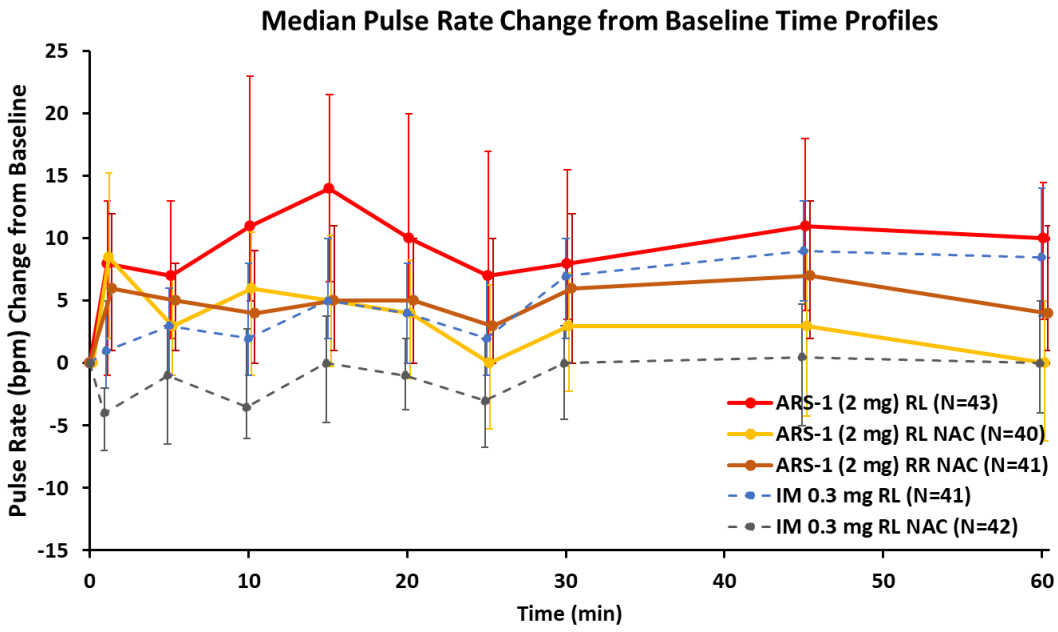
C. Median Change of DBP From Baseline

Source: Reviewer's analysis based on adxd.xpt dataset for EPI 18.
Error bar represents 25% and 75% percentile of PD values.
Average Pre-NAC PD baseline values for each individual was calculated by taking the mean of -45 and -30 min values.
Abbreviations: IM, intramuscular (Adrenalin), R, right; L, left; NAC, nasal allergen challenge; PD, pharmacodynamic; SBP, systolic blood pressure; PR, pulse rate; DBP, diastolic blood pressure.

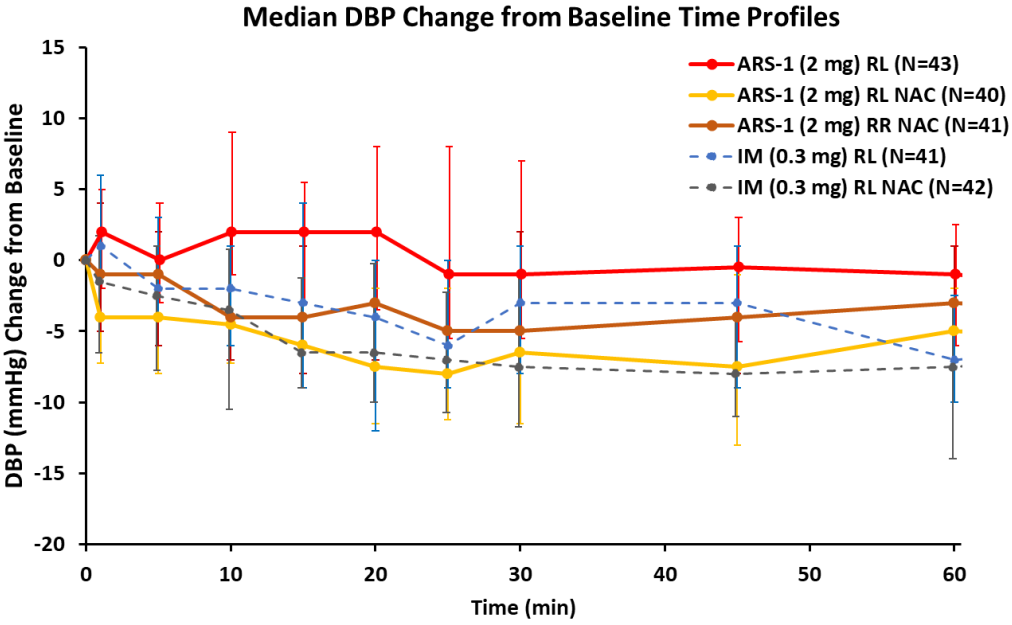
Figure 14. Median PD (SBP, PR, and DBP) Change From Baseline in EPI 18 (Using Average Post-NAC Baseline to Calculate Change in NAC Treatment Periods)



A. Median Change of SBP From Baseline



B. Median Change of PR From Baseline



C. Median Change of DBP From Baseline

Source: Reviewer's analysis based on adxd.xpt dataset for EPI 18. Error bar represents 25% and 75% percentile of PD values. Average Post-NAC PD baseline values for each individual was calculated by taking the mean of -10 and -5 min values.
Abbreviations: IM, intramuscular (Adrenalin), R, right; L, left; NAC, nasal allergen challenge; PD, pharmacodynamic; SBP, systolic blood pressure; PR, pulse rate; DBP, diastolic blood pressure.

For normal nasal conditions treatment periods (i.e., without NAC), the maximum SBP and PR responses (i.e., the maximum change from baseline) within 60 minutes following the first dose is shown in Table 15. Similar to other studies, the SBP and PR responses are generally higher following ARS-1 than Adrenalin in normal nasal conditions.

Table 15. Maximum SBP and PR Response Following Two Doses of Adrenalin or ARS-1 With Normal Nasal Conditions in EPI 18

Parameter	Adrenalin 0.3 mg R/L Without NAC N=41	ARS-1 2 mg R/L Without NAC N=43
Maximum SBP response over 60 minutes		
Mean (SD) (mmHg)	15.20 (7.98)	29.40 (15.73)
Median (range) (mmHg)	16 (0, 39)	28 (2, 71)
Median T_{max} (range) (min)	45 (0, 240)	20 (1, 120)
Maximum PR response over 60 minutes		
Mean (SD) (BPM)	14.56 (9.06)	23.88 (11.56)
Median (range) (BPM)	13 (2, 53)	23 (6, 57)
Median T_{max} (range) (min)	45 (1, 240)	15 (1, 180)

Source: Reviewer's analysis based on adxd.xpt dataset for EPI 18.
Abbreviations: BMP, beats per minute; NAC, nasal allergen challenge; PR, pulse rate; SBP, systolic blood pressure; SD, standard deviation; Tmax, time at maximum concentration; L, left; R, right.

For NAC treatment periods, the maximum SBP and PR responses (i.e., the maximum change form baseline) within 60 minutes following the first dose are shown in Table 16 (using average pre-NAC baseline) and Table 17 (using average post-NAC baseline). The maximum SBP and PR responses for both IM and ARS-1 appeared greater using pre-NAC baseline compared to using post-NAC baseline.

Table 16. Maximum SBP and PR Response Following Two Doses of Adrenalin or ARS-1 With NAC (Using Pre-NAC Baseline) in EPI 18

Parameter	Adrenalin (0.3 mg) R/L With NAC N=42	ARS-1 (2 mg) R/L With NAC N=40	ARS-1 (2 mg) R/R With NAC N=41
Maximum SBP response over 60 minutes			
Mean (SD) (mmHg)	13.50 (7.75)	18.25 (11.55)	21.27 (1.23)
Median (range) (mmHg)	13.5 (0, 34)	16 (0, 44)	21 (2, 45)
Median T_{max} (range) (min)	30 (0, 240)	15 (0, 180)	25 (1, 120)
Maximum PR response over 60 minutes			
Mean (SD) (BPM)	14.57 (6.80)	21.83 (9.93)	21.73 (10.19)
Median (range) (BPM)	13.5 (1, 38)	22.5 (3, 44)	19 (7, 47)
Median T_{max} (range) (min)	30 (1, 240)	10 (1, 240)	15 (1, 240)

Source: Reviewer's analysis based on adxd.xpt dataset for EPI 18.
Abbreviations: BMP, beats per minute; NAC, nasal allergen challenge; PR, pulse rate; SBP, systolic blood pressure; SD, standard deviation; Tmax, time at maximum concentration; L, left; R, right.

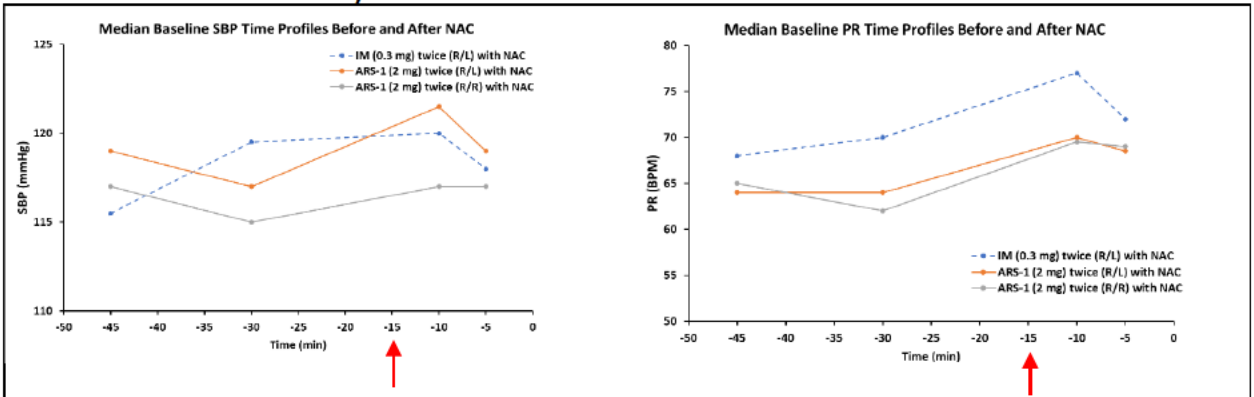
Table 17. Maximum SBP and PR Response Following Two Doses of Adrenalin or ARS-1 With NAC (Using Post-NAC Baseline) in EPI 18

	Adrenalin (0.3 mg) R/L With NAC N=42	ARS-1 (2 mg) R/L With NAC N=40	ARS-1 (2 mg) R/R With NAC N=41
Maximum SBP response over 60 minutes			
Mean (SD) (mmHg)	12.05 (7.61)	14.70 (10.18)	18.90 (11.23)
Median (range) (mmHg)	13.5 (0, 31)	13.50 (0, 35)	19 (0, 46)
Median T_{max} (range) (min)	30 (0, 240)	15 (0, 180)	25 (0, 120)
Maximum PR response over 60 minutes			
Mean (SD) (BPM)	8.52 (6.19)	15.8 (9.29)	17 (10.24)
Median (range) (BPM)	8 (0, 27)	15.5 (0, 36)	16 (0, 47)
Median T_{max} (range) (min)	22.5 (0, 240)	7.5 (0, 240)	15 (0, 240)

Source: Reviewer's analysis based on adxd.xpt dataset for EPI 18.
Abbreviations: BMP, beats per minute; NAC, nasal allergen challenge; PR, pulse rate; SBP, systolic blood pressure; SD, standard deviation; Tmax, time at maximum concentration; L, left; R, right.

When comparing the baseline PD (SBP and PR) values prior to dosing in NAC treatment periods, a trend of increase in both SBP and PR was observed post-NAC compared to pre-NAC, as shown in Figure 15 and Table 18, which suggested that NAC alone may have an small impact on SBP and PR.

Figure 15. Median Pre-Dose SBP and PR Time Profiles Before and After NAC In EPI 18 (NAC Administration: -15 Minutes)



A. Median Pre-Dose SBP-Time Profiles Before and After NAC (NAC Administration: -15 min)

B. Median Pre-Dose PR-Time Profiles Before and After NAC (NAC Administration: -15 min)

Source: Reviewer's analyses based on adxd.xpt for EPI 18.
Red arrow indicates the timing of NAC administration.
Abbreviations: NAC, nasal allergen challenge; PR, pulse rate; SBP, systolic blood pressure; L, left; R, right.

Table 18. Median (Range) Difference Between Pre-NAC and Post-NAC Baseline SBP and PR Values Prior to Dosing in NAC Treatment Periods in EPI 18

	Median (Range) Difference Between Pre-NAC and Post-NAC Baseline Values Prior to Dosing (Average Post-NAC Value − Average Pre-NAC Value)*	
Treatment	**SBP (mmHg)**	**PR (BMP)**
Two doses IM (0.3 mg) R/L	3.5 (-16, 17)	6.5 (-3, 38)
Two doses ARS-1 (2 mg) R/L	3.5 (-10, 15)	6.5 (-5, 24)
Two doses ARS-1 (2 mg) R/R	2 (-13, 20)	4 (-5, 16)

Source: Reviewer's analyses based on adxd.xpt for EPI 18.
* The average pre-NAC PD value for each individual was calculated as a mean for PD values obtained at -45 min and -30 min; The average post-NAC PD value for each individual was calculated as a mean for PD values obtained at -10 min and -5 min.
Abbreviations: BMP, beats per minute; IM, intramuscular (Adrenalin); R, right; L, left; PR, pulse rate; SBP, systolic blood pressure; NAC, nasal allergen challenge; mmHg, millimeter of mercury.

Nasal Conditions Assessed by TNSS Scores:

Pre-NAC/Pre-Dose TNSS

A washout period of at least 3 weeks was implemented between screening and Treatment Period 1 and between each treatment under NAC conditions (Treatment Periods 3 to 5). The TNSS score was assessed prior to dosing and NAC induction at beginning of each treatment, as shown in Table 19. With a score of 0 to 1 for each category, the result suggests that the washout period was sufficient to allow adequate recovery of nasal conditions from previous NAC induction period.

Table 19. Distribution of Pre-NAC Baseline TNSS Scores Prior to Dosing in Each Treatment Period in EPI 18

Variable	Period 1 N=43 n (%)	Period 2 N=43 n (%)	Period 3 N=42 n (%)	Period 4 N=41 n (%)	Period 5 N=41 n (%)
Time	-15 min	-15 min	-30 min	-30 min	-30 min
Congestion score					
0 to 1	43 (100%)	43 (100%)	40 (95.2%)	41 (100%)	40 (97.6%)
2 to 3	0 (0%)	0 (0%)	2 (4.8%)	0 (0%)	1% (2.4%)
Rhinorrhea score					
0 to 1	43 (100%)	42 (97.7%)	40 (95.2%)	41 (100%)	41 (100%)
2 to 3	0 (0%)	1 (2.3%)	2 (4.8%)	0 (0%)	0 (0%)
Itching score					
0 to 1	42 (97.7%)	42 (97.7%)	41 (97.6%)	41 (100%)	41 (100%)
2 to 3	1 (2.3%)	1 (2.3%)	1 (2.4%)	0 (0%)	0 (0%)
Sneezing score					
0 to 1	43 (100%)	42 (97.7%)	41 (97.6%)	41 (100%)	41 (100%)
2 to 3	0 (0%)	1 (2.3%)	1 (2.4%)	0 (0%)	0 (0%)

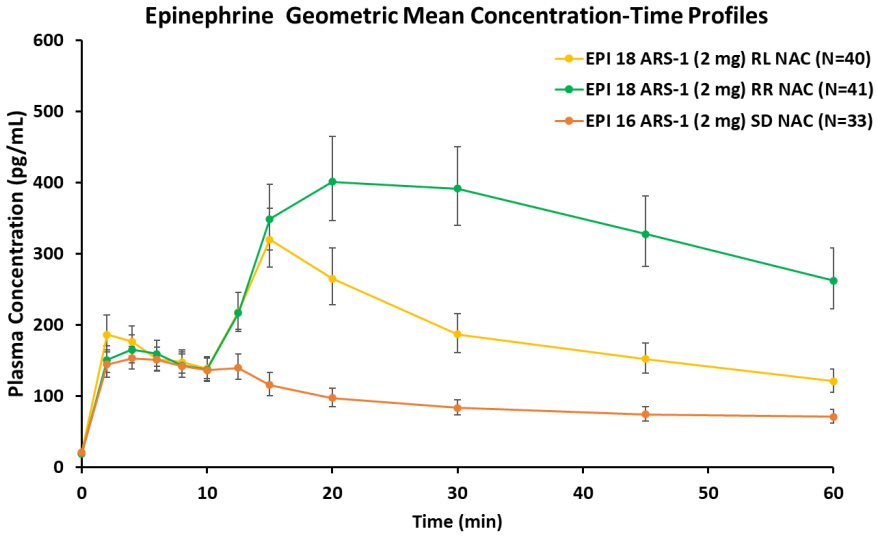
Source: reviewer's analysis based on adyn.xpt dataset for EPI 18.
Abbreviations: NAC, nasal allergen challenge; TNSS, Total Nasal Symptom Score.

Post-NAC/Pre-Dose TNSS in Treatment Periods 3 to 5

In NAC treatment periods, no TNSS scores were assessed post-NAC induction and prior to dosing. Of note, the allergen concentrations used for each subject at the beginning of these treatments were 5-fold higher than the established concentrations that were used to successfully induce nasal edema and congestion in that subject during Screening. See Section 6 for details. The TNSS assessment at time 0 was a post-dose assessment with an allowed window within 2 minutes post-dose.

A single-dose NAC trial was conducted in subjects with allergic rhinitis (EPI 16) and was reviewed in the original NDA. See NDA Multidisciplinary Review dated September 19, 2023. Highly similar PK profiles were observed within 10 minutes after first dose ARS-1 administration under NAC between EPI 18 and EPI 16 based on a cross-study comparison, as shown in Figure 16, which suggested a similar NAC induction effect was achieved in EPI 16 and EPI 18.

Figure 16. Cross-Study Comparison of Epinephrine Plasma Geometric Mean Concentration Time Profiles of ARS-1 (2 mg) With NAC in Trial EPI 16 (One Dose) and EPI 18 (Two Doses)

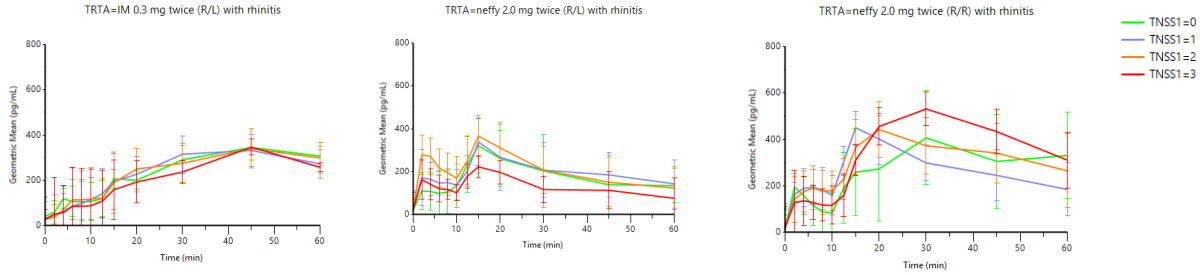


Source: reviewer's analysis based on adyn.xpt dataset for EPI 18.
For EPI 16, the dose was administered 0 min; For EPI 18, the two doses were administered at 0 and 10 minutes.
Abbreviations: R, right; L, left; SD, single dose; NAC, nasal allergen challenge.

PK and PD Subgroup Analysis by Rhinorrhea and Congestion

In EPI 18 NAC treatment periods (Treatment Periods 3 to 5), the impact of nasal conditions on PK was explored based on the scores for rhinorrhea and nasal congestions at drug administration (0 to 2 minutes post dose), as shown in Figure 17. In general, no consistent effect of rhinorrhea or nasal congestion severity on epinephrine PK following Adrenaline IM injection or ARS-1 administration in the same nostril was observed. However, subjects with the most severe rhinorrhea/nasal congestion generally had the lowest epinephrine PK profile when ARS-1 is administered in the alternate nostril.

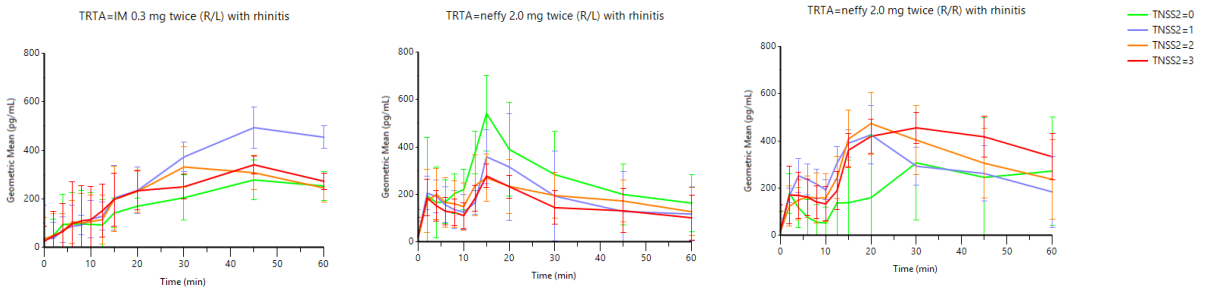
Figure 17. Plasma Epinephrine Geometric Mean Concentrations for Two-Dose Adrenalin (0.3 mg) vs. ARS-1 (2 mg) With NAC Grouped by Rhinorrhea or Nasal Congestion Scores at Drug Administration (0-2 Minutes Post-Dose) In EPI 18



A. Two-Dose IM (0.3 mg) (R/L) With NAC Grouped by Rhinorrhea

B. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Rhinorrhea

C. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Rhinorrhea

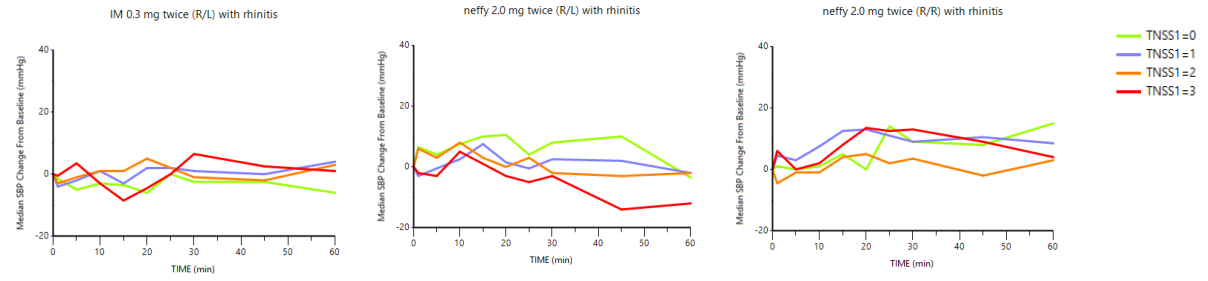


D. Two-Dose IM (0.3 mg) (R/L) With NAC Grouped by Congestion **E. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Congestion** **F. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Congestion**

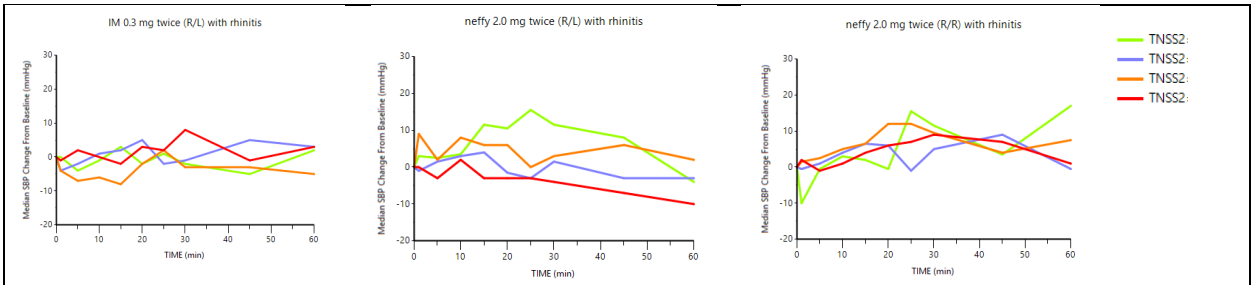
Source: reviewer's analysis based on adyn.xpt and adpc.xpt datasets for EPI 18.
Abbreviations: IM, intramuscular (Adrenalin); L, left; R, right; NAC, nasal allergen challenge; TNSS1, rhinorrhea score; TNSS2, congestion score.

The impact of nasal conditions on PD (SBP and PR) was explored based on scores for rhinorrhea and nasal congestions assessed at drug administration (0 to 2 minutes post dose), as shown in Figure 18 for SBP responses and Figure 19 for PR responses. The PD (SBP and PR) responses were determined using post-NAC baseline SBP and PR values prior to dosing. In general, no consistent effect of rhinorrhea or nasal congestion severity on PD responses following Adrenaline IM injection or ARS-1 administration in the same nostril was observed. However, subjects with the most severe rhinorrhea/nasal congestion generally had the lowest PD responses when ARS-1 was administered in the alternate nostril.

Figure 18. Median SBP Change From Post-NAC Baseline (Average of -10 and -5 min) for Two-Dose Adrenalin (0.3 mg) vs. ARS-1 (2 mg) With NAC Grouped by Rhinorrhea or Nasal Congestion Scores at Drug Administration (0 Minutes) In EPI 18



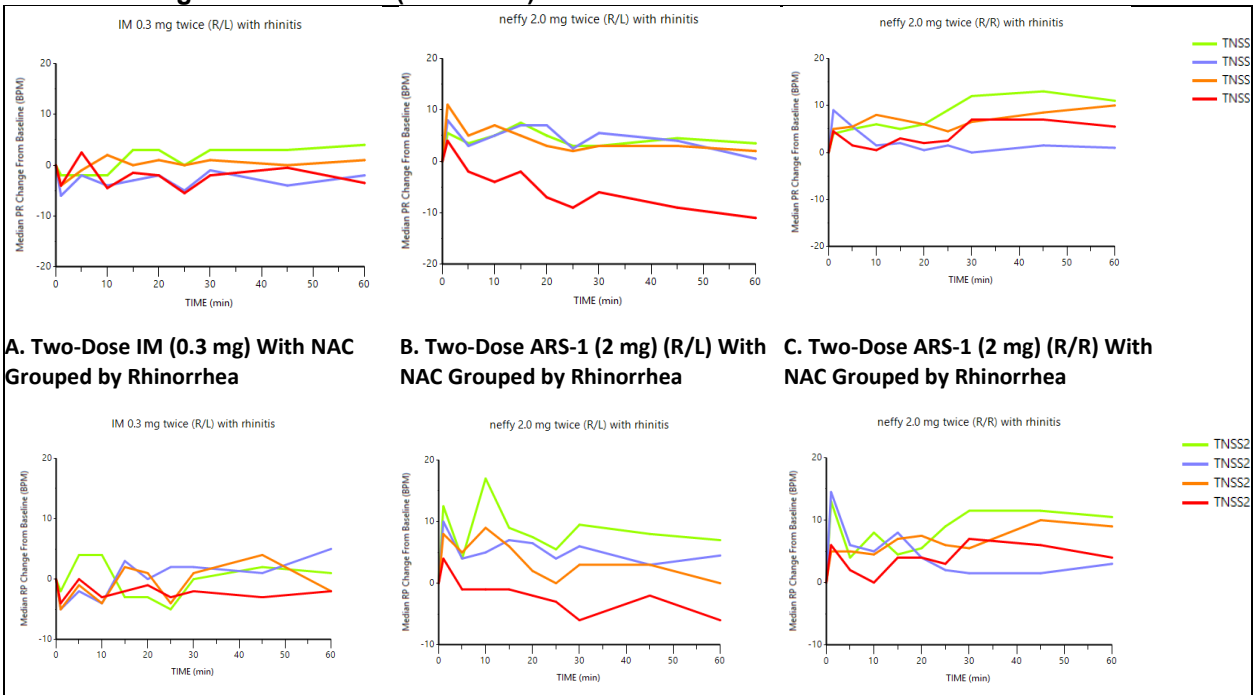
A. Two-Dose IM (0.3 mg) With NAC Grouped by Rhinorrhea **B. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Rhinorrhea** **C. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Rhinorrhea**



D. Two-Dose IM (0.3 mg) With NAC Grouped by Congestion **E. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Congestion** **F. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Congestion**

Source: reviewer's analysis based on adyn.xpt and adxd.xpt datasets for EPI 18.
Abbreviations: IM, intramuscular (Adrenalin); L, left; R, right; NAC, nasal allergen challenge; TNSS1, rhinorrhea score; TNSS2, congestion score.

Figure 19. Median PR Change From Post-NAC Baseline (Average of -10 and -5 min) for Two-Dose Adrenalin (0.3 mg) vs. ARS-1 (2 mg) With NAC Grouped by Rhinorrhea or Nasal Congestion Scores at Drug Administration (0 Minutes) in EPI 18



A. Two-Dose IM (0.3 mg) With NAC Grouped by Rhinorrhea **B. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Rhinorrhea** **C. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Rhinorrhea**

D. Two-Dose IM (0.3 mg) With NAC Grouped by Congestion **E. Two-Dose ARS-1 (2 mg) (R/L) With NAC Grouped by Congestion** **F. Two-Dose ARS-1 (2 mg) (R/R) With NAC Grouped by Congestion**

Source: reviewer's analysis based on adyn.xpt and adxd.xpt datasets for EPI 18.
Abbreviations: IM, intramuscular (Adrenalin); L, left; R, right; NAC, nasal allergen challenge; TNSS1, rhinorrhea score; TNSS2, congestion score.

Conclusions

PK

- The geometric mean epinephrine plasma concentrations following two doses of ARS-1 into the same nostril 10 minutes apart with NAC were higher than those of two doses of Adrenalin with and without NAC within 40 minutes post-dose and became similar afterwards.
- The geometric mean plasma concentrations following two doses of ARS-1 into the alternate nostril 10 minutes apart with NAC were higher than those of two doses of Adrenalin with and without NAC for around 25 to 30 minutes but became lower afterwards.
- The bioequivalence analysis demonstrated 40 to 80 percent higher partial AUCs (0 to 10 minutes, 0 to 20 minutes, 0 to 30 minutes, and 0 to 60 minutes) for two doses of ARS-1 into same nostril with NAC compared to two doses of Adrenalin with NAC. The partial AUCs for two doses of ARS-1 into alternate nostrils with NAC initially had higher early partial AUCs (0 to 10 minutes, 0 to 20 minutes, and 0 to 30 minutes) compared to two doses of Adrenalin with NAC. However, the $AUC_{0\text{-}60min}$ of two doses ARS-1 into alternate nostrils became lower than two doses of Adrenalin with NAC.
- The geometric mean epinephrine systemic exposure within 60 minutes following two doses of ARS-1 into the same nostril with NAC was overall comparable to that of two doses of ARS-1 into the alternate nostril without NAC.

PD

Using post-NAC value as baseline to calculate change in NAC treatment periods:

- For treatment periods with normal nasal conditions, two doses of ARS-1 into alternate nostrils demonstrated higher SBP and PR responses compared to those of two doses of Adrenalin.
- For NAC treatment periods, two doses of ARS-1 into the same nostril generally had higher SBP and PR responses compared to those of two doses of Adrenalin.
- For NAC treatment periods, two doses of ARS-1 into alternate nostrils had higher or comparable median PR and SBP responses within 60 minutes compared to those of two doses of Adrenalin after NAC, except for the lower SBP following ARS-1 into the alternate nostril at 60 minutes post dose.

Using a pre-NAC value as the baseline to calculate the change in NAC treatment periods did not impact the conclusion of the comparison results between two doses of ARS-1 into same nostril and two doses of Adrenalin with NAC. The median SBP and PR responses for two doses of ARS-1 administered into alternate nostrils with NAC were higher or comparable to those of two doses of Adrenalin with NAC, except that they were relatively lower at the last time point (i.e., 60 minutes post-dose).

Effects of NAC on PK and PD

- NAC slightly increased the endogenous epinephrine concentrations prior to dosing by around 2 to 10 pg/mL.
- NAC also increased baseline SBP (2 to 3.5 mmHg) and PR (4 to 6.5 beats per minute) prior to dosing.

PK and PD Subgroup Analysis by Nasal Conditions

- In general, no consistent effect of rhinorrhea or nasal congestion severity on epinephrine PK following Adrenaline IM injection or ARS-1 administration in the same nostril was observed. However, subjects with the most severe rhinorrhea/nasal congestion generally had the lowest epinephrine PK profile when ARS-1 was administered in the alternate nostril.
- In general, no consistent effect of rhinorrhea or nasal congestion severity on PD responses following Adrenaline IM injection or ARS-1 administration in the same nostril was observed. However, subjects with the most severe rhinorrhea/nasal congestion generally had the lowest PD responses when ARS-1 was administered in the alternate nostril.

15.3.2. Bioanalytical Assay Review

The bioanalytical method used for EPI 18 was summarized in the Applicant's Response to Information Request submitted dated April 8, 2024. The Applicant used an existing bioanalytical method (MV(C)-193-23) to assess plasma epinephrine concentration with a detection range of 10.99 pg/mL to 1501.58 pg/mL. Both the clinical site (Novum Pharmaceutical Research Services, Las Vegas NV) and the bioanalytical site (b) (4) (b) (4) for this trial were previously used for EPI 17 and were inspected in the original NDA review. See Multidisciplinary Review dated September 19, 2023, regarding the Office of Study Integrity and Surveillance (OSIS) inspection results summary.

The bioanalytical method validation and in study performance are in line with the guidance and are acceptable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MIYA O PATERNITI
08/05/2024 03:06:59 PM

NDA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214697
Priority or Standard	Standard
Submit Date(s)	August 19, 2022
Received Date(s)	August 19, 2022
PDUFA Goal Date	September 19, 2023
Division/Office	Division of Pulmonology Allergy, and Critical Care, Office of Immunology and Inflammation
Review Completion Date	September 19, 2023
Established/Proper Name	epinephrine nasal spray
(Proposed) Trade Name	Neffy
Pharmacologic Class	(b) (4) alpha- and beta- adrenergic agonist
Code name	ARS-1
Applicant	ARS Pharmaceuticals
Dosage form	Nasal spray
Applicant proposed Dosing Regimen	2 mg as needed for allergic reactions including anaphylaxis. In the absence of clinical improvement or (b) (4) after the initial treatment a second may be administered approximately (b) (4) minutes ((b) (4) minutes) after the first dose.
Applicant Proposed Indication(s)/Population(s)	Immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥30 kg
Recommendation on Regulatory Action	Complete Response

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Reviewers of Multidisciplinary Review and Evaluation

Regulatory Project Manager	Ji Hyun LaRose, PharmD
Nonclinical Reviewer	Xiaochun Chen, PhD
Nonclinical Team Leader	Carol Galvis, PhD
Office of Clinical Pharmacology Reviewer(s)	Qianni Wu, PharmD
Office of Clinical Pharmacology Team Leader(s)	Yunzhao Ren, MD, PhD
Clinical Reviewer	Jennifer Lan, MD
Clinical Team Leader	Miya Paterniti, MD
Statistical Reviewer and Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Miya Paterniti, MD
Associate Director for Therapeutic Review	Kelly Stone, MD, PhD
Division Director	Sally Seymour, MD

Additional Reviewers of Application

OPQ	DS: Sharon Kelly/ Lawrence Perez DP: Xin Feng/ Craig Bertha Process/Facilities: Quamrul Majumder/Christine Falabella Microbiology: Catherine Gilbert/Yan Zheng RBPM: Anika Lalmansingh/Emma Gimose Cai Hong Nina Ni
PLT	Nyedra Booker/Marcia Williams
Microbiology	Catherine Gilbert/ Yan Zheng
OPDP	Quynh-Nhu Capasso/Kyle Snyder
OSIS	Yiyue Zhang/Gopa Biswas/Arindam Dasgupta
OSE/DMEPA	Matthew Barlow/Oluwamurewa Oguntimein/Jason Flint Scott Janiczak/ Lisa Wolf Lissa Owens/ Idalia Rychlik Cristina Attinello/Ameet Joshi
CDRH	Porsche Bennett/Courtney Evans/Alan Stevens
Associate Director for Labeling	Jessica Lee
DPMH	Ndidi Nwokorie/Mona Khurana Katherine Kratz/Miriam Dinatale/Lynne P. Yao

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; CDRH, Center for Devices and Radiological Health; PLT, Patient Labeling Team; OSIS, Office of Study Integrity and Surveillance; DPMH: Division of Pediatric and Material Health

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Xiaochun Chen	Office of New Drugs (OND)/Office of Immunology and Inflammation (OII)/Division of Pharmacology Toxicology for Immunology and Inflammation (DPT-II)	Sections: 5	Select one: _X__ Authored ___ Approved
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S Date: 2023.09.19 10:28:17 -04'00'			
Nonclinical Supervisor	Carol Galvis	OND/OII/DPT-II	Sections: 5	Select one: ___ Authored _X__ Approved
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S Date: 2023.09.19 10:28:48 -04'00'			
Clinical Pharmacology Reviewer	Qianni Wu	Office of Translational Sciences (OTS)/ Office of Clinical Pharmacology (OCP)/ Division of Inflammation and Immune Pharmacology (DIIP)	Section:8, 20.4	Select one: _x__ Authored ___ Approved
	Signature: Qianni Wu -S Digitally signed by Qianni Wu -S Date: 2023.09.19 10:37:03 -04'00'			
Clinical Pharmacology Team Leader	Yunzhao Ren	OTS/OCP/DIIP	Section: 8, 20.4	Select one: _X_ Authored __x_ Approved
	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S Date: 2023.09.19 10:50:59 -04'00'			
Clinical Pharmacology Deputy Division Director	Suresh Doddapaneni	OTS/OCP/DIIP	Section: 8, 20.4	Select one: __ Authored __x_ Approved
	Signature: Suresh N. Doddapaneni -S Digitally signed by Suresh N. Doddapaneni -S Date: 2023.09.19 12:20:24 -04'00'			
Clinical Reviewer	Jennifer Lan	OND/OII/Division of Pulmonology, Allergy, and Critical Care (DPACC)	Sections:1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 13, 15.1, 15.2	Select one: _x__ Authored ___ Approved
	Signature: Jennifer P. Lan -S Digitally signed by Jennifer P. Lan -S Date: 2023.09.19 12:31:36 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Miya Paterniti	OND/OII/DPACC	Sections: 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 13, 15.1, 15.2	Select one: _x__ Authored _x_ Approved
	Signature: Miya Paterniti -S Digitally signed by Miya Paterniti -S Date: 2023.09.19 12:46:04 -04'00'			
Associate Director for Therapeutic Review (Clinical)	Kelly Stone, MD, PhD	OND/ODII/DPACC	Authored: 14 Approved: all	Select one: _x_ Authored _x_ Approved
	Signature: Kelly D. Stone -S Digitally signed by Kelly D. Stone -S Date: 2023.09.19 12:58:02 -04'00'			
Division Director (Clinical)	Sally Seymour, MD	OND/ODII/DPACC	Authored: 14 Approved: all	Select one: _x_ Authored _x_ Approved
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S Date: 2023.09.19 13:04:27 -04'00'			

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
DDM	n-dodecyl-β-D-maltoside
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
IN	intranasal
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
NAC	nasal allergen challenge
NCS	nasal congestion score
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
PADAC	Pulmonary-Allergy Drugs Advisory Committee Advisory Committee
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PMC	postmarketing commitment
PREA	Pediatric Research Equity Act
SAE	serious adverse event
TEAE	treatment-emergent adverse event

1. Executive Summary

1.1. Product Introduction

ARS Pharmaceuticals (the Applicant) submitted a new drug application (NDA) for epinephrine nasal spray (ARS-1) for "the immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥30 kg." Epinephrine administered by injection (intramuscular or subcutaneous), or intravenously in monitored settings, is currently first-line and the only life-saving treatment for anaphylaxis. Epinephrine is a direct-acting, nonselective, sympathomimetic, alpha- and beta-adrenergic agonist that, at high plasma and tissue concentrations, can correct the pathophysiologic conditions of anaphylaxis within minutes (Brown et al. 2020) through vasoconstriction, relaxation of smooth muscle, and increased rate and force of cardiac contractions, leading to decreased mucosal edema, bronchodilation, and increased cardiac output. ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection. ARS-1 is a single-dose (2 mg) epinephrine nasal spray that has a (b) (4) (n-dodecyl-β-D-maltoside (DDM)) to enhance absorption of epinephrine. The solution is packaged into a nasal spray device; the device used is the same as naloxone nasal spray for the treatment of opioid overdose, as well as other approved nasal sprays. The proposed dose is 2 mg administered as one spray (100 µl) into one nostril for children and adults weighing ≥30 kg; if symptoms progress after (b) (4) minutes or any error occurs in administering ARS-1, the Applicant recommends administration of a second dose with a new device. In the remainder of this document, we refer to the 2 mg epinephrine nasal spray product as ARS-1, unless otherwise specified.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is a Complete Response of ARS-1 for the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and children who weigh ≥30 kg, based on uncertainties on the durability of effect in patients with allergen-induced acute rhinitis, which can occur in some patients with anaphylaxis.

To support this application, the Applicant conducted four clinical pharmacology pharmacokinetic (PK)/pharmacodynamic (PD) trials with the proposed 2-mg dose to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. PK/PD trials were not conducted in subjects who were undergoing anaphylaxis and clinical efficacy trials in anaphylaxis were not conducted due to feasibility challenges, specifically limitations in obtaining clinically meaningful data (Section 3.2). Rather, the Applicant proposed to establish substantial evidence of effectiveness by PK bracketing to Adrenalin and EpiPen, as well as supportive hemodynamic PD results (systolic blood pressure (SBP) and pulse rate (PR) change from baseline), in healthy adults and subjects with Type 1 allergic diseases, namely allergic rhinitis; demonstration of effectiveness relies on FDA's prior finding of effectiveness for these listed products (Section 3.1). For this program, Adrenalin and EpiPen were selected as comparators since they are administered with different delivery

systems (i.e., needle-syringe and autoinjector) and demonstrate different PK/PD profiles, with both demonstrating effectiveness based on clinical experience.

In the ARS-1 clinical program, three trials were conducted in adults (18-55 years of age) and one trial was conducted in pediatric subjects (≥30 kg) using the to-be-marketed ARS-1 product:

1. Single and repeat dose trial in healthy adults (EPI 15): Results of this PK/PD trial demonstrated that the PK profile of a single dose of ARS-1 is bracketed by Adrenalin and EpiPen in healthy adults after 10 minutes, and PD responses (SBP and PR) from baseline were generally higher for ARS-1 compared to the listed epinephrine injection products; PK bracketing for the first 10 minutes is based on results from EPI 17, using a cross-study comparison. Repeat injection with epinephrine is recommended for severe persistent anaphylaxis; the PK/PD profile of two, repeat doses of ARS-1 in healthy adults was similar to the results for two, repeat doses of EpiPen, when both were administered 10 minutes apart.
2. Self-administration trial in healthy adults (EPI 17): Self-administration of a single-dose of ARS-1 to adults did not introduce meaningful changes to the PK/PD profile.
3. Nasal allergen challenge trial in adults with seasonal allergic rhinitis (EPI 16): Acute onset rhinitis, with nasal congestion and rhinorrhea, can be features of anaphylaxis; alterations of the nasal mucosa (e.g., vasodilation) may affect the local absorption of epinephrine and rhinorrhea may more rapidly clear ARS-1 from the surface of the nasal mucosa. The nasal allergen challenge approach to inducing acute rhinitis was incorporated into the development program to mimic, in part, findings that may occur in some patients with anaphylaxis, and is critical for demonstrating substantial evidence of effectiveness for this development program that does not include a clinical efficacy trial. In subjects with acute, allergen-induced rhinitis, ARS-1 demonstrated a more rapid absorption phase during the first 10 minutes, compared to Adrenalin, followed by a more rapid decline in epinephrine plasma concentration, with epinephrine mean plasma concentrations dropping below Adrenalin starting around 20 minutes postdose, demonstrating lower PK sustainability. Although hemodynamic PD responses (SBP and PR change from baseline) for ARS-1 in subjects with allergen-induced rhinitis also demonstrated a more rapid increase postdose compared to Adrenalin, the median SBP change from baseline remained comparable to that of Adrenalin 0.3 mg throughout 60 minutes postdose; however, the median PR response for ARS-1, became lower than Adrenalin after 5 minutes.

   The decline of mean epinephrine plasma concentration following ARS-1 in subjects with allergen-induced rhinitis at 20 minutes postdose, compared to epinephrine injection, raises concerns with the durability of effect in anaphylaxis patients with acute, allergen-induced rhinitis. The sustained ARS-1 SBP through 60 minutes compared to Adrenalin is not sufficient to obviate this concern as PD sustainability was not demonstrated for PR, and uncertainty remains on the translatability of PD from healthy volunteers to patients with anaphylaxis.

   The rapid PK decline also raises concern for the potential for more frequent need for an additional ARS-1 dose compared to the rates reported for epinephrine injection products.

Repeat dose administration under nasal allergen challenge conditions was not evaluated in this development program. Whether two doses of ARS-1 will have sufficient durability of effect for patients with allergen-induced acute rhinitis who require one dose of epinephrine injection or patients with severe persistent anaphylaxis who require two doses of epinephrine injection is unknown. The lack of PK/PD data with repeat administration under nasal allergen challenge conditions raises uncertainty of effectiveness in anaphylaxis patients with allergen-induced rhinitis, if a second dose is needed. Therefore, a repeat dose study in patients with acute allergen-induced rhinitis is needed to provide the needed PK/PD profile to reduce this uncertainty.

4. Pediatric single dose trial in pediatric subjects ≥30 kg with systemic (Type I) allergies that require epinephrine prescription (EPI 10): For the pediatric population ≥30 kg, ARS-1 demonstrated PK/PD similarity of ARS-1 in subjects who weigh ≥30 kg compared to that of adults. The age of the cohort ranged from 8 to 17 years of age, with a median of 14 years of age. Given that there is a high degree of similarity in anaphylaxis between adult and pediatric subjects, with both resulting from acute activation of mast cells and/or basophils, and that there is an established response to treatment with epinephrine in pediatric subjects that is highly similar to that observed in adults, extrapolation of efficacy from adults is reasonable.

Due to the novel route of administration and the complexities of this development program, including reliance on PK and PD bridging and the lack of clinical efficacy trials, this NDA was discussed at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting on May 11, 2023. The majority of the PADAC indicated that a clinical efficacy trial was not needed, given the challenges in designing an interpretable trial for anaphylaxis, and voted in support of a favorable benefit-risk assessment of ARS-1 for adults (16 yes, 6 no) and children ≥30 kg (17 yes, 5 no) based on the available PK/PD data (Section 10). However, while many panel members voted for approval of the product, in part based on the ease of administration and, therefore, likely improved compliance and earlier administration compared to epinephrine injection products, they did relay residual uncertainty that may or may not be addressed with further studies, and that they would want to see additional studies under a postmarketing commitment or requirement, including clinical data. Many members relayed uncertainty in PK/PD data and translatability to anaphylaxis treatment and noted the need for additional data in patients with anaphylaxis given the consequences of having an ineffective product for treatment of a life-threatening condition in the setting of available therapies. Overall, many of the members noted the benefits of the nasal route of administration may outweigh risks based on residual uncertainty, which was described as a “leap of faith” by one PADAC member.

Overall, the PK/PD results from the adult studies, EPI 15 and EPI 17, and the pediatric study in children <18 years of age and ≥30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products to demonstrate substantial evidence of effectiveness, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and >100 years of use. The PK/PD results under the nasal allergen challenge conditions from EPI 16, in adults ≥18 years of age with allergic rhinitis, demonstrated adequate PK and PD responses in the first 20 minutes postdose; however, the lack of sustainability of epinephrine

concentrations for ARS-1 after 20 minutes when compared to Adrenalin raises uncertainty as to the durability of effect in anaphylaxis patients with allergen-induced acute rhinitis. The discrepant SBP and PR comparison results between ARS-1 and Adrenalin made interpretation of the PK/PD results even more challenging. Due to the complex interaction between nasal congestion and local pharmacologic effect of epinephrine following the initial administration of ARS-1, there is uncertainty in leveraging the PK/PD results from trials EPI 15 and 16 to simulate the epinephrine PK/PD profiles following the repeat dose of ARS-1 under nasal allergen challenge conditions. Anaphylaxis is a life-threatening emergency and approval for this indication requires a high level of confidence in the PK/PD results under conditions likely to be encountered by the target population. Approximately 10% of patients with anaphylaxis require a second dose of epinephrine Injection products; due to the lack of sustainability of PK following single dose of ARS-1 under nasal allergen challenge conditions, a higher percentage of patients may require a second dose. In addition, proposed labeling for ARS-1, in alignment with labeling for approved epinephrine injection products, recommends administration of a second dose for patients with severe persistent anaphylaxis. Adequate PK/PD data for repeat dose administration under nasal allergen challenge conditions are needed to have confidence in the results sufficient to support approval. In addition, since the initial dose of ARS-1 administered under acute rhinitis conditions may impact the PK/PD profile of a subsequent dose administered in the same naris, a repeat dose study should also address PK/PD profiles with repeat dosing under nasal allergen challenge conditions when administered in the ipsilateral or contralateral naris, reflective of anticipated real-world use.

Due to the lack of observed PK/PD data from repeat dose administration under nasal allergen challenge conditions, including uncertainty of PK/PD profile with ipsilateral and contralateral naris administration, the application does not adequately demonstrate substantial evidence of effectiveness or a favorable benefit-risk assessment for ARS-1 in the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and children who weigh ≥30 kg. As a result, the recommended regulatory action is **Complete Response**.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Epinephrine administered by injection (intramuscular or subcutaneous), or intravenously in a monitored setting, is currently first-line and the only life-saving treatment for anaphylaxis. The use of epinephrine injection for the treatment of anaphylaxis is based on historical and anecdotal use for >100 years; adequate and well-controlled clinicals trials to demonstrate efficacy have not been conducted. Early administration of epinephrine is recommended as fatal anaphylaxis is associated, in some cases, with delayed administration of epinephrine. Barriers to administration of epinephrine for treatment of anaphylaxis are multifactorial, but they include fear of injection. Availability of alternative routes of administration of epinephrine, such as by the nasal route, may improve compliance and time to administration for epinephrine, and result in improved outcomes.

ARS-1, an epinephrine nasal spray, was developed for the emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥30 kg. ARS-1 is the first epinephrine product proposed for treatment of anaphylaxis that is not administered via injection. The Applicant conducted four PK/PD trials to support a 505(b)(2) pathway, by establishing a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via PK bracketing, with additional support provided by hemodynamic PD results, namely SBP and PR change from baseline. No clinical efficacy studies were conducted for ARS-1 administered during anaphylaxis and no PK/PD studies were conducted in patients undergoing anaphylaxis due to feasibility concerns.

Three PK/PD trials were conducted in adults (EPI 15, EPI 16, and EPI 17) and one was conducted in pediatric subjects ≥30 kg (EPI 10). ARS-1 PK was bracketed by Adrenalin and EpiPen following single dose administration, and administration of two doses of ARS-1 demonstrated similar PK/PD findings to two doses of EpiPen in healthy subjects (EPI 15). PD response (SBP and PR change from baseline) was generally higher for ARS-1, compared to epinephrine injection. Self-administration of ARS-1 did not introduce meaningful changes to the PK/PD profile (EPI 17). ARS-1 administered under acute, allergen-induced rhinitis conditions was assessed as acute allergen-induced rhinitis can occur in anaphylaxis. ARS-1 declined to below the PK of Adrenalin at 20 minutes; PD responses, specifically SBP, remained comparable to Adrenalin 0.3 mg throughout 60 minutes postdose. Despite the durability of PD, the decline in PK at 20 minutes, compared to epinephrine injection, raises concerns with the durability of the effect in patients with acute allergen-induced rhinitis and whether this would lead to more patients requiring a second dose of ARS-1, or whether patients with severe persistent anaphylaxis would be adequately treated with a second dose of ARS-1. Proposed labeling for ARS-1, in alignment with labeling for approved epinephrine injection products, recommends a second dose for patients with severe persistent anaphylaxis. Repeat dose administration of ARS-1 under acute allergen-induced rhinitis was not assessed in this development program. A repeat dose study in patients with acute allergen-induced rhinitis is needed to fully inform the PK/PD for a repeat dose of ARS-1 compared to a repeat dose of epinephrine injection.

The PK/PD of single-dose ARS-1 was assessed in children ≥30 kg (8-17 years of age) with systemic Type 1 allergy requiring an epinephrine prescription. ARS-1 demonstrated PK/PD similarity of ARS-1 in pediatric subjects who weigh ≥30 kg compared to that of the adults. Given that there is a high degree of similarity in anaphylaxis between adult and pediatric subjects, with both resulting from acute activation of mast cells and/or basophils, and that there is an established

response to treatment with epinephrine in pediatric subjects that is highly similar to that observed in adults, extrapolation of efficacy to children is reasonable.

For safety, ARS-1 systemic safety relies on the safety of epinephrine injection listed products as epinephrine exposure with ARS-1 is not higher than approved injection products. The limited systemic safety adverse event profile of ARS-1 from the PK studies did not raise any safety concerns. As this is a new route of administration, local nasal adverse events are of interest. Local adverse events included nasal discomfort, rhinorrhea, and throat discomfort. Although the overall safety database was small, the local adverse event profile of ARS-1 did not raise any concerns. As the studies were limited with the majority of subjects receiving only one dose, the local adverse event profile is not well defined for more frequent use.

The review team recommends a Complete Response due to the uncertainty of durability of effect in subjects with allergen-induced acute rhinitis, which can be seen in anaphylaxis, including in patients with severe persistent anaphylaxis who require two doses. Overall, the PK/PD results from adults and children ≥30 kg provide a scientific bridge to approved epinephrine injection products to rely on FDA's prior findings of safety and effectiveness of EpiPen and Adrenalin. However, since this development program relies solely on bridging PK/PD to approved epinephrine injection products, anaphylaxis is a life-threatening emergency, and approval for this indication requires a high level of confidence in the PK/PD results under conditions likely to be encountered by the target population, the PK/PD results from the nasal allergen challenge model are not adequate to demonstrate substantial evidence of effectiveness for this new route of administration. Although the Agency acknowledges the ease of administration of a non-injection route of administration, and therefore, likely improved compliance and earlier administration compared to epinephrine injection products, complete PK/PD data under allergen-induced, acute rhinitis conditions, including repeat administration in the ipsilateral or contralateral naris, are needed to have confidence that two doses of ARS-1 will provide PK/PD results comparable to those from two doses of a listed epinephrine injection product to support a favorable benefit-risk assessment for ARS-1 in the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and children who weigh ≥30 kg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Anaphylaxis is an acute, potentially life-threatening, systemic allergic reaction; approximately 200 deaths occur per year in the United States. • A large population in the US is at risk of anaphylaxis, primarily due to allergy to foods, drugs, and Hymenoptera venom, among other causes. • Although risk factors for fatal anaphylaxis have been described, it is not possible to identify patients at risk for fatal reactions based solely on these risk factors	Anaphylaxis is an emergency condition that can occur suddenly and can be rapidly progressive and fatal.
Current Treatment Options	• Epinephrine injection is the first-line and only available life-saving treatment for anaphylaxis. Adequate and well-controlled clinicals trials to demonstrate efficacy have not been conducted; evidence for efficacy is based on animal models, case series, expert opinion, and >100 years of use. • Approved epinephrine injection products include vials, prefilled syringes, and auto-injectors for adults and children • Early administration of epinephrine reduces morbidity and mortality from anaphylaxis • Epinephrine injection products are frequently underused or administration is delayed, increasing the risk of morbidity and mortality. Causes for delayed administration, or failure to administer epinephrine, include epinephrine being unavailable at the time of reaction, anaphylaxis not being recognized, and hesitation to inject due to needle-phobia.	Epinephrine injection products are safe and effective. Barriers to administration of epinephrine injection for treatment of anaphylaxis include needle phobia. There is an unmet need for alternative routes of administration for epinephrine that may increase use and reduce time to administration.
Benefit	• ARS-1 provides an alternative to the injection route of epinephrine administration, which may improve compliance and earlier administration of epinephrine. • Clinical efficacy trials were not conduced due to feasibility concerns	Early administration of epinephrine is the cornerstone of anaphylaxis management. This new ROA has the potential to address barriers to epinephrine administration by fostering improved compliance and earlier administration compared to epinephrine injection products. Efficacy of ARS-1 is established through PK bracketing to Adrenalin and EpiPen, and supportive hemodynamic PD markers, with reliance on the Agency's finding of safety and effectiveness of both listed products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• PK/PD studies in adults and children, not undergoing anaphylaxis, establish a scientific bridge to approved epinephrine injection products (EpiPen and Adrenalin) to rely on FDA's prior findings of safety and effectiveness – The PK profile of a single dose of ARS-1 is bracketed by Adrenalin and EpiPen. – The PK profile of two doses of ARS-1 was similar to two doses of EpiPen dosed 10 minutes apart. – ARS-1 PD (SBP and PR) was generally higher compared to EpiPen and Adrenalin and is supportive. • Lack of sustainable PK under allergen-induced acute rhinitis conditions raises concerns regarding the durability of effect of ARS-1 – ARS-1 administration during allergen-induced acute rhinitis was notable for epinephrine PK dropping below Adrenalin at 20 minutes, raising questions regarding durability of effect. ARS-1 SBP (but not PR) is above Adrenalin through 60 minutes post administration. – Repeat doses of ARS-1 under allergen-induced acute rhinitis conditions were not assessed; the PK/PD compared to single and repeat dose epinephrine injection is unknown. – Impact on PK/PD of the initial dose of ARS-1 on a repeat dose of ARS-1 under acute rhinitis conditions in the same naris is unknown.	Allergen-induced acute rhinitis can occur with anaphylaxis. Single-dose ARS-1 in patients with allergen-induced acute rhinitis demonstrated a decline in PK at 20 minutes, compared to Adrenalin, which raises concerns with the durability of the effect, and whether this would lead to more patients requiring a second dose of ARS-1 or whether patients with severe persistent anaphylaxis would be adequately treated with a second dose of ARS-1. Based on the severity of the indication and lack of clinical efficacy studies, approval for this new route of administration requires a high level of confidence on the PK/PD results. The PK/PD results in subjects with allergen-induced acute rhinitis are not adequate to demonstrate substantial evidence of effectiveness.
Risk and Risk Management	• Systemic safety relies on the known safety profile of epinephrine injection products. Systemic adverse reactions include headache, nausea, vomiting, anxiety, apprehensiveness, restlessness, tremor, weakness, sweating, palpitations, pallor, and respiratory difficulties. • Local safety is based on the safety data obtained from the ARS-1 development program, most of which includes only single dose administration. Local adverse reactions observed with ARS-1 included nasal discomfort, rhinorrhea, and throat irritation. The majority of adverse events were reported as mild. • Local safety with administration of multiple doses of ARS-1 was limited.	The adverse event profile of ARS-1 did not result in an unexpected safety profile. The single and repeat dose PK studies did not raise safety concerns beyond the established systemic safety of epinephrine injection products. The local adverse event profile for more frequent use is not well defined. The risks can be managed through labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		As epinephrine is used in the emergency setting and will likely be of infrequent and/or intermittent use, the safety data obtained from single and repeat dose PK studies is reasonable.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient-reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
X	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports		September 9, 2021, externally led Patient-Focused Drug Development for food allergy
	□	Observational survey studies designed to capture patient experience data		
	X	Other: (Please specify):		Public comments at Pulmonary-Allergy Drugs Advisory Committee meeting to discuss application
	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly, usually after contact with an allergy-causing substance in a sensitized individual (Sampson et al. 2006). Anaphylaxis is a complex condition and presenting symptoms can be varied and progression can be unpredictable. Typical symptoms include, but are not limited to, 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.

The lifetime prevalence of anaphylaxis is estimated to range from 1.6% to 5.1% (Shaker et al. 2020). Risk factors for severe anaphylaxis include cardiovascular disease, asthma, older age, and additional coexisting comorbid conditions (Shaker et al. 2020). An estimated 1% of hospitalizations and 0.1% of emergency department admissions for anaphylaxis result in a fatal outcome (Turner et al. 2017). Fatal anaphylaxis usually occurs within 60 minutes of exposure to an allergenic substance, and most frequently within 5 to 35 minutes of exposure (Pumphrey 2000). Although fatal anaphylaxis is rare, a significant number of people are at risk for anaphylaxis, such as those who have food allergy, venom allergy, and drug allergy, among others Systemic reactions to Hymenoptera venom affect around 3% of the U.S. population, while food allergy impacts approximately 10% of the U.S. population, and adverse drug reactions (not limited to hypersensitivity reactions) affect up to 10% of the population. In a review of International Classification of Diseases, 10th Edition codes from a U.S. National Morality Database (1999 to 2010), 2458 fatal anaphylaxis cases were coded leading to an estimated prevalence of fatal anaphylaxis of 0.69 per million (approximately 232 deaths/year based on the U.S. population) (Jerschow et al. 2014).

2.2. Analysis of Current Treatment Options

Epinephrine injection is approved for treatment of anaphylaxis and is considered the first-line and only life-saving treatment for anaphylaxis. Early recognition and prompt administration is the cornerstone of management for anaphylaxis (Shaker et al. 2020). The use of epinephrine for the treatment of anaphylaxis is based on historical and anecdotal use and is considered the standard of care by national and international guidelines. Epinephrine is a direct-acting, nonselective, sympathomimetic, alpha and beta-adrenergic agonist that, at high plasma and tissue concentrations, can correct the pathophysiologic conditions of anaphylaxis within minutes (Brown et al. 2020). Epinephrine causes vasoconstriction, relaxation of airway smooth muscle, and increased rate and force of cardiac contractions, leading to decreased mucosal edema, bronchodilation, and increased cardiac output (Simons and Simons 2010). In addition, epinephrine has been shown to prevent additional release of histamine, tryptase, and other mediators, preventing escalation of anaphylaxis (Sampson et al. 2006).

Epinephrine injection (IM or subcutaneous route) is approved for the emergency treatment of anaphylaxis in: 1) unsupervised community settings with fixed doses, and 2) healthcare settings where dosing can be administered at approved fixed doses or as a mg/kg dose, with upper limit doses established (Table 1). The currently approved epinephrine products for the treatment of anaphylaxis are listed in (Table 2). Of note, dosing can be repeated with severe persistent anaphylaxis, with national and international guidelines recommending dosing every 5 to 15 mins (Sampson et al. 2006). Epinephrine injection products prescribed for the community setting are generally dispensed as a two-pack. Although there is limited information regarding the proportion of subjects who require more than one dose of epinephrine injection, literature reports rates as high as 20% (Boyce et al. 2010).

Table 1. Approved Doses of Epinephrine in the Medical and Community Settings

Setting	7.5 kg to 15 kg	15 kg to 30 kg	≥30 kg
Community	0.1 mg	0.15 mg	0.3 mg
Medical	<30 kg		≥30 kg
	0.01 mg/kg up to 0.3 mg		0.3 – 0.5 mg

Source: Prescribing information

Table 2. Approved Epinephrine Products

Type of Product Drug Product *(Sponsor)*	Year of Approval	Dosage Strength	Dosage Form
Autoinjectors			
EpiPen/EpiPen JR and authorized generic *(Mylan Specialty LP)*	1987	0.15 mg/injection 0.3 mg/injection	Single dose, autoinjector
Adrenaclick and authorized generic (*Impax Labs, Inc.)*	2003	0.15 mg/injection 0.3 mg/injection	Single dose, autoinjector
Auvi-Q *(Kaleo, Inc.)*	2012	0.1 mg/injection 0.15 mg/injection 0.3 mg/injection	Single dose, autoinjector
Generic EpiPen/EpiPen JR *Teva*	2018	0.15 mg/injection 0.3 mg/injection	Single dose, autoinjector
(b) (4) syringe (home use)			
Symjepi *(Adamis Pharms Corp)*	2017	0.3 mg/0.3 mL	Single dose, prefilled syringe
Vial-syringe (medical setting only)			
Adrenalin and epinephrine injection *(Multiple companies)*	2012	1 mg base/mL	Single use and multidose vial

Source: Clinical and clinical pharmacology reviewers

Although the approved fixed doses have been used in the community for decades, the optimal epinephrine dose for treatment of anaphylaxis is unknown. No dose-ranging or clinical efficacy trials have been conducted to support the recommended epinephrine dose for treatment of anaphylaxis (Simons 2011); the weight-based and fixed-dose IM or subcutaneous doses are based on anecdotal clinical experience. Of note, the 0.1-mg dose in children weighing 7.5 to 15 kg was approved based on extrapolated PK results, with reasonable allometric scaling.

Although epinephrine is the first-line treatment for anaphylaxis, underuse and delayed use of epinephrine are common. Review of epinephrine for treatment of anaphylaxis across multiple countries demonstrated varying use from 14% to 56% of anaphylaxis subjects receiving epinephrine (Lieberman and Wang 2020). The reasons for this underuse include:

1. Not recognizing anaphylaxis: Subjects, caregivers, and healthcare providers may not recognize signs and symptoms of anaphylaxis. Education on anaphylaxis, however, does not fully explain the lack of epinephrine use. In one Emergency Department trial in Minnesota, despite education on signs of anaphylaxis and epinephrine use to Emergency Department staff members, actual real-world epinephrine use in the Emergency Department only increased from 33% to 51% for those who required epinephrine despite having the education and access to epinephrine (Manivannan et al. 2014).
2. Lack of access to epinephrine: In the United States, high cost, supply chain, and injection device issues lead to issues with procurement (Westermann-Clark et al. 2018; FDA 2022).
3. Lack of immediate access to epinephrine: Studies have shown that many subjects do not fill epinephrine prescriptions or fail to keep epinephrine near them at all times (Warren et al. 2018). Studies attempting to increase epinephrine carriage with text reminders and financial incentives found these attempts did not lead to a robust increase in the overall carriage rate (Spina et al. 2012; Cannuscio et al. 2015).
4. Having immediate access to epinephrine but failing to use it: Although this issue is less common than not having an epinephrine injection product during a reaction, some subjects, despite having access to an epinephrine injection product at the time of anaphylaxis, fail to use it. Studies found that the patient or caregiver did not administer epinephrine as they 1) did not believe the reaction was serious, 2) did not understand how to use the device, and/or 3) had a fear of using the device (Fleischer et al. 2012; Warren et al. 2018).

A needleless route of epinephrine administration may foster improved compliance and earlier use of epinephrine to treat anaphylaxis for subjects and caregivers who hesitate to use or administer an injection.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Epinephrine Regulatory History

Epinephrine has been marketed in the U.S. since 1901, predating both the original Federal Food and Drugs Act (1906), which prohibited interstate commerce of adulterated or misbranded drugs, and the Federal Food, Drug, and Cosmetic Act of 1938, which required that new drugs be demonstrated to be safe for approval. In 1962, Congress passed the Kefauver-Harris amendment to the Federal Food, Drug, and Cosmetic Act of 1938, adding the new requirement that new drugs be shown to be effective, as well as safe, to obtain approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of drug products

that had been approved by the Agency as safe between 1938 and 1962; the Agency's administrative implementation of the effectiveness evaluations was called the Drug Efficacy Study Implementation process. Since epinephrine had been marketed since 1901, preceding passage of the 1938 Federal Food, Drug, and Cosmetic Act, it was not subject to a Drug Efficacy Study Implementation review. However, epinephrine was still required to comply with good manufacturing procedures and adequate labeling to ensure safe use.

In 1987 EpiPen and EpiPen Jr. were the first epinephrine injection products approved that remain on the market today. EpiPen was approved by FDA based upon literature support for efficacy and safety; clinical trials and PK/PD data were not required. More recent approvals of epinephrine injection products for anaphylaxis have been based on the established efficacy and safety of an FDA approved epinephrine injection product for anaphylaxis (e.g., EpiPen), chemistry/manufacturing/device data, and human factor assessments to evaluate the user interface with the drug-device combination. PK and in vivo bioequivalence data were not required for the approval of more recent epinephrine injection products because of similarity of the formulations and route of administration between the new epinephrine injection product and the approved reference epinephrine product. Therefore, approved epinephrine injection products on the market today for the treatment of anaphylaxis were not required to submit bioequivalence or clinical data for approval.

3.2. Summary of Presubmission/Submission Regulatory Activity

Presubmission Development

ARS PK/PD Program Development

ARS first engaged FDA about its epinephrine nasal spray program in 2018. There was no regulatory precedence for development of alternative route of administration for epinephrine. ARS proposed a PK/PD development program utilizing a 505(b)(2) regulatory pathway, relying on FDA's previous finding of safety and effectiveness of an approved epinephrine injection product. The major focus of discussions between FDA and ARS during product development was the scope of the program necessary for ARS to establish a scientific and regulatory bridge to an approved epinephrine injection product. FDA raised concerns regarding reliance solely on PK/PD data. Early discussions included whether the focus should be on PK or PD parameters (discussed in more detail below). There were questions about the most relevant PK parameter(s) to predict efficacy, as well as concerns that changes in the nasal mucosa during anaphylaxis may impact epinephrine absorption. The need for clinical efficacy trials was considered and clinical trial scenarios were discussed, but feasibility concerns were acknowledged. Ultimately, the Applicant and FDA agreed on a clinical pharmacology program to provide data to provide a scientific bridge/justification to establish the efficacy and safety for ARS-1. Because of uncertainties with a PK/PD approach, FDA noted that this program would need discussion by an FDA advisory committee.

In interactions with the Applicant during the development of ARS-1, FDA identified the following concerns and challenges that ARS would need to address.

Carryover Effect and Dose Selection

ARS initially intended to develop a 1 mg epinephrine dose for adults, as a crossover Trial, EPI 3, demonstrated that the mean epinephrine PK profile of 1 mg ARS-1 summarized from several nasal spray treatment periods was within the range of PK profiles from two dose levels of Adrenalin (i.e., 0.3 mg and 0.5 mg) IM injection. However, a subsequent analysis indicated that this mean PK profile of 1 mg ARS-1 was inflated because the epinephrine PK profiles for ARS-1 in the later nasal spray treatment periods of EPI 3 were several times higher than the first nasal spray treatment period. Further, this inflated mean PK profile following ARS-1 administration was consistently confirmed in all the previously conducted PK studies with crossover design for the epinephrine nasal spray treatment periods. Although the cause was unclear, the phenomenon was referred to as a *carryover effect*.

Interestingly, this carryover effect was not immediately observed for the second dose of ARS-1 administered 10 minutes after the first dose but peaked around 2 days following the previous ARS-1 administration. Therefore, the mean epinephrine PK profile of 1 mg ARS-1 summarized from EPI 3 is not representative of the actual epinephrine PK profile for a single or repeat dose. Of note, the carryover effect was not observed following IM epinephrine injection in the same crossover design. On review of nonclinical studies, it is hypothesized that reversible nasal mucosal damage may take some time (i.e., no immediate carryover effect) to develop following the first nasal spray administration; and the damage peaks in 1 to 2 days, which allows for an increased absorption from the second dose of epinephrine nasal spray.

ARS successfully mitigated the carryover effect by substantially expanding the washout period between intranasal (IN) treatment periods in crossover trials. After the identification of the carryover effect and implementation of a longer washout period, the Applicant reassessed ARS-1 with additional formulation-exploration and dose-ranging studies. Based on the results from these studies, a 2 mg ARS-1 product was selected to move forward in the program.

Challenges for PK Bridging

General Considerations for PK Extrapolation From Healthy Subjects to Subjects With Anaphylaxis

The Division considered that well overlayed PK profiles, between ARS-1 and a listed epinephrine injection product, could reflect similarity of real-time absorption, distribution, and elimination of epinephrine following the two routes of administration in healthy subjects. The Division was concerned that the absorption phase of the PK could be different in subjects with nasal edema, which could occur in subjects with anaphylaxis. Therefore, the Division requested the Applicant characterize the epinephrine PK profile of ARS-1 under a condition mimicking the nasal mucosa edema seen in anaphylaxis. The Division and Applicant agreed that nasal congestion induced by nasal allergen challenge (NAC) in subjects with seasonal allergic rhinitis was a reasonable model to address this concern.

PK Data Variability, Critical PK Parameters, Bracketing Approach

The Division noted the high inter- and ultraproduct PK variability between epinephrine injection products, as well as variability between batches within one product. This PK variability

introduces uncertainties in comparative studies, particularly when there is an absence of clinical data to establish critical PK parameters for efficacy. Thus, selection of appropriate and representative comparators in these comparative PK studies is critical to support accurate interpretation of trial results.

In addition to traditional PK parameters, such as C_{max} and $AUC_{0\text{-}inf}$/$AUC_{0\text{-}t}$, the Division also considered the following PK characteristics as meaningful in the evaluation of any epinephrine product to be used to treat anaphylaxis:

- The initial epinephrine absorption rate/early partial AUC values.
- The sustainability of epinephrine plasma concentration.

The Division acknowledges that there are no threshold values available for the absorption rate, critical plasma concentration, and sustained time for critical plasma concentrations of epinephrine for the treatment of subjects with anaphylaxis. Therefore, bracketing to approved epinephrine injection products allows us to establish a reasonable, relative reference range for the PK profiles. Bracketing with 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. Accordingly, the objective of the dedicated PK matching trial is to reasonably bracket the epinephrine PK profile from the epinephrine nasal spray by the PK profiles from at least two listed epinephrine injection products using a crossover design. The concept of "PK matching" through a bracketing strategy is the foundation for a scientific and regulatory bridge between ARS-1 and listed epinephrine injection products in the ARS-1 clinical pharmacology program.

Impact of IN Epinephrine on Absorption

Unlike the vasodilatory effect observed in skeletal muscle following IM injection of epinephrine, IN administration of epinephrine is expected to cause vasoconstriction in the nasal mucosa, a mechanism utilized by alpha adrenergic agonistic nasal decongestants. The Division questioned whether the absorption of a second IN dose of epinephrine, if needed, may be impaired due to local vasoconstriction following the first IN dose of epinephrine. Therefore, the Division requested ARS to evaluate and compare epinephrine PK profiles following a second dose, between ARS-1 and the listed epinephrine injection products. We note that the effect of IN epinephrine on the absorption of subsequent IN doses could differ between healthy volunteers and subjects with anaphylaxis due to the pathophysiology of anaphylaxis, such as nasal mucosal edema, affecting epinephrine pharmacology.

Impact of HF and Actual Use

A HF assessment was required for this development program to assess the user interface. The goal of HF validation studies is to demonstrate that the final finished user interface supports safe and effective use of the product by intended users, for intended uses, and under the expected conditions (including environment(s) of use).

To reduce PK variability caused by administration differences, trial staff administered ARS-1 to subjects in all the clinical pharmacology studies; this represented an idealized use situation. Whether self-administration changed the PK profile of ARS-1 was a question that FDA raised. Therefore, the Division requested the Applicant conduct an actual use PK trial (e.g., self-administration clinical trial) to characterize epinephrine PK profiles in subjects following self-administered IN spray.

Pediatric Considerations

To comply with the Pediatric Research Equity Act, which requires a pediatric trial plan due to the change of administration route of approved epinephrine injection products, the Applicant proposed an ARS-1 pediatric drug development program. Given differences in shape, size, and surface area of the nasal cavity in children compared to adults, the Division requested a dose-ranging trial in pediatric subjects across all ages and body weights.

PD as Supportive Endpoint

There are expected differences between healthy volunteers and subjects with anaphylaxis in hemodynamics, vasoactive hormone/cytokine levels, and baroreceptor responses; whether PD results in healthy volunteers translate to similar benefits in the setting of anaphylaxis is unknown. While PD responses (i.e., SBP, DBP, HR) may reflect expected physiologic changes based on the mechanism of action of epinephrine that are important for effective treatment of anaphylaxis, and may support PK matching results, PD and PK results did not always correlate to the same extent in the ARS-1 development program. In addition, different trends of PK and PD comparison results were observed between ARS-1 and EpiPen without a clear mechanism to explain this discrepancy (i.e., ARS-1 PK is lower, but had higher PD). The Division believes that comparative PD results, between ARS-1 and epinephrine injection products, provide supportive evidence to the PK matching approach that is needed for scientific and regulatory bridging in the ARS-1 clinical pharmacology program. Therefore, the Division places emphasis on the PK bracketing results, and views PD results as supportive.

Clinical Efficacy Trial Feasibility

The feasibility of performing a clinical efficacy trial in anaphylaxis was discussed with the Applicant and within the FDA. There are no adequate and well-controlled clinical trials with epinephrine in patients with anaphylaxis; thus, there was no precedence that we could follow. Approaches to designing a clinical efficacy trial that were explored in these discussions included:

- A trial in emergency departments, in which subjects with anaphylaxis would be treated with IN epinephrine as first-line therapy, with rescue epinephrine injection administered as back-up, if needed.
- A trial in the setting of oral food challenges or subcutaneous allergen immunotherapy.

There were concerns with delaying standard of care (epinephrine injection) for potentially life-threatening reactions where the timing of treatment is critical for preventing serious outcomes.

As development progressed, trial design concerns remained including the spontaneous nature of events would require a long trial duration and large sample size and challenges in determining meaningful endpoints (e.g., improvement in symptoms, treatment failure). Due to these challenges, it was determined that a clinical efficacy trial had feasibility issues and the development program would focus on the PK/PD data. The Division noted that whether the PK/PD data would be sufficient would be the topic for an advisory committee.

Development of Other Emergency-Use IN Products

As there is no regulatory precedent for approval of a noninjectable epinephrine product for treatment of anaphylaxis, the development programs for two approved IN therapeutics, naloxone nasal spray (approved November 2015) and diazepam nasal spray (approved January 2020), were considered in evaluation of the IN epinephrine development program, as both are used as emergency treatment and were originally approved with a different route of administration (naloxone injection and diazepam rectal gel). However, due to pharmacologic and safety differences, the approaches used for the naloxone and diazepam nasal spray PK development programs have important differences that limit the applicability to the development of IN epinephrine.

Naloxone Nasal Spray

Naloxone nasal spray, an opioid antagonist, uses the same device as ARS-1 and is approved for the emergency treatment of known or suspected opioid overdose for all ages. This approval was based on one PK trial in healthy adults in which the bioavailability of the IN spray was compared to a single IM naloxone injection; no clinical efficacy trials were conducted. Naloxone is unique in that it has a wide safety margin with a relatively high systemic exposure following IN administration that is 5- to 10-fold over the minimum therapeutic threshold.,12 Therefore, surpassing the therapeutic threshold is the goal of development as safety is not a concern with higher exposures. The higher exposure overcame concerns with translation of PK in healthy volunteers to subjects with opioid overdose. While there may be similarities with Narcan, there are important differences with IN epinephrine that require additional considerations.

Diazepam Nasal Spray

Diazepam nasal spray is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures), that are distinct from a patient's usual seizure pattern in subjects with epilepsy 6 years of age and older. The IN route of administration uses the same device as ARS-1. Approval was based on comparable bioavailability (IN versus rectal) in healthy subjects and subjects with epilepsy relying on adequate and well-controlled efficacy studies for rectal diazepam. A PK trial was conducted in adults and pediatric subjects with epilepsy comparing seizure versus nonseizure

[1] See the Cross-Discipline Team Leader Review for Narcan Nasal Spray (NDA 208411) dated 20 January 2016, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000CrossR.pdf.
[2] See the FDA Review for Narcan Nasal Spray (NDA 208411) dated 9 November 2015, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000TOC.cfm.

states to address potential differences in PK in healthy subjects compared to subjects with epilepsy. Overall, while the diazepam nasal spray program is an example of a nasal spray for emergency use that relied on PK to bridge the efficacy, the diazepam nasal spray program has limitations in its applicability to the ARS-1 program.

Listed Drugs

The Applicant submitted this application as a 505(b)(2) with Adrenalin (NDA 204200) as the listed drug of reference. During the review, the Applicant was asked to also submit documentation for use of EpiPen (NDA 019430) as their application relies on both drugs for efficacy and safety. This was done in conjunction with advice from the 505(b)(2) committee in the Office of Regulatory Products. Both EpiPen and Adrenalin are the referenced listed drug for this NDA.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Study Integrity and Surveillance

The Office of Study Integrity and Surveillance (OSIS) inspections were requested for both clinical sites and analytical sites of three PK/PD studies, which are the pivotal single- and repeat-dose PK/PD trial (EPI 15), the self-administration trial (EPI 17) and the pediatric single dose PK/PD trial (EPI 10). Inspection requests were declined for clinical sites and analytical sites for EPI 15 and EPI 17 as well as the analytical site for EPI 10 (same site used for EPI 15), as inspections or Remote Regulatory Assessment (RRA) were previously conducted for these sites under other NDAs or ANDAs within the surveillance interval and data from these sites were deemed reliable.

Inspections were conducted for the three clinical sites used for Trial EPI 10: Site #1 Children's Hospital Colorado, Aurora, CO (DARRTS Reference ID: 5152432), Site #2 Institute for Asthma and Allergy, P.C., Chevy Chase, MD and Site #3 University of South Florida, Tampa, FL (DARRTS Reference ID: 5176656). No significant objectionable items were identified for Site #1 and #3 and trial data is deemed reliable. However, objectionable conditions were observed for Site #2 and FDA issued a one-item Form FDA 483 regarding lack of the second parent's signature in the informed consent forms (ICF) in all 24 subjects enrolled in this site. In addition, 7 out 10 subjects enrolled in Site #1 and 2 out of 28 subjects enrolled in Site #3 reported a single-parent signature on the ICF as protocol deviations in the Clinical Study Report. The lack of a second parent's signature is acknowledged but does not impact the data or its interpretation. Refer to the Bioequivalence Establishment Inspection Report Review dated May 23, 2023, for the further discussion.

Additional issues, such as concomitant medication usage, fasting time shorter than 8-hour requirement by protocol, and unclear rounding rules for the body mass index (BMI) etc., were observed during the inspection for Site #2 and OSIS recommended the Division assess impact

on results and safety. The issues observed for subjects enrolled in trial group ARS-1 1 mg (≥30 kg) and ARS-1 2 mg (≥30 kg) are related to [redacted] the trial or the BMI. These findings are not likely to impact the PK/PD trial outcomes.

4.2. Product Quality

Epinephrine will be delivered via a single-use device which administers one 2 mg in 100 µL nasal spray. The formulation includes a [redacted] of epinephrine, and the product has a 25 µL overfill to assure 100 µL can be delivered (note that [redacted] for approved epinephrine injection products range from [redacted]%). The formulation contains a noncompendial [redacted] (Aegis' Intravail A3® which is a water-soluble nonionic detergent n-dodecyl-β-D-maltoside (DDM)), [redacted] (sodium metabisulfite), [redacted] (disodium edetate), and other common excipients used in nasal sprays. The formulation contains a [redacted] concentration of sodium metabisulfite than is typical for epinephrine injection products, however stability testing shows that the formulation shows [redacted] impact on spray pattern is not considered a risk. In addition, the Applicant agreed to test stability samples for particulates and apply the requirements for injections as per USP. The stability data provided support a 24-month shelf-life.

Of note, stability of the product was conducted outside of the blister packages in which the device will be dispensed, per labeling. Although this does not follow guidance that indicates that "stability testing should be conducted on the dosage form packaged in their container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label)," based on the design of the primary device, the presence of the blister packaging would not have altered the stability of the product to any significant extent.

[redacted] FDA expects manufacturers and applicants to ascertain the presence of nitrosamine impurities, including NDSRIs. On August 7, 2023, FDA published a guidance for industry, *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023) (NDSRI Guidance). The guidance is a final guidance, to be implemented immediately upon publication. With respect to pending applications, the NDSRI Guidance states that "[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the [acceptable intake] [AI] limits recommended in this guidance." If an NDSRI is detected above the recommended AI limit (not more than [redacted] ng/day for [redacted] based on the predicted carcinogenic potency categorization approach), the applicant should amend the application as appropriate. The NDA, as submitted, does not include data or information, such as a risk assessment and/or

confirmatory testing data as needed, demonstrating that the applicant has ascertained the presence of NDSRIs, specifically (b) (4) in ARS-1, and is therefore inadequate.

Other than submitting the necessary information to demonstrate ascertainment of the presence of NDSRIs, the data provided in this application support the conclusion that the proposed presentation combined with in process, release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. See the review by Craig Bertha located in the Integrated Quality Assessment.

4.3. Clinical Microbiology

The Division of Microbiology Assessment recommends approval based on review of the product quality microbiology and sterility assurance. For further details, see the reviews by Catherine Gilbert and Yan Zheng located in the Integrated Quality Assessment.

4.4. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health reviewed the device constituent of the combination product and recommends approval. The Applicant addressed device deficiencies during the review process adequately, however, additional testing for the (b) (4) device constituent part of the proposed combination product is needed, but is not an approvability issue. An adequate irritation assessment is important because exposure to the device (if it includes even a small amount of an irritant) can result in a localized non-specific inflammatory response which can lead to redness, swelling, itching, dryness, cracking of the skin, blistering or pain. See the CDRH review by Porsche Bennett for additional details.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Early in development of ARS-1, the Applicant requested advice on the nonclinical program. It was agreed that a single-dose GLP IN toxicology study in rats was needed with the initial IND submission. The ARS-1 formulation contains n-dodecyl-β-D-maltoside (DDM), an absorption enhancer for the IN route of administration. At the time of the opening IND, DDM was not present in any FDA-approved IN products. Therefore, the IN toxicology study included a formulation control to evaluate the safety of DDM for the IN route. The study report was provided in the IND submission on December 27, 2018. Subsequently, based on the approval of sumatriptan nasal spray on January 25, 2019, that contains DDM at levels higher than the levels in ARS-1, further toxicity qualification of DDM was not considered necessary.

In a non-GLP PK study in rats, ARS-1 that contained (b) (4)% DDM was found to have enhanced absorption compared to a formulation with no DDM or (b) (4) DDM ((b) (4)%).

Given the limitations of conducting clinical efficacy trials in anaphylaxis, to determine the potential impact of anaphylaxis on the PK of ARS-1, a GLP cardiovascular telemetry study in anesthetized non-naïve beagle dogs was conducted. Dogs with or without Tween-80-induced anaphylaxis received 1 mg ARS-1 via IN administration. An increase in epinephrine exposure (total and baseline-adjusted) was noted within the first 10 minutes after ARS-1 administration in dogs under anaphylaxis. The Cmax and AUC_{0-45} doubled under anaphylaxis, suggesting that anaphylaxis appears to increase absorption of ARS-1. This study also included measurements of arterial blood pressure and histamine. However, this study did not have a Tween-80 challenge-only group (no ARS-1 treatment), precluding conclusions on any PD effects of ARS-1.

In a single-dose GLP IN toxicity study, treatment of ARS-1 in rats induced epinephrine-related histopathology changes in the nose, such as minimal ulceration of the exposed mucosa (at ≥2.3-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area), and nasal passages, such as minimal to mild necrosis in the nasal turbinate and parietal wall in the rostral-most level (at ≥1.2-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area) were noted on Day 2. These findings were often associated with minimal to mild neutrophilic inflammation. Although histopathological examination at early timepoints was not planned, it is believed that these changes don't necessarily happen immediately but take time to develop. All these changes were minimal to mild severity, observed at low frequency, absent from recovery groups on Day 15, and considered clinically monitorable.

See Sections 5.4 and 5.5.1 for additional information on the nonclinical assessment.

5.2. Referenced NDAs, BLAs, DMFs

No reference related to nonclinical pharmacology and toxicology.

5.3. Pharmacology

No additional pharmacology studies of ARS-1 were conducted due to the extensive clinical history of epinephrine and pharmacology data from literature.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Study (b) (4) 285501: A Pharmacokinetic Assessment of Three Different Epinephrine Formulations of ARS-1 following Nasal Administration to Male Sprague Dawley Rats	Enhanced systemic epinephrine absorption in rats was noted following nasal administration of ARS-1 that contained (b) (4) % DDM.
Study 1021-4072: A Cardiovascular Telemetry Study With LVP Monitoring in the Anaesthetized Non-Naïve Beagle Dogs	Compared to normal condition, the Cmax and AUC0-45 for epinephrine doubled under anaphylaxis in dogs given ARS-1.
Distribution	Not available
Metabolism	Not available
Excretion	Not available
TK data from general toxicology studies	Not available
TK data from reproductive toxicology studies	Not available
TK data from Carcinogenicity studies	Not available

5.5. Toxicology

5.5.1. General Toxicology

A single-dose IN toxicity study of ARS-1 in rats was conducted. The study included histopathological examinations of a complete panel of organs and tissues from the respiratory system and gastrointestinal tract for local toxicity assessment for the IN route. Epinephrine-related nasal mucosa and nasal passage findings were noted on Day 2 and were reversible by Day 15. The formulation alone did not induce any local toxicity.

Study Title/ Number

Expanded Acute Intranasal Toxicity Study of ARS-1 in Rats (Study # 2555-002)

Conducting Laboratory and Location

(b) (4)

GLP Compliance

Yes

Methods

Dose and frequency of dosing	Single dose; 0 (saline), 0 (formulation buffer), 0.2 (LD), 0.4 (MD), and 0.8 (HD) mg/day
Route of administration	Nasal
Formulation/vehicle	(b) (4)% DDM, (b) (4)% BZK ((b) (4)%), (b) (4)% sodium chloride, (b) (4)% disodium EDTA (b) (4) in water for injection at pH (b) (4) adjusted by hydrochloric acid
Species/strain	Rat/ SPRAGUE-DAWLEY
Number/sex/group	10/sex/group for main study on Day 2; 5/sex/group for main study on Day 15
Age	9-11 weeks
Satellite groups unique design	3-6/sex /group for TK analysis; however, TK analysis was done outside of the validated period regarding the long-term stability. Therefore, TK data is included for review purpose.
Deviation from study protocol affecting interpretation of results	No

Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No drug-related findings
Clinical Signs	No drug-related findings
Body Weights	No drug-related findings
Ophthalmoscopy	No drug-related findings
ECG	No drug-related findings
Hematology	HD: +11% fibrinogen in males on Day 2, resolved on Day 15
Clinical Chemistry	No drug-related findings
Urinalysis	No drug-related findings
Gross Pathology	No drug-related findings
Organ Weights	No drug-related findings
Histopathology Adequate battery: Yes	Nose: Epinephrine-related minimal ulceration of the exposed mucosa associated with minimal neutrophilic inflammation was observed in 1 MD animal and 2 HD animals. Nasal passages: Epinephrine-related minimal to mild necrosis in the nasal turbinates and parietal wall in the rostral most level was noted in 1 LD animal, 2 MD animals, and 3 HD M animals. Minimal to mild acute neutrophilic inflammation were noted in 1 LD animal, 7 MD animals, and 7 HD M animals.

Abbreviations: LD: low-dose; MD: mid-dose; HD: high dose
+ indicates increase in parameters compared to control.

General Toxicology: Additional Studies

None

5.5.2. Genetic Toxicology

No new studies were submitted for ARS-1.

5.5.3. Carcinogenicity

No new studies were submitted for ARS-1.

5.5.4. Reproductive and Developmental Toxicology

No new studies were submitted for ARS-1.

5.5.5. Other Toxicology Studies

An ocular tolerability study of ARS-1 in New Zealand white rabbits was submitted. There were no drug-related ocular findings after a single administration of ARS-1 as ocular drops (b) (4)

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 3. ARS Pharmacology Trials

Study Name	Study Design	Objective of the Study	Test Product	Number of Subjects	Population
EPI 11b Dose-ranging	Phase 1, two-group, five-period, five-treatment, single-dose, crossover study	Assess the comparative bioavailability of different formulations of ARS-1 with various strengths of absorption enhancing excipient	Group 1 (single dose): Symjepi 0.3 mg ARS-1 1.3 mg (0.25% DDM) ARS-1 1.5 mg (0.25% DDM) ARS-1 1.5 mg (0.30% DDM) ARS-1 1.8 mg (0.30% DDM) Group 2 (single dose): EpiPen 0.3 mg ARS-1 1 mg (0.25% DDM) ARS-1 1 mg (0.25% DDM) ARS-1 1.5 mg (0.30% DDM, (b) (4) ARS-1 2.0 mg (0.30% DDM)	26 enrolled Group 1: 13 Group 2: 13 All subjects included in the PK analysis	Healthy adults
EPI 15 Single and repeat dose	Phase 1, two-part, six-treatment, six-period, single and repeat-dose crossover study	Assess the comparative bioavailability and PD response of epinephrine after ARS-1 2.0 mg, EpiPen 0.3 mg, and epinephrine IM injection 0.3 mg	Part 1 (single dose): ARS-1 2.0 mg EpiPen 0.3 mg epinephrine IM 0.3 mg Part 2 (two doses, 10 min apart): ARS-1 2.0 mg both doses in right naris ARS-1 2.0 mg, one dose in left and one in right naris EpiPen 0.3 mg, one dose in left and one in right thigh	59 enrolled (including 5 re-enrollment) Included in PK analysis: Total: 58 (26 subjects participated in both parts with PK data) Part 1: ARS-1: 42 EpiPen: 42 Epinephrine IM: 41 Part 2: ARS-1 (L/R): 39 ARS-1 (R/R): 39 EpiPen (L/R): 42	Healthy adults

Study Name	Study Design	Objective of the Study	Test Product	Number of Subjects	Population
EPI 16 Nasal allergen challenge	Phase 1, single-dose, partially randomized, four-treatment, crossover trial	Assess the comparative bioavailability of epinephrine after ARS-1 2.0 mg, epinephrine IM 0.3 mg and epinephrine IM 0.5 mg in subjects with seasonal allergic rhinitis after nasal challenge	ARS-1 2.0 mg Epinephrine IM 0.3 mg Epinephrine IM 0.5 mg ARS-1 2.0 mg after nasal challenge	36 enrolled Included in PK analysis: ARS-1 (normal): 36 Epinephrine IM 0.3 mg: 31 Epinephrine IM 0.5 mg: 31 ARS-1 (challenge): 33	History of seasonal allergic rhinitis
EPI 17 Self-administration	Phase 1, single-dose, two-treatment, two-period, randomized crossover trial	Assess the comparative bioavailability of epinephrine after self-administration of ARS-1 2.0 mg or staff-administered epinephrine IM injection	ARS-1 2.0 mg, self-administered Epinephrine IM 0.3 mg, staff administered	45 enrolled Included in PK analysis: ARS-1: 42 Epinephrine IM: 42	Type I allergies
EPI 10 Pediatric	Phase 1, single-dose, single-treatment trial	Assess the PK/PD of three doses of ARS in pediatric allergy subjects	ARS-1 0.65 mg ARS-1 1.0 mg ARS-1 2.0 mg	57 (at time of interim analysis) enrolled Included in PK analysis >30 kg: ARS-1 2 mg: 16 ARS-1 1 mg: 25 15 and 30 kg ongoing	Pediatric subjects 4 to <18 years of age with Type I allergies to food, venom, or drugs that require that the subject be prescribed an epinephrine product

Source: FDA Clinical Reviewer.
Subjects who received at least one dose of treatment and have ≥3 PK samples within 30 minutes postdose were included in the PK analysis conducted by FDA.
The formulation used in EPI11b is not the final to-be-marketed formulation used in other studies.
Abbreviations: IM, intramuscular; L, left; PD, pharmacodynamic; PK, pharmacokinetic; R, right; DDM, n-dodecyl-β-D-maltoside

6.2. Review Strategy

No clinical efficacy studies were conducted for this NDA. This review focuses on the four clinical pharmacology trials submitted (EPI 15, EPI 16, EPI 17, and EPI 10). The review will include a brief description of the clinical pharmacology protocols in Section 7, followed by the clinical pharmacology results in Section 8. Safety of these trial is discussed in Section 9. Of note, the investigation of PK/PD in children weighing 15 to <30 kg from the pediatric trial EPI 10 was ongoing at the time of NDA submission. Therefore, this review only covers PK/PD results obtained from children weighing ≥30 kg from the pediatric trial EPI 10.

7. Pivotal Trials Protocols

7.1. Review of Relevant Individual Trials Used To Support Efficacy

7.1.1. EPI 15: A Two-Part, Six-Period, Six-Treatment, Crossover Trial of the Pharmacokinetics of Epinephrine After Single and Repeat Administration of Intranasal ARS-1 or Epinephrine Injection to Healthy Volunteers

Administrative Information

Trial Dates

July 14, 2021, to September 19, 2021

Trial Sites

One trial center: WCCT Global, Inc. 5630 Cerritos Avenue, Cypress, CA 90630

Trial Report Date

July 19, 2022

Trial Design

This is a two-part, six-treatment, six-period, single and repeat dose, crossover trial.

Trial Part 1

The bioavailability of a single dose of ARS-1 (2.0 mg) compared to a single dose of EpiPen (0.3 mg IM epinephrine autoinjector) and a single dose of Adrenalin (0.3 mg IM epinephrine administered with a needle and syringe) was assessed. Each dose in Part 1 was separated by a 24 hour wash out period, as there was only one IN treatment period. Part 1 was fully randomized between the three treatments. Each subject was randomized to receive the following treatments:

- A single dose of ARS-1 in the left naris

- A single EpiPen dose in the left anterolateral thigh
- A single dose of Adrenalin in the right anterolateral thigh

Trial Part 2

The bioavailability of two doses of ARS-1 compared to two doses of EpiPen was assessed. The second dose was administered 10 minutes after the first dose. Each subject in Part 2 received the following treatments:

- Two doses of ARS-1, both in the right naris
- Two doses of ARS-1, one in the left and one in the right nares
- Two doses of EpiPen in the left and right anterolateral thigh

Administration of trial drug, blood samples, and vitals were given or taken in sitting position. If there was excessive nasal drip, the nose was permitted to be wiped before dosing ARS-1. The protocol did not specify instructions as to whether sniffing the spray

Because there were two IN treatment period in Part 2, to avoid carryover effect (see Section 3.2), a partial randomized schedule was employed so that there were at least 6 days between treatments with 12 days between IN dosing.

Trial Endpoints

PK and PD endpoints. See Section 8.

Statistical Analysis Plan

Not applicable.

Protocol Amendments

There were three protocol amendments (May 20, 2021, June 21, 2021, and July 13, 2021). Minor amendments were made to clarify PK timepoints and to ensure sufficient time was given to adjust for the carry over effect of epinephrine.

7.1.1.1. Trial Results

Compliance With Good Clinical Practices

EPI 15 was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 15.2 of this review for additional details.

Patient Disposition

A total of 59 subjects were enrolled in the trial. An additional Cohort with 17 subjects were enrolled due to an error in processing PK samples at the clinical site, where approximately 10 times the acid was added, destroying the samples for that cohort; five of these 17 subjects were subjects from Cohort 1 who re-enrolled. Therefore, there are 54 total unique subjects who received at least one dose of trial drug are included in the demographic summary.

A total of 59 subjects were enrolled, with 50 (85%) subjects completing the trial. All 59 subjects received at least one dose of trial medication. Nine subjects withdrew prematurely.

Protocol Violations/Deviations

During the trial, there were 261 protocol deviations over 49 subjects, as follows:

- 207: PK blood draws not being done, or being done outside the window
- 35: PD and/or vital signs not being collected or being collected outside the window
- 9: ECG data not being collected in the specified window or not being evaluated by the Investigator
- 5: VAS not being collected
- 2: nasal irritation evaluations not being recorded
- 2: TNSS score not being recorded
- 1: ARS-1 dosing nostril not being recorded

Deviated samples were included in the pharmacological datasets. Only up to 4% of samples were affected. Given the intensive sampling time and narrow window to obtain sampling, the deviation is not expected to have significant impact on PK/PD analysis.

Demographics

As outlined in Table 4 the average age was 40 years, ranging from 21 to 54 years. Thirty-eight subjects (70%) were male, 30 (56%) were White, 17 subjects (32%) were Black or African American, four subjects (7%) were Asian, and three subjects (6%) were "Other."

Table 4. EPI 15 Trial Demographics

Demographics	(N=54) n (%)
Age	
Mean (SD)	40 (9)
Median	40
Minimum, Maximum	21, 54
Gender	
Male	38 (0)
Female	16 (30)

Demographics	(N=54) n (%)
Race	
White	30 (56)
Black or African American	17 (32)
Asian	4 (7)
Other	3 (6)
Ethnicity	
Hispanic or Latino	21 (39)
Not Hispanic or Latino	33 (61)

Source: Applicant CSR. Table 14.1.2.2, Listing 16.2.4.1
Abbreviations: N, total number of subjects; n, percent of subjects, SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Subjects were healthy volunteers between 18 and 55 years old. Subjects with a history of hypertension or cardiovascular disease in the last 10 years were excluded. Subjects had to have a Total Nasal Symptom Congestion Score of 0 at screening and prior to dosing. Subjects with history of nasal facture, nasal injury, or nasal disorders (including nasal polyps) were also excluded.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Over-the counter medications 3 days prior to the trial or any prescription medication (except hormonal contraceptives) within 14 days of the trial were prohibited. Nasal decongestants within 12 days prior to the trial and systemic steroid containing products (excluding topical steroids) in the past 30 days were also prohibited.

Efficacy Results – Primary Endpoint

See Section 8.

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

OSIS inspections were requested for both clinical sites and analytical sites of three PK/PD studies, which are the pivotal single- and repeat-dose PK/PD trial (EPI 15), the self-administration trial (EPI 17) and the pediatric single dose PK/PD trial (EPI 10). See Section 4.1 for inspection results detail.

7.1.2. EPI 16: A Four-Treatment, Partially-Randomized Crossover Trial of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS-1 or Epinephrine in Subjects With Allergic Rhinitis

Administrative Information

Trial Dates

October 5, 2020, to October 9,2020

Trial Sites

One trial center: Altasciences Clinical Los Angeles, Inc. 5630 Cerritos Avenue, Cypress, CA 90630

Trial Report Date

July 12, 2022

Trial Design

This is a phase 1, single dose, four period, partially randomized, cross-over trial that consisted of a screening period, baseline period, and an open-label treatment period. Subjects enrolled had diagnosed and confirmed seasonal rhinitis. The bioavailability of a single dose of ARS-1 with and without induction of rhinitis was assessed and compared to single dose of 0.3 mg and 0.5 mg epinephrine IM injection administered with a standard needle and syringe. Each dose was separated by a 24-hour washout period.

Each subject received the following treatments:

- A single dose of ARS-1 in the left (L) naris under normal nasal conditions
- A single dose of IM injection of 0.3 mg epinephrine with standard needle and syringe in the left anterolateral thigh
- A single dose of 0.5 mg epinephrine IM injection with standard needle and syringe in the right anterolateral thigh
- A single dose of ARS-1 in the right naris after nasal challenge

Because there were two IN treatment periods in Trial EPI 16, to avoid the carry-over effect, a partial randomization schedule was used so that the IN treatments were the first and last treatment groups.

Approximately 36 eligible male or female subjects, 18 to 55 years of age, with seasonal allergies (positive case history of seasonal allergic rhinitis related to tree or grass allergens with positive skin prick test within 12 months of enrollment and positive NAC with Allergen Panel at Screening between 21 and 60 days prior to treatment in the trial) were enrolled. For the screening, subjects are first challenged with escalating IN allergen at 15 minute intervals until a positive reaction (i.e., TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3) is reached. TNSS and congestion score were recorded every 15 minutes. If the subject reached the highest concentration of 1:2 without qualifying, the subject was excluded. The TNSS is a standardized patient-reported questionnaire that measures 4 symptoms (congestion, runny nose, itching and sneezing) on a scale of 0 (none) to 3 (severe). The score for each symptom is added for a total score of 0-12, with 12 being the worst score. Subjects were tested outside the pollen season.

On treatment arm under NAC, TNSS was recorded before the allergen is applied and every 15 minutes after the allergen is applied until a positive reaction is reached. The allergen dose that achieved reaction during screening was applied by giving 2 puffs in the right nostril. ARS-1 was then administered on the right nostril (was administered on left nostril under normal conditions).

Trial Endpoints

PK and PD endpoints. See Section 8.

Statistical Analysis Plan

Not applicable

Protocol Amendments

There were no protocol amendments.

7.1.2.1. Trial Results

Compliance With Good Clinical Practices

EPI 16 was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 15.2 of this review for additional details.

Patient Disposition

A total of 36 subjects were enrolled, with 34 subjects completing the trial. Two subjects withdrew prematurely.

Protocol Violations/Deviations

During the trial, there were 110 protocol deviations over 27 subjects.

- There were four instances of vital signs not being assessed or being assessed outside the assessment window.
- There were 106 instances of PK blood draws not being conducted or being conducted outside the window.
- Deviated samples were included in the datasets. Up to 4% were affected but were not expected to have significant impact on PK/PD analysis.

Demographics

A total of 36 subjects were enrolled in the trial; all 36 subjects received at least one dose of trial drug. Demographics are summarized in Table 5. The mean age was 38 years, ranging from 20 to 52 years. Twenty subjects (56%) were male, 16 subjects (44%) were White, eight subjects (22%) were Black or African American, eight subjects (22%) were Asian, one subject (3%) was Native Hawaiian or Other Pacific Islander; and three subjects (8%) were Other.

Table 5. EPI 16 Trial Demographics

Demographics	(N=36) n (%)
Age	
Mean (SD)	38 (8)
Median	38
Minimum, Maximum	20, 52
Gender	
Male	20 (56)
Female	16 (44)
Race	
White	16 (44)
Black or African American	8 (22)
Asian	8 (22)
Native Hawaiian or Other Pacific Islander	1 (3)
Other	3 (8)
Ethnicity	
Hispanic or Latino	5 (14)
Not Hispanic or Latino	31 (86)

Source: Applicant CSR. Table 14.1.2.2, Listing 16.2.4.1
Abbreviations: N, total number of subjects; n, percent of subjects, SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Subjects were healthy volunteers between 18 and 55 years old. Subjects with a history of hypertension or cardiovascular disease in the last 10 years were excluded. In treatment periods under normal nasal condition, subjects had to have a Total Nasal Symptom Congestion Score of 0 at screening and prior to dosing. Subjects with history of nasal facture, nasal injury or nasal disorders were also excluded. Unlike EPI 15, subjects had to also have a history of seasonal allergic rhinitis demonstrated with a positive skin prick (Positive skin prick (wheal ≥3 mm over negative control) and/or intradermal test to allergen(s) within 12 months of enrollment; Subjects had a TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3 with NAC at screening).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Same as EPI 15.

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

7.1.3. EPI 17: A Two-Period, Two-Treatment, Randomized, Crossover Trial of the Pharmacokinetics, Pharmacodynamics, and Dosing Errors After Self-Administration of Epinephrine With Intranasal ARS-1 as Compared to IM Injection in Subjects With Type I Allergies.

Administrative Information

Trial Dates

April 8, 2022, to May 14, 2022

Trial Sites

One trial center: Novum Pharmaceutical Research Services, 3760 Pecos McLeod, Las Vegas, NV 89121

Trial Report Date

July 28, 2022

Trial Design

This is a phase 1, single-dose, two treatment, randomized crossover trial that assessed the bioavailability of a single dose of ARS-1 (2.0 mg epinephrine) after self-administration compared to a single dose of IM injection (0.3 mg epinephrine autoinjector) administered by trial staff.

Training on ARS-1 was done during the screening period (between -28 to -7 days prior to dosing) which included review of the Instructions for Use and Quick Reference Guide along with a training video. After reviewing the materials, the subjects were asked to demonstrate product use with a training device. Mistakes were corrected. After the initial training, subjects were not provided with any labeling or instructional materials to allow time to forget use instruction as in real life situations.

Prior to self-administration of ARS-1, subjects were given a scenario where they pretended they were experiencing a severe allergic reaction and provided ARS-1 in its secondary blister packaging with the Quick Reference Guide on the back of the blister. The subject would then proceed to self-administer ARS-1 without assistance, but they were permitted to review any labeling on the device or secondary packaging prior to administer. Subjects were only allowed up to 5 minutes to self-administer.

For the IM injection period, trial personnel administered the standard 0.3 mg epinephrine autoinjector into the right anterolateral thigh.

Trial Endpoints

PK and PD endpoints. See Section 8.

Statistical Analysis Plan

Not applicable.

Protocol Amendments

No amendments were made.

7.1.3.1. Trial Results

Compliance With Good Clinical Practices

EPI 17 was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 15.2 of this review for additional details.

Patient Disposition

A total of 45 subjects were enrolled, with 41 subjects completing the trial. All 45 subjects

received at least one dose of trial drug. Four subjects withdrew, prior to receiving both doses of medication as per physician decision.

Protocol Violations/Deviations

During the trial, there were 42 protocol deviations over 21 subjects all due to PK sampling not done in the necessary window. The deviations did not compromise the subject's safety or continuation in the trial and did not have any effect on the integrity of the trial or trial data per Applicant. Deviated samples were included in the datasets and not likely impact PK/PD analysis.

Demographics

Demographics for EPI 17 are summarized in Table 6. The mean age was 39 years, ranging from 23 to 53 years. Twenty-six subjects (58%) were male, 14 subjects (31%) were White, 17 subjects (38%) were Black or African American, six subjects (13%) were Asian, three subject (7%) were Native American or Alaska Native, one subject (2%) was Hawaiian or Other Pacific Islander; and four subjects (9%) were Other.

Table 6. EPI 17 Trial Demographics

Demographics	(N=45) n (%)
Age	
n	45
Mean (SD)	39 (9)
Median	40
Minimum, Maximum	23,53
Gender	
Male	26 (58)
Female	19 (42)

Demographics	(N=45) n (%)
Race	
White	14 (31)
Black or African American	17 (38)
Asian	6 (13)
American Indian or Alaska Native	3 (7)
Native Hawaiian or Other Pacific Islander	1 (2)
Other	4 (9)
Ethnicity	
Hispanic or Latino	11 (24)
Not Hispanic or Latino	34 (76)

Source: Table 14.1.2.2, Listing 16.2.4.1
Abbreviations: N, total number of subjects; n, percent of subjects, SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Same as EPI 15

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Same as EPI 15

Efficacy Results – Primary Endpoint

PK and PD endpoints. See Section 8.

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

7.1.4. EPI 10: A Single-Period, Single-Dose Trial of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Pediatric Subjects With Systemic Allergies

Administrative Information

Interim Trial Dates

July 17, 2020, to March 15, 2021

Trial Sites

- Children's Hospital Colorado, 13 123 East 16th Avenue, Aurora, CO 80045
- University of South Florida, 13801 Bruce B Downs Blvd., Tampa, FL 33613
- Institute for Asthma & Allergy, P.C., 2 Wisconsin Circle, Chevy Chase, MD 20185

Trial Report Date

July 21, 2022

Trial Design

This was a phase 1, single dose trial that assessed the PK/PD of either a 0.65 mg, 1.0 mg, or 2.0 mg ARS-1 in pediatric subjects with systemic (Type I) allergies that require epinephrine prescription. Each subject received one dose of ARS-1 based on body weight.

Trial Part 1

- Subjects 15 to <30 kg received a single 0.65 mg/100 µL dose of ARS-1 in the left nares
- Subjects ≥30 kg received a single 1.0 mg/100 µL dose of ARS-1 in the left nares.

Trial Part 2

- Subjects 15 to <30 kg received a single 1.0 mg/100 µL dose of ARS-1 in the left nares
- Subjects ≥30 kg or received a single 2.0 mg/100 µL dose of ARS-1 in the left nares.
- The trial was ongoing for subjects weighing <30 kg is at the time of NDA submission. Subjects ≥30 kg were the focus of the review to support the proposed indication.

Trial Endpoints

PK and PD Endpoints. See Section 8.

Statistical Analysis Plan

Not applicable

Protocol Amendments

There have been four protocol amendments. The first amendment submitted March 24, 2020, took into account the recommendations made by the Agency which incorporated advice from the FDA. Specifically, the trial was expanded to include children 4 to 11 years of age, a change from 6 to 11 years. The Applicant also modified their trial to include staggered enrollment, assessing adolescents prior to the younger cohorts. PK/PD sampling was aligned and modifications to the trial procedure were made to make the children more comfortable (e.g., provide entertainment materials).

The second amendment, submitted June 29, 2020, took into account suggestions from the European Medicines Agency (EMA). Specifically, EMA disagreed that children were excluded if they had congestion given that in real life, children may be congested at baseline when receiving IN product. Therefore, children were allowed to have baseline congestion, but needed to be off antihistamine and nasal decongestants for at least 3 days prior to treatment.

The third amendment, submitted December 22, 2020, updated the formulations of ARS-1, assessing two strengths of the excipient DDM and therefore increased the number of targeted subjects to enroll (approximately 60 subjects to 70 subjects).

The fourth amendment submitted September 8, 2021, provided additional safety data from the adult trial (2.0 mg) and also minor edits to the trial document with no substantive changes.

7.1.4.1. Trial Results

Compliance With Good Clinical Practices

EPI 10 was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection.

Financial Disclosure

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 15.2 of this review for additional details.

Patient Disposition

As of the interim analysis cutoff date, there were 42 subjects weighing ≥30 kg. Twenty-six of these subjects received ARS-1 1.0 mg, and 16 of these subjects received ARS-1 2.0 mg**.**

Protocol Violations/Deviations

As of the interim analysis cutoff date there were 80 protocol deviations over 30 subjects. The majority of the deviations involved PK and/or PD measurements being taken outside the specified window or a failure of both parents to sign the ICF. Deviated samples were included in the datasets and are not likely to impact PK/PD analysis

Demographics

Demographics for EPI 10 are summarized in Table 7. As of the interim analysis cutoff date (March 15, 2021), a total of 16 subjects were enrolled for those who weigh 30 kg or more; all 16 subjects received at least one dose of trial drug. Subjects ranged in age from 8 to 17 years. Thirty-two subjects (63%) were male, 12 subjects (75%) were White, two subjects (13%) were Black or African American, and two subjects (13%) were Asian.

Table 7. EPI 10 Demographics in Subjects Who Received ARS-1 2.0 mg.

Demographic	ARS-1 1.0 mg (15-30 kg) (N=3) n (%)	ARS-1 1.0 mg (≥30 kg) (N=26) n (%)	ARS-1 2.0 mg (≥30 kg) (N=16) n (%)
Age (year)			
n	3	26	16
Mean (SD)	10 (1)	13 (2)	14 (3)
Median	9.0	14	15
Minimum, Maximum	9, 11	9, 17	8, 17
Sex			
Male	1 (33)	15 (58)	10 (63)
Female	2 (67)	11 (42)	6 (38)
Race			
White	3 (100)	18 (69)	12 (75)
Black or African American	0 (0)	6 (23)	2 (13)
Asian	0 (0)	2 (8)	2 (13)
Ethnicity			
Hispanic or Latino	0 (0)	2 (8)	0 (0)
Not Hispanic or Latino	3 (100)	24 (92)	16 (100)

Source: Table 14.1.2.2, Listing 16.2.4.1
Abbreviations: N, total number of subjects; n, percent of subjects, SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Subjects enrolled in both cohorts (<30 kg and ≥30 kg) were between 4 and <18 years old with the following BMI:

- Boys
  - Age 4 to 8: BMI ≤19 kg/m2
  - Age 9 to 11: BMI ≤21 kg/m2
  - Age 12 to 17: BMI ≤26 kg/m2
- Girls
  - Age 4 to 8: BMI ≤18 kg/m2
  - Age 9 to 11: BMI ≤20.5 kg/m2
  - Age 12 to 17: BMI ≤25 kg/m2

They had to have a history of Type 1 allergies to food, insects, venom, or drugs that required the subject to been prescribed an epinephrine.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No concomitant medications were permitted during the course of this trial (except hormonal contraceptives) or medications necessary to manage chronic conditions which could not have

been discontinued in the opinion of the PI and approved by the Medical Monitor as unlikely to have resulted in an impact on PKs and safety.

Efficacy Results – Primary Endpoint

PK and PD endpoints. See Section 8.

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

8. Clinical Pharmacology

8.1. Executive Summary

ARS Pharmaceuticals submitted an NDA for ARS-1 for the treatment of allergic reactions (Type I) including anaphylaxis. This is a new route of administration for epinephrine. This application is based on PK and PD data for ARS-1 compared to approved epinephrine injection products, Adrenalin and EpiPen, in healthy subjects and subjects with allergic rhinitis or Type I allergies. No clinical efficacy trials were conducted given feasibility concerns, specifically limitations in obtaining clinically meaningful data (Section 3.2). The Applicant proposes a 2-mg dose for adults and children weighing ≥30 kg. The pediatric program for those weight <30 kg is ongoing.

ARS submitted their application under the 505 (b)(2) pathway with reference to Adrenalin (NDA 204200) and EpiPen (NDA 019430) as their listed drugs. To support the new route of administration, the Applicant conducted four clinical pharmacology studies with 2 mg of ARS-1 to fulfill the 505(b)(2) pathway. An additional dose-ranging study (EPI 11b) was conducted. All five trials are shown in Table 3 in Section 6.1.

The key clinical pharmacology review questions focus on the appropriateness of PK bracketing of ARS-1 by Adrenalin and EpiPen, with supportive PD, the PK of two-doses or ARS-1 in comparison to two-doses of EpiPen, with supportive PD, self-administration of ARS-1, the impact of allergen-induced allergic rhinitis on epinephrine PK and PD following ARS-1, and the systemic exposure of epinephrine comparison between adults and pediatric subjects.

8.1.1. Recommendation

The Office of Clinical Pharmacology have reviewed the information contained in NDA 214697 and concluded that the epinephrine PK profile of the ARS-1 product is bracketed by the two listed epinephrine injection products (EpiPen and Adrenalin) and the PD profile of ARS-1 product is higher than the two listed epinephrine injection products in healthy subjects under normal nasal conditions. Therefore, a scientific bridge has been established between ARS-1 and the listed products, Adrenalin and EpiPen, such that we can rely on the Agency's finding of safety and effectiveness of both listed products under normal nasal conditions. In addition, the similar PK/PD findings in children ≥30 kg compared to adults support the extrapolation to this

population, as there is an established response to treatment with epinephrine that is highly similar between pediatric subjects and adults based on the clinical experience with approved epinephrine injection products.

In the NAC trial EPI 16, which is designed to mimic allergen induced acute rhinitis conditions that may been seen in anaphylaxis to assess the impact on PK/PD of ARS-1, the PK profile of a single dose ARS-1 under NAC demonstrates a relatively more rapid absorption phase during the first 10 minutes followed by a relatively less sustained phase in which epinephrine concentration becomes lower than the that of epinephrine injection products around 20 minutes. Although hemodynamic PD responses (SBP and PR change from baseline) following ARS-1 in subjects with allergen-induced rhinitis followed a similar pattern, the comparison results with Adrenalin is different. The median SBP response remained comparable to that of Adrenalin 0.3 mg throughout 60 minutes postdose. Meanwhile, the median PR response for ARS-1 was initially higher than Adrenalin within 5 minutes post-dose but became lower afterwards.

When compared to Adrenalin, the less sustained epinephrine mean plasma concentration after 20 minutes postdose and the lower median PR response after 5 minutes postdose following a single dose of ARS-1 under NAC raises concerns regarding the durability of effect in patients with allergen induced acute rhinitis, which can occur in some patients with anaphylaxis. Although it is a common practice that a second dose of epinephrine may be administered in the absence of clinical improvement or if deterioration or rebound occurs after the initial treatment of anaphylaxis, there is an uncertainty regarding the PK and PD profiles following the second dose of ARS-1, as the repeat doses of ARS-1 under NAC have not been evaluated in ARS-1 clinical program. Without assessing the PK and PD in a clinical trial, the epinephrine exposures following repeat doses of ARS-1 under NAC and the PD responses cannot be reliably predicted, given the complex interaction between nasal congestion and pharmacologic effect of epinephrine following the initial administration of ARS-1, notwithstanding a potential additional effect of nasal conditions on the PD responses.

Therefore, the clinical pharmacology review team supports the Complete Response decision that an additional trial assessing the PK/PD following repeat doses of ARS-1 under NAC conditions is needed to address the remaining uncertainties of using ARS-1 in the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and children who weigh ≥30 kg.

8.2. Summary of Clinical Pharmacology Assessment

8.2.1. Pharmacology and Clinical Pharmacokinetics

The available epinephrine PK/PD data in the ARS-1 clinical pharmacology program is derived from healthy subjects, and subjects with allergic rhinitis or Type I allergies. Highlights from the epinephrine PK/PD literature are summarized below.

Mechanism of Action

Epinephrine is an endogenous, nonselective adrenergic agonist. The two major classes of adrenergic receptors are alpha- and beta-adrenergic receptors and they are differentially expressed in various organs and tissues. Alpha-1 receptors are located in vascular (especially precapillary arterioles) smooth muscle and are responsible for vasoconstriction when activated. Alpha-2 receptors are involved in autoregulation of norepinephrine release and are located in multiple nerve endings and in the central nervous system. Beta-1 receptors are mainly located in the heart and activation increases cardiac inotropy and chronotropy (i.e., force of contractility and heart rate). Beta-2 receptors are located in airway smooth muscle, and skeletal muscle arteries; activation of beta-2 receptors increases bronchodilation, and vasodilation in the skeletal muscles (Westfall 2011).

Pharmacokinetics of Epinephrine Following Injection Products

Endogenous plasma epinephrine concentrations fluctuate in healthy subjects, but average levels are approximately 35 pg/mL, with a plasma half-life in the systemic circulation of about 2 to 3 min. The major metabolizing enzymes for epinephrine are monoamine oxidases and catechol-O-methyltransferase (Ebert 2013).

Following intramuscular administration of exogenous epinephrine, plasma epinephrine concentrations demonstrate high intersubject and intrasubject variability. Using Auvi-Q and EpiPen autoinjectors, the coefficient of variation for the mean C_{max} and AUC ranged from 51% to 80%; the T_{max} ranged from 5 to 60 min. These results reflect the highly variable nature of epinephrine PK. [3] A second peak of epinephrine plasma concentration was observed in some subjects, at approximately 30 minutes following IM injection; the magnitude of this second peak is variable when compared to that of the first peak, which also contributes to the variability of the T_{max}. Although the mechanism underlying this second peak is unclear, it is speculated to be a secondary effect of vasodilation in the skeletal muscle due to stimulation of beta-2 receptors, with resultant increased absorption (Westfall 2011). This unique combination of physiological and pharmacological properties provides a potential advantage of epinephrine administration via IM injection for ensuring that injected epinephrine is rapidly and thoroughly absorbed into the systemic circulation.

Pharmacodynamics of Epinephrine Following Injection

At therapeutic concentrations, epinephrine injection increases SBP, decreases DBP, reduces peripheral resistance, increases heart rate, increases skeletal muscle blood flow, and decreases cutaneous and renal blood flow in humans (Westfall 2011). Epinephrine exerts a concentration-dependent effect on PD (vital signs) responses following continuous IV infusion. In a trial of healthy volunteers receiving sequential fixed rates (0.1, 0.5, 1.0, 2.5, and 5.0 µg/min) of continuous epinephrine IV infusion while in supine posture, there was an approximate linear relationship between the real-time epinephrine plasma concentrations and change from

[3] See the FDA Clinical Pharmacology Review for Epinephrine (NDA 201739), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/201739Orig1s000ClinPharmR.pdf.

baseline values for SBP (increase), DBP (decrease), and HR (increase). The author suggested several threshold epinephrine plasma concentrations that were required for changes in HR (50 to 100 pg/mL), SBP (75 to 125 pg/mL), and DBP (150 to 200 pg/mL). A simple linear regression model estimated that plasma epinephrine concentrations of approximately 200 pg/mL increased HR by ~10 bpm and SBP by ~10 mmHg. The magnitude of vital sign changes was generally proportional to epinephrine plasma concentration from the threshold of 80 to 200 pg/mL up to approximately 1000 pg/mL (Clutter et al. 1980). The Agency acknowledges that:

- There are ranges of threshold concentrations that predict PD responses in this trial.
- Selected epinephrine threshold concentrations may vary due to the high intersubject variability (including PD responsiveness).
- PD responses vary by route of administration.
- The trial results were obtained from healthy volunteers; whether those PD responses can be extrapolated to subjects experiencing anaphylaxis is unclear (Bautista et al. 2002; Mink et al. 2004).
- There is uncertainty in target thresholds that correlate with efficacy for treatment of anaphylaxis.

8.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed 2 mg of ARS-1 as a single IN administration into one nostril for emergency treatment of allergic reactions (Type I), including anaphylaxis, in adults and children who are ≥30 kg. If symptoms progress after (b) (4) minutes or any error occurs in administering ARS-1, the Applicant recommends administration of a second dose with a new device. More than two sequential doses of epinephrine should be only administered under direct medical supervision.

Therapeutic Individualization

There was no dose adjustment proposed for renal or hepatic impairment, elderly, or various body weights in adults.

Pediatric subjects weighing 30 kg or greater who received ARS-1 2 mg demonstrated similar epinephrine exposure to healthy adults who received the same dose.

Outstanding Issues

None

8.3. Comprehensive Clinical Pharmacology Review

8.3.1. General Pharmacology and Pharmacokinetic Characteristics

Summary of Clinical Pharmacology and Pharmacokinetics

Pharmacology	
Review Issue(s)	**Recommendations and Comments**
Mechanism of action (Adrenalin USPI)	Epinephrine acts on both alpha and beta-adrenergic receptors. Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation and helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis. Epinephrine alleviates pruritus, urticaria, and angioedema. It may also relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.
Pharmacodynamics	
Review Issue(s)	**Recommendations and Comments**
Healthy volunteers	Following administration of a single or repeat-dose of ARS-1 in the same or opposite naris, the systolic blood pressure (SBP) and pulse rate (PR) increased from baseline while the diastolic blood pressure (DBP) remained relatively stable from baseline over 60 minutes postdose. Following a single dose administration, the median/mean SBP and PR responses (change from baseline) for ARS-1 were within the range of EpiPen and Adrenalin IM injection during the first 10 minutes postdose. Thereafter, the median/mean SBP and PR responses for ARS-1 were higher than both epinephrine injection products over 60 minutes postdose. A similar trend in median/mean SBP and PR responses were noted following two-doses of ARS-1 in comparison to two-doses of EpiPen.
Allergic rhinitis subjects' postnasal allergen challenge	When ARS-1 is administered in subjects with allergen-induced acute rhinitis, the median SBP and PR of ARS-1 following NAC initially increased from baseline, but the median responses (change from baseline) were lower than ARS-1 under normal conditions after 5 to 15 minutes postdose. The median SBP response of ARS-1 following NAC was higher than Adrenalin 0.3 mg within 20 minutes postdose and became similar afterwards. The median PR response of ARS-1 following NAC was higher than Adrenalin 0.3 mg within 5 minutes postdose and became lower than Adrenalin afterwards.
Pediatrics	Following administration of 2 mg ARS-1 in pediatric subjects with Type I allergies weighing ≥30 kg, both median SBP and median PR responses (change from baseline) were slightly lower than that of adults over the 60 minutes postdose.

<table>
<tr><th colspan="2">General PK Information</th></tr>
<tr><th>Review Issue(s)</th><th>Recommendations and Comments</th></tr>
<tr><td>Bioanalysis</td><td>Validated liquid chromatography with tandem mass spectrometry methods by (b) (4) (for Trials EP 15, 16, 10) and (b) (4) (EPI 17).</td></tr>
<tr><td>General PK characteristics</td><td>Table 8. Geometric Mean (CV%) PK Parameters for ARS-1
<table>
<tr><th></th><th>Trial EPI 15 Single Dose In HVs (N=42)</th><th>Trial EPI 15 Repeat Dose in HVs[a] (N=39)</th><th>Trial EPI 16 Induced Nasal Congestion in Allergic Rhinitis Subjects (N=33)</th><th>Trial EPI 10 Pediatric Type I Allergy Subjects (N=16)</th></tr>
<tr><td>C_{max} (pg/mL)</td><td>341 (114)</td><td>706 (104)</td><td>260 (64)</td><td>433 (80)</td></tr>
<tr><td>$AUC_{0\text{-}10min}$ (pg/mL)</td><td>712 (93)</td><td>836 (118)</td><td>1446 (58)</td><td>989 (112)</td></tr>
<tr><td>$AUC_{0\text{-}20min}$ (pg/mL)</td><td>2596 (102)</td><td>3664 (123)</td><td>2789 (60)</td><td>3147 (90)</td></tr>
<tr><td>$AUC_{0\text{-}30min}$ (pg/mL)</td><td>4901 (109)</td><td>8106 (119)</td><td>3792 (60)</td><td>6231 (78)</td></tr>
<tr><td>$AUC_{0\text{-}60min}$ (pg/mL)</td><td>10925 (116)</td><td>21083 (110)</td><td>6354 (60)</td><td>15126 (76)</td></tr>
</table>
Source: Reviewer's analysis based on adpc.xpt for Trial EPI 15, 16, and 10.
a As the systemic exposures of two-doses of ARS-1 administered ipsilaterally or contralaterally are similar, the PK parameters for ARS-1 (L/R) is reported

Following two doses of ARS-1, the C_{max} and $AUC_{0\text{-}60\ min}$ increased roughly dose proportionally compared to single dose ARS-1 in healthy adults. The systemic exposures of two-doses of ARS-1 administered into the same or opposite naris were generally similar.
In subjects with allergic rhinitis administered with ARS-1 following NAC, the plasma epinephrine concentrations following a single dose of ARS-1 initially increased relatively rapidly within 10 minutes postdose followed by a less sustained phase and became lower than Adrenalin 0.3 mg after 20 minutes postdose. The $AUC_{0\text{-}60min}$ for ARS-1 under the induced nasal congestion conditions was lower than that of Adrenalin 0.3 mg.
In pediatric subjects with Type I allergies weighing 30 kg or greater, following a single dose of 2 mg ARS-1, the mean plasma epinephrine concentrations were slightly higher than that of healthy adults receiving the same dose based on a cross-trial comparison.</td></tr>
<tr><th colspan="2">Absorption</th></tr>
<tr><th>Review Issue(s)</th><th>Recommendations and Comments</th></tr>
<tr><td>T_{max} [intranasal]</td><td>Following a single dose ARS-1 administration, the median T_{max} was 30 minutes in healthy adults with normal nasal conditions, while the median T_{max} was 6 minutes in adult allergic rhinitis subjects under induced nasal congestion conditions. The median T_{max} in pediatric Type I allergies subjects was 25 minutes.</td></tr>
<tr><th colspan="2">Distribution</th></tr>
<tr><th>Review Issue(s)</th><th>Recommendations and Comments</th></tr>
<tr><td>Volume of distribution</td><td>N/A</td></tr>
<tr><th colspan="2">Elimination</th></tr>
<tr><th>Review Issue(s)</th><th>Recommendations and Comments</th></tr>
<tr><td>Mean terminal elimination half-life (Adrenalin USPI)</td><td>Following intravenous injection, epinephrine is rapidly cleared from the plasma with an effective half-life of <5 minutes.</td></tr>
</table>

Metabolism	
Review Issue(s)	**Recommendations and Comments**
Primary metabolic pathway(s) (Adrenalin USPI)	Epinephrine is extensively metabolized with only a small amount excreted unchanged. Epinephrine is rapidly degraded to vanillylmandelic acid, an inactive metabolite, by monoamine oxidase and catechol-O-methyltransferase that are abundantly expressed in the liver, kidneys, and other extra neuronal tissues. The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).
Drug Interaction	
Review Issue(s)	**Recommendations and Comments**
Effect on other nasal spray products	ARS-1 may alter nasal mucosa for up to 2 weeks after administration, thus affecting systemic absorption of other nasal products. Concomitant use of other nasal sprays (e.g., corticosteroid nasal spray) may potentially increase the exposure of these nasal spray products, which may increase adverse reactions.

8.3.2. Clinical Pharmacology Questions

Many of these issues are also discussed in Section 3.2.

How Was Epinephrine Plasma Concentration Data Handled During the Review?

All plasma concentration of epinephrine time profiles in this review are presented with geometric mean values, as they are less influenced by the extreme outliers.

The plasma concentrations that were below limit of quantification (BLQ) at predose and postdose were imputed as one-half of the lower limit of quantification (LLOQ/2=10 pg/mL for Trial EPI 15, 16 and 10, and LLOQ/2=5.519 pg/mL for Trial EPI 17). Missing data was not imputed. Subjects with insufficient number of postdose plasma epinephrine samples (N <3) collected within 30 minutes were excluded from PK and PD analyses (n=7 in EPI 15 and n=13 in EPI 16; subjects had insufficient number of samples in multiple treatment periods were counted as separate individual).

The baseline concentration of epinephrine was calculated as a mean value from the PK samples collected at 10 and 5 minutes predose in all the clinical pharmacology studies in the ARS-1 clinical program. The mean and median baseline concentrations were similar across all treatment periods (geometric mean: 17 to 22 pg/mL and median: 10 to 27 pg/mL) and treatment arms in all the studies, and the values are close to the literature reported baseline epinephrine value of 35 pg/mL (Lake et al. 1984). A representative baseline epinephrine mean value across different treatment arms in Trial EPI 15 is shown in Table 9.

Table 9. Representative Geometric Mean and Median Epinephrine Baseline Values, Trial EPI 15

	Part 1 Single Dose					
	ARS-1 2 mg		Adrenalin 0.3 mg		EpiPen 0.3 mg	
Time	-10 min (n=41)	-5 min (n=42)	-10 min (n=42)	-5 min (n=42)	-10 min (n=42)	-5 min (n=42)
Geometric Mean (CV%)	18 (47)	17 (59)	18 (65)	21 (61)	20 (58)	21 (64)
Median (Range)	23 (10 to 38)	10 (10 to 51)	21 (10 to 63)	23 (10 to 64)	23 (10 to 57)	27 (10 to 75)
	Part 2 Repeat Dose					
	ARS-1 2 mg (L/R)		ARS-1 2 mg (R/R)		EpiPen 0.3 mg (R/R)	
Time	-10 min (n=38)	-5 min (n=37)	-10 min (n=38)	-5 min (n=37)	-10 min (n=41)	-5 min (n=40)
Geometric Mean (CV%)	20 (69)	21 (85)	19 (68)	17 (64)	22 (275)	22 (258)
Median (Range)	24 (10 to 72)	22 (10 to 128)	20 (10 to 62)	10 (10 to 46)	22 (10 to 857)[a]	22.2 (10 to 783)[a]

Source: clinical pharmacology reviewer's analysis based on adpc.xpt of Trial EPI 15. L = left; R = right
[a] One subject treated with EpiPen (L/R) had baseline epinephrine concentration of 857 and 783 at -10 and -5 minutes.

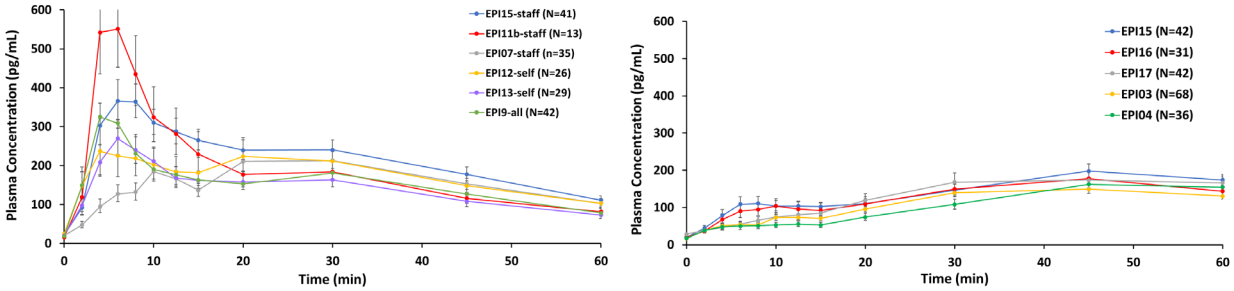
The Division agreed with the Applicant that it was not necessary to adjust epinephrine plasma concentrations by baseline values during the analysis for the following reasons: 1) the mean baseline epinephrine plasma concentrations were generally less than 10% of the mean C_{max} values following the epinephrine treatment; 2) a few subjects had some postdose epinephrine concentrations lower than their baseline values, which resulted in negative baseline-adjusted values that become invalid for calculating geometric mean values during the traditional PK analysis; 3) the baseline-uncorrected value of epinephrine plasma concentration is expected to be more clinically relevant during the PK/PD analysis. Therefore, only the mean/median baseline values by different treatment arms were reported for reference purpose.

Is the PK Bracketing Approach Between Approved Epinephrine Injection Products Reasonable To Support the Approval of ARS-1?

During the ARS-1 drug development program, the Applicant and FDA noted that there were substantial differences in the shape of the PK profiles and values of PK parameters between different epinephrine injection products and within the same injection products (Figure 1). These substantial differences were observed even within the same trial with a crossover design (a design to reduce PK variability).

Figure 1. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profile for Single-Dose EpiPen 0.3 mg (A) and Single-Dose Adrenalin 0.3 mg (B) Across Studies in ARS-1 Clinical Program

A. Single-Dose EpiPen 0.3 mg B. Single-Dose Adrenalin 0.3 mg



Source: Clinical Pharmacology Reviewer.
Adrenalin was administered by staff. Studies EPI 3, 4, 7 were clinical pharmacology trials that compared 1 mg ARS-1 with epinephrine injection products in healthy subjects; EPI 12 and 13 were clinical pharmacology trials conducted in subjects with Type 1 allergies that evaluated 1 mg ARS-1 and 2 mg ARS-1, respectively, in comparison to epinephrine injection products. Trial EPI 11b was a dose-ranging trial in healthy subjects that compared the PK of multiple dose levels of ARS-1 with epinephrine injection products.
Abbreviations: All, staff- and self-administration; self, self-administration; staff, staff-administration

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. Given the paucity of available PK data, this observation was not previously reported, and the root cause is unknown. 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. Although Adrenalin is intended for use within a medical setting, the needle-syringe PK profile is generally close to Symjepi, a prefilled syringe approved for home use. Moreover, although EpiPen demonstrates higher intra-product PK variability, EpiPen is widely prescribed for community use and is therefore considered a clinically relevant comparator.

What PK Parameters Are Considered When Comparing the PK Profiles of ARS-1 and Epinephrine Injection Products?

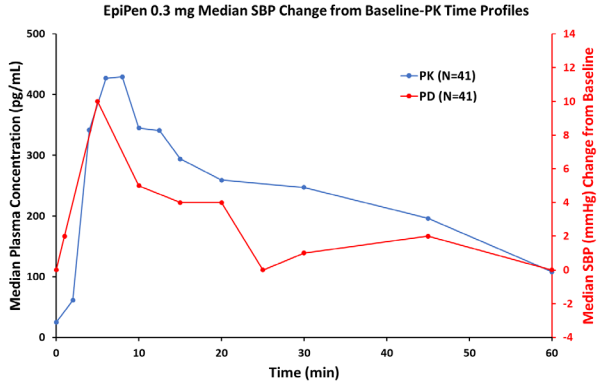
Anaphylaxis is an acute life-threatening disease that presents with rapid onset. Data from fatal anaphylaxis cases suggest that the interval between initial development of anaphylaxis and death can be <30 minutes. For example, registry data from the U.K. note that the median time interval between anaphylaxis onset and respiratory and cardiac arrest was 30 minutes in food-induced fatal anaphylaxis cases (Pumphrey 2000). Thus, the Division focused our analysis on the totality of the PK profiles within the first 60 minutes postdose during the review. PK parameters including C_{max}, partial AUCs ($AUC_{0\text{-}10\ min}$, $AUC_{0\text{-}20\ min}$, $AUC_{0\text{-}30\ min}$, and $AUC_{0\text{-}60min}$) are selected for relative bioavailability comparison between products.

What Is the Role of PD Endpoints in Supporting the Bridge Between ARS-1 and Epinephrine Injection Products?

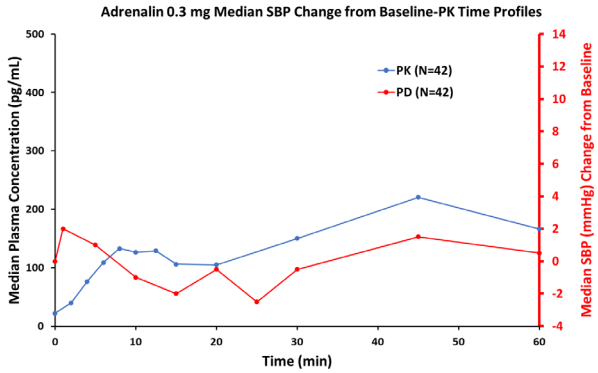
Based on trial EPI 15, the PK/PD relationship in healthy subjects appear different for each epinephrine product (EpiPen, Adrenalin and ARS-1) with ARS-1 having a generally higher and more sustained systolic blood pressure change from baseline after 10 minutes postdose regardless of its generally lower PK profile compared to EpiPen, as shown in Figure 2. The mechanism of this observation is unclear. A more sustained PD effect compared to PK was also observed for ARS-1 under NAC (see Figure 12 and Figure 13).

Figure 2. Median Plasma Epinephrine Concentration vs. Median PD Response (Change of SBP From Baseline) Following a Single Dose EpiPen 0.3 mg, Adrenalin 0.3 mg or ARS-1 2 mg, Trial EPI 15

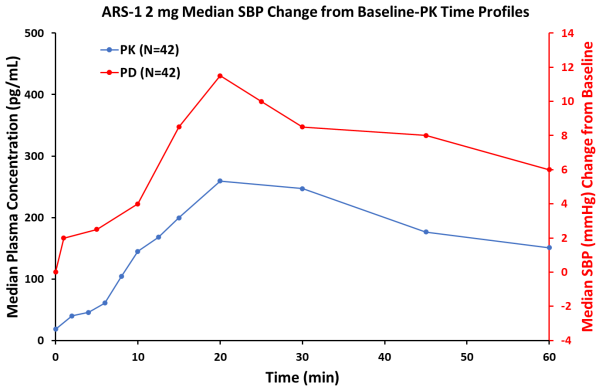
A. Single Dose EpiPen 0.3 mg IM



B. Single Dose Adrenalin 0.3 mg IM



C. Single-Dose ARS-1 2 mg IN



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 15

While PD responses (i.e., SBP, DBP, HR) may reflect hemodynamic changes that are important to treatment of anaphylaxis, there is an uncertainty whether the PD responses are similar between healthy subjects and anaphylaxis patients, as the hemodynamic conditions may be altered during anaphylaxis, which may affect the systemic responses to epinephrine. The PD responses of ARS-1 has not been evaluated in anaphylaxis patients. In addition, given different PK/PD relationship observed between ARS-1 and injection products in healthy subjects and reduction of PD response for ARS-1 under NAC conditions, there could be some additional

factors, including nasal conditions that may attribute to various PD responses. This raises the concerns to extrapolate the higher PD response trend for ARS-1 to anaphylaxis patients unless the Applicant provides a definitive understanding of the mechanism of action based on the anatomy, physiology, and pharmacology. The Division considers that the PD comparison results between ARS-1 and epinephrine injection products provide supportive evidence to the PK bracketing approach when justifying the needed scientific and regulatory bridging in the ARS-1 clinical pharmacology program.

In contrast to PD responses, the reviewer is more confident that a similar amount (as measured by AUC) of epinephrine delivered by ARS-1 is expected to be absorbed into systemic circulation in healthy subjects and anaphylaxis patients, as long as the nasal conditions are similar between the two populations (i.e., same normal nasal conditions in two populations or NAC conditions in rhinitis subjects mimicking the nasal edema of anaphylaxis patients). The reviewer acknowledges that the epinephrine PK profile could be different in healthy subjects and anaphylaxis patients due to the different hemodynamics. However, as long as the absorbed epinephrine amount delivered by ARS-1 matches to the epinephrine amount delivered by injection products, the factors (distribution, metabolism, and elimination) that could affect systemic epinephrine PK exposure are the same for the same subject (healthy subject or anaphylaxis patient) once epinephrine enters systemic circulation, regardless of the administration route of epinephrine. Therefore, the Division places more emphasis on the PK bracketing results, and views PD results as supportive.

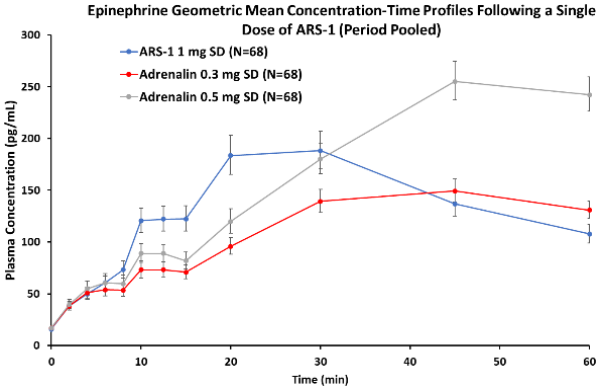
As ARS-1 has demonstrated a comparable PK profile to at least one listed product with a reasonable duration as well as overall sustained PD effect (especially SBP) throughout 60 minutes postdose across studies, the trend of sustained PD effect of ARS-1 can further support the establishment of the scientific bridge to the listed products in conjunction with PK comparison results.

What Is the Carryover Effect and How Does It Affect the Epinephrine PK Following ARS-1 Administration?

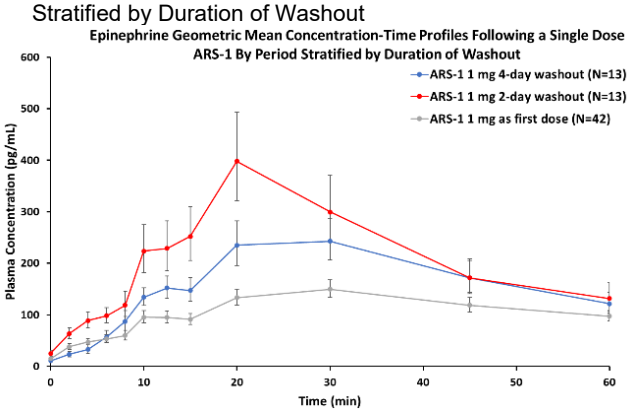
ARS initially intended to develop a 1 mg epinephrine dose for adults, as a crossover Trial, EPI 3, demonstrated that the mean epinephrine PK profile following 1 mg ARS-1 summarized from several IN treatment periods was within the range of PK profiles following two dose levels of Adrenalin (i.e., 0.3 mg and 0.5 mg) IM injection (Figure 3A). However, a subsequent analysis indicated that the mean PK profile from EPI 3 for 1 mg ARS-1 was inflated because the epinephrine PK profiles following ARS-1 from treatment periods that were preceded by earlier IN period were several times higher than the first IN treatment period in EPI 3 (Figure 3B). This phenomenon was termed “carryover effect.”

Figure 3. Epinephrine Geometric Mean Concentration-Time Profile Following a Single Dose of ARS-1, Trial EPI 3

A. Mean Epinephrine PK Profiles of ARS-1 (Period Pooled)



B. Mean Epinephrine PK Profiles of ARS-1 by Period Stratified by Duration of Washout



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 3.
Abbreviation: IN, intranasal; PK, pharmacokinetic

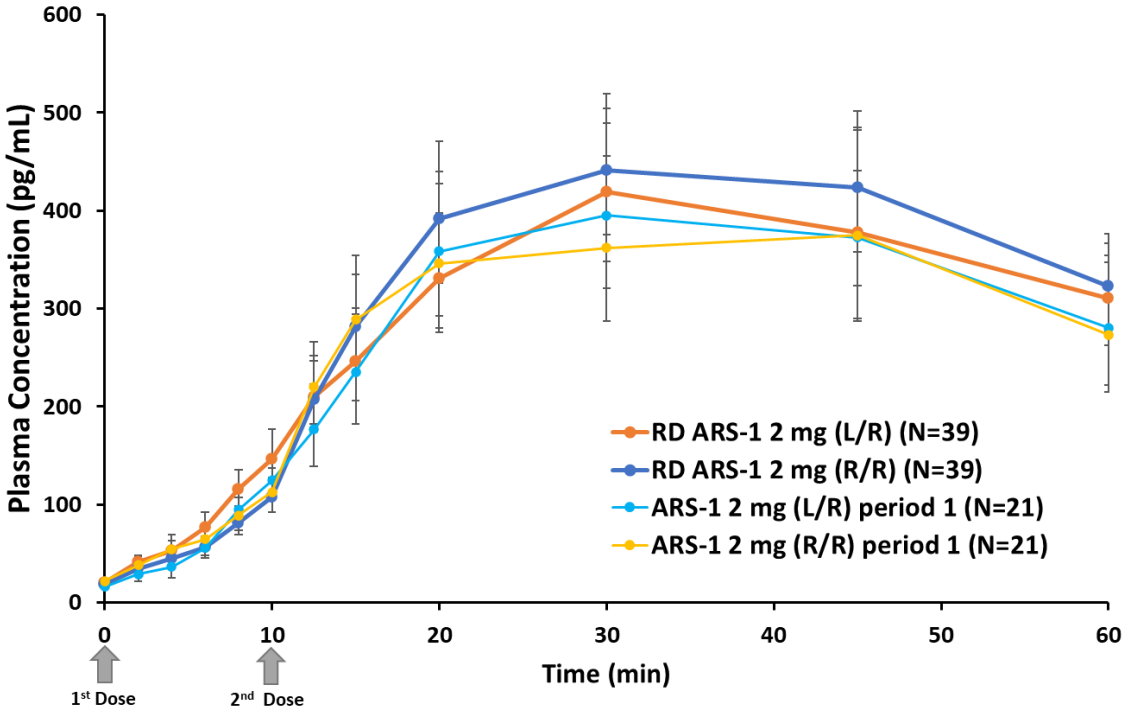
Further, this carryover effect was consistently confirmed in all the ARS-1 1 mg PK studies with crossover designs for the IN treatment periods. Therefore, the mean epinephrine PK profile of 1 mg ARS-1 summarized from EPI 3 is not representative of the actual epinephrine PK profile for single dose of ARS-1. Although a patient could use ARS-1 again if they experience another anaphylaxis episode within a few days, the higher epinephrine PK following ARS-1 for the treatment of the second anaphylaxis due to the carryover effect is generally within the epinephrine systemic exposure of EpiPen (Figure 5 and Figure 9) and would not be considered a safety concern. In addition, as patients are (b) (4) the safety of more than one dose of ARS-1 administered within a short time period (e.g., 2 days) will be appropriately monitored by healthcare providers. Of note, the carryover effect was not observed following IM epinephrine injection in the same crossover design.

On review of nonclinical studies, it is hypothesized that reversible nasal mucosal changes may take some time (i.e., no immediate carryover effect) to develop with the change peaking in 1 to 2 days, which allows for an increased absorption from the second dose of IN epinephrine if delivered during this period. See Section 5 for summary of nonclinical review of local nasal toxicity in rats. The carryover effect was not observed following the second dose of ARS-1 administered 10 minutes after the first dose, as the PK profile of epinephrine following two doses of ARS-1 administered in the same naris (same absorption site) was similar compared to that of two doses of ARS-1 administered in the opposite nares (different absorption site) (see Section 15.4.1.1 and Figure 4). However, the carryover effect was most noticeable when the second dose is administered around 2 days following the previous ARS-1 administration (although dosing intervals between 10 minutes and 2 days were not investigated) (Figure 3).

To mitigate the carryover effect, the Applicant substantially expanded the washout period to 12 days between IN treatment periods or administered ARS-1 in a different naris in trials with IN crossover design. No apparent carryover effect was observed during the ARS-1 2 mg program

after implementation of these mitigation strategies. Representative PK results for evaluation of carryover effect from Trial EPI 15 are shown in Figure 4.

Figure 4. Epinephrine Concentration-Time Profiles of Repeat-Dose ARS-1 (Period Pooled vs. Period 1), Trial EPI 15



Washout period between two IN treatment period was 12 days.
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 15

Are the PK Profiles of Epinephrine Following ARS-1 2 mg Sufficiently Bracketed by the Approved Epinephrine Injection Products Under Normal Nasal Conditions?

Trial EPI 15 was a two-part, six-treatment, six-period, single and repeat dose, incomplete crossover PK/PD trial. The purpose of this trial was to provide pivotal PK and PD data comparing ARS-1 with approved epinephrine injection products (EpiPen 0.3 mg and Adrenalin 0.3 mg) following a single and repeat dose. For additional details, see Section 7.1.1 for the protocol and Section 15.4.1.1 for trial results.

Part 1 was a single-dose comparative bioavailability trial in which subjects (N=42) were randomized to receive each of the following treatments in each period: a single dose of ARS-1 in the left naris, a single dose of EpiPen IM 0.3 mg in the left thigh, and a single dose of Adrenalin IM 0.3 mg in the right thigh. The washout period between each treatment period was 24 hours.

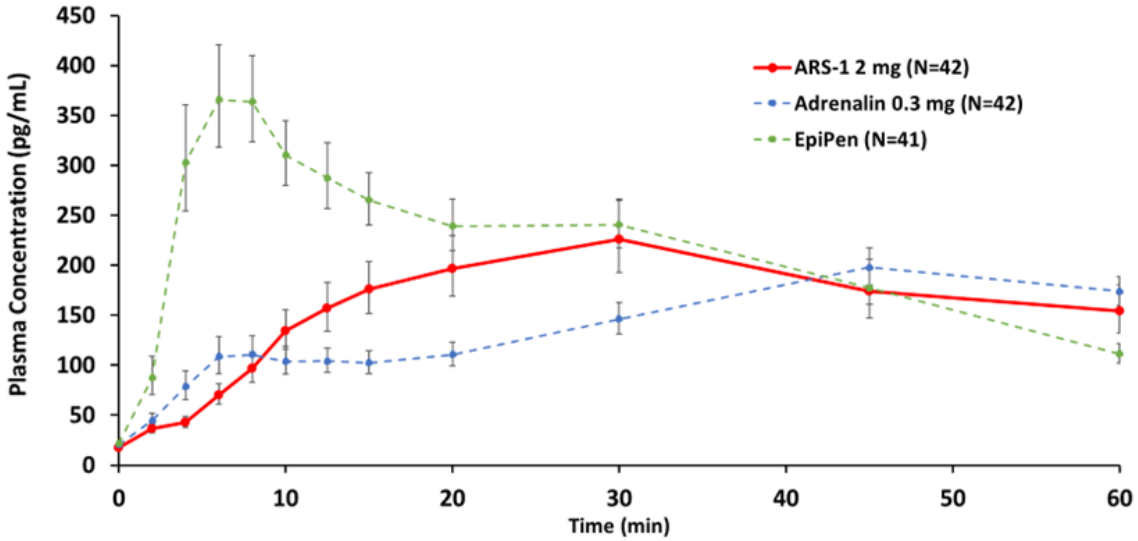
Part 2 was a repeat-dose comparative bioavailability trial. Subjects (N=42) received two doses of either ARS-1 (same naris or opposite naris) or EpiPen IM 0.3 mg, separated by 10 minutes between each dose. The trial sequence adopted a sandwich design (ARS-1 → EpiPen → ARS-1)

with a washout period of 6 days between each treatment period to mitigate the carryover effect. A total of 26 subjects participated in both Part 1 and Part 2.

Single-Dose PK Results

For Part 1, the epinephrine concentration-time profiles within 60 minutes postdose and PK parameters including C_{max} and partial AUCs up to 60 minutes following a single dose of ARS-1, Adrenalin 0.3 mg or EpiPen 0.3 mg are displayed in Figure 5 and Table 10, respectively.

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, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. One subject from EpiPen arm was excluded due to an insufficient number of postdose samples (N <3) collected within 30 min.

Table 10. 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, Trial EPI 15

	Geometric Mean (CV%)			
Parameter	**ARS-1 (N=42)**	**Adrenalin 0.3 mg IM (N=42)**	**EpiPen 0.3 mg IM (N=41)[b]**	**Bracketed (Y/N)[c]**
C_{max} (pg/mL)	341(114)	283 (63)	618 (79)	Y
T_{max} (min)[a]	30	45	6	---
$AUC_{0\text{-}10min}$ (pg·min/mL)	712 (93)	889 (118)	2979 (98)	N (lower than both)
$AUC_{0\text{-}20min}$ (pg·min/mL)	2596 (102)	2040 (102)	6007 (77)	Y
$AUC_{0\text{-}30min}$ (pg·min/mL)	4901 (109)	3439 (77)	8759 (67)	Y
$AUC_{0\text{-}60min}$ (pg·min/mL)	10925 (116)	9242 (59)	14772 (56)	Y

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
a Median.
b One subject from EpiPen arm was excluded due to an insufficient number of postdose samples (N <3) collected within 30 min.
c See Table 11 for statistical analysis.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IN, intranasal; IM, intramuscular; N, no; T_{max}, time to maximum plasma concentration; Y, yes

The bioequivalence (BE) assessment shown in Table 11 indicates that the epinephrine C_{max} and AUCs for ARS-1 were generally bracketed by EpiPen and Adrenalin (i.e., the high 90% CI boundary of geometric mean ratio of ARS-1/EpiPen is less than 125% and the low 90% CI boundary of geometric mean ratio of ARS-1/Adrenalin is greater than 80%) except $AUC_{0\text{-}10\ min}$, which the low 90% CI boundary of geometric mean ratio of ARS-1/Adrenalin is less than 80%. The lower $AUC_{0\text{-}10\ min}$ of epinephrine following ARS-1 compared to both EpiPen and Adrenalin implies a slower initial absorption rate following ARS-1 administration in Trial EPI 15. However, as substantial cross-study PK variability was noted especially within the initial absorption phase for Adrenalin among different studies in ARS-1 clinical program, the initial absorption rate for ARS-1 was within the range of Adrenalin based on a cross-study comparison (Figure 7). Thus, the PK profile for ARS-1 from EPI 15 within 10 minutes postdose is reasonably bracketed by PK profiles of Adrenalin from different studies.

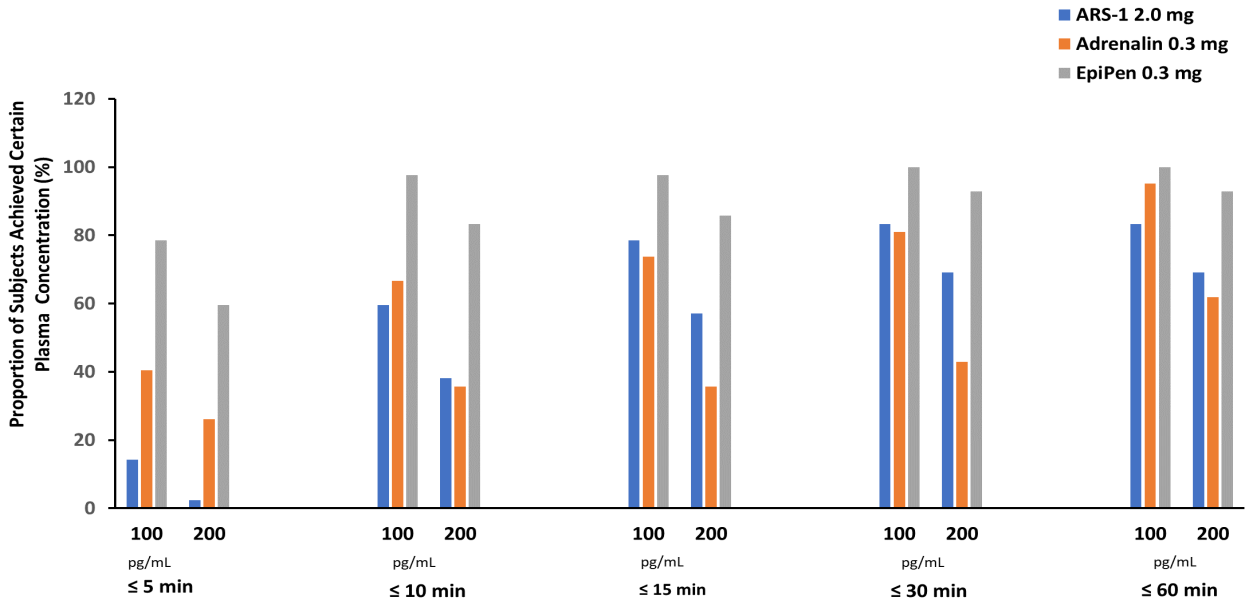
Table 11. Bioequivalence Assessment Between a Single Dose of ARS-1 and a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

	Test: ARS-1 2 mg (N=42) vs. Reference: Adrenalin 0.3 mg (N=42) GMR (%) [90% CI]	**Test: ARS-1 2 mg (N=42) vs. Reference: EpiPen 0.3 mg (N=41) GMR (%) [90% CI]**
C_{max} (pg/mL)	120.2 [94.5, 152.9]	56.2 [44.2, 71.4]
$AUC_{0\text{-}10}$ (pg*min/mL)	**80.1 [61.8, 103.9]**	24.6 [19.0, 31.9]
$AUC_{0\text{-}20}$ (pg*min/mL)	127.3 [101.1, 160.2]	44.0 [34.9, 55.3]
$AUC_{0\text{-}30}$ (pg*min/mL)	142.5 [114.1, 177.9]	56.5 [45.3, 70.6]
$AUC_{0\text{-}60}$ (pg*min/mL)	118.2 [95.8, 145.7]	74.2 [60.2, 91.5]

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; IN, intranasal; IM, intramuscular; N, no

The therapeutic threshold for epinephrine is unknown. The proportion of subjects whose epinephrine concentration reached 100 pg/mL or 200 pg/mL, arbitrary threshold concentrations suggested by literature following continuous IV infusion (Clutter et al. 1980), at different time points within 60 minutes post–single dose is shown in Figure 6. The proportion of subjects who failed to reach 100 pg/mL within 30 minutes and 60 minutes is shown in Table 12.

Figure 6. Proportion of Subjects With Epinephrine Concentrations of 100 and 200 pg/mL or Greater by Time Following a Single Dose of ARS-1, Adrenalin 0.3 mg, or EpiPen 0.3 mg, Trial EPI 15



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

Table 12. Proportion of Subjects Who Failed To Reach 100 pg/mL Following a Single Dose of ARS-1 2 mg, Adrenalin 0.3 mg, or EpiPen 0.3 mg, Trial EPI 15

Elapsed Time	ARS-1	Adrenalin 0.3 mg	EpiPen 0.3 mg
Within 30 min	7/42 (17%)	7/42 (17%)	0/41 (0%)
Within 60 min	7/42 (17%)	2/42 (5%)	0/41 (0%)

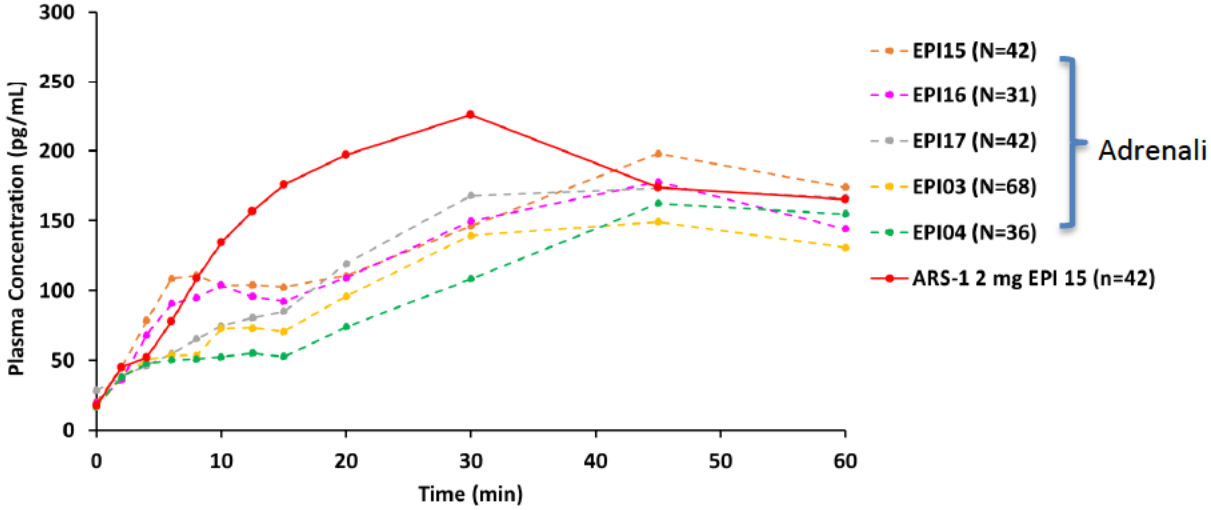
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15

EpiPen 0.3 mg administration resulted in higher proportion of subjects achieving epinephrine concentrations of 100 pg/mL and 200 pg/mL than ARS-1 and Adrenalin for all time points within 60 minutes postdose. The proportion of subjects who achieved 100 pg/mL and 200 pg/mL was initially low following both ARS-1 and Adrenalin 0.3 mg administration. Although the proportions for both ARS-1 and Adrenalin gradually increased over time, the values remained lower than EpiPen at 60 minutes postdose. The proportion of subjects who achieved 100 pg/mL and 200 pg/mL following ARS-1 was noticeably lower when compared to Adrenalin within 5 minutes postdose, however, the proportion of subjects who achieved threshold values between Adrenalin and ARS-1 became comparable thereafter. Of note, the clinical relevance of 100 or 200 pg/mL is unclear in the treatment of anaphylaxis.

Cross-Trial PK Comparison With All Adrenalin Results

When comparing the epinephrine PK profiles of ARS-1 from Trial EPI 15 to that of Adrenalin from other studies conducted under the ARS-1 clinical program in a cross-trial manner, as shown in Figure 7, the epinephrine PK profile of ARS-1 appears to be generally bracketed by PK profiles of Adrenalin within 10 minutes postdose. Of note, the epinephrine PK profile of Adrenalin from EPI 15 appears to have the highest absorption rate within 10 minutes among all the studies using Adrenalin as a comparator in the ARS-1 program.

Figure 7. Cross-Trial Comparison of Geometric Mean Concentration-Time Profiles

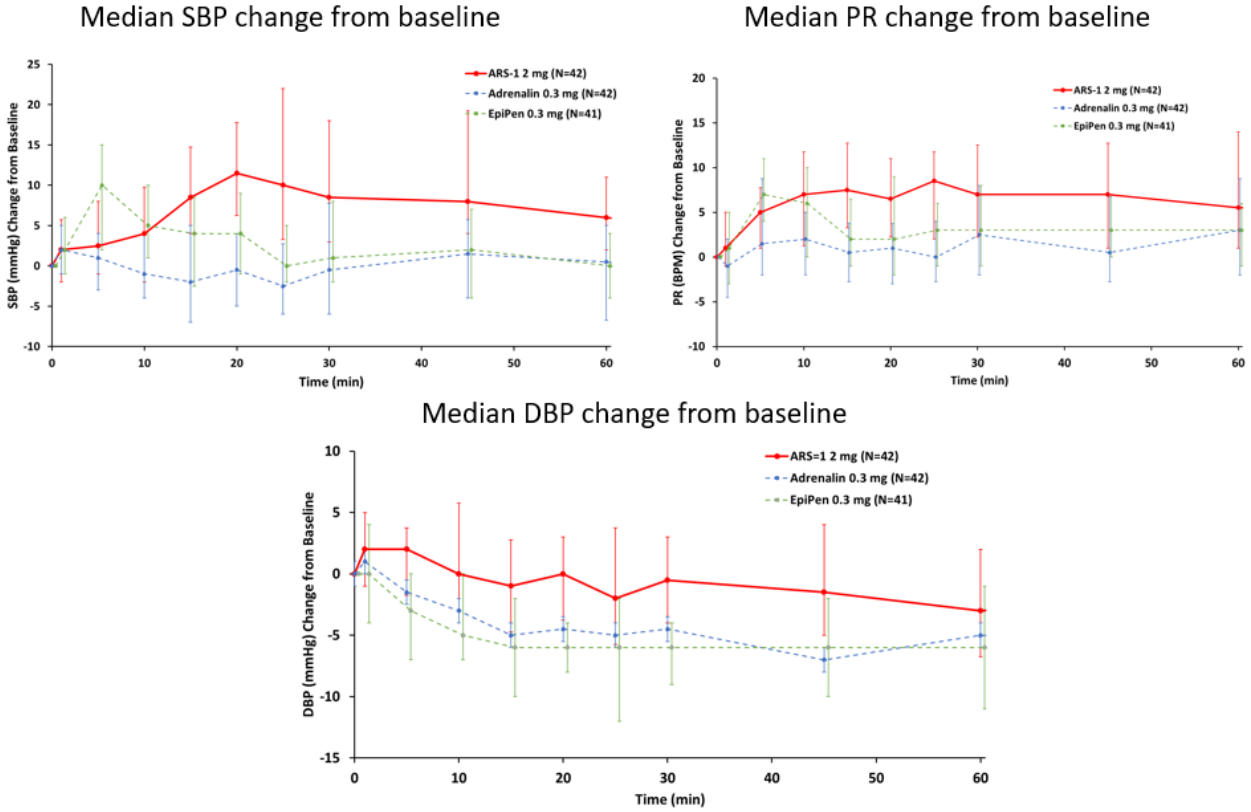


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15, EPI 16, EPI 17, EPI 3 and EPI 4.

Single-Dose PD Results

The PD responses (SBP, DBP and PR change from baseline)-time profiles following a single dose of ARS-1, Adrenalin 0.3 mg, or EpiPen 0.3 mg are displayed in Figure 8. The mean and median maximum SBP changes from baseline in 60 minutes and the median time to reach the maximum SBP change following a single dose are shown in Table 13.

Figure 8. 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, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15. 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: DBP, diastolic blood pressure; PD, pharmacodynamic; PK, pharmacokinetic; PR, pulse rate; SBP, systolic blood pressure

Table 13. Maximum Change of SBP From Baseline in 60 Minutes Following a Single Dose, Trial EPI 15

Parameter	ARS-1 (n=42)	EpiPen 0.3 mg (n=41)	Adrenalin 0.3 mg (n=42)
Mean (SD) (mmHg)	23 (16)	17 (15)	12 (10)
Median (range) (mmHg)	19 (0, 72)	15 (0, 90)	9 (0, 41)
Median T_{max} (range) (min)	25 (0, 60)	5 (0, 60)	15 (0, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15. Subjects who were included in the PK analysis were included in the PD analysis.
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic; SBP, systolic blood pressure; Tmax time to maximum plasma concentration

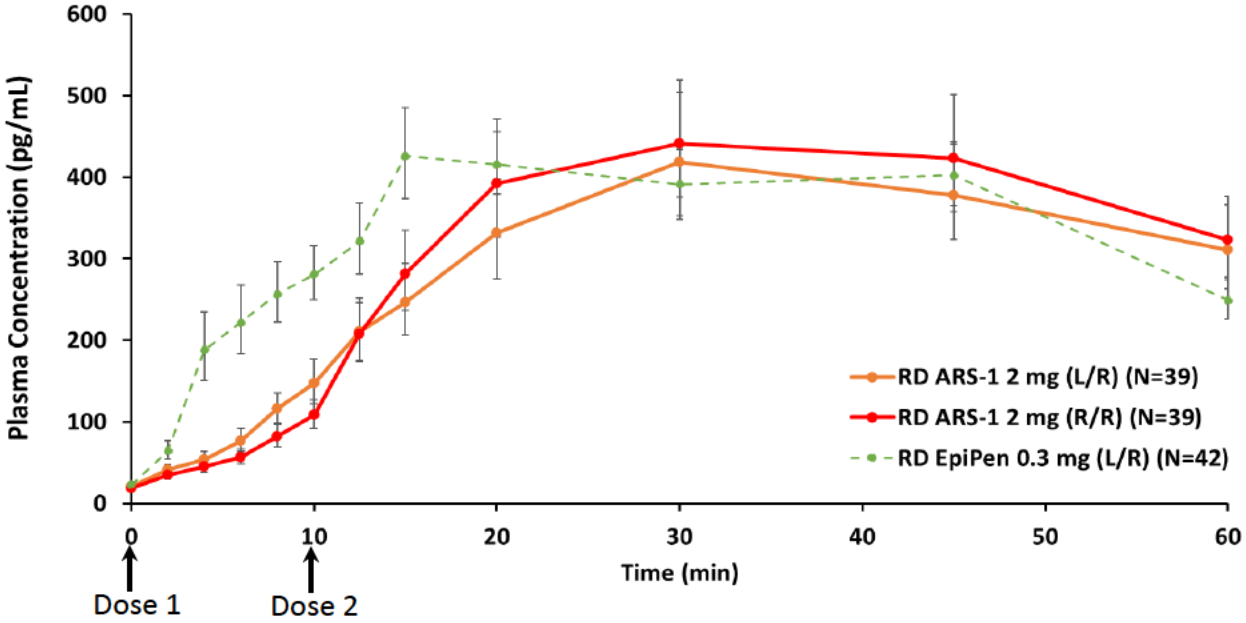
The median SBP and PR responses following single-dose administration of ARS-1 are generally bracketed by EpiPen and Adrenalin within 10 minutes postdose. However, the magnitudes of SBP and PR responses are generally higher and more sustained for ARS-1 compared to both injection products thereafter despite the geometric mean epinephrine concentration of ARS-1 being generally lower compared to that of EpiPen. The exact mechanism underlying the discrepancy of PK and SBP/PR comparison results between ARS-1 and EpiPen is unclear. In

addition, a more stable DBP-time profile was observed following ARS-1 when compared to apparent declined profiles from both injection products.

Repeat-Dose PK Results

In Part 2 of EPI 15, two doses of ARS-1 or EpiPen were given 10 minutes apart. The second dose of ARS-1 was administered in the same naris in one period and in the opposite naris in another period. The epinephrine concentration-time profiles following the first dose (Time 0 minute) and second dose (Time 10 min) are shown in Figure 9. The PK parameters from the repeat dosing are reported in Table 14.

Figure 9. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profile Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. Three subjects each in the ARS-1 (R/R) and ARS-1 (L/R) arms discontinued early and did not have PK data.
Abbreviations: L, left; PK, pharmacokinetic; R, right; RD, repeat doses

Table 14. PK Parameters Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

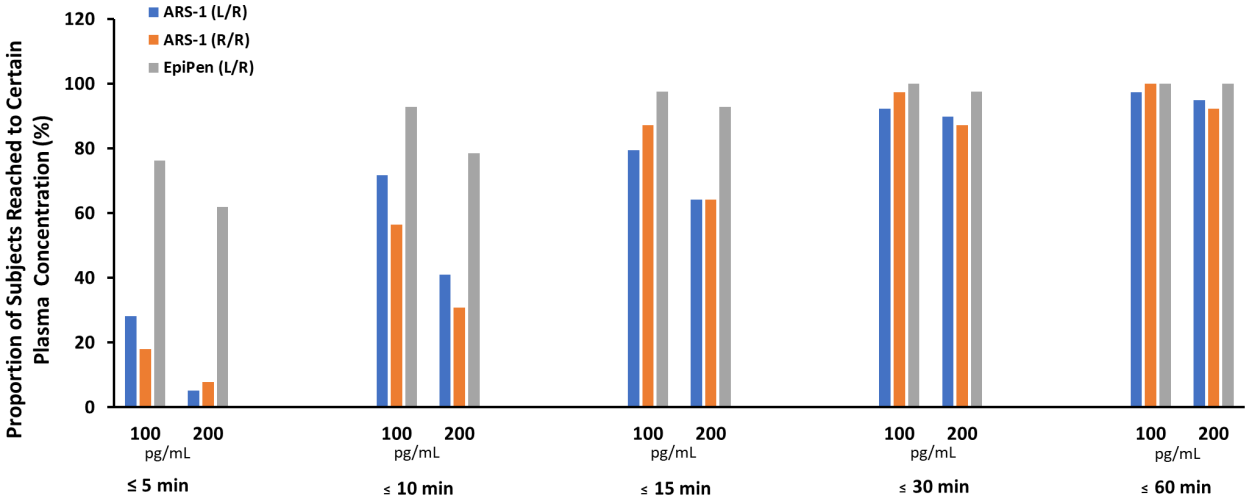
	Geometric Mean (CV%)		
Parameter	Repeat-Dose ARS-1 2 mg (L/R) (N=39)	Repeat-Dose ARS-1 2 mg (R/R) (N=39)	Repeat-Dose EpiPen 0.3 mg (L/R) IM (N=42)
C_{max} (pg/mL)	706 (104)	729 (99)	721 (61)
T_{max} (min)[a]	30	30	15
$AUC_{0\text{-}10min}$ (pg·min/mL)	836 (117.5)	627 (111)	2147 (104)
$AUC_{0\text{-}20min}$ (pg·min/mL)	3664 (123)	3626 (128)	6363 (78)
$AUC_{0\text{-}30min}$ (pg·min/mL)	8106 (119)	8291 (119)	10735 (67)
$AUC_{0\text{-}60min}$ (pg·min/mL)	21083 (110)	22034 (110)	23034 (54)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. Three subjects each in the ARS-1 (R/R) and ARS-1 (L/R) arms discontinued early and did not have PK data.
a Median is reported.
Abbreviations: L, left; R, right; PK, pharmacokinetic

Based on the results of EPI 15 Part 2, the epinephrine C_{max} and $AUC_{0\text{-}60min}$ following two doses of EpiPen only increased about 20% and 50%, respectively, compared to that following single-dose administration in Part 1. However, the epinephrine C_{max} and $AUC_{0\text{-}60min}$ values following two doses of ARS-1 approximately doubled compared to single-dose administration in Part 1. Therefore, the epinephrine C_{max} and $AUC_{0\text{-}60min}$ values following two doses of ARS-1 are comparable to that of two doses of EpiPen. The epinephrine concentration following two doses of ARS-1 remains lower than that of EpiPen during the first 20 to 30 minutes post-first dose and becomes numerically comparable thereafter. Although repeat doses of Adrenalin were not assessed in the repeat dose comparison in EPI 15, a cross study comparison was performed between EPI 15 and repeat doses Adrenalin results from EPI 3, a study that was previously conducted by the Applicant to support 1-mg dose. The results demonstrated that the PK profile of repeat doses of ARS-1 was comparable to that of repeat doses of Adrenalin 0.3 mg during first 10 minutes postdose and became higher afterwards (see 15.4.1.1, Figure 27 for more details). In addition, epinephrine PK profiles and systemic exposures were similar between ARS-1 administered in the same naris and opposite naris.

The proportion of subjects whose epinephrine concentration reached 100 pg/mL or 200 pg/mL at different time points within 60 minutes following two doses of ARS-1 or EpiPen 0.3 mg is shown in Figure 10. The proportion of subjects whose epinephrine concentration failed to reach 100 pg/mL within 30 minutes and 60 minutes is shown in Table 15.

Figure 10. Proportion of Subjects With Epinephrine Concentrations of 100 pg/mL and 200 pg/mL or Greater Following Two Doses of ARS-1 in Same Naris (R/R) or Opposite Naris (L/R), and Two Doses of EpiPen 0.3 mg, Trial EPI 15



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

Table 15. Proportion of Subjects Who Failed to Reach 100 pg/mL Following Two Doses of ARS-1 2 in Same Naris (R/R) or Opposite Naris (L/R), and Two Doses of EpiPen 0.3 mg

Elapsed Time	ARS-1 L/R	ARS-1 R/R	EpiPen L/R
Within 30 min	2/38 (5%)	0/38 (0%)	0/42 (0%)
Within 60 min	1/38 (3%)	0/38 (0%)	0/42 (0%)

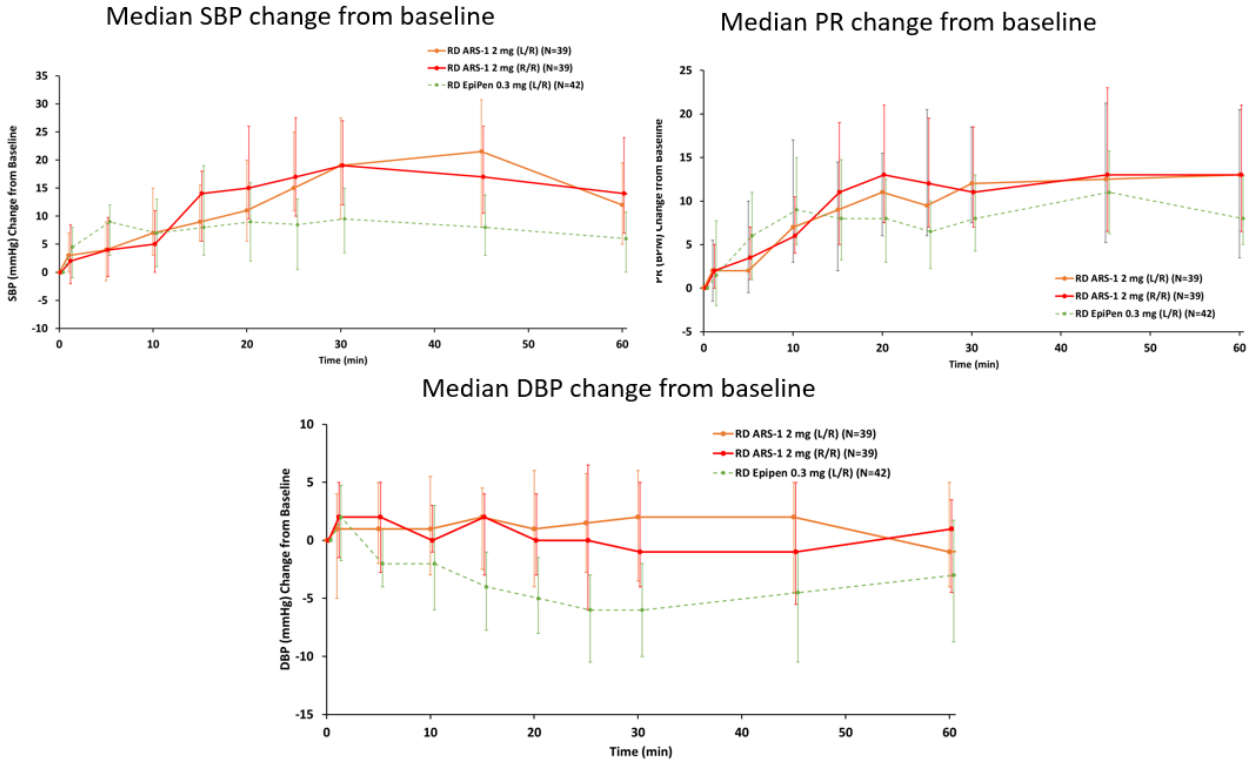
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
Abbreviations: L, left; R, right

Similar to Part 1, the proportions of subjects whose epinephrine concentration reached the threshold of 100 pg/mL and 200 pg/mL were initially low following ARS-1 dosing and gradually increased over time. The proportion following two doses of ARS-1 approached that following two doses of EpiPen at 60 minutes postdose. Higher proportions of subjects whose epinephrine concentrations reached 100 pg/mL and 200 pg/mL following two doses of ARS-1 in Part 2 than single dose in Part 1 starting 15 minutes postdose.

Repeat-Dose PD Results

The PD responses (SBP, PR, and DPB change from baseline)-time profiles following two doses of ARS-1 and EpiPen 0.3 mg are shown in Figure 11. The mean and median of the maximum SBP change from baseline within 60 minutes as well as the median time to reach the maximum change following repeat doses are shown in Table 16.

Figure 11. Median PD Responses (SBP, PR, and DBP Change From Baseline) Following Two Doses of ARS-1 in Same Naris (R/R) or Opposite Naris (L/R), and Two Doses of EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15.
Error bars represent 25% and 75% percentile of the PD values.

Table 16. Maximum SBP Change From Baseline in 60 Minutes Following Repeat Doses, Trial EPI 15

Parameter	ARS-1 (L/R) (n=38)	ARS-1 (R/R) (n=38)	EpiPen 0.3 mg (L/R) (n=42)
Mean (SD) (mmHg)	29 (14)	29 (13)	19 (9)
Median (range) (mmHg)	29 (6, 67)	26 (11, 64)	19 (3, 42)
Median T_{max} (range) (min)	28 (1, 60)	30 (5, 60)	15 (1, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15.
Abbreviations: L, left; PD, pharmacodynamic; PK, pharmacokinetic; R, right; Tmax, time to maximum plasma concentration

Similar to the PD results from Part 1, higher and more sustained SBP and PR responses following two doses of ARS-1 were observed when compared to two doses of EpiPen in Part 2, despite the comparable $AUC_{0\text{-}60min}$ values between treatments. In addition, the magnitude of SBP and PR responses are higher following two doses of ARS-1 in Part 2 than following single dose of ARS-1 in Part 1. However, the magnitude of SBP and PR responses following two doses of EpiPen in Part 2 is similar to that following a single dose of EpiPen in Part 1, except for improved sustainability. In addition, a more stable DBP time profile following ARS-1 2 mg administration was observed compared to EpiPen.

PK/PD Summary in Healthy Subjects With Normal Nasal Condition

Overall, based on results from EPI 15 in healthy adults, the PK profile of epinephrine for ARS-1 was reasonably bracketed by Adrenalin and EpiPen following a single dose after 10 minutes postdose and the PK profile of epinephrine following repeat doses of ARS-1 was similar to repeat-dose EpiPen, except for the lower concentration within 20 minutes postdose.

Based on a cross-trial comparison with Adrenalin results in the ARS-1 clinical program, the PK profile for ARS-1 from EPI 15 within 10 minutes postdose was reasonably bracketed by PK profiles of Adrenalin from different studies. The 10-minute PK profile of Adrenalin was the highest from EPI 15. A higher intersubject PK variability shown by CV% was noted for ARS-1 when compared to epinephrine injection products (Table 10 and Table 14).

In general, the median PD (SBP and PR) responses following ARS-1 were generally bracketed by EpiPen and Adrenalin within 10 minutes following single dose administration. After 10-minutes post dose, the median PD responses following ARS-1 are numerically higher and more sustained than both injection products. The median maximum PD responses are higher following two doses of ARS-1 than a single dose of ARS-1. The PD comparison results in healthy subjects under normal nasal condition generally supports the PK bracketing approach for the ARS-1 drug development program.

Does Allergen-Induced Acute Rhinitis Affect the PK and PD Response Following ARS-1 Administration?

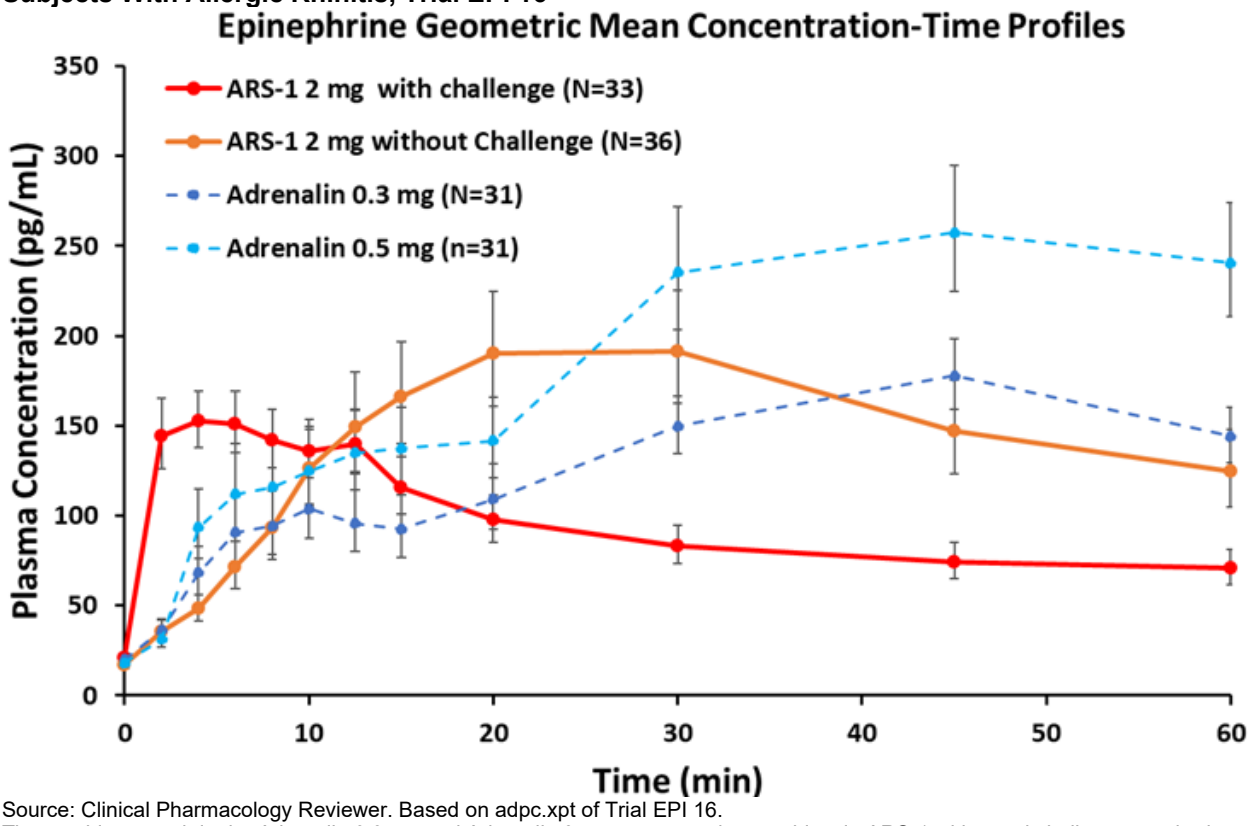
In Trial EPI 16, epinephrine PK and PD profiles following ARS-1 were evaluated in subjects with allergic rhinitis with or without NAC (used to include allergen-induced acute rhinitis). Adrenalin 0.3 mg and Adrenalin 0.5 mg were administered in this trial as comparators. Anaphylaxis can impact multiple organ systems, including the nasal mucosa—the administration site of ARS-1. Allergen-induced acute rhinitis can occur in anaphylaxis and cause symptoms, such as rhinorrhea and nasal congestion; alterations of the nasal mucosa (e.g., vasodilation) may affect the local absorption of epinephrine. The rates of rhinitis and conjunctivitis range from 2% to 11% in anaphylaxis subjects (Brown et al. 2001; Braganza et al. 2006; Gonzalez-Estrada et al. 2017). However, these statistics are limited given these are from retrospective case trial reviews. FDA and the Applicant agreed that NAC of subjects with allergic rhinitis with known allergen sensitization may reasonably mimic the local findings that could occur in anaphylaxis.

Trial EPI 16 was a four-treatment, partially randomized, crossover trial involving adult subjects with allergic rhinitis (N=36). The trial sequence was of sandwich design (ARS-1 → Adrenalin → Adrenalin → ARS-1) with a washout period of 12 days between the two ARS-1 treatment periods to mitigate the carryover effect. For additional details, see Section 7.1.2 for the protocol and Section 15.4.1.2 for trial results.

PK in Allergen-Induced Acute Rhinitis

The epinephrine concentration-time profiles within 60 minutes postdose are shown in Figure 12.

Figure 12. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis, Trial EPI 16



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 16.
Three subjects each in the Adrenalin 0.3 mg and Adrenalin 0.5 mg arms and one subject in ARS-1 with nasal challenge arm had insufficient number of postdose samples (n <3) collected within 30 min. Two subjects each in the Adrenalin 0.3 mg, Adrenalin 0.5 mg, and the ARS-1 with nasal allergen challenge did not have PK data.

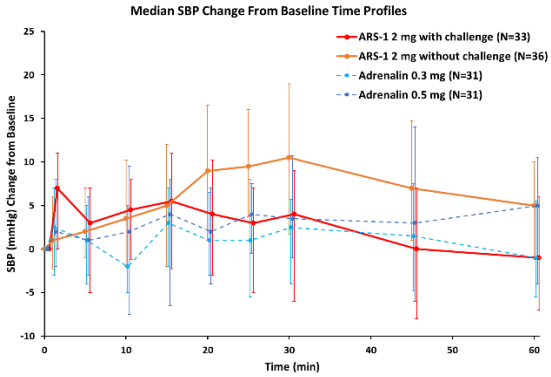
Under normal nasal conditions, the epinephrine concentration-time profile for ARS-1 was similar to that from Trial EPI 15 (Figure 5). The exposure was reasonably within the range of 0.3 mg and 0.5 mg of Adrenalin within 60 minutes postdose. Under the NAC conditions, the epinephrine geometric mean concentration following ARS-1 increased more rapidly than the two Adrenalin dose arms followed by a decline phase in which the epinephrine concentrations became lower than ARS-1 under normal nasal conditions 10 minutes postdose and lower than Adrenalin 0.3 mg 20 minutes postdose.

PD in Allergen-Induced Acute Rhinitis

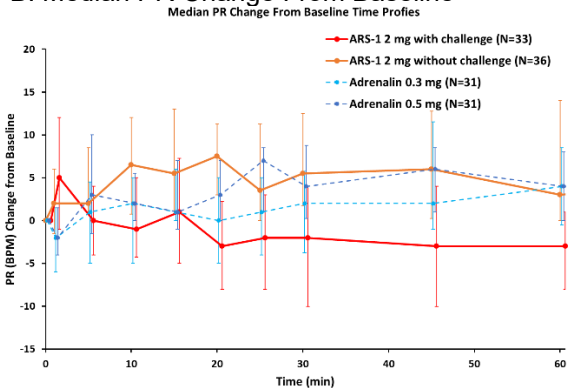
The PD responses (SBP and PR change from baseline)-time profiles over 60 minutes are shown in Figure 13. The mean and median of maximum SBP change from baseline within 60 minutes and median T_{max} to reach maximum change are shown in Table 17.

Figure 13. Median PD Responses (SBP and PR Changes From Baseline) in Subjects With Allergic Rhinitis, Trial EPI 16

A. Median SBP Change From Baseline



B. Median PR Change From Baseline



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial 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, pharmacodynamic; PK, pharmacokinetic; PR, pulse rate; SBP, systolic blood pressure

Table 17. Maximum SBP and PR Change From Baseline in 60 Minutes in Subjects With Allergic Rhinitis, Trial EPI 16

Parameter	ARS-1 Normal (N=36)	ARS-1 NAC (N=33)	Adrenalin 0.3 mg (N=31)	Adrenalin 0.5 mg (N=31)
SBP				
Mean (SD) (mmHg)	20 (17)	15 (13)	12 (9)	13 (10)
Median (range) (mmHg)	18 (-24, 88)	13 (-12, 68)	12 (-4, 28)	16 (-19, 32)
Median T_{max} (range) (min)	25 (1, 60)	10 (1, 60)	20 (1, 60)	25 (1, 60)
PR				
Mean (SD) (BPM)	18 (13)	10 (13)	10 (8)	12 (8)
Median (range) (BPM)	14 (-4, 58)	9 (-17, 53)	11 (-6, 26)	11 (1, 37)
Median T_{max} (range) (min)	20 (1, 60)	1 (1, 60)	25 (1, 60)	20 (1, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI16.
Subjects who were included in the PK analysis were included in the PD analysis.
Abbreviations: BPM, beats per minute; PR, pulse rate; SBP, systolic blood pressure; Tmax, time to maximum plasma concentration; NAC, nasal allergen challenge

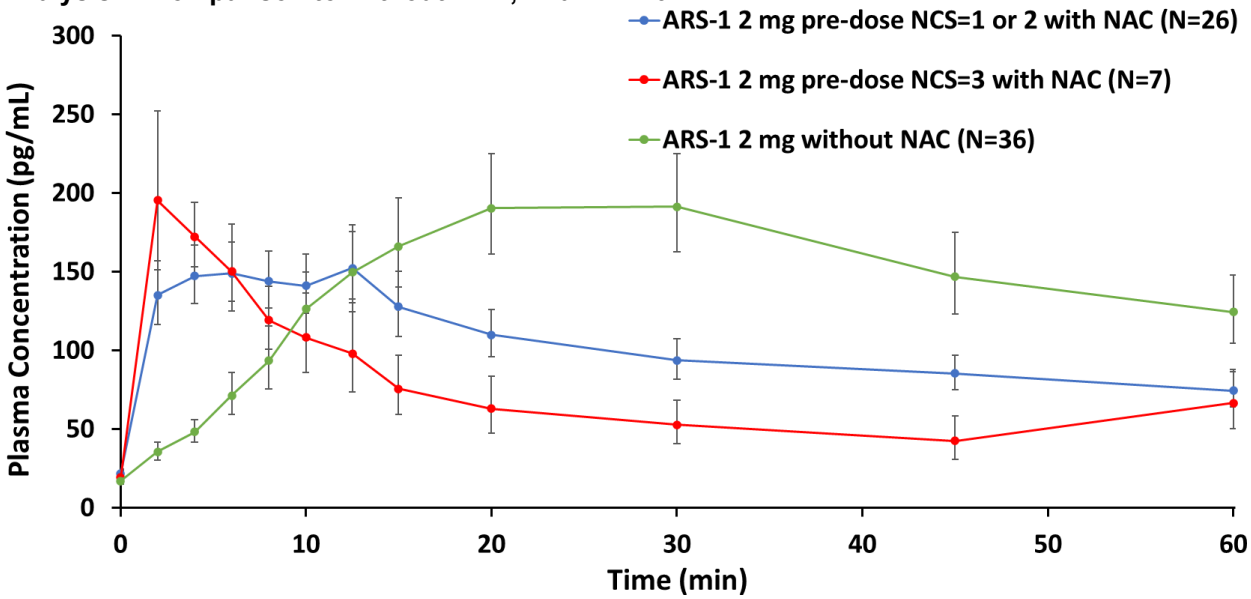
Similar to the PK profile, initially higher median SBP response was observed following ARS-1 under NAC conditions. However, the SBP response declined to lower than that of ARS-1 without NAC after about 15 minutes postdose. The median SBP response for ARS-1 with NAC was initially higher than the median SBP response for 0.3 mg Adrenalin through 20 minutes postdose and became comparable through 60 minutes postdose. The initially higher median PR response following ARS-1 under NAC conditions declined lower than that of ARS-1 without NAC conditions and Adrenalin 0.3 mg after about 5 minutes postdose. Further, the median PR following ARS-1 under NAC conditions was generally lower than baseline level after 10 minutes postdose. By comparing the shape of PK and PD profiles, additional effect of nasal condition on PD response other than PK cannot be excluded.

Impact of Nasal Congestion on PK

To further explore the effect of NAC on epinephrine PK following ARS-1, the reviewer reviewed predose (i.e., pre-ARS-1) nasal congestion score (NCS) under NAC conditions, as nasal congestion may affect the systemic absorption of ARS-1. The reviewer also found that under NAC conditions, 10 of the 34 subjects treated with ARS-1 continued to have some degree of nasal congestion for more than 30 minutes post-ARS-1 dose, with 7 of those subjects experiencing nasal congestion for 120 minutes or longer. This indicates nasal congestion may not be fully relieved by ARS-1 treatment in some subjects.

The severity of allergen-induced nasal congestion prior to ARS-1 administration impacted the PK profile of ARS-1, as shown in Figure 14.

Figure 14. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles of ARS-1 in Subjects With Allergic Rhinitis Under NAC Conditions by Predose NCS Subgroup Analysis in Comparison to Without NAC, Trial EPI 16



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt and adyn.xpt of Trial EPI 16. Predose refers to prior to ARS-1 administration but after nasal allergen challenge.
Abbreviations: NAC, nasal allergen challenge, NCS, nasal congestion score

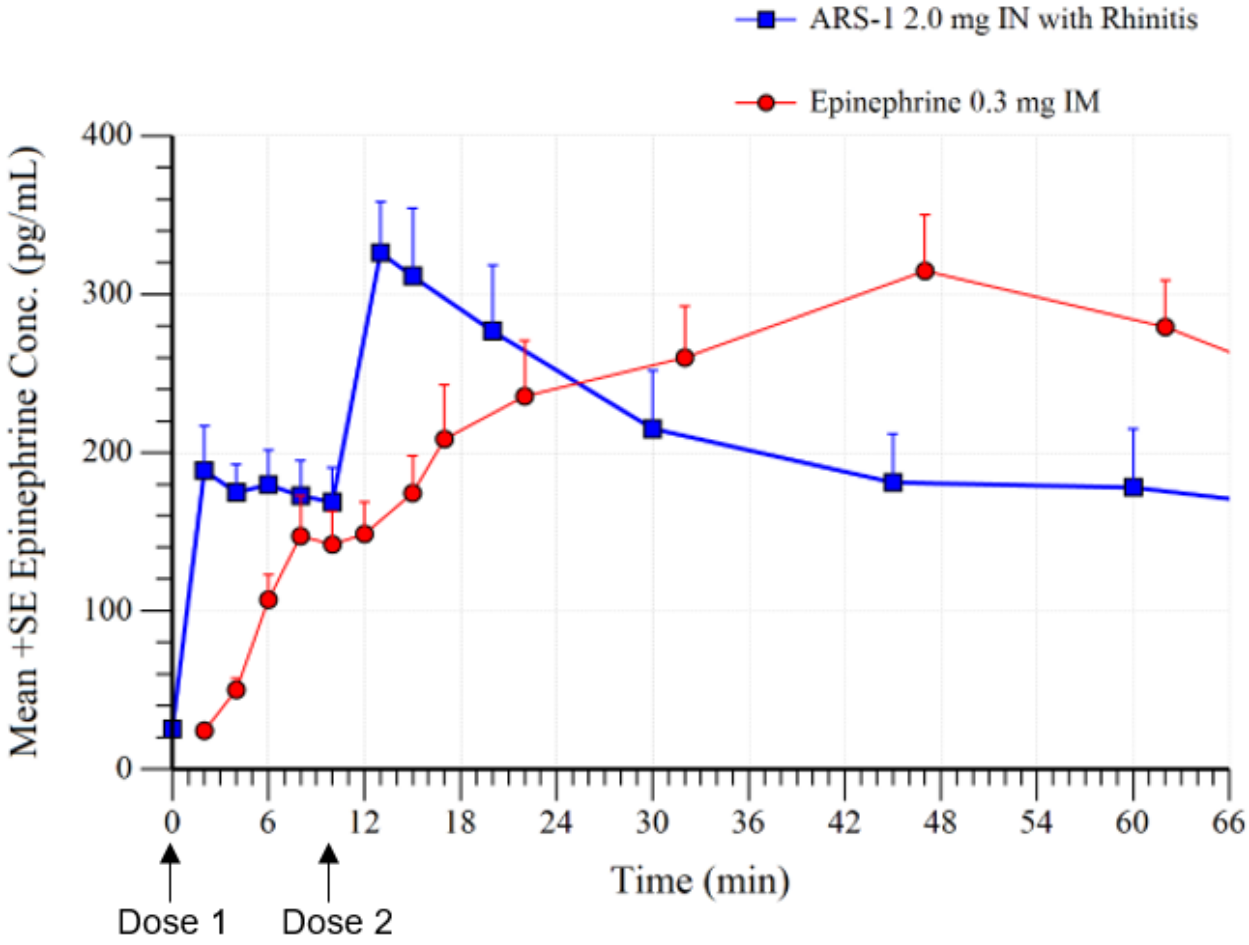
The PK of epinephrine in subjects with severe nasal congestion (NCS =3) prior to ARS-1 administration had a slightly faster absorption rate followed by a faster decline, in comparison to subjects with mild to moderate predose nasal congestion (NCS =1 or 2).

Theoretically, rhinorrhea may lead to a faster nasal mucosal clearance and affect absorption of drug delivered to the nasal mucosal membrane. The impact of postdose rhinorrhea on PK was also explored in a post hoc subgroup analysis. However, no noticeable impact was observed. See Section 15.4.1.2 for details.

PK Modeling for Repeat Doses of ARS-1 under NAC

As the repeat doses of ARS-1 was not assessed under NAC conditions, the Applicant estimated the epinephrine exposures following two dose of ARS-1 (spaced by 10 minutes) under NAC as well as two doses of Adrenalin 0.3 mg IM (also spaced by 10 minutes) using a modeling and simulation approach based on single dose PK data from EPI 16, as shown in Figure 15.

Figure 15. Simulated Epinephrine Concentration Profiles Following Two Does of ARS-1 and Two Doses of Adrenalin 0.3 mg Under NAC Conditions



Source: Applicant's Clinical Information Amendment Dated March 17, 2023.
Abbreviations: NAC, nasal allergen challenge

The Applicant's predicted epinephrine exposures following two doses of ARS-1 under NAC is higher than that of two doses of Adrenalin during first 25 minutes post–first dose but becomes lower thereafter. The potential impact of lower exposure after 25 minutes on PD responses cannot be predicted, as additional effects of allergen-induced acute rhinitis on PD response other than PK cannot be excluded. Furthermore, it is unclear whether PK following administration of the second dose of ARS-1 into the same nostril will be similar to contralateral nares administration as the first dose may impact the absorption of the second dose under NAC due to mucosa change by ARS-1 and the vasoconstrictive effect of epinephrine. The impact of the first dose of ARS-1 on the absorption of the second dose under NAC, especially when administered into the same nostril, cannot be adequately predicted without clinical data.

Although repeat doses of ARS-1 were evaluated in healthy subjects with normal nasal conditions in EPI 15, the PK/PD may differ in subjects with allergen-induced acute rhinitis and therefore observation from EPI 15 may not be applicable to subjects under NAC conditions.

Although it is expected that a repeat dose of ARS-1 under NAC will increase the epinephrine exposure as well as the duration of PD effects, the exact change in PK and PD cannot be predicted based on the reasons mentioned above. Without clinical PK/PD data for two doses of ARS-1 under NAC, the impact on the effectiveness of ARS-1 in patients with allergen-induced acute rhinitis whose anaphylaxis symptoms may require repeat doses of epinephrine is unknown. Therefore, we recommend a repeat-dose PK/PD study conducted under NAC conditions to minimize the uncertainties.

PK/PD Summary in Allergen-Induced Nasal Congestion

Overall, when ARS-1 was administered under NAC, the epinephrine PK profile demonstrated an initial faster absorption phase followed by a decline phase. The geometric mean plasma epinephrine concentrations for ARS-1 under NAC conditions were lower than ARS-1 under normal nasal condition 10 minutes postdose and lower than Adrenalin 0.5 mg and 0.3 mg arms after around 10 and 20 minutes postdose, respectively.

The PD responses (median SBP and PR change from baseline) for ARS-1 under NAC conditions also demonstrated a similar pattern (i.e., higher response followed by faster decline) in comparison to normal nasal conditions, although the median SBP response remained comparable to that of Adrenalin 0.3 mg throughout 60 minutes postdose. The median PR response of ARS-1 under NAC was higher than Adrenalin within 5 minutes but lower afterwards, despite that the PK profiles were comparable up to around 20 minutes. By comparing the shape of PK and PD profiles, additional effect of allergen-induced acute rhinitis on PD responses other than PK cannot be excluded.

The reviewer acknowledges that the epinephrine PK/PD profile following the second dose of ARS-1 is currently unavailable. Therefore, to confirm the epinephrine PK/PD, a repeat-dose PK/PD trial under NAC conditions to characterize the epinephrine PK/PD profiles following two doses ARS-1 2 mg in nasal congested conditions will be required.

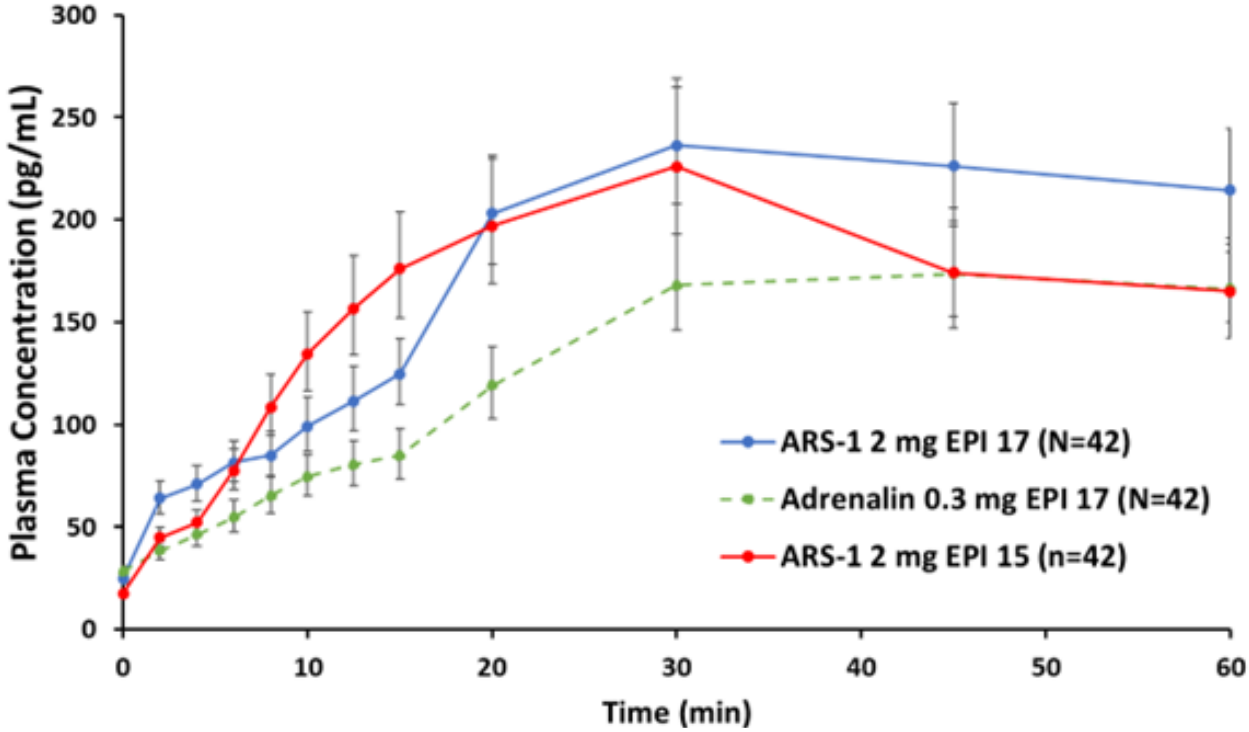
How Does Administration Methods/Errors Impact PK/PD of ARS-1?

In all the previously discussed clinical pharmacology studies, ARS-1 was administered by trial staff to reduce the potential PK variability by ensuring consistent administration. However, ARS-1 is proposed for self-administration and the impact of self-administration on the PK profile was a question raised during development of ARS-1 (see Section 3.2). Therefore, the Division requested the Applicant conduct a PK trial to characterize the epinephrine PK profiles in subjects following self-administration of ARS-1.

The impact of self-administration on the epinephrine PK profile was assessed in Trial EPI 17, a two-period, two-treatment, randomized, crossover trial in adult subjects with Type 1 allergies. Subjects (N=42) were randomized to receive either a single dose of self-administered ARS-1 or a single dose of staff-administered Adrenalin 0.3 mg. The concentration-time profiles for self-

administered ARS-1, staff-administered Adrenalin 0.3 mg as well as staff-administered ARS-1 from Trial EPI 15 are shown in Figure 16. Trial EPI 17 did not include a staff-administered ARS-1 treatment arm, so a cross-trial comparison was performed. For additional details, see Section 7.1.3 for the protocol and Section 15.4.1.3 for trial results.

Figure 16. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Single Dose of ARS-1 (Self-Administered From Trial EPI 17), Adrenalin 0.3 mg (Staff-Administered From Trial EPI 17) and Single Dose of ARS-1 (Staff-Administered From Trial EPI 15)



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 17 and EPI 15.

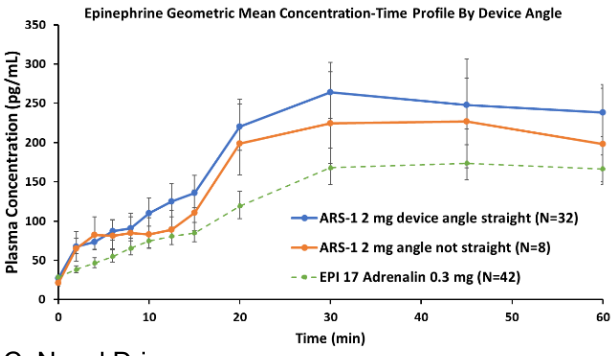
The epinephrine PK profile following self-administration of single dose ARS-1 was generally higher than that following staff-administered Adrenalin 0.3 mg. The cross-trial comparison of the PK profile for ARS-1 between Trial EPI 15 (staff-administered) and EPI 17 (self-administered) demonstrated a similar pattern. A cross trial comparison of epinephrine PK profile of Adrenalin from EPI 17 with other studies is displayed in Figure 7.

Some deviations identified in the HF studies were also noted in the self-administration trial. For example, there were subjects who inserted the device at an incorrect angle (nozzle is supposed to be inserted straight and not toward the septum or side wall of the naris), did not completely insert the nozzle fully, those who sniffed after administration, and those who reported nasal drip after use. The reviewer conducted subgroup PK analyses to assess if there was a difference in PK profile for some of these observations. Based on the subgroup PK analyses, nasal drip, device insertion angle, and incomplete insertion of nozzle into the nose appear not to lower the epinephrine PK profile. However, sniffing lowered the epinephrine PK profile to a certain extent following nasal administration, as shown in Figure 17. Of note, the mean PK profiles of ARS-1 with all these deviations remained higher than that of Adrenalin.

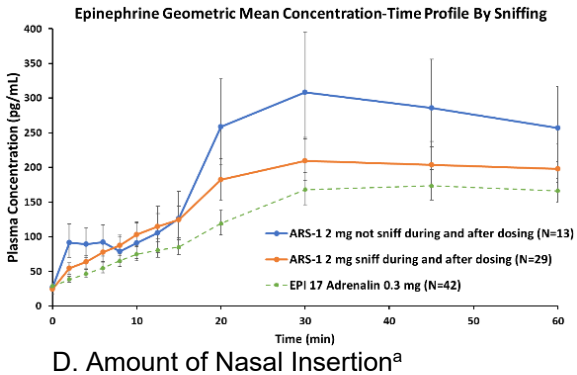
Sneezing, premature activation of device, and not activating the device were not observed in Trial EPI 17.

Figure 17. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Self-Administered Single Dose of ARS-1 2 mg by Administration Issue, Trial EPI 17

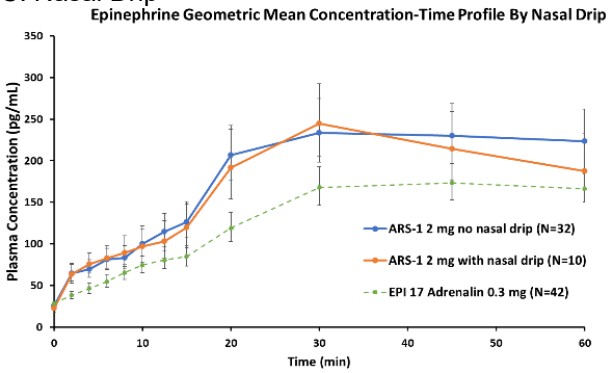
A. Device Angle[a]



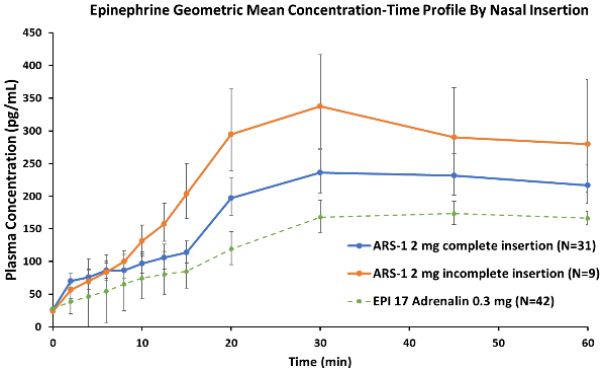
B. Sniffing During and After Dosing



C. Nasal Drip



D. Amount of Nasal Insertion[a]



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt and adyh.xpt for Trial EPI 17.
a Two subjects were unable to have the device angle or amount of nasal insertion determined due to subjects' hand obstructing a clear view of dosing based on the CSR. They were excluded in the subgroup analysis. These two subjects had low epinephrine exposures with unclear reason.
Abbreviation: CSR, clinical trial report

Is a Single Arm Pediatric PK Trial Sufficient To Support the Use of ARS-1 in Children Weighing 30 kg and Above?

The Applicant is conducting a single-arm PK/PD trial (EPI 10) in children 4 to 17 years of age with a systemic (Type 1) allergy that requires an epinephrine prescription to assess the PK/PD of ARS-1 in pediatric subjects. The trial includes two groups divided by weight: 15 to <30 kg and ≥30 kg. Subjects in the 15 to <30 kg group receive either 0.65 mg or 1 mg of ARS-1; subjects in the ≥30 kg group receive either 1 mg or 2 mg of ARS-1. This pediatric trial is ongoing, but the Applicant conducted an interim analysis and has included PK/PD data for pediatric subjects with a body weight ≥30 kg in this application to support the proposed indication. Of note, an epinephrine injection comparator was not included in EPI 10 because of ethical considerations related to injection of epinephrine in pediatric subjects. Thus, a cross-trial comparison of PK/PD results between children and adults is performed to support the proposed pediatric dose. Since the trial is currently ongoing in children weighing 15 to <30 kg, this population will not be discussed in this review. For additional details, see Section 7.1.4 for the protocol and Section 15.4.1.4 for trial results.

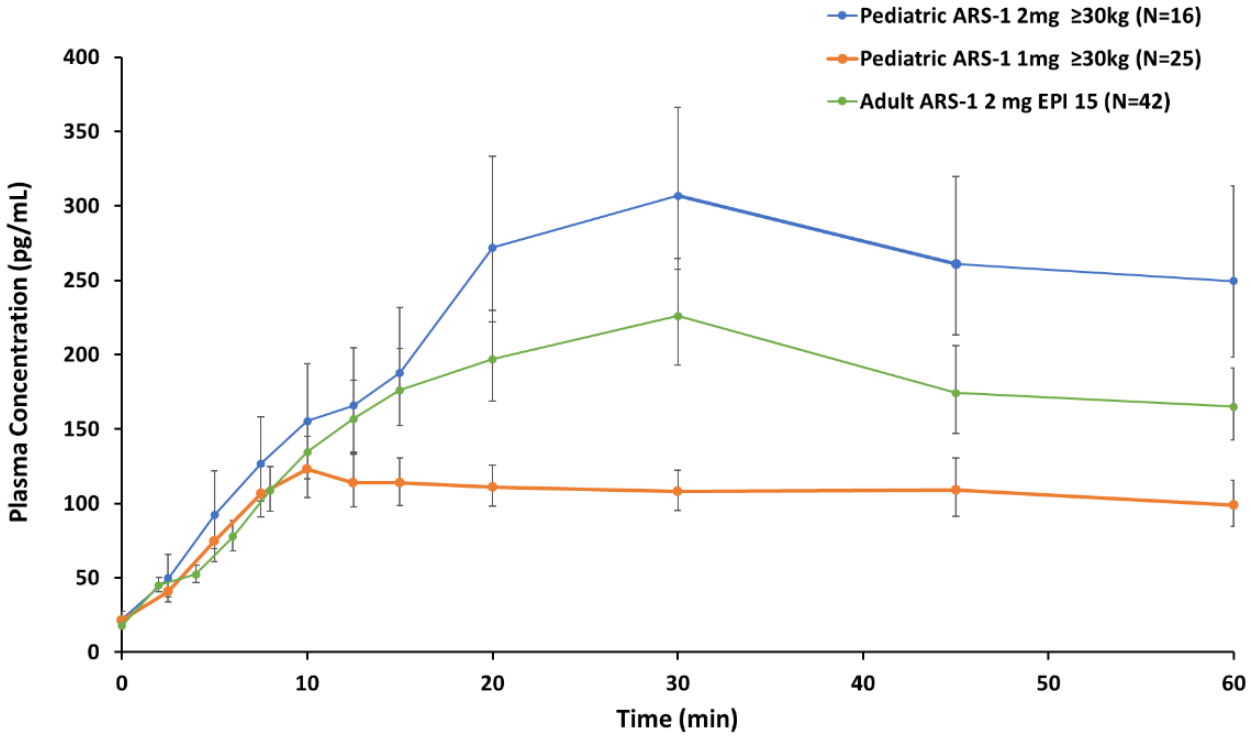
A total of 42 pediatric subjects weighing ≥30 kg (body weight range: 31 kg to 95 kg; age range: 8 to 17 years) were evaluated for PK at the time of interim analysis cutoff date, with 16 subjects receiving a 2-mg dose of ARS-1 and 26 subjects receiving a 1-mg dose of ARS-1. In the 2-mg dosing group (N=16), there were two subjects aged 8 and 11 years old who had a body weight between 30 kg and 33 kg, while the other subjects had a body weight >45 kg. A discrepancy was noted between the trial protocol and PK dataset for EPI 10 in terms of body weight groups. The trial protocol grouped pediatric subjects by 15 to <30 kg and ≥30 kg, while the body weight groups in the dataset are 15 to 30 kg and >30 kg. This discrepancy did not affect the PK assessment, as the lowest body weight patient included in the 2-mg dosing group is 31 kg, close to 30 kg.

Of note, among the 42 pediatric subjects weighing ≥30 kg, 10 subjects who were treated with a 1-mg dose were re-enrolled to receive a 2-mg dose after at least 1 year. One subject who was planned to be enrolled for 2 mg received 1 mg. As a result, this subject was actually treated with 1 mg twice separated by 1 year. Overall, there were only 30 unique subjects who weighed ≥30 kg evaluated with either 1 mg or 2 mg of ARS-1 (14 and 6 subjects treated only with 1 mg or 2 mg, respectively, and 10 subjects treated with both 1 mg and 2 mg separated by at least 1 year).

For PK analysis, PK data from both periods from the subject who received two periods of 1-mg dose by incidence were included. In addition, another subject who weighed ≥30 kg that received a 1-mg dose had all PK samples below the limit of quantification. Per Applicant, this subject and was not included in the PK dataset. Thus, 25 subjects (24 unique subjects) in the 1-mg dose group were included in the PK analysis.

The epinephrine PK profiles in this population, in comparison to adults who received 2 mg ARS-1 in Trial EPI 15, are shown in Figure 18. The PK parameters are shown in Table 18. The PK results demonstrated that the PK profile of pediatric subjects weighing ≥30 kg on ARS-1 2 mg was similar to that of adults during the first 15 minutes postdose and generally higher than that of adults afterwards based on a cross-study comparison. The slightly higher epinephrine systemic exposure in children after the initial absorption phase was likely due to the lower body weight in children (mean body weight 56.4±14.3 kg) compared to adults (mean body weight 82.5±12.1 kg following single dose ARS-1 in EPI 15. The PK profile for the 1-mg dose in pediatric subjects weighing ≥30 kg was generally lower compared to adults following administration of ARS-1 2 mg after 10 minutes postdose.

Figure 18. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥30 kg From Trial EPI 10 and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 10 and EPI 15.

Table 18. PK Parameters Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥30 kg From Trial EPI 10 and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Trial EPI 15

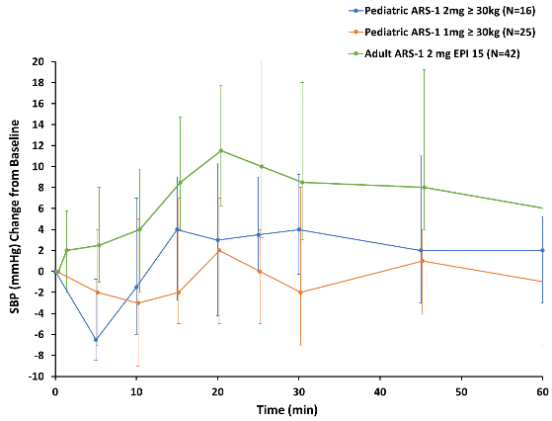
	Geometric Mean (CV%)		
	Pediatric Subjects ≥30 kg		Adults from Trial EPI 15
	ARS-1 2 mg (N=16)	ARS-1 1 mg (N=25)	ARS-1 2 mg (N=42)
C_{max} (pg/mL)	433 (80)	203 (78)	341 (114)
T_{max} (min) [a]	25	20	30
AUC_{0-10} (pg*min/mL)	989 (112)	796 (96)	712 (93)
AUC_{0-20} (pg*min/mL)	3147 (90)	1997 (81)	2596 (102)
AUC_{0-30} (pg*min/mL)	6231 (78)	3202 (71)	4901 (109)
AUC_{0-60} (pg*min/mL)	15126 (76)	6883 (69)	10925 (116)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 10 and EPI 15.
[a] median

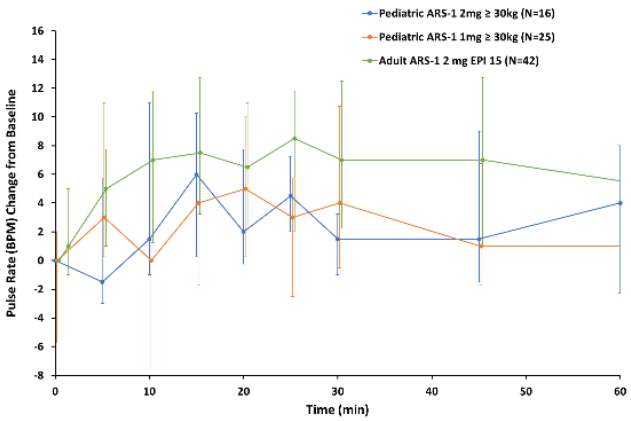
In general, pediatric subjects weighing ≥30 kg on ARS-1 2 mg demonstrated slightly numerically lower median PD responses than adults following the same dose of ARS-1 in EPI 15 (Figure 19). In a review of the EPI 10 trial, it was noted that pediatric subjects were in a semisupine position for vital sign measurements and drug administration, while adults in all studies were in the sitting position. It is unclear if the difference in position partly contributed to the observed PK/PD differences between pediatric and adult subjects (Reid 1986) or if there is a difference between epinephrine PD responses in pediatric subjects compared to adults .

Figure 19. Median PD Responses (SBP, PR and DBP Change From Baseline) Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥30 kg From Trial EPI 10 and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Trial EPI 15

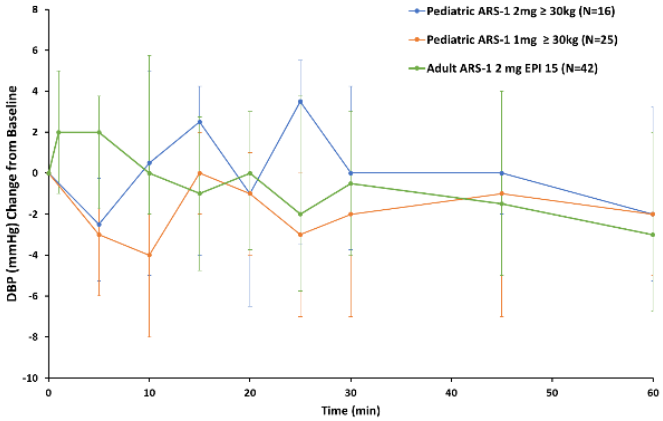
A. Median SBP Change From Baseline



B. Median PR Change From Baseline



C. Median DBP Change From Baseline



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI10.
Error bars represent 25% and 75% percentile of the PD values.
Abbreviations: PD, pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

A substantial carryover effect was noted when ARS-1 was administered in multiple treatment periods, which is hypothesized to be associated with alteration in nasal mucosa by ARS-1 and thus affecting the systemic absorption of nasally administered drugs. ARS-1 induced nasal mucosal changes were also demonstrated in nonclinical studies. Therefore, concomitant use of other nasal products with ARS-1 may result in an increased systemic exposure of other nasal products and adverse events. Given that a washout period between IN treatments (12 days) was used in EPI 15 to mitigate the carryover effect, we caution that this potential DDI could occur for at least 2 weeks.

9. Clinical and Evaluation

9.1.1. Assessment of Efficacy Across Trials

To support this application, the Applicant conducted four clinical pharmacology PK/PD trials with the proposed 2-mg dose to establish a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway. PK/PD trials were not conducted in subjects who were undergoing anaphylaxis and clinical efficacy trials in anaphylaxis were not conducted due to feasibility challenges, specifically limitations in obtaining clinically meaningful data (Section 3.2). Rather, the Applicant proposed to establish substantial evidence of effectiveness by PK bracketing to Adrenalin and EpiPen, as well as supportive hemodynamic PD results (SBP and PR change from baseline), in healthy adults and subjects with Type 1 allergic diseases, namely allergic rhinitis; demonstration of effectiveness relies on FDA's prior finding of effectiveness for these listed products (Section 3.1). For this program, Adrenalin and EpiPen were selected as comparators since they are administered with different delivery systems (i.e., needle-syringe and autoinjector) and demonstrate different PK/PD profiles, with both demonstrating effectiveness based on clinical experience.

In Section 8, we summarized key results from the pivotal clinical pharmacology studies in the ARS-1 program. Based on the results from the submitted clinical pharmacology studies, we have the following main observations that we believe are important to highlight. To provide scientific bridging to the listed products, using the to-be-marketed product, three trials were conducted in adults (18-55 years of age) and one trial was conducted in pediatric subjects (≥ 30 kg):

1. Single and repeat dose trial in healthy adults (EPI 15): Results of this PK/PD trial demonstrated that the PK profile of a single dose of ARS-1 is bracketed by Adrenalin and EpiPen in healthy adults after 10 minutes, and PD responses (SBP and PR) were generally higher, from baseline, for ARS-1 compared to the listed epinephrine injection products; PK bracketing for the first 10 minutes is based on results from EPI 17, using a cross-study comparison. Repeat injection with epinephrine is recommended for severe persistent anaphylaxis; the PK/PD profile of two, repeat doses of ARS-1 in healthy adults were similar to the results for two, repeat doses of EpiPen, when both were administered 10 minutes apart.
2. Self-administration trial in healthy adults (EPI 17): Self-administration of a single-dose of ARS-1 to adults did not introduce meaningful changes to the PK/PD profile.
3. Nasal allergen challenge trial in adults with seasonal allergic rhinitis (EPI 16): Acute onset rhinitis, with nasal congestion and rhinorrhea, can be features of anaphylaxis; alterations of the nasal mucosa (e.g., vasodilation) may affect the local absorption of epinephrine and rhinorrhea may more rapidly clear ARS-1 from the surface of the nasal mucosa. The nasal allergen challenge approach to inducing acute rhinitis was incorporated into the development program to mimic, in part, findings that may occur in some patients with anaphylaxis, and is critical for demonstrating substantial evidence of effectiveness for this

development program that does not include a clinical efficacy trial. In subjects with allergen-induced acute rhinitis, ARS-1 demonstrated a more rapid absorption phase during the first 10 minutes, compared to Adrenalin, followed by a more rapid decline in epinephrine plasma concentration, with epinephrine mean plasma concentrations dropping below Adrenalin starting around 20 minutes postdose, demonstrating lower PK sustainability. Although hemodynamic PD responses (SBP and PR change from baseline) for ARS-1 in subjects with allergen-induced acute rhinitis also demonstrated a more rapid increase postdose compared to Adrenalin, the median SBP change from baseline remained comparable to that of Adrenalin 0.3 mg throughout 60 minutes postdose; however, the median PR response for ARS-1, became lower than Adrenalin after 5 minutes.

The decline of mean epinephrine plasma concentration following ARS-1 in subjects with allergen-induced rhinitis at 20 minutes postdose, compared to epinephrine injection, raises concerns with the durability of effect in anaphylaxis patients with acute, allergen-induced rhinitis. The sustained ARS-1 SBP through 60 minutes compared to Adrenalin is not sufficient to obviate this concern as PD sustainability was not demonstrated for PR, and uncertainty remains on the translatability of PD from healthy volunteers to patients with anaphylaxis.

The rapid PK decline also raises concern for the potential for more frequent need for an additional ARS-1 dose compared to the rates reported for epinephrine injection products. Repeat dose administration under nasal allergen challenge conditions was not evaluated in this development program. Whether two doses of ARS-1 will have sufficient durability of effect for patients with allergen-induced acute rhinitis who require one dose of epinephrine injection or patients with severe persistent anaphylaxis who require two doses of epinephrine injection is unknown. The lack of PK/PD data with repeat administration under nasal allergen challenge conditions raises uncertainty of effectiveness in anaphylaxis patients with allergen-induced acute rhinitis, if a second dose is needed. Therefore, a repeat dose study in patients with acute allergen-induced rhinitis is needed to provide the needed PK/PD profile to reduce this uncertainty.

4. Pediatric single dose trial in pediatric subjects ≥30 kg with systemic (Type I) allergies that require epinephrine prescription (EPI 10): For the pediatric population ≥30 kg, ARS-1 demonstrated PK/PD similarity of ARS-1 in subjects who weigh ≥30 kg compared to that of the adults. The age of the cohort ranged from 8 to 17 years of age with a median of 14 years old. Given that there is a high degree of similarity in anaphylaxis between adult and pediatric subjects, with both resulting from acute activation of mast cells and/or basophils, and that there is an established response to treatment with epinephrine in pediatric subjects that is highly similar to that observed in adults, extrapolation of efficacy from adults is reasonable.

Overall, the PK/PD results from the adult studies EPI 15 and EPI 17, and the pediatric study in children < 18 years of age and ≥ 30 kg, EPI 10, provide an adequate scientific bridge to approved epinephrine injection products to demonstrate substantial evidence of effectiveness. The PK/PD results under NAC, in adults ≥18 years of age with allergic rhinitis, from EPI 16 demonstrated adequate PK and PD responses in the first 20 minutes postdose; however, the

lack of sustainability of epinephrine concentrations for ARS-1 after 20 minutes when compared to Adrenalin raises uncertainty as to the durability of effect in anaphylaxis patients with allergen-induced acute rhinitis. The discrepant SBP and PR comparison results between ARS-1 and Adrenalin made interpretation of the PK/PD results even more challenging.

Anaphylaxis is a life-threatening emergency and approval for this indication requires a high level of confidence in the PK/PD results under conditions likely to be encountered by the target population. Adequate PK/PD data for repeat dose administration under nasal allergen challenge conditions are needed to have confidence in the results to support approval. In addition, since the initial dose of ARS-1 administered under acute rhinitis conditions may impact the PK/PD profile of a subsequent dose administered in the same naris, a repeat dose study should also address PK/PD profiles with repeat dosing under nasal allergen challenge conditions when administered in the ipsilateral or contralateral naris, reflective of anticipated real-world use.

Due to the lack of observed PK/PD data from repeat dose administration under nasal allergen challenge conditions, including uncertainty of PK/PD profile with ipsilateral and contralateral naris administration, the application does not adequately demonstrate substantial evidence of effectiveness for ARS-1 in the emergency treatment of allergic reactions (Type I) including anaphylaxis for adults and children who weigh ≥30 kg.

9.2. Review of Safety

9.2.1. Safety Review Approach

The safety review of ARS-1 primarily relies on the determination of safety of approved epinephrine injection products, as the epinephrine exposure with ARS-1 is not higher than approved products. Adverse reactions of systemic epinephrine from epinephrine injection reported in observational trials and case reports include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.[4] Local adverse events (AEs) from IN administration rely only on the data presented from the ARS-1 development program.

The safety review consisted of pooling AE data from the three adult pivotal trials: EPI 15, EPI 16 and EPI 17. As EPI 10 enrolled pediatric subjects, EPI 10, was reviewed separately and was not included in the safety pool. For our analysis, N is reported as the number of subjects (per each treatment received) and not number of exposures. Furthermore, our review does not differentiate whether ARS-1 was given during normal conditions or after NAC as no notable differences were noted in the AE profile with and without NAC. The epinephrine injection treatment arms were combined given the small number of AEs along with no differences seen in AEs between autoinjector and the needle and syringe.

4 See the EpiPen label at https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=7560c201-9246-487c-a13b-6295db04274a&type=pdf.

9.2.2. Review of the Safety Database

Overall Exposure

Of the three pivotal adult trials, 134 subjects received at least one dose of ARS-1. Given the trials were crossover design, subjects received more than one exposure to ARS-1 per trial which equaled a total of 268 exposures of ARS-1 across the three trials. There were 76 subjects who received more than one exposure (N=36 for 2 exposures, N=4 for 3 exposures, N=1 for 4 exposures, N=30 for 5 exposures and N=5 for 6 exposures) to ARS-1 among three trials.

Adequacy of the Safety Database

Overall, the safety database is of sufficient size and duration for an emergency use medication.

9.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

See Section 4 for overview of data integrity and submission quality.

Categorization of Adverse Events

The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocols. AEs were captured from signing of informed consent through the trial. Treatment-emergent AEs were events that were not present at baseline, or if present at baseline, worsened in severity. For the trials, blood pressure increased and heart rate increased were not considered an AE unless such event required treatment due to the known mechanism of action of epinephrine. AEs were coded using the MedDRA dictionary version 22.0. The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. Of note, a reporting bias towards nasal pain, irritation, and discomfort was noted as these symptoms were solicited, but injection site discomfort was not solicited.

9.2.4. Safety Results

Deaths

There were no deaths during the three pivotal trials.

Serious Adverse Events

There were no SAEs in the three pivotal trials.

Dropouts and/or Discontinuations Due to Adverse Effects

There was one subject who received ARS-1 and two subjects in the epinephrine injection 0.3 mg arm who discontinued from the trial due to AEs. Two subjects discontinued due to syncope after administration of IM epinephrine. The one subject who discontinued after ARS-1 withdrew after developing syncope with the initiation of blood sampling that occurred shortly after ARS-1 administration.

Common Adverse Events

Common AEs that occurred in the ARS-1 treatment arm were nasal discomfort (10%), headache (6%), dizziness (3%), rhinorrhea (3%), nausea (3%), throat irritation (2%), and vomiting (2%). The majority of adverse events were reported as mild. The common AEs that occurred greater than the comparator epinephrine injection are seen in Table 19. The common local AEs reported (nasal discomfort, throat irritation, and rhinorrhea) were anticipated given the route of administration. Headache, dizziness, and nausea have been reported with epinephrine injection. There were no safety concerns related to the higher exposure and no notable PD related (elevated BP or HR) AEs. Nasal examinations were performed, and local AEs were minimal. The safety profile of ARS-1, however, is limited given that nearly half of the subjects only received one dose of ARS-1. It is uncertain if there would be an increased incidence of local AEs from frequent and/or long-term use of ARS-1. However, as this product is intended for acute use, frequent and/or long-term use is unlikely.

Table 19. Common Adverse Events Occurring at ≥3% Frequency in ARS-1 and Greater Than Epinephrine Injection Comparator, Primary Safety Population, Safety Pooling, Trials EPI 15, EPI 16, and EPI 17

		ARS-1 (N=134)		Epinephrine Injection 0.3 mg* (N=189)	
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%
Nervous system disorders	Headache	8	6%	4	2%
	Dizziness	4	3%	2	1%
Gastrointestinal disorders	Nausea	4	3%	4	2%
Respiratory, thoracic, and mediastinal disorders	Nasal discomfort	13	10%	0	0%
	Rhinorrhea	4	3%	0	0%

Source: FDA Clinical Reviewer
*Includes both EpiPen 0.3 mg and Adrenalin 0.3 mg injection.

Laboratory Findings

Routine clinical laboratory values were only obtained at screening/baseline for this trial.

Vital Signs

Vital signs were not pooled across trials. See Pharmacodynamic analysis discussed in Section 8.

Electrocardiograms (ECGs)

ECGs were obtained as baseline along with at -10 and -5 minutes predose and at 10, 20, 30, 60 minutes postdose in the trials. Abnormal ECG results were observed in the majority of subjects at baseline and following all treatments. These high proportions were due to the liberal features that were used to define abnormal ECGs, none of which are considered clinically significant. The percentage of the abnormal ECGs were similar among ARS-1 and epinephrine injection treatments and timepoints. ECGs were not pooled for safety evaluations.

Pediatric Safety—EPI 10

The safety pool for EPI 10 included 21 subjects who received 2 mg ARS-1. Common AEs reported in these subjects included nasal discomfort (19%), IN paresthesia (19%), rhinorrhea (14%), sneezing (14%), paresthesia (10%), fatigue (10%), and feeling jittery (10%), as listed in Table 20. A 1-mg dose of ARS-1 was also assessed in some subjects who weighed over 30 kg to assess dose ranging. There does appear to be some dose related AEs (i.e., IN paresthesia, epistaxis, fatigue, feeling jittery) when compared to subjects who received the 1.0-mg dose (Table 20), although this conclusion is limited given the small sample size. In general, the AEs reported were numerically higher in the pediatric population of EPI 10 compared to the adult population; however, safety conclusions from EPI 10 are limited due to the small size and single arm design with no comparator.

Table 20. EPI 10 Common Adverse Events Occurring at ≥10% Frequency in 2.0 mg ARS-1 With the 1.0 mg ARS-1 Comparison

	ARS-1 1.0 mg (>30 kg) N=26		ARS-1 2.0 mg (≥30 kg) (N=21)	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Intranasal paresthesia	0	(0)	4	(19)
Nasal discomfort	3	(12)	4	(19)
Rhinorrhea	3	(12)	3	(14)
Sneezing	2	(8)	3	(14)
Epistaxis	0	(0)	2	(10)
Fatigue	0	(0)	2	(10)
Feeling jittery	0	(0)	2	(10)
Paresthesia	1	(4)	2	(10)
Rhinalgia	2	(8)	2	(10)

Source: Clinical Review, OCS Analysis Studio, Safety Explorer

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

9.2.5. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

ARS-1 is not approved outside of the United States; therefore, no safety concerns have been identified for use of ARS-1 through postmarket experience. Epinephrine injection products have an established postmarket safety profile that will be included in labeling to inform the systemic safety of ARS-1.

Expectations on Safety in the Postmarket Setting

ARS-1 will continue to be monitored through routine pharmacovigilance in the postmarket setting.

9.2.6. Integrated Assessment of Safety

The safety review of ARS-1 primarily relies on the determination of safety of epinephrine injection listed products as ARS-1 epinephrine exposure is not higher than approved epinephrine injection products. The limited systemic safety adverse event profile of ARS-1 did not raise any safety concerns. There were no deaths, SAEs and common AEs were mild and expected given route of administration along with mechanism of action. Given ARS-1 is a new route of administration, local safety was established based on the clinical pharmacology studies to support approval. Local adverse events included nasal discomfort, throat irritation, and rhinorrhea. The nonclinical studies in rats did show minimal ulceration at a dose 2.3 fold higher than ARS-1 at the 2-mg dose. However, nasal exams were performed during these trials were minimal. As almost half of the safety population only received ARS-1 once, the local safety profile from more frequent use is not well defined; however, as this is an acute use product, frequent use is unlikely. Similar adverse events were seen in the pediatric population.

10. Advisory Committee Meeting and Other External Consultations

This application was discussed at a virtual meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on May 11, 2023. The purpose of the meeting was to discuss the novel route of administration, the lack of regulatory precedence, and the PK/PD data submitted to support an emergency indication without clinical efficacy trials.

The Agency sought the PADAC's feedback on whether the available PK/PD data for ARS-1 supported a favorable benefit-risk assessment for adults and children who weigh ≥30 kg.

The PADAC discussed multiple uncertainties to establishing a scientific bridge for ARS-1 to epinephrine injection products, including

- Unknown therapeutic thresholds due to lack of adequate and well-controlled trials with epinephrine for treatment of anaphylaxis
- Variability of PK both within and across epinephrine injection products
- Potential changes in PK and PD during anaphylaxis

After discussion of the available data from the development program as presented by the Agency and Applicant (briefing documents and live presentations), the committee voted for in favor of the benefit-risk assessment of ARS-1 for adults ≥18 years (16 yes, 6 no). The committee voted similarly for the benefit-risk assessment of ARS-1 children who weigh ≥30 kg (17 yes, 5 no).

The committee members that voted against a favorable benefit-risk assessment cited concerns with the differences in PK/PD compared to epinephrine injection products for a new route of administration, concerns with not having data in patients with anaphylaxis, the consequences of having an ineffective product for treatment of a life-threatening condition, as well as the

availability of approved therapies. Many of these members stated that clinical data in patients with anaphylaxis was necessary.

Most committee members agreed with the uncertainties, but that the benefits of the nasal route of administration may outweigh risks based on residual uncertainty. Some members questioned the utility of conducting additional PK/PD studies to address these uncertainties. The majority concluded that a clinical efficacy trial was not needed pre- approval, given the challenges in designing an interpretable trial in anaphylaxis.

Many committee members noted the completed PK/PD trials were sufficient to support a favorable benefit-risk assessment; several committee members were more convinced by general higher PD response following ARS-1 administration than epinephrine injection products than the PK bracketing results. Overall, while many panel members voted for approval of the product, in part based on the ease of administration and, therefore, likely improved compliance and earlier administration compared to epinephrine injection products, they did relay residual uncertainty that may or may not be addressed with further studies, and that they would want to see additional studies under a postmarketing commitment or requirement, including clinical data.

11. Pediatrics

This application triggers PREA due to a new route of administration. In accordance with 21 CFR 314.55(c)(3)(i) and 314.55(a) and Sections 505B(a)(4)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, the Applicant requested a partial waiver for children <4 years of age and <15 kg in this NDA submission as studies are impossible or highly impracticable in subjects less than 4 years of age given that the device is not fit-for-purpose for children <4 years of age, the immaturity of their nasal physiology precluding efficient absorption of drug, and that there is less assurance that a proper dose will be administered due to patient noncompliance at this age. The Applicant conducted trials in pediatric subjects as the differing nasal anatomy and size may affect epinephrine absorption. At the time of NDA submission, the Applicant had interim analysis results from EPI 10, a single-arm PK/PD trial (EPI 10) in children 4 to 17 years of age and ≥15 kg who have a significant systemic (Type 1) allergy and are at risk for anaphylaxis to assess the PK/PD of ARS-1 in pediatric subjects. The Applicant submitted safety data in 21 children and PK/PD data in 16 children ≥30 kg who received 2 mg ARS-1 to support including children ≥30 kg in the indication.

In considering the pediatric program, pediatric extrapolation from the adult PK/PD program is necessary given the limitations of the pediatric data; an epinephrine injection comparator was not included due to ethical considerations related to administration of epinephrine in pediatric subjects not undergoing anaphylaxis. Pediatric extrapolation can extend what is known about the adult populations (e.g., efficacy) to pediatric subjects if the course of the disease and the expected response to therapy would be sufficiently similar in the pediatric and adult population (ICH 2022). Given that there is a high degree of similarity in anaphylaxis between adult and

pediatric subjects, with both resulting from acute activation of mast cells and/or basophils, and that there is an established response to treatment with epinephrine in pediatric subjects that is highly similar to that observed in adults, extrapolation of efficacy from adults is reasonable. Extrapolation based on PK considerations has been used previously for epinephrine for anaphylaxis, e.g., approval of 0.1 mg epinephrine injection for the lowest weight group (7.5 to 15 kg).

12. Labeling Recommendations

Not applicable

13. Postmarketing Requirements and Commitment

Not applicable.

14. Division Director and Associate Director for Therapeutic Review Comments

ARS Pharmaceuticals submitted a 505 (b)(2) NDA, 214697, for epinephrine nasal spray (ARS-1) for the proposed indication of emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥30 kg. ARS-1 is a single-dose IN epinephrine spray. The proposed dose is 2 mg administered as one spray (100 µL) into one nostril for children and adults weighing ≥30 kg; if symptoms progress after (b) (4) minutes or any error occurs in administering ARS-1, the Applicant recommends administration of a second dose with a new device.

Background

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs rapidly, generally after contact with an allergen to which an individual is sensitized. Up to 5% of the U.S. population has experienced an anaphylactic reaction. Although fatal anaphylaxis is rare, with an estimated 250 deaths per year in the United States, a significant number of people are at risk for anaphylaxis, such as those with allergy to food, Hymenoptera venom, and drugs, among others. Fatal anaphylaxis usually occurs within 60 minutes of exposure to an allergenic substance, and most frequently within 5 to 35 minutes of exposure. Factors associated with fatal anaphylaxis from food allergy registries include age (adolescents and young adults), history of peanut allergy, comorbid asthma, and delayed administration of epinephrine. For drug and Hymenoptera venom allergy, risk factors for fatal anaphylaxis include increased age and cardiovascular comorbidities. Notably, the severity of past anaphylaxis episodes is not sufficient to predict the severity of future reactions.

For patients with Type 1 allergy at risk for anaphylaxis, such as children and adults with food allergy, standard of care includes allergen avoidance and treatment with an epinephrine injectable product if anaphylaxis occurs. Epinephrine injection is first-line and the only life-saving treatment for anaphylaxis. Although early administration of epinephrine is recommended, epinephrine administration is frequently avoided or delayed, including due to needle phobia. In addition, epinephrine is often underprescribed in patients at risk for anaphylaxis. As discussed by the Applicant in this application, by patients and caregivers at a Patient-Focused Drug Development session with the Agency on September 9, 2021, and by AC members and in public testimony at the May 11, 2023, PADAC meeting, availability of alternative routes of administration of epinephrine, such as by the nasal route, may improve the compliance and time to administration for epinephrine.

Regulatory History

Epinephrine has been marketed in the United States since 1901, predating both the original Federal Food and Drugs Act (1906) and the Federal Food, Drug, and Cosmetic Act of 1938. Furthermore, since epinephrine had been marketed since 1901, preceding passage of the 1938 Federal Food, Drug, and Cosmetic Act, it was not subject to a Drug Efficacy Study Implementation review as required by passage of the 1962 Kafauver-Harris Amendment to the FD&C Act. As a result, clinical efficacy trials were never performed.

In 1987, EpiPen and EpiPen Jr. were the first epinephrine injection products approved; they remain on the market today. EpiPen was approved by FDA based upon literature support for efficacy and safety; clinical trials and PK/PD data were not required. More recent approvals of epinephrine injection products for anaphylaxis were based on the established efficacy and safety of an FDA approved epinephrine injection product for anaphylaxis (e.g., EpiPen), chemistry/manufacturing/device data, and human factor assessments to evaluate the user interface with the drug-device combination. PK and in vivo bioequivalence data were not required for the approval of more recent epinephrine injection products because of similarity of the formulations and route of administration between the new epinephrine injection product and the approved reference epinephrine product. Therefore, approved epinephrine injection products on the market today for the treatment of anaphylaxis were not required to submit bioequivalence or clinical data for approval.

There is no regulatory precedent for an epinephrine nasal spray product for the treatment of anaphylaxis. As a result, there have been extensive discussions with the Applicant regarding details of a program to facilitate development of this product.

Below are key aspects of the ARS-1 development program and interactions with the Agency.

Chemistry Manufacturing Controls

ARS-1 is a single dose aqueous nasal spray packaged in a Unit Dose Sprayer (UDS). The formulation is a solution that contains the active pharmaceutical ingredient of epinephrine, a (b) (4) dodecyclymaltoside (DDM) to enhance absorption of epinephrine, sodium metabisulfite as (b) (4) and other inactive ingredients that are common excipients used

in nasal sprays. Each spray delivers 2 mg of epinephrine in 100 mcl of solution. An important issue for epinephrine is stability and shelf life as epinephrine is prone to (b) (4) degradation. Submitted stability data support a 24-month shelf-life.

The May 11, 2023, Integrated Quality Assessment identified deficiencies related to (b) (4)

(b) (4)

On August 7, 2023, FDA published a guidance for industry, *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August 2023) (NDSRI Guidance)*. The guidance states that FDA expects manufacturers and applicants to ascertain the presence of nitrosamine impurities, including NDSRIs, using a 3-step mitigation strategy described in the FDA guidance for industry, *Control of Nitrosamine Impurities in Human Drugs (Feb. 2021) (Nitrosamine Guidance)*. (b) (4)

(b) (4)

(b) (4) Although the guidance was released in August 2023, late in the review cycle, it specifies that "[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the [acceptable intake] [AI] limits recommended in this guidance." The applicant will need to provide information regarding potential NDSRIs as recommended in the NDSRI Guidance, specifically with respect to (b) (4)

There are no remaining outstanding CMC issues.

Device Considerations

The aqueous epinephrine solution is filled into unit dose 400 mcl glass vials and closed with a rubber stopper and then assembled into a UDS device. The device is a (b) (4) dispenser delivering a 100 mcl spray. The UDS device is packaged into individual single use blisters. The UDS for ARS-1 has been used in other approved nasal spray products. Because ARS-1 is for emergency use, a high degree of product reliability is expected, 99.999% or 1:100,000 failure rate. The CDRH review team identified major deficiencies that were conveyed to the Applicant in the May 24, 2023, correspondence. One issue was the lack of biocompatibility and irritation testing. In addition, there were deficiencies related to the Applicant's fault tree analysis (FTA),

which was submitted to support the product reliability expectations. In response, the Applicant submitted additional information to address the biocompatibility and FTA deficiencies. These submissions were also considered part of the major amendment for extension of the PDUFA goal date.

The Center for Devices and Radiological Health reviewed the device constituent of the combination product and recommends approval. The Applicant addressed device deficiencies during the review process adequately; however, one remaining deficiency remained at time of approval, specifically providing irritation data for one of the companies supplying the container components. As irritation testing is not essential for the safe and effective use of the product, irritation testing data can be established after approval if necessary.

Nonclinical

The nonclinical program for ARS-1 was limited. The DDM absorption enhancer is included in another approved IN product (sumatriptan nasal spray) at higher amounts than in ARS-1, so toxicological qualification of DDM was not necessary. A single dose IN toxicology study in rats showed some local histological changes in the nose, including ulceration; these findings were generally mild in severity. These types of local nasal findings are not unusual for a nasal spray and are considered monitorable. The Applicant also conducted a study to assess the absorption and PD effects of ARS-1 administered to dogs in which anaphylaxis was induced by Tween-80. Findings suggested that administration of ARS-1 increased epinephrine exposure in dogs experiencing anaphylaxis. However, there are limitations with this study, including the unclear relevance of this anaphylaxis model to human anaphylaxis, and a lack of comparator group experiencing anaphylaxis that did not receive ARS-1. There are no outstanding nonclinical issues.

Clinical and Clinical Pharmacology

Since clinical efficacy trials were not included in the development program, the design of the clinical pharmacology program was a focus of interactions with the Applicant. The following is a summary of the key issues discussed during the development phase of ARS-1.

PK/PD Program

Initial discussions of the development program focused on the scope of the program necessary to establish a scientific and regulatory bridge from ARS-1 to an approved epinephrine injection product. The main question was whether a PK/PD development program compared to approved epinephrine products would be sufficient or whether a clinical efficacy trial was needed. FDA raised concerns regarding reliance solely on PK/PD data, particularly because it was unclear whether PK/PD data from healthy volunteers would be similar to patients experiencing anaphylaxis. Clinical efficacy trials were considered, and a number of different clinical trial scenarios were discussed; however, no adequate and well-controlled clinical efficacy trials for epinephrine injection products have ever been conducted, so there is no precedent to follow. The Applicant indicated that a clinical efficacy trial of ARS-1 in patients with anaphylaxis was not feasible. FDA recognized the challenges of conducting a clinical trial,

including identifying the appropriate clinical trial scenario, identifying meaningful endpoints, inclusion of an active control, and questions regarding sample size and powering a trial. After extensive discussion, FDA agreed to a PK/PD development program with the caveat that the need for clinical efficacy data would be discussed with an FDA advisory committee.

During the development program, the Applicant discovered that there was a delayed carryover effect of epinephrine that peaked around 2 days due to the crossover design of the studies and insufficient washout between treatment arms. The Applicant had to repeat some of the clinical pharmacology studies, including dose finding, using a longer washout period.

Bracketed Approach

As described above, there are limited available PK/PD data for the approved epinephrine injection products. Therefore, the PK/PD endpoints critical to establish efficacy have not been determined and the approved doses of epinephrine have not been validated by clinical efficacy trials. As the ARS-1 PK/PD program progressed, the variability of the epinephrine PK data for approved epinephrine injection products became apparent. There was substantial variability noted in the PK profile for epinephrine autoinjectors versus epinephrine injected with needle and syringe, and even variability within the same product. The PK variability coupled with the lack of clarity on the critical PK parameters to ensure efficacy led to a bracketed PK approach, in which the PK profile of ARS-1 would be reasonably bracketed between the PK profile of two different approved epinephrine injection products. The Applicant chose Adrenalin and EpiPen as the comparator products for their PK/PD program.

Role of PD Data

The mechanism of action of epinephrine in the treatment of anaphylaxis is through agonism of α- and β-adrenergic receptors, leading to increased blood pressure and heart rate, bronchodilation, and inhibition of mediator release from mast cells and basophils. Since the most relevant PD parameters are systolic blood pressure (SBP) and pulse rate (PR), the Applicant proposed the use of PD data as a surrogate for efficacy. As a result, the Applicant collected PD parameters in the clinical pharmacology studies. While the Applicant advocated for use of PD markers as a surrogate for efficacy, FDA considered the PD findings as necessary supportive data.

Repeat Dose

The proposed use of ARS-1 includes the potential for a second dose; therefore, repeat dose data was needed. IN administration of epinephrine has the potential to constrict local blood vessels, potentially changing the absorption of epinephrine and impacting systemic plasma concentrations. This may be particularly important to consider if a second dose of epinephrine is needed. Therefore, FDA requested the Applicant evaluate the epinephrine PK/PD profile of ARS-1 following a second dose in a repeat-dose trial in healthy volunteers. This included the assessment of repeat dose of ARS-1 in the same nares or opposite nares.

Self-Administration

To minimize PK variability caused by administration differences, trial staff administered ARS-1 to subjects in the pivotal PK/PD studies; this represented an idealized use situation. FDA requested the Applicant conduct a self-administration PK/PD trial to represent actual use to ensure there were no significant differences in the PK/PD profile following self-administration of ARS-1.

Nasal Allergen Challenge

The main concern with relying solely on PK/PD data for the ARS-1 program is the question of whether PK/PD data from healthy volunteers would be similar to patients experiencing anaphylaxis. As it is infeasible to conduct a useful clinical trial in anaphylaxis, the Division and the Applicant assessed whether any component of anaphylaxis could potentially inhibit or alter the absorption of ARS-1. Rhinitis, with findings of rhinorrhea and nasal congestion, can be a feature of anaphylaxis; alterations of the nasal mucosa (e.g., vasodilation) may affect the local absorption of epinephrine and rhinorrhea may interfere with absorption, including through more rapid clearance from the nasal cavity. FDA and the Applicant agreed that NAC of subjects with allergic rhinitis with known allergen sensitization may reasonably mimic the nasal edema findings that could occur in anaphylaxis. Therefore, FDA requested that the Applicant evaluate the PK/PD profile of ARS-1 under NAC conditions. Of note, repeat dosing of ARS-1 was not studied in the NAC setting.

ARS-1 Development Program—Clinical and Clinical Pharmacology

As discussed above, the ARS-1 development program is based upon PK/PD assessment of ARS-1 compared to approved epinephrine injection products. Table 21 lists the key PK/PD studies in the ARS-1 program. Details of the trial design and results are described in the body of this review. The following is a summary of the relevant findings from the program.

Table 21. ARS-1 Development Program

PK/PD/Safety Trial	Purpose
Dose ranging (EPI 11b)	Determine an appropriate IN epinephrine dose compared to epinephrine injection in healthy volunteers based on PK similarity.
PK matching (EPI 15)	Bracket the single-dose PK profile of ARS-1 in healthy volunteers with epinephrine injection products with support of comparable safety and PD profiles.
Second dose (EPI 15)	Assess the PK/PD and safety of two doses of ARS-1 in healthy volunteers compared to two doses of epinephrine injection.
Nasal allergen challenge (EPI 16)	Assess the effect of rhinitis (nasal congestion and rhinorrhea) in patients with Type 1 allergy following allergen challenge on the PK/PD and safety of ARS-1 compared to epinephrine injection.
Self-administration (EPI 17)	Assess if self-administration of ARS-1 changes the PK/PD and safety compared to epinephrine injection (staff-administered).
Pediatric PK (EPI 10)	Assess the PK/PD and safety of various doses of IN epinephrine in pediatric allergy subjects.

Abbreviations: IN, intranasal; PK, pharmacokinetic; PD, pharmacodynamic

Dose Selection

EPI 11b is the pivotal dose ranging trial that assessed a single dose of various doses of ARS-1, ranging from 1 mg to 2 mg, and different strengths of the DDM excipient in healthy volunteers. EpiPen autoinjector and Symjepi prefilled syringe were included as comparator arms. Results from the trial showed a dose response for ARS-1. The PK profile of EpiPen was notable for a higher peak and more rapid decline compared to ARS-1 and Symjepi, which demonstrated lower peaks that were sustained. Around 15 minutes, the exposure for ARS-1 2 mg exceeded the exposure of EpiPen. Based upon data from this trial, the Applicant selected the ARS-1 2-mg dose, which was the highest dose studied.

Single and Repeat Dose in Healthy Volunteers

EPI 15 is the pivotal trial that assessed the PK/PD of single and repeat dose of ARS-1 compared to epinephrine injection products in healthy volunteers. Repeat dose of ARS-1 in the same or opposite naris was assessed in this trial. EpiPen and Adrenalin were included as comparators.

Results of EPI 15 showed that, after 10 minutes, the exposure of a single dose of ARS-1 was bracketed between the two reference comparators (Adrenalin and EpiPen). In the first 10 minutes, the exposure of ARS-1 was lower than both Adrenalin and EpiPen. Threshold analyses of the proportion of subjects who achieved certain plasma concentrations of epinephrine (e.g., ≥100 pg/mL) showed a similar pattern. While the issue of lower exposure in the first 10 minutes raised concerns, results from EPI 17, which compared self-administration of ARS-1 to Adrenalin in healthy volunteers, showed that exposure of ARS-1 was higher than Adrenalin in the first 10 minutes. This difference in exposure across studies was primarily due to the variability of the PK profile of Adrenalin. Based upon the data from EPI 15 and EPI 17, the exposure from a single dose of ARS-1 was bracketed between Adrenalin and EpiPen in healthy volunteers. PK results are further supported by clinically relevant PD results, namely increased SBP and PR equal to or greater than with the comparators, to provide further confidence in the PK results.

Repeat dose administration of ARS-1 was only evaluated in EPI 15. A second dose of ARS-1 (in the same and opposite naris) at 10 minutes was compared to a second dose of EpiPen at 10 minutes. In terms of the comparison to EpiPen, the PK profile of ARS was less than EpiPen in the first 20 minutes but overlapped with EpiPen around 20 minutes through 60 minutes. Epinephrine exposure approximately doubled between single and repeat dose of ARS-1. The SBP and PR for ARS-1 were similar to repeat dose of EpiPen, providing support for a similar PD effect, despite the lower exposure of ARS-1 in the first 20 minutes. Repeat dose data for Adrenalin are not available in EPI 15; however, we note that a single dose of Adrenalin provides a different PK profile than EpiPen with a slower peak that is more similar to ARS-1 in the first 10 to 20 minutes. As noted above, in EPI 17 the exposure for Adrenalin was lower than ARS-1 throughout the first 20 minutes, which provides support for single and repeat dose of ARS-1 in healthy volunteers.

Self-Administration

EPI 17 is the pivotal trial to assess if self-administration of IN epinephrine spray changes the PK/PD and safety compared to staff-administered epinephrine injection. Results showed the PK

profile of self-administered ARS-1 was consistently higher than the PK profile of Adrenalin administered by staff.

Nasal Allergen Challenge

EPI 16 is the pivotal trial to assess the effect of rhinitis (nasal congestion and rhinorrhea) in patients with Type 1 allergy following allergen challenge on the PK/PD and safety of ARS-1 compared to epinephrine injection. EPI 16 was a single dose trial that evaluated the PK/PD of ARS-1 prior to NAC and after NAC, as well as Adrenalin 0.3 mg and Adrenalin 0.5 mg as comparators. Results showed that the PK profile of ARS-1 was different without NAC versus with NAC. Following NAC, the PK profile of ARS-1 showed a more rapid peak followed by a more rapid decline around 20 minutes in the exposure of epinephrine compared to ARS-1 without NAC. A similar pattern was noted for the PK of ARS-1 following NAC compared to Adrenalin, i.e., earlier peak for ARS-1 (NAC) and more rapid decline in exposure. The more rapid peak of ARS-1 in the setting of NAC is reassuring as there is no evidence of decreased absorption. However, the more rapid decline raised concerns about the durability of the exposure of ARS-1 under NAC conditions, specifically whether this would lead to more patients requiring a second dose of ARS-1 or whether patients who had more severe anaphylaxis would be adequately treated with a second dose. A major issue was whether repeat dose data under NAC were necessary to support approval.

To determine whether repeat dose data under NAC were necessary to support approval, we considered the following information:

- While we note there are differences in the ARS-1 PK profile with and without NAC, the relevant comparison remains the ARS-1 PK profile compared to an approved epinephrine injection product.
- The epinephrine geometric mean concentration following ARS-1 increased more rapidly than Adrenalin, followed by a fast decline and the epinephrine concentrations became lower than Adrenalin 0.3 mg about 20 minutes postdose.
- It is unclear if the more rapid decline in PK exposure seen with ARS-1 under NAC may lead to diminished sustainability of effect in severe anaphylaxis or to more patients with anaphylaxis requiring a second dose of ARS-1 compared to an epinephrine injection product.
- The SBP response for ARS-1 following NAC was higher than Adrenalin 0.3 mg within 20 minutes postdose and became similar afterwards, suggesting the SBP PD effect was sustained longer than the PK exposure; however, the PR more closely followed the PK profile of ARS-1.
- Epinephrine injection product instructions for use include a recommendation for a 2nd dose after 10 minutes if symptoms progress. (b) (4) (b) (4) Although a second dose of ARS-1 given after 10 minutes is expected to increase the epinephrine exposure, we do not have data to understand the PK/PD profile following the

second dose of ARS-1 under NAC and whether ARS-1 would provide sustained exposure, comparable to repeat dosing of an epinephrine injection product.

- Local effects of ARS-1 on the nasal mucosa following administration of the first dose under NAC conditions, may affect the absorption of ARS-1 following repeat dosing. In addition, PK/PD findings following repeat dosing may differ when administered in the ipsilateral or contralateral naris. This data is important to inform labeling.
- The remaining uncertainty regards patients with severe reactions who may require a more sustained epinephrine exposure. Although the duration and level of epinephrine exposure necessary to assure efficacy for these high-risk patients are unknown, the uncertainty in PK/PD profile with repeat dosing under NAC conditions, and with administration in the ipsilateral or contralateral naris, precludes approval.
- A repeat dose trial of ARS-1 under NAC needs to be conducted preapproval, to characterize the PK/PD effects with repeat use, including following repeat administration in the ipsilateral or contralateral naris.

Safety

The safety of ARS-1 is informed by the systemic safety profile of epinephrine injection products and local nasal effects observed in the ARS-1 PK/PD studies. Although the safety data from this program are limited, the PK profile of ARS-1 does not show a significant increase in epinephrine exposure compared to epinephrine injection that would raise safety concerns. Local adverse events identified include nasal discomfort and rhinorrhea, and these are considered monitorable. However, as most of the safety population received only a single dose of ARS-1, the local adverse event profile from more frequent use is unknown.

Pulmonary and Allergy Drugs Advisory Committee

The ARS-1 development program was discussed at a May 11, 2023, meeting of the Pulmonary and Allergy Drugs Advisory Committee. The PADAC panel discussed the PK/PD approach, uncertainty of translation of PK/PD data from healthy volunteers and NAC model to anaphylaxis, and whether clinical data were needed. Overall, the feedback from the panel was diverse and included the following: 1) the PD data were compelling; 2) ARS-1 exposure in the NAC trial was still within the therapeutic range despite dropping below epinephrine injection, 3) concern regarding the lower ARS-1 exposure in the first 10 minutes; 4) limited number of pediatric patients; 5) clinical data are not feasible or necessary; and 6) clinical data should be collected given the limitations of translating PK/PD data from healthy subjects to patients with anaphylaxis. The panel did consistently agree upon the benefits of a needle-free delivery system for epinephrine, particularly in the pediatric population. The panel voted on two questions regarding whether the PK/PD results support a favorable benefit-risk assessment for ARS-1 for the emergency treatment of anaphylaxis in adults (16 Yes, 6 No) and in children <18 years of age ≥30 kg (17 Yes, 5 No). If approved, the panel recommended collecting clinical outcome data through postmarketing surveillance.

Pediatrics

This NDA triggers PREA due to the new route of administration for epinephrine. Anaphylaxis occurs in pediatric patients and epinephrine injection products are approved for pediatric patients; therefore, a pediatric development program is required for ARS. The Applicant is conducting a single-arm PK/PD trial (EPI 10) in children 4 to 17 years of age, who have a significant systemic (Type 1) allergy and are at risk for anaphylaxis, to assess the PK/PD of ARS-1 in pediatric patients. The Applicant requested a partial waiver for children <4 years of age and <15 kg as studies are impossible or highly impracticable in subjects less than 4 years of age given that the device is not fit-for-purpose for children <4 years of age, the immaturity of their nasal physiology precluding efficient absorption of drug, and that there is less assurance that a proper dose will be administered due to patient noncompliance at this age.

EPI 10 is a single arm trial that includes two groups divided by weight: 15 to <30 kg and ≥30 kg. Subjects in the 15 to <30 kg group receive either 0.65 mg or 1 mg of ARS-1; subjects in the ≥30 kg group receive either 1 mg or 2 mg of ARS-1. The Applicant submitted interim data from EPI 10 in patients ≥30 kg to support inclusion of pediatric patients ≥30 kg in the proposed indication. The submitted data includes PK/PD data from 16 children ≥30 kg who received ARS-1 2 mg and PK/PD data in 26 subjects who received a 1-mg dose of ARS-1. Data from the 15 to <30 kg pediatric population is not available at this time. EPI 10 is a single-arm trial, so cross-trial comparison was performed to compare data to adults who received ARS-1. Results show that pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 had a similar PK profile compared to adults who received 2 mg ARS-1 for the first 15 minutes; after 15 minutes, the PK curves were higher compared to adults. PD results for SBP and PR were lower in pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 compared to adults who received 2 mg ARS-1.

Pediatric extrapolation can extend what is known about the adult populations (e.g., efficacy) to pediatric subjects if the course of the disease and the expected response to therapy would be sufficiently similar in the pediatric and adult population. Given that there is a high degree of similarity in anaphylaxis between adult and pediatric subjects and an established response to treatment with epinephrine in pediatric subjects, extrapolation is reasonable. Extrapolation based on PK considerations has been used previously for epinephrine for anaphylaxis, e.g., approval of epinephrine injection for the lowest weight group (7.5 to 15 kg). The PK data shows that the 2-mg dose of ARS-1 is necessary to ensure epinephrine exposure is higher than adults who receive the 2-mg dose of ARS-1. Safety data, albeit limited, did not identify new safety signals. Overall, the submitted data support ARS-1 2 mg for the treatment of pediatric patients ≥30 kg in the proposed indication, based on extrapolation, if substantial evidence of effectiveness is established in adults.

505(b)(2) and Substantial Evidence of Effectiveness

This 505(b)(2) application relies upon the Agency's finding of effectiveness and safety of approved epinephrine injection products. The development program for ARS-1 was based upon a scientific bridge of PK/PD data to approved epinephrine injection products. As described above, FDA and the Applicant agreed upon a bracketing strategy, meaning that the PK/PD data for ARS-1 would be reasonably bracketed by the PK/PD profile of approved epinephrine

injection products. Adrenalin and EpiPen were the approved epinephrine injection products used in the ARS-1 development program and the listed drugs for this 505(b)(2) program. Demonstration of substantial evidence of effectiveness requires establishment of a scientific bridge of PK/PD data to approved epinephrine injection products, under expected conditions of use, to rely upon the Agency's findings of effectiveness of the approved epinephrine injection products, specifically Adrenalin and EpiPen.

Benefit/Risk Assessment and Recommendation

The nasal route of administration for epinephrine has the potential benefit of improving compliance with anaphylaxis treatment recommendations, including more frequent and more timely administration of epinephrine in the setting of anaphylaxis; this benefit may reasonably be expected to translate into improved outcomes. However, despite this potential advantage, in the absence of a clinical efficacy trial, the results of the clinical pharmacology program are expected to be sufficiently robust to ensure adequate systemic delivery of epinephrine in the setting of anaphylaxis. The PK results from the healthy volunteer trial (EPI 15), including with repeat dosing, show that ARS-1 is sufficiently bracketed between the two reference comparators (Adrenalin and EpiPen) to provide support for approval. Although ARS-1 PK lags behind the comparator with the lowest PK curve (Adrenalin) for the first 10 minutes in EPI 15, there is wide variability of Adrenalin PK seen between trials. For example, results from EPI 17, showed that exposure of ARS-1 was higher than Adrenalin in the first 10 minutes. Overall, the PK results in healthy volunteers are sufficient to demonstrate comparable results to approved epinephrine injection products. The favorable PK results are further supported by clinically relevant PD results, namely increased SBP and PR equal to or greater than with the comparators, to provide further confidence in trial results.

The nasal route of administration, however, introduces additional uncertainty in the setting of anaphylaxis since local nasal mucosa changes related to both anaphylaxis and topical administration of epinephrine may alter absorption. To address this area of uncertainty, the Applicant proposed a PK/PD trial using a NAC model (EPI 16) to replicate, in part, changes in nasal mucosa expected in some patients with anaphylaxis, including nasal congestion and rhinorrhea. PK results from trial EPI 16 demonstrate an earlier peak (Tmax) epinephrine concentration compared to the Adrenalin comparator (second comparator not included in trial), but concentrations are not sustained, falling below Adrenalin PK starting at 20 minutes. The rapid decline in PK and PR response with ARS-1, compared to Adrenalin, may result in more frequent requirement for a second ARS-1 dose to sustain clinical benefit, as recommended in labelling. A remaining uncertainty with the ARS-1 development program is the absence of PK/PD data from repeat dosing in the NAC model. Although it is reasonably expected that with repeat dose of ARS-1, PK will rise above levels seen with an epinephrine injection product, the effects of nasal epinephrine on local vasculature and the effects of rhinorrhea on further absorption are unknown and introduce additional uncertainty. The impact of such changes on PK/PD findings when the repeat dose is administered in the ipsilateral or contralateral naris is also unknown. Since sustained epinephrine PK/PD may be needed in cases of severe, persistent anaphylaxis requiring a second dose, PK/PD data from repeat dosing of ARS-1 compared to single and repeat doses on an epinephrine injection product are needed, including results when

the second dose is administered in the ipsilateral or contralateral naris, to address residual uncertainty.

The safety of ARS-1 is informed by the systemic safety profile of epinephrine injection products and local nasal effects observed in the ARS-1 PK/PD studies. Although the safety data from this program are limited, the PK profile of ARS-1 does not show a significant increase in epinephrine exposure compared to epinephrine injection that would raise safety concerns and local adverse events are considered monitorable.

Overall, the results of PK/PD studies do not support a favorable benefit risk assessment. Anaphylaxis is a life-threatening emergency and approval for this indication, in the absence of clinical efficacy trials, requires a high level of confidence in the PK/PD results under conditions likely to be encountered by the target population. Since PK/PD data were not obtained from subjects with anaphylaxis, a nasal allergen challenge approach was agreed upon with the Applicant to reflect changes in the nasal mucosa that may be present in some patients with anaphylaxis; these changes may impact absorption of ARS-1. In addition, proposed labeling for ARS-1, in alignment with labeling for approved epinephrine injection products, recommends administration of a second dose for patients with severe persistent anaphylaxis. The PK/PD of ARS-1 following repeat dosing under NAC conditions, and comparison to PK/PD findings from single and repeat doses of the listed epinephrine injection products is unknown. Similarly, the effects of ARS-1 administered under NAC conditions on absorption of a repeat dose of ARS-1 administered in the ipsilateral or contralateral naris is unknown. Additional data from a PK/PD trial(s) assessing PK/PD following a repeat dose of ARS-1 compared to repeat doses of epinephrine injection product(s) under allergen-induced allergic rhinitis conditions is needed to demonstrate substantial evidence of effectiveness; the trial(s) should also assess PK/PD findings when the second dose is administered in the ipsilateral and contralateral naris.

15. Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): EPI 10, 15, 16, 17

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 41		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

None.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Individual Trial Review

Table 22. All Submitted Clinical Pharmacology Clinical Studies[c]

Trial ID	Trial Date	Phase	Trial Objective(s)	Trial Design	Subjects Completed	Treatment Groups
Pivotal Clinical Pharmacology Studies						
EPI 15	7/14/2021-9/19/2021	1	SD and RD PK/PD	OL, R, CO	Total: 50 HS Part 1: 38 HS Part 2: 36 HS (24 HS participated in both Parts)	Part 1: ARS-1 2 mg IN Adrenalin 0.3 mg IM EpiPen 0.3 mg IM Part 2: ARS-1 2 mg (L/R) IN EpiPen 0.3 mg (L/R) IM ARS-1 2 mg (R/R) IN Washout between ARS-1 periods: 12 days
EPI 16	12/6/2021-2/4/2022	1	SD NAC PK/PD	OL, R, CO	34 Rhinitis Subjects	ARS-1 2 mg IN (L) (normal) Adrenalin 0.3 mg IM Adrenalin 0.5 mg IM ARS-1 2 mg IN (R) (NAC)
EPI 17	4/8/2022-5/14/2022	1	SD self-administration PK/PD	OL, R, CO	41 Type I Allergy Subjects	ARS-1 2 mg IN (self) Adrenalin 0.3 mg IM (staff)
EPI 10	7/17/2020-3/15/2021 (ongoing)	1	SD PK/PD	OL	≥30 kg: 42 Type I Allergy Pediatric Subjects	≥30 kg: ARS-1 2 mg IN ARS-1 1 mg IN 15 to <30 kg: (ongoing) ARS-1 1 mg IN ARS-1 0.65 mg IN

Trial ID	Trial Date	Phase	Trial Objective(s)	Trial Design	Subjects Completed	Treatment Groups
Supportive Clinical Pharmacology Studies						
EPI 3	3/19/2019-4/30/2019	1	SD PK/PD	OL, R, CO	67 HS	ARS-1 1 mg IN (L) ARS-1 1 mg IN, twice (L/R) Adrenalin 0.3 mg IM Adrenalin 0.3 mg IM, Twice Adrenalin 0.5 mg IM Washout between ARS-1 periods: 2 to 4 days
EPI 4	2/13/2019-4/7/2019	1	SD NAC PK/PD	OL, R, CO	33 Rhinitis Subjects	ARS-1 1 mg IN (L) (normal) Adrenalin 0.3 mg IM Adrenalin 0.3 mg SC ARS-1 1 mg IN (L) (NAC) Adrenalin 0.5 mg IM Washout between ARS-1 periods: 3 days
EPI 7	7/10/2019-7/17/2019	1	SD and RD PK/PD	OL, R, CO	35 HS	ARS-1 1 mg IN (L) ARS-1 1 mg twice (L/R) ARS-1 1 mg twice (R/R) EpiPen 0.3 mg EpiPen 0.3 mg twice Washout between ARS-1 periods: 24 hours
EPI 9	6/15/2020-9/2/2020	1	SD self-administration PK/PD	OL, R, CO	53 Type I Allergy Subjects	ARS-1 1 mg (self and staff) EpiPen 0.3 mg (self and staff) Symjepi 0.3 mg (self and staff)

Trial ID	Trial Date	Phase	Trial Objective(s)	Trial Design	Subjects Completed	Treatment Groups
EPI 11b	3/29/2021-4/28/2021	1	Dose ranging	OL, R, CO	25 HS	Group 1: ARS-1 1.3 mg (0.25% DDM) ARS-1 1.5 mg (0.25% DDM) Symjepi 0.3 mg ARS-1 1.5 mg (0.3% DDM) ARS-1 1.8 mg (0.3% DDM) Group 2: ARS-1 1 mg (0.25% DDM) (lot: 190932) ARS-1 1 mg (0.25% DDM) (lot: 202130) EpiPen 0.3 mg ARS-1 1.5 mg (0.3% DDM, (b) (4)) ARS-1 2 mg (0.3% DDM)[a] ARS-1 was administered in alternate naris; Washout between ARS-1 in same naris: 12 days
EPI 12	1/12/2021-3/19/2021	1	Self-administration	OL, R, CO	36 Type I Allergy Subjects	ARS-1 1 mg (0.25% DDM) (L or R) (self) EpiPen 0.3 mg (self) Symjepi 0.3 mg (self) ARS-1 1 mg (0.35% DDM) (L or R) (self) Washout between ARS-1 periods: 3 days
EPI 13[b]	9/21/2021-12/2/2021	1	Self-administration	OL, R, CO	42 Type I Allergy Subjects	ARS-1 2 mg (self) EpiPen 0.3 mg (self) Symjepi 0.3 mg (self)

Abbreviations: CO, cross-over; DB, double-blind; RD, repeat-dose; OL, open-label; R, randomized; SD, single-dose; NAC, nasal allergen challenge; IN, intranasal; IM, intramuscular; L, left; R, right; HS, healthy subjects; DDM, n-dodecyl-β-D-maltoside
a formulation is different from to-be-marketed
b Major protocol deviations were noted for packaging/labeling (ARS-1) and device training
c Including additional six trials investigated 1 mg ARS-1.

15.4.1.1. Trial EPI 15

Trial Type

Phase 1 single- and repeat-dose PK trial in healthy subjects

Trial Dates

July 14, 2021, to September 19, 2021

Formulation

- ARS-1 2 mg (Lot: 210928A)
- EpiPen 0.3 mg (Lot: 1FM201, 1FM209, 1FM286, 1FM287, 1FM338)
- Adrenalin 0.3 mg (Lot: 29671 and 36224)

Title

A Two-Part, Six-Period, Six-Treatment, Crossover Trial of the Pharmacokinetics of Epinephrine After Single and Repeat Administration of Intranasal ARS-1 or Epinephrine Injection to Healthy Volunteers (EPI 15)

Objective

The primary objectives were to assess the comparative bioavailability of epinephrine after IN administration of ARS-1 2 mg, intramuscular (IM) injection with EpiPen 0.3 mg (autoinjector) and IM injection with Adrenalin 0.3 mg (needle and syringe) in healthy volunteers under fasted conditions, and to evaluate the comparative PD response between products and doses based on Systolic blood pressure (SBP), Diastolic blood pressure (DBP), and pulse rate (PR) using an automated blood pressure monitoring (ABPM) device between treatment groups.

The secondary objectives were to assess the relative bioavailability of two doses of ARS-1 2 mg given in the right and left nares as compared to two doses in the right naris, and to evaluate the safety and tolerability of ARS-1 and EpiPen in healthy volunteers.

Trial Design and Method

This was a Phase 1, two-part, six-treatment, six-period, single and repeat doses, crossover trial that consisted of a screening period, baseline period, and an open-label randomized treatment period. The trial was conducted in two parts.

In Part 1, subjects were randomized to receive the following treatments in 3 treatment periods, with one treatment in each treatment period separated by a 24-hour washout period:

- A single IN dose of ARS-1 2 mg in the left naris,
- A single IM dose of EpiPen 0.3 mg with autoinjector in the left anterolateral thigh,
- A single IM dose of Adrenalin 0.3 mg with standard needle and syringe in the right anterolateral thigh.

After at least 12-day washout period, subjects from Part 1 returned for Part 2 were randomized to one of the following treatment sequence, with an at least 6 days washout period between each treatment:

- Two IN doses of ARS-1 2 mg both in the right naris (R/R) spaced 10 minutes apart followed by two IM doses of EpiPen 0.3 mg in left and right thigh (L/R) spaced 10 minutes apart followed by Two IN doses of ARS-1 2 mg in left and right (L/R) nares spaced 10 minutes apart
- Two IN doses of ARS-1 2 mg in left and right nares (L/R) spaced 10 minutes apart followed by two IM doses of EpiPen 0.3 mg in left and right thigh (L/R) spaced 10 minutes apart followed by Two IN doses of ARS-1 2 mg both in the right naris (R/R) spaced 10 minutes apart

ARS-1 was administered under a seated position. Subjects remained in a seated (slight recline for comfort is permitted) position and calm without stimulation for 60 minutes prior to dosing, at the time of dosing and throughout the first 120 minutes after dosing. Subjects remained seated and not engaged in any activities that may cause excitement. Nasal conditions were assessed at baseline and predose of each dosing period using Total Nasal Symptom Score (TNSS). Subjects had a TNSS Congestion Score of 0 at baseline or prior to dosing on Day 0 were enrolled.

PK blood samples for measurement of epinephrine concentrations were collected predose (at -10 and -5 minutes) and serially at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240 and 360 minutes postdose. Actual blood collection times were permitted to vary as follows: (1) ±1minute for the -10 to 20 minutes samples, (2) ±2 minutes for the 30 to 90 minutes samples, and (3) ±5 minutes for the 120 to 360 minutes samples. Epinephrine plasma concentration data were analyzed using noncompartmental method.

Human plasma samples obtained during the trial were analyzed for epinephrine concentrations using a validated liquid chromatography with tandem mass spectrometry methods (ATM-2648 and ATM-2662) at (b) (4) The lower limit of quantification for epinephrine was 20 pg/mL.

Pharmacodynamic measurements included pulse rate and blood pressure (systolic and diastolic pressure) using an automated blood pressure measuring device in a sitting position on Day 0 through Day 3. Pulse rate and BP measurement were taken at baseline, predose (twice after at least 20 minutes in a sitting position and at least 5 minutes apart) and serially at 5 (±2 min), 10 (±2 min), 15 (±2 min), 20 (±2 min) 25 (±2 min), 30 (±2 min), 45 (±5 min), 60 (±5 min), 90 (±5 min) and 120 (±5 min) minutes after dosing.

Protocol Deviation

The Applicant reported that there were 261 protocol deviations over 49 subjects. There were 207 instances of PK blood draws not being done or being done outside the window; there were 35 instances of PD and/or vital signs not being collected or being collected outside the window. Samples collected outside the window are included in the dataset.

As PK and PD samples were collected following an intensive sampling schedule for every 2 to 15 minutes with allowed window between ±1 to ±5 minutes during the first 1 hour postdose and only up to ~4% of samples were affected, the deviation from predefined sampling collection window in first 1 hour is not expected to have a significant impact on the PK and PD analyses.

Demographic

A total of 59 healthy adult subjects (including 5 re-enrolled subjects) were enrolled and received at least one dose. PK samples from 14 subjects (Subjects (b) (6)) collected on Day 0 in Period 1, Part 1 could not be measured due to error in processing PK samples noted by the Applicant. Therefore, Part 1 data from these subjects were excluded. An additional 17 subjects (Subjects (b) (6)) were enrolled. The list of subjects included in each Part of the trial is shown in Table 23.

Table 23. List of Subjects Who Participated, Trial EPI 15

	n	Subject ID
Included in part 1 only	16	(b) (6)
Included in part 2 only	16	
Included in parts 1 and 2	26	
Excluded from entire trial	1	

a Discontinued before Part 2, Period 1
b PK sample excluded from Part 1 due to error in processing
c Discontinued after 1 day (Part 1, Period 1)
d Discontinued before Part 2, Period 3 (No ARS-1 2 mg L/R)
e Discontinued before Part 2, Period 3 (No ARS-1 2 mg R/R)
f Subjects samples failed due to processing error during Part 1 and re-enrolled in Part 1 ((b) (6) (b) (6)

The baseline age and body weight of subjects for EPI 15 is shown in Table 24.

Table 24. Baseline Demographics, Trial EPI 15

Demographic	(N=59)
Age (years)	
Mean (SD)	40.6 (9.73)
Median	41
Minimum, maximum	21, 54
Body Weight (kg)	
Mean (SD)	82.5 (12.13)
Median	81.6
Minimum, maximum	54.7, 114.9

Source: clinical pharmacology reviewer's analysis based on adsl.xpt for EPI 15.

The baseline epinephrine concentrations for each treatment are shown in Table 25. The median and geometric mean of baseline epinephrine concentrations were similar across all treatment arms and generally no greater than 10% of mean C_{max} values. In both Part 1 and Part 2, all subjects except two subjects from EpiPen (L/R) had a mean baseline value (average of -10 and-5 minutes values) <100 pg/mL.

Table 25. Baseline Epinephrine Concentrations, Trial EPI 15

	Part 1 Single Dose						Part 2 Repeat Dose					
	ARS-1 2 mg		Adrenalin 0.3 mg		EpiPen 0.3 mg		ARS-1 2 mg (L/R) [a]		ARS-1 2 mg (R/R) [a]		EpiPen 0.3 mg (L/R) [a]	
Time	-10 min (n=41)	-5 min (n=42)	-10 min (n=42)	-5 min (n=42)	-10 min (n=42)	-5 min (n=42)	-10 min (n=38)	-5 min (n=37)	-10 min (n=38)	-5 min (n=37)	-10 min (n=41)	-5 min (n=40)
Geometric Mean (CV%)	18.06 (47.08)	17.00 (59.02)	18.40 (65.49)	20.93 (61.61)	20.35 (57.50)	21.48 (64.14)	19.78 (68.86)	20.86 (84.85)	18.59 (68.12)	17.32 (63.54)	21.51 (275.48)	22.03 (257.87)
Median (Range)	22.5 (10 to 38.3)	10 (10 to 51.3)	21.2 (10 to 63)	23.25 (10 to 64.3)	23.1 (10 to 56.8)	27.2 (10 to 74.9)	23.7 (10 to 71.7)	22 (10 to 128)	20.35 (10 to 62.3)	10 (10 to 46.2)	21.7 (10 to 857)	22.2 (10 to 783)

Source: clinical pharmacology reviewer's analysis based on adpc.xpt of Trial EPI 15. L = left; R = right
a One subject each in ARS-1 (R/R), ARS-1 (L/R) and EpiPen (L/R) did not have any baseline concentrations collected. Sensitivity analysis including or excluding these subjects from these treatment arms did not result in meaningful changes in PK results.

PK Endpoints

C_{max}, T_{max}, partial AUCs 10, 20, 30, and 60 minutes postdose (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, and AUC_{0-60}). As epinephrine is a critical medication that treats life-threatening symptoms of anaphylaxis as soon as symptoms occurs. The concentrations within 60 minutes are considered most clinically relevant. Therefore, PK analysis for all studies focused on evaluating the PK parameters mentioned above.

PD Endpoints

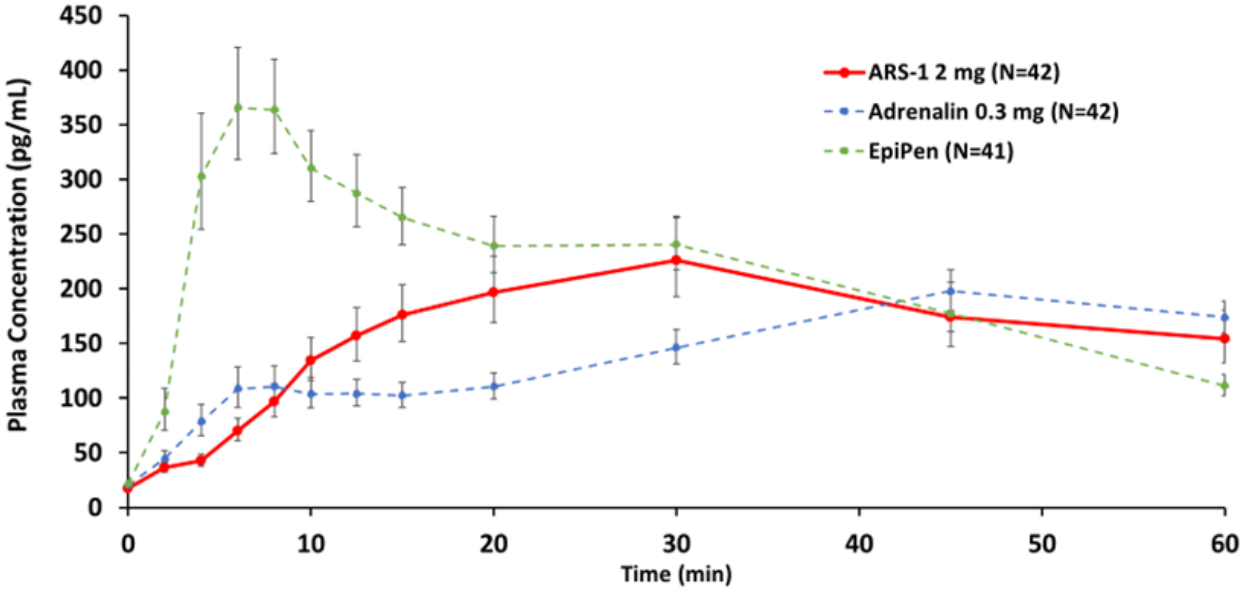
SBP, DBP and PR change from baseline over time, especially within 60 minutes postdose.

Results

Single Dose PK Results

Following a single dose administration of ARS-1, EpiPen or Adrenalin, the geometric mean epinephrine concentration-time profile, summary of PK Parameters and bioequivalence assessment are present in Figure 20, Table 26 and Table 27, respectively.

Figure 20. 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, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. One subject from EpiPen arm was excluded due to an insufficient number of postdose samples (N <3) collected within 30 min.

Table 26. 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, Trial EPI 15

	Geometric Mean (CV%)			
Parameter	**ARS-1 (N=42)**	**Adrenalin 0.3 mg IM (N=42)**	**EpiPen 0.3 mg IM (N=41)[b]**	**Bracketed (Y/N)**
C_{max} (pg/mL)	341(114)	283 (63)	618 (79)	Y
T_{max} (min)[a]	30 (6 to 150)	45 (4 to 90)	6 (2 to 45)	---
$AUC_{0\text{-}10min}$ (pg·min/mL)	**712 (93)**	**889 (118)**	**2979 (98)**	**N (lower than both)**
$AUC_{0\text{-}20min}$ (pg·min/mL)	2596 (102)	2040 (102)	6007 (77)	Y
$AUC_{0\text{-}30min}$ (pg·min/mL)	4901 (109)	3439 (77)	8759 (67)	Y
$AUC_{0\text{-}60min}$ (pg·min/mL)	10925 (116)	9242 (59)	14772 (56)	Y

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
A Median (range).
B One subject from EpiPen arm was excluded due to an insufficient number of postdose samples (N <3) collected within 30 min.
Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; IN, intranasal; IM, intramuscular; N, no; Tmax, time to maximum plasma concentration; Y, yes

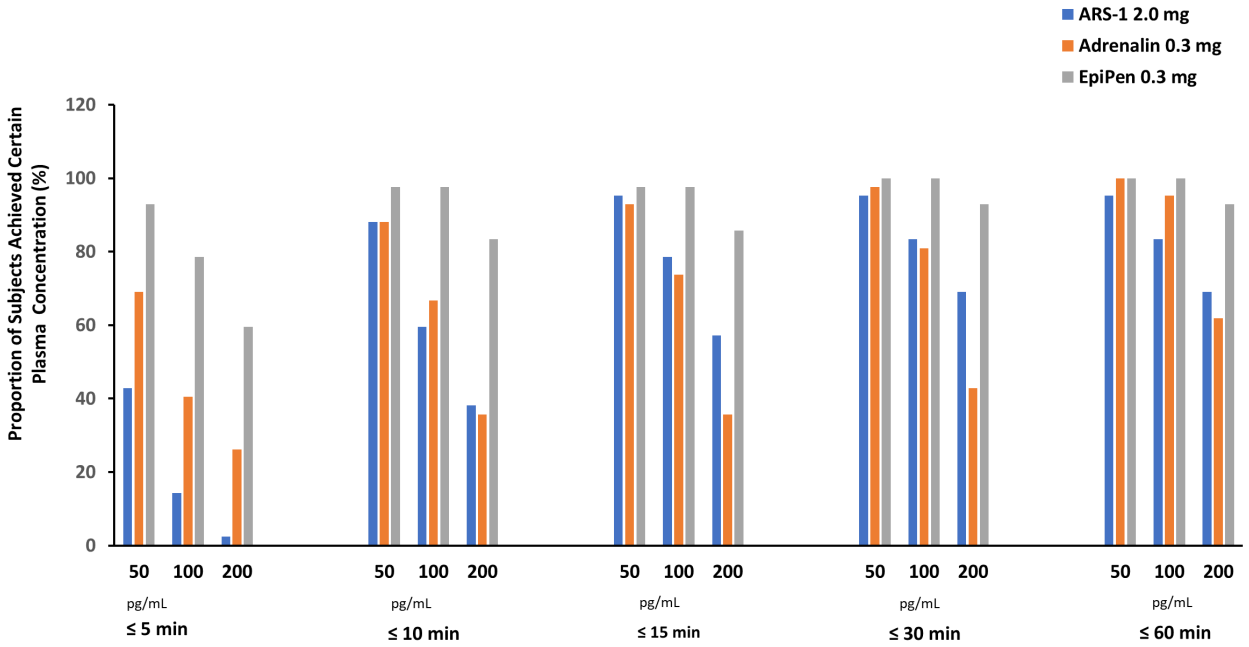
Table 27. Bioequivalence Assessment Between a Single Dose of ARS-1 and a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

	Test: ARS-1 2 mg (N=42) vs. Reference: Adrenalin 0.3 mg (N=42) GMR (%) [90% CI]	Test: ARS-1 2 mg (N=42) vs. Reference: EpiPen 0.3 mg (N=41) GMR (%) [90% CI]
C_{max} (pg/mL)	120.2 [94.5, 152.9]	56.2 [44.2, 71.4]
AUC0-10 (pg*min/mL)	**80.1 [61.8, 103.9]**	24.6 [19.0, 31.9]
AUC0-20 (pg*min/mL)	127.3 [101.1, 160.2]	44.0 [34.9, 55.3]
AUC0-30 (pg*min/mL)	142.5 [114.1, 177.9]	56.5 [45.3, 70.6]
AUC0-60 (pg*min/mL)	118.2 [95.8, 145.7]	74.2 [60.2, 91.5]

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; GMR, geometric mean ratio; IN, intranasal; IM, intramuscular

The proportion of subjects that achieved the arbitrarily selected plasma concentration 50, 100 and 200 pg/mL is shown in Figure 21. The proportion of subjects whose epinephrine concentration failed to reach 100 pg/mL within 30 minutes and 60 minutes is shown in Table 28.

Figure 21. Proportion of Subjects With Epinephrine Concentrations of 50, 100, and 200 pg/mL or Greater by Time Following a Single Dose of ARS-1, Adrenalin 0.3 mg, or EpiPen 0.3 mg, Trial EPI 15



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

Table 28. Proportion of Subjects Who Failed to Reach 100 pg/mL Following Two Doses of ARS-1 2 in Same Naris (R/R) or Opposite Naris (L/R), and Two Doses of EpiPen 0.3 mg, Trial EPI 15

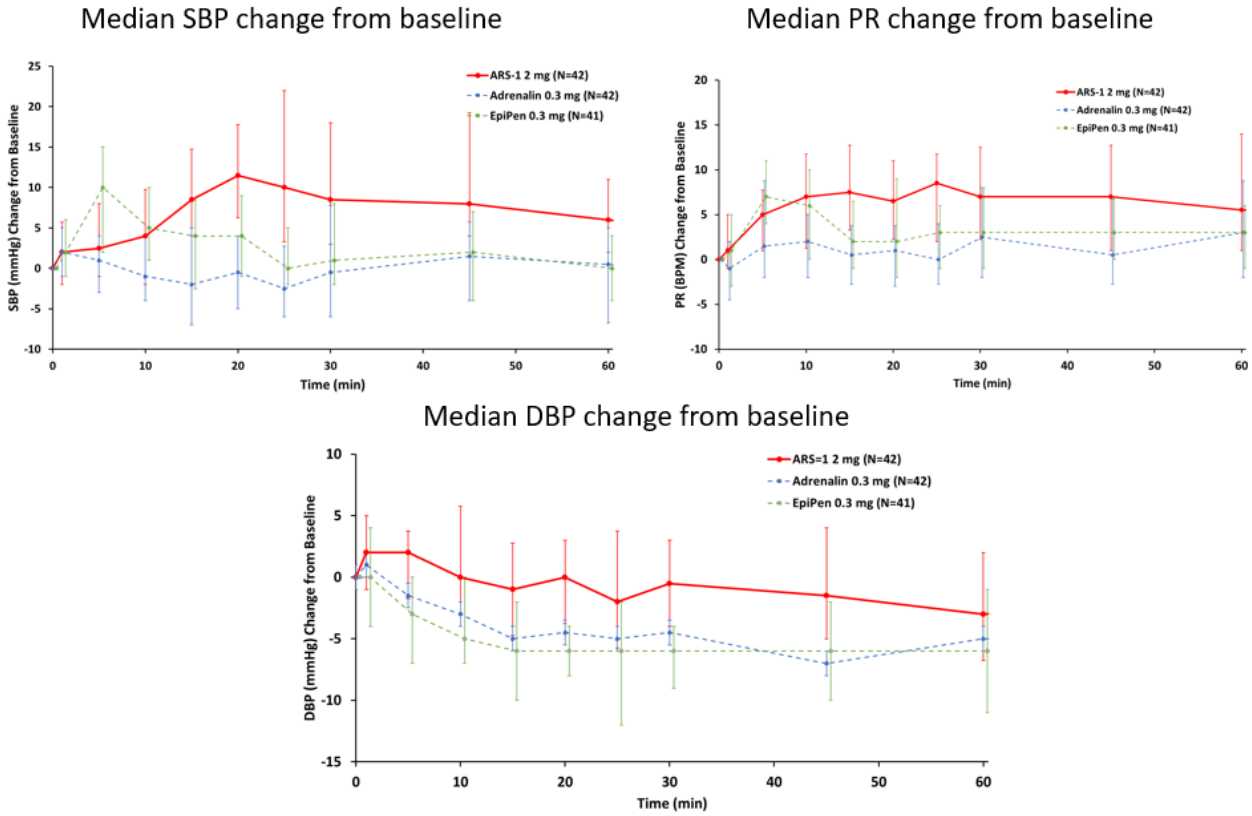
Elapsed Time	ARS-1	Adrenalin 0.3 mg	EpiPen 0.3 mg
50 pg/mL			
Within 30 min	2/42 (5%)	1/42 (2%)	0/41 (0%)
Within 60 min	2/42 (5%)	0/42 (0%)	0/41 (0%)
100 pg/mL			
Within 30 min	7/42 (17%)	7/42 (17%)	0/41 (0%)
Within 60 min	7/42 (17%)	2/42 (5%)	0/41 (0%)

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

Single Dose PD Results

The PD responses, SBP, DBP and PR, following a single dose of ARS-1, Adrenalin 0.3 mg, or EpiPen 0.3 mg are displayed in Figure 22. The mean and median maximum SBP changes from baseline in 60 minutes and the median time to reach the maximum SBP change following a single dose are shown in Table 29.

Figure 22. 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, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15. 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: DBP, diastolic blood pressure; PD, pharmacodynamic; PK, pharmacokinetic; PR, pulse rate; SBP, systolic blood pressure

Table 29. Maximum Change of SBP From Baseline in 60 Minutes Following a Single Dose, Trial EPI 15

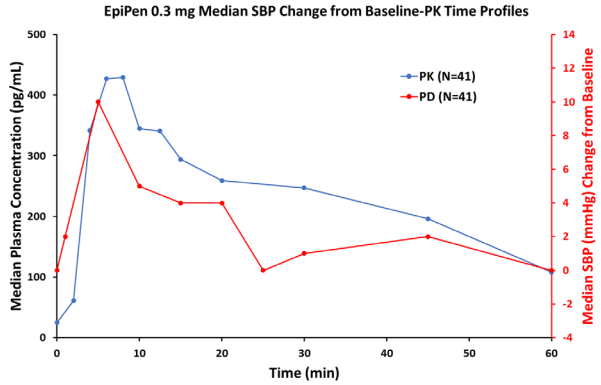
Parameter	ARS-1 (n=42)	EpiPen 0.3 mg (n=41)	Adrenalin 0.3 mg (n=42)
Mean (SD) (mmHg)	23 (16)	17 (15)	12 (10)
Median (range) (mmHg)	19 (0, 72)	15 (0, 90)	9 (0, 41)
Median T_{max} (range) (min)	25 (0, 60)	5 (0, 60)	15 (0, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15. Subjects who were included in the PK analysis were included in the PD analysis.
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic; SBP, systolic blood pressure; Tmax time to maximum plasma concentration

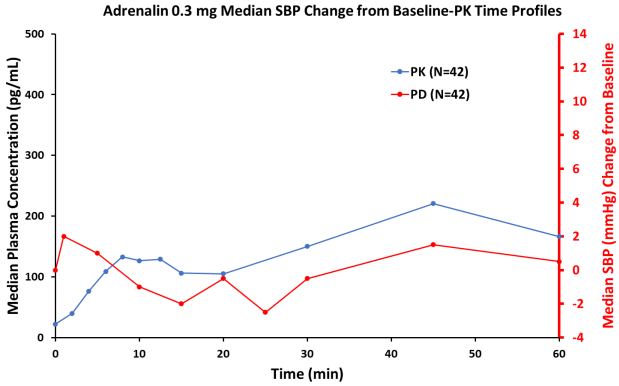
The PK/PD relationship following a single dose of EpiPen, Adrenalin and ARS-1 is shown in Figure 23, which demonstrates different relationships among these three products.

Figure 23. Median Plasma Epinephrine Concentration vs. Median PD Response (Change of SBP From Baseline) Following A Single Dose EpiPen 0.3 mg, Adrenalin 0.3 mg or ARS-1 2 mg, Trial EPI 15

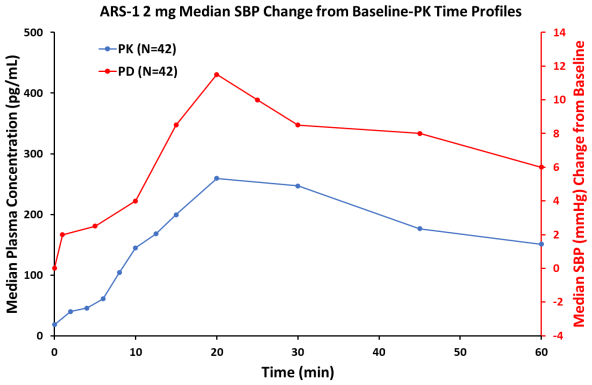
A. A Single Dose EpiPen 0.3 mg IM



B. A Single Dose Adrenalin 0.3 mg IM



C. A Single Dose ARS-1 2 mg IN

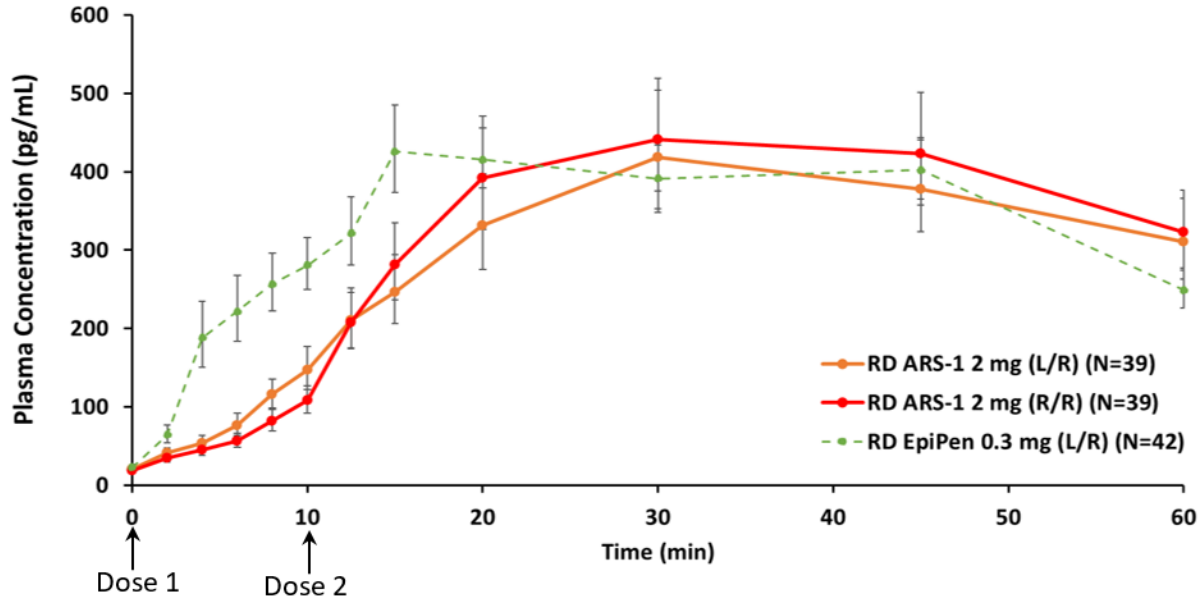


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt and adxd.xpt for Trial EPI 15

Repeat Dose PK Results

Following repeat doses (i.e., 2 doses separated by 10 minutes) administration of ARS-1 (ipsilaterally or contralaterally) or EpiPen on both thighs, the geometric mean epinephrine concentration-time profile, summary of PK Parameters and bioequivalence assessment are present in Figure 24, Table 30 and Table 31, respectively.

Figure 24. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profiles Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. Three subjects each in the ARS-1 (R/R) and ARS-1 (L/R) arms discontinued early and did not have PK data.
Abbreviations: L, left; PK, pharmacokinetic; R, right; RD, repeat doses

Table 30. PK Parameters Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

	Geometric Mean (CV%)		
Parameter	**Repeat-Dose ARS-1 (L/R) IN (N=39)**	**Repeat-Dose ARS-1 2 mg (R/R) IN (N=39)**	**Repeat-Dose EpiPen 0.3 mg (L/R) IM (N=42)**
C_{max} (pg/mL)	706 (104)	729 (99)	721 (61)
T_{max} (min)[a]	30 (6 to 150)	30 (4 to 150)	15 (0 to 360)
$AUC_{0\text{-}10min}$ (pg·min/mL)	836 (118)	627 (111)	2147 (104)
$AUC_{0\text{-}20min}$ (pg·min/mL)	3664 (123)	3626 (128)	6363 (78)
$AUC_{0\text{-}30min}$ (pg·min/mL)	8106 (119)	8291 (119)	10735 (67)
$AUC_{0\text{-}60min}$ (pg·min/mL)	21083 (110)	22034 (110)	23034 (54)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. Three subjects each in the ARS-1 (R/R) and ARS-1 (L/R) arms discontinued early and did not have PK data.
A Median (range)
Abbreviations: IN, intranasal; L, left; R, right; PK, pharmacokinetic

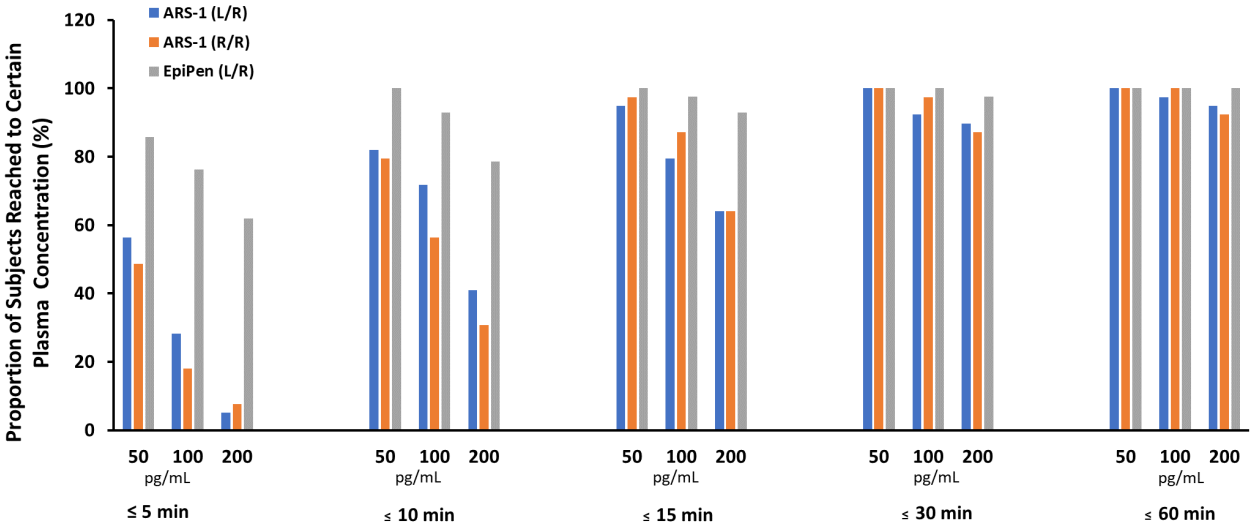
Table 31. Bioequivalence Assessment Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

	ARS-1 2 mg (L/R) (test) vs. EpiPen (L/R) (reference) GMR (%) [90% CI]	ARS-1 2 mg (R/R) (test) vs. EpiPen (L/R) (reference) GMR (%) [90% CI]	ARS-1 2 mg (L/R) (test) vs. ARS-1 2 mg (R/R) (reference) GMR (%) [90% CI]
C_{max} (pg/mL)	96.3 [76.3, 121.5]	99.9 [79.2, 126.1]	96.4 [75.3, 122.3]
$AUC_{0\text{-}10\ min}$ (pg*min/mL)	38.8 [29.5, 51.0]	29.3 [22.3, 38.6]	132.3 [99.9, 175.1]
$AUC_{0\text{-}20\ min}$ (pg*min/mL)	56.9 [44.2, 73.3]	57.3 [44.5, 73.9]	99.3 [76.6, 128.7]
$AUC_{0\text{-}30\ min}$ (pg*min/mL)	74.1 [57.8, 95.1]	77.3 [60.2, 99.1]	96.0 [74.4, 123.8]
$AUC_{0\text{-}60\ min}$ (pg*min/mL)	90.0 [70.4, 115.0]	94.9 [74.3, 121.2]	94.8 [73.8, 121.8]

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15. Three subjects each in the ARS-1 (R/R) and ARS-1 (L/R) arms discontinued early and did not have PK data.

The proportion of subjects whose epinephrine concentration reached 50, 100 or 200 pg/mL at different time points within 60 minutes following two doses of ARS-1 or EpiPen 0.3 mg is shown Figure 25.

Figure 25. Proportion of Subjects With Epinephrine Concentrations of 50, 100, and 200 pg/mL or Greater by Time Following Two Doses of ARS-1 Given in Same Naris (R/R) or Opposite Naris (L/R) vs. Two Doses of Intramuscular Injection Using EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15

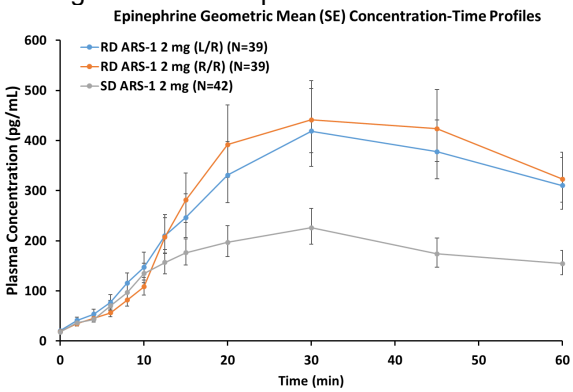


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.

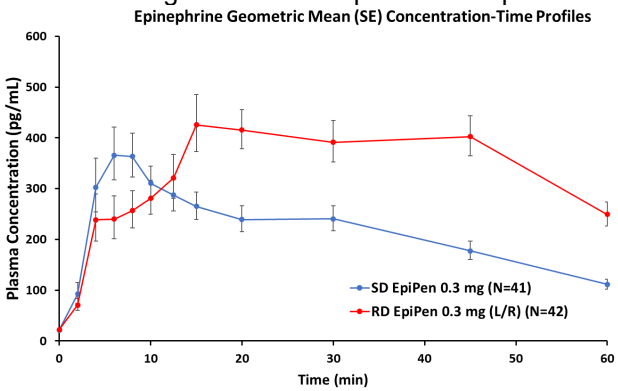
The single dose versus repeat dose PK profiles comparison for ARS-1 and EpiPen is shown in Figure 26 and the PK parameters comparison is shown in Table 32.

Figure 26. Single- vs. Repeat-Dose PK Profiles Comparison for ARS-1 and EpiPen, Trial EPI 15

A. Single-Dose vs. Repeat-Dose ARS-1



B. Single-Dose vs. Repeat-Dose EpiPen



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

Table 32. Single- vs. Repeat-Dose PK Parameters Comparison for ARS-1 and EpiPen, Trial EPI 15

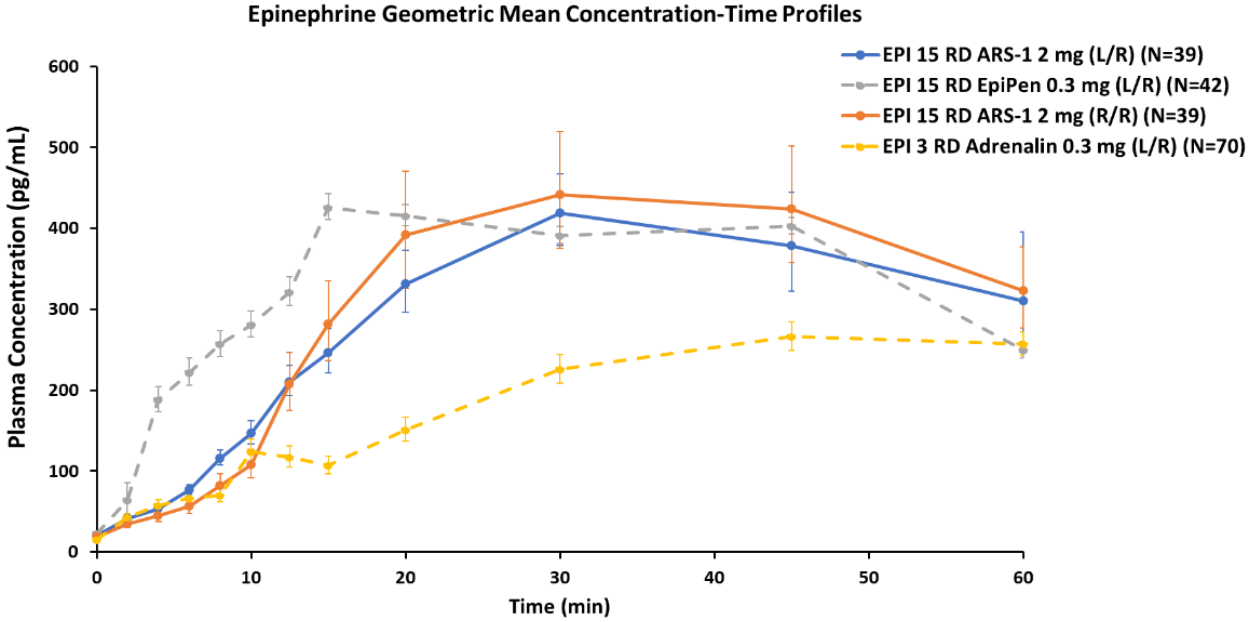
Geometric Mean PK Parameters	Single Dose	Repeat Doses[a]	Fold Difference (Repeat/Single)
ARS-1			
C_{max}	341	706	2
$AUC_{0\text{-}60min}$	10925	21083	1.9
EpiPen			
C_{max}	618	721	1.2
$AUC_{0\text{-}60min}$	14772	23034	1.5

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15.
a ARS-1 (L/R) PK parameters was used.

The Epinephrine exposure is approximately doubled following two-dose ARS-1 compared to single-dose ARS-1, while two-dose EpiPen increased the C_{max} by 20% and $AUC_{0\text{-}60\ min}$ by 50% compared to single-dose EpiPen. The different PK proportionality between ARS-1 and EpiPen may explain why exposure following two doses of ARS-1 can catch up to that of two doses of EpiPen, whereas the epinephrine exposure following single dose ARS-1 is lower than that of single dose of EpiPen. The mechanism of less than dose proportional PK for EpiPen is unclear.

Although the repeat doses of ARS-1 were not compared to that of repeat doses Adrenalin 0.3 mg in EPI 15, a cross study comparison was performed using the repeat doses of Adrenalin data from EPI 3, as shown in Figure 27.

Figure 27. Geometric Mean Epinephrine Time Profiles of Repeat Doses of ARS-1 2 mg (Trial EPI 15) vs. Repeat Doses of Adrenalin 0.3 mg (Trial EPI 3)



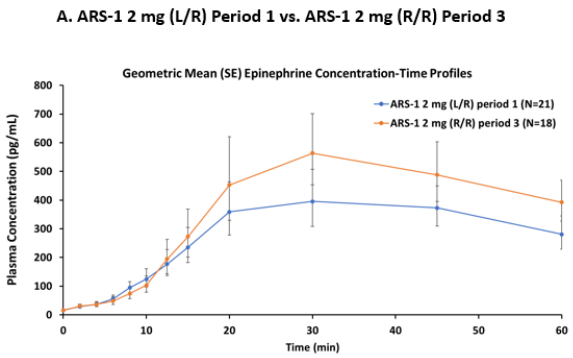
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 15 and EPI 3.

PK Carryover Effect Assessment

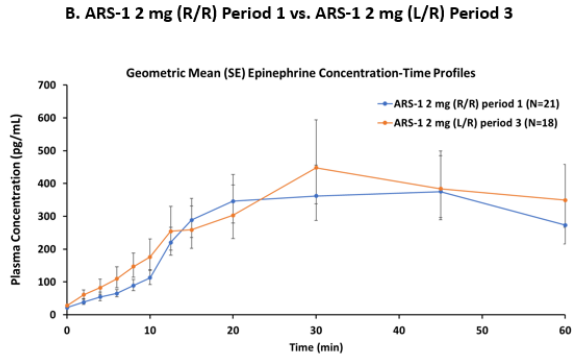
In repeat-dose trial, the two repeat-dose ARS-1 treatment periods were separated by the EpiPen treatment period, with a washout period of 6 days between each treatment period. This results in a 12-day washout period between two ARS-1 treatment periods. With a cross-over design, subjects who received ARS-1 (L/R) in period 1 were treated with ARS-1 (R/R) in period 3, while subjects who received ARS-1 (R/R) in period 1 were treated with ARS-1 (L/R) in period 3. The epinephrine exposures of AR—1 by treatment sequence sis shown in Figure 28.

Figure 28. Epinephrine Concentration-Time Profiles of Repeat Dose ARS-1 by Treatment Sequences, Trial EPI 15, Part 2

A. Treatment Sequence 1



B. Treatment Sequence 2

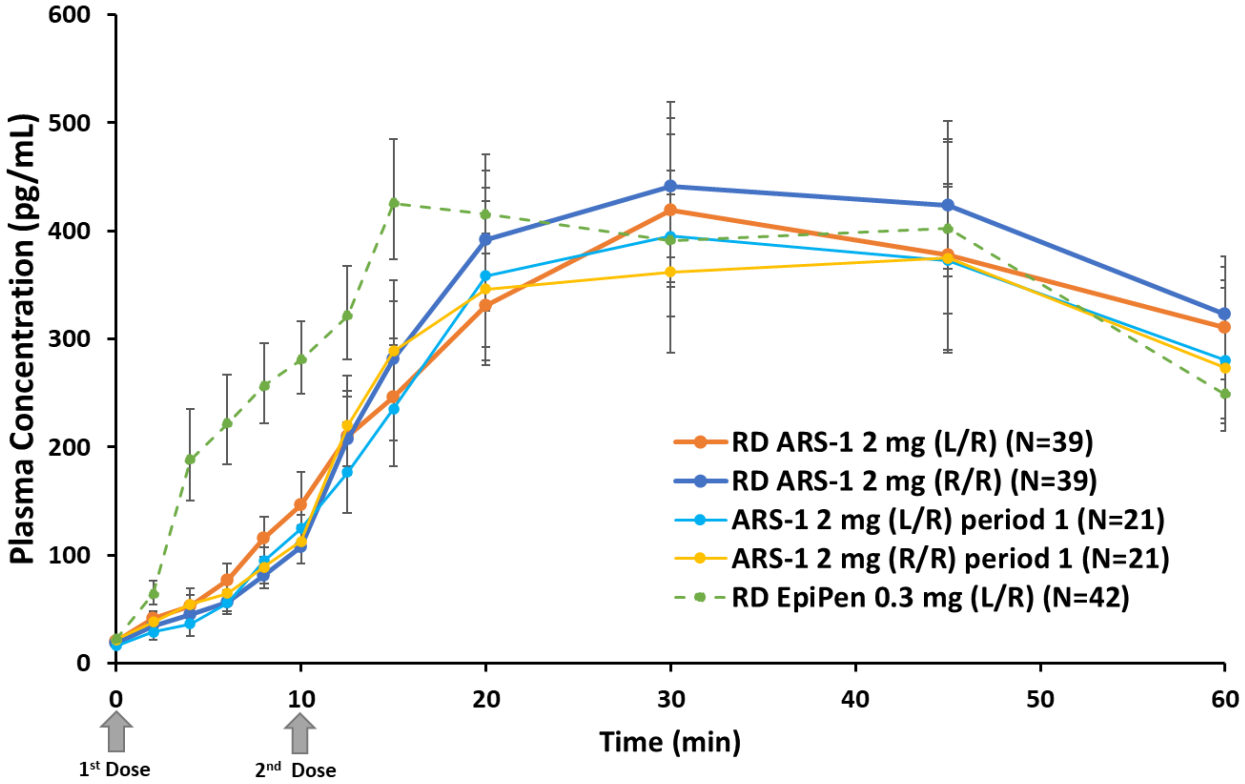


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 15

Given that the difference in PK profiles for two ARS-1 treatment periods were not consistent in the same direction between the two treatment sequences, the carryover effect was determined to be minimized following a 12-day washout period. The PK Profiles for repeat-dose

ARS-1 in Treatment Period 1 was compared to pooled results from both Period 1 and 3 as well as repeat-dose EpiPen in Figure 29. The PK profiles for repeat-dose ARS-1 given ipsilaterally or contralaterally in Treatment Period 1 were similar to pooled results of ARS-1 as well as two-dose EpiPen after 20 minutes postdose. Therefore, pooled PK results for ARS-1 was used for the PK assessment for EPI 15 part 2 (Figure 24,Table 30 and Table 31).

Figure 29. Epinephrine Concentration-Time Profiles of Repeat-Dose ARS-1 in Period 1 and Pooled vs. Repeat-Dose EpiPen, Trial EPI 15

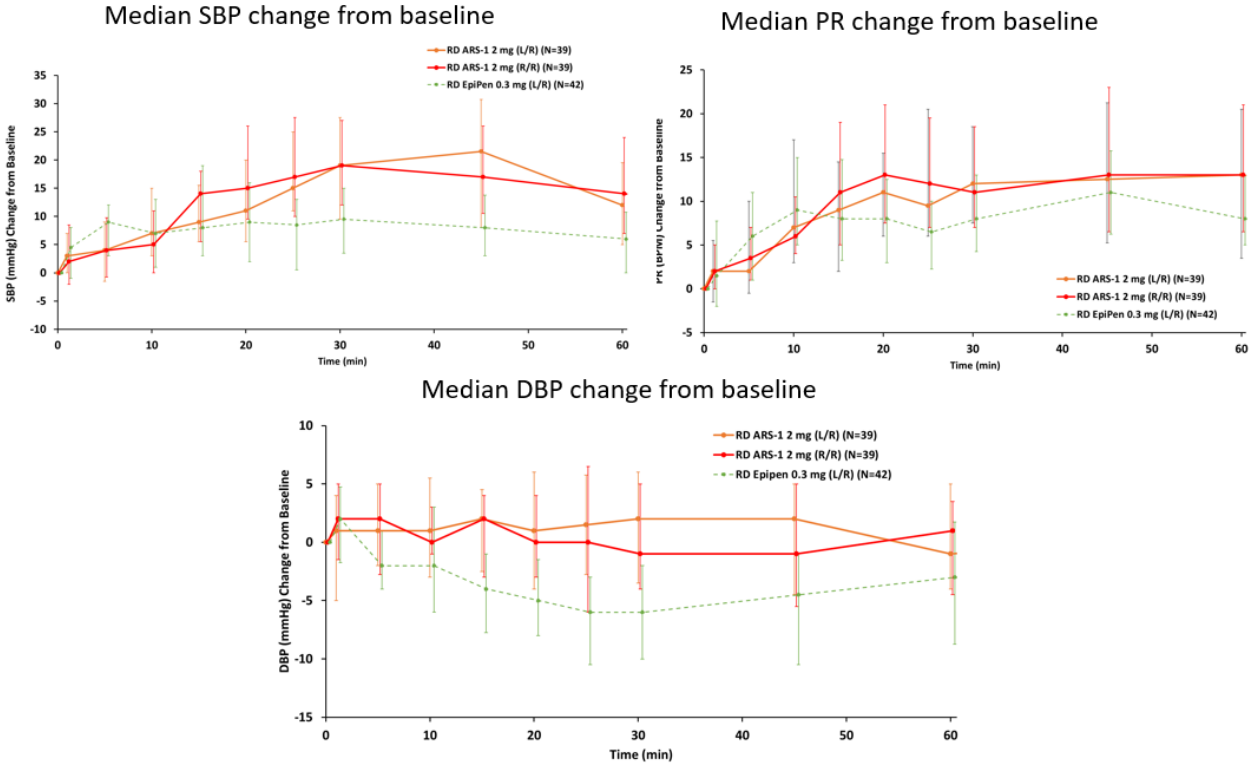


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for Trial EPI 15

Repeat-Dose PD Results

The PD responses following two doses of ARS-1 2 mg and EpiPen 0.3 mg are shown in Figure 30. The mean and median of the maximum SBP change from baseline within 60 minutes as well as the median time to reach the maximum change following repeat doses are shown in Table 27.

Figure 30. Median PD Responses (SBP, PR, and DBP Change From Baseline) Following Two Doses of ARS-1 in Same Naris (R/R) or Opposite Naris (L/R), and Two Doses of EpiPen 0.3 mg in Healthy Subjects, Trial EPI 15



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15.

Table 33. Maximum SBP Change From Baseline in 60 Minutes Following Repeat Doses, Trial EPI 15

Parameter	ARS-1 (L/R) (n=38)	ARS-1 (R/R) (n=38)	EpiPen 0.3 mg (L/R) (n=42)
Mean (SD) (mmHg)	29 (14)	29 (13)	19 (9)
Median (range) (mmHg)	29 (6, 67)	26 (11, 64)	19 (3, 42)
Median T_{max} (range) (min)	28 (1, 60)	30 (5, 60)	15 (1, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 15.
Abbreviations: L, left; PD, pharmacodynamic; PK, pharmacokinetic; R, right; Tmax, time to maximum plasma concentration

Conclusion

Single Dose

- PK: Within 60 minutes following the single dose administration in healthy subjects, the mean epinephrine concentrations for ARS-1 were lower than Adrenalin and EpiPen within 10 minutes postdose and became bracketed by these two injection products after 10 minutes.
- PD: Within 60 minutes following single dose administration in healthy subjects, the median PD responses (SBP and PR) for ARS-1 were numerically bracketed by EpiPen and Adrenalin within 10 minutes postdose and became higher than both EpiPen and Adrenalin afterwards.

The DBP profile for ARS-1 was more stable from baseline compared to the two injection products.

Repeat Dose

- PK: Within 60 minutes following the repeat doses (i.e., 2 doses separated by two minutes) administration in healthy subjects, the mean epinephrine concentrations following two doses of ARS-1 were lower than two doses of EpiPen during the first 20 to 30 minutes post–first dose and became numerically comparable thereafter. The PK profiles and systemic exposures were similar between ARS-1 administered in the same naris and opposite naris.
- PD: Within 60 minutes following the repeat doses (i.e., 2 doses separated by two minutes) administration in healthy subjects, the PD responses (SBP and PR) were initially lower that EpiPen during first ~10 post-first dose and became higher than EpiPen afterwards. The DBP response was more stable from baseline for repeat-dose ARS-1 compared to repeat-dose EpiPen.

15.4.1.2. Trial EPI 16

Trial Type

Phase 1 single-dose PK trial in subjects with allergic rhinitis

Trial Date

December 6, 2021, to February 4, 2022

Formulation

- ARS-1 2 mg (Lot: 210928A)
- Adrenalin 0.3 mg and 0.5 mg (Lot: 36224)

Title

A Four-Treatment, Partially Randomized, Crossover Trial of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis (EPI 16)

Objective

The primary objective is to evaluate the comparative bioavailability after IN administration of a 2-mg dose of ARS-1 in subjects with and without induced allergic rhinitis (nasal allergen challenge) and to evaluate the impact of nasal edema and congestion on the absorption of epinephrine.

The secondary objective is to evaluate the comparative bioavailability of ARS-1 and IM epinephrine injection when administered in subjects under normal conditions and to evaluate the safety and tolerability of ARS-1 in subjects after IN administration of epinephrine as compared to the IM epinephrine administration.

Trial Design and Method

This was a phase 1, single-dose, four-period, partially randomized, cross-over trial on subjects with allergic rhinitis subjects. Subjects were randomized to receive the following treatment sequences, with a washout period of 24 hour between each treatment:

- A single dose of ARS-1 2 mg in left naris under normal nasal condition followed by A single dose of Adrenalin 0.3 mg IM in left thigh followed by A single dose of Adrenalin 0.5 mg IM in the right thigh followed by A single dose of ARS-1 2 mg in right naris after NAC
- A single dose of ARS-1 2 mg in left naris under normal nasal condition followed by A single dose of Adrenalin 0.5 mg IM in right thigh followed by A single dose of Adrenalin 0.3 mg IM in the left thigh followed by A single dose of ARS-1 2 mg in right naris after NAC

ARS-1 was administered in a seated position. Subjects remained in a seated (slight recline for comfort is permitted) position and calm without stimulation for 60 minutes prior to dosing, at the time of dosing and throughout the first 120 minutes after dosing. Subjects remained seated and not engaged in any activities that may cause excitement

In Treatment period 4, NAC was initially conducted with the same allergen challenge dose that was established at screening. Subjects' nasal conditions were assessed by total nasal symptoms scores (TNSS), which is a standard patient-reported questionnaire that evaluates various symptoms including congestion, runny nose, itching and sneezing, each on a scale of 0 to 3. Zero corresponds to no symptoms, while 3 corresponds to severe symptoms. The nasal NCS is one of the components that measure the congestion condition. As subjects were assessed out of their allergy season, they would not be expected to have rhinitis symptoms at time of enrollment and before undergoing NAC. TNSS was recorded before and after the allergen is applied. If the initial allergen dose did not induce a positive reaction (TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3) after 15 minutes, a second administration of allergen with up to a 4-fold increase in concentration from the previous dose may have been applied (up to a maximum up dilution of 1:2).

PK blood samples for measurement of epinephrine concentrations were collected predose (at -10 and -5 minutes) and serially at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240 and 360 minutes postdose. Actual blood collection times were permitted to vary as follows: 1) ±1 minute for the -10 to 20 minutes samples, 2) ±2 minutes for the 30 to 90 minutes samples, and 3) ±5 minutes for the 120 to 360 minutes samples. Epinephrine plasma concentration data were analyzed using noncompartmental method.

Human plasma samples obtained during the trial were analyzed for epinephrine concentrations using a validated liquid chromatography with tandem mass spectrometry methods (ATM-2662) at (b) (4) The lower limit of quantification for epinephrine was 20 pg/mL.

Pharmacodynamic measurements included SBP, DBP, and PR after each dosing arm using an ABPM device. Blood pressure and PR measurements were taken at baseline, predose each treatment period (at -10 and -5 minutes) after sitting relaxed with back supported, legs

uncrossed, and upper arm bared (slight recline for comfort is permitted) for at least 20 minutes, and at 1, 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes after dosing.

Protocol Deviation

During the trial, there were 110 protocol deviations over 27 subjects. There were four instances of vital signs not being assessed or being assessed outside the assessment window. There were 106 instances of PK blood draws not being conducted or being conducted outside the window.

As PK and PD samples were collected following an intensive sampling schedule for every 2 to 15 minutes with allowed window between ±1 to ±5 minutes during the first 1 hour postdose and only up to ~4% samples were affected, the deviation from predefined sampling collection window in first 1 hour is not expected to have a significant impact on the PK and PD analyses.

Demographic

A total of 36 subjects were enrolled and received at least one dose of trial drug. Subjects (b) (6) and (b) (6) withdrew early from the trial after Period 1 and Period 3, respectively. Subjects ranged in age from 20 to 52 years. Twenty subjects (55.6%) were male, and 16 subjects (44.4%) were female. Sixteen subjects (44.4%) were White, eight subjects (22.2%) were Black or African American, eight subjects (22.2%) were Asian, one subject (2.8%) was Native Hawaiian or Other Pacific Islander; and three subjects (8.3%) were Other.

Following subjects in Table 34 did not have adequate number of postdose samples (<3) collected within 30 minutes postdose in the treatment period listed below and were excluded from PK analysis. Subjects who were excluded from PK analysis were also excluded from PD analysis.

Table 34. Excluded Subjects From EPI 16 PK/PD Analysis

Subjects	Treatment	Number of postdose samples in 30 minutes	Reason
(b) (6)	ARS-1 2 mg (NAC)	0	No PK Sample collected
	Adrenalin 0.3 mg IM	0	No PK Sample collected
	Adrenalin 0.5 mg IM	0	No PK Sample collected
	ARS-1 2 mg (NAC)	0	No PK Sample collected
	ARS-1 2 mg (after nasal challenge)	0	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.3 mg IM	1	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.5 mg IM	1	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.3 mg IM	0	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.5 mg IM	0	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.3 mg IM	0	Insufficient PK sample (<3) collected within 30 minutes
	Adrenalin 0.5 mg IM	0	No PK Sample collected
	Adrenalin 0.3 mg IM	0	No PK Sample collected [a]
	Adrenalin 0.5 mg IM	0	Insufficient PK sample (<3) collected within 30 minutes

a Subject (b) (6) only had one PK sample at 360 minutes and is considered as one subject with no PK data

The baseline age and body weight of subjects for EPI 16 is shown in Table 35.

Table 35. Baseline Demographic, Trial EPI 16

Demographics	N=36
Age (years)	
Mean (SD)	37.8 (8.28)
Median	38
Minimum, maximum	20, 52
Body Weight (kg)	
Mean (SD)	73.6 (10.68)
Median	74.7
Minimum, maximum	52.6, 97.8

Source: Clinical pharmacology reviewer's analysis based on adsl.xpt for EPI 16

The baseline epinephrine concentration for Trial EPI 16 is shown in Table 36. All subjects except one in ARS-1 without NAC had a mean baseline (average of -10 min and -5 min values) <100 pg/mL.

Table 36. Baseline Epinephrine Concentrations, Trial EPI 16

	ARS-1		Adrenalin 0.3 mg		Adrenalin 0.5 mg		ARS-1 with NAC	
Time	-10 min (N=35)	-5 min (N=35)	-10 min (N=29)	-5 min (N=30)	-10 min (N=30)	-5 min (N=29)	-10 min (N=31)	-5 min (N=33)
Geometric Mean (CV%)	17.0 (92.5)	16.6 (116.8)	19.0 (74.7)	19.6 (69.3)	17.9 (72.8)	18.3 (87.4)	19.9 (69.8)	20.6 (79.8)
Median (range)	10 (10, 88.6)	10 (10, 120)	21.4 (10, 89.6)	22.25 (10, 59.1)	15.4 (10, 64.3)	10 (10, 81.5)	24.8 (10, 84.9)	23.3 (10, 103)

Source: clinical pharmacology reviewer's analysis based on adpc.xpt.xpt for EPI 16.

PK Endpoints

C_{max}, T_{max}, partial AUCs 10, 20, 30, and 60 minutes postdose (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, and AUC_{0-60})

PD Endpoints

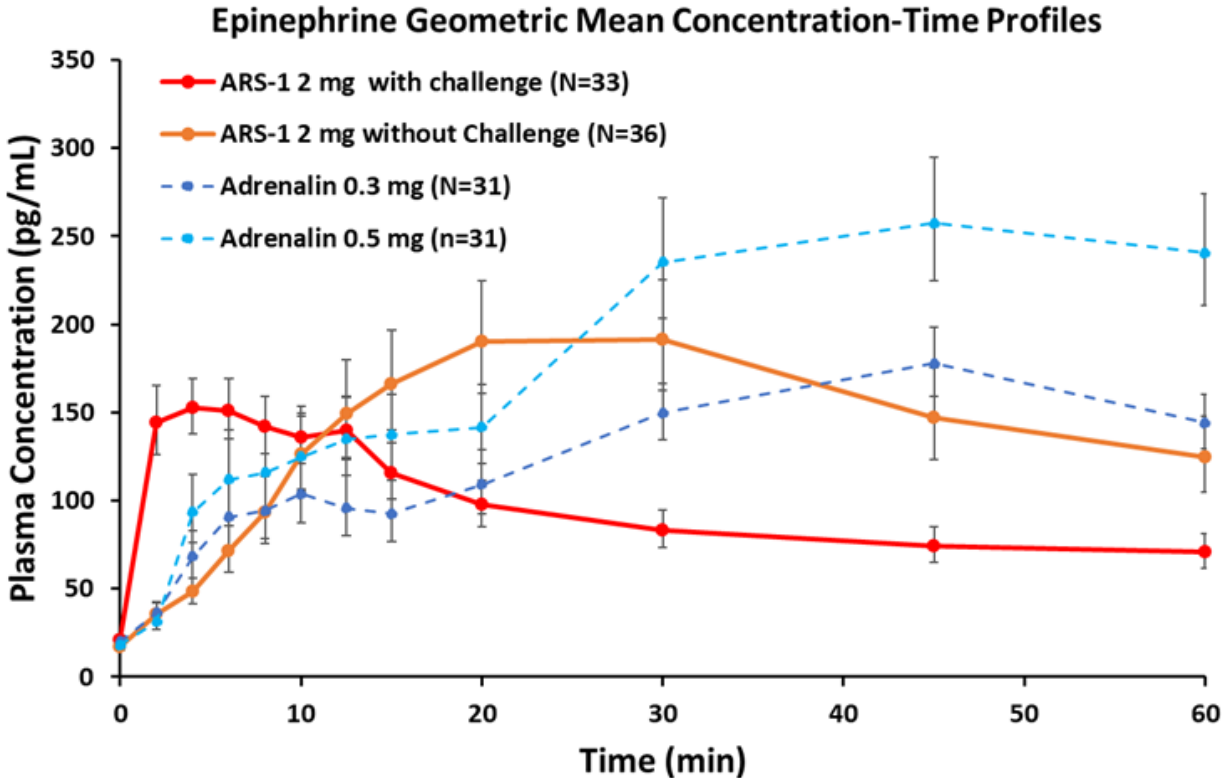
SBP, DBP, and PR change from baseline over time, especially within 60 minutes postdose.

Results

PK Results

The epinephrine concentration-time profile, PK parameters and bioequivalence assessment following single dose of ARS-1 under normal nasal condition and after nasal challenge in comparison to Adrenalin 0.3 mg or 0.5 mg are shown in Figure 31, Table 37, and Table 38, respectively.

Figure 31. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis, Trial EPI 16



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 16.
Three subjects each in the Adrenalin 0.3 mg and Adrenalin 0.5 mg arms and one subject in ARS-1 with nasal challenge arm had insufficient number of postdose samples (n <3) collected within 30 min. Two subjects in each in the Adrenalin 0.3 mg, Adrenalin 0.5 mg arm, and the ARS-1 with nasal challenge arm did not have PK data.

Table 37. PK Parameters, Trial EPI 16

	Geometric Mean (CV%)			
	ARS-1 2 mg IN w/o NAC (N=36)	**ARS-1 2 mg IN with NAC (N=33)**	**Adrenalin 0.3 mg IM (N=31)**	**Adrenalin 0.5 mg IM (N=31)**
C_{max} (pg/mL)	386.0 (90.1)	260.0 (63.5)	244.9 (61.7)	345.9 (85.5)
T_{max} (min) [a]	20	6	45	45
$AUC_{0\text{-}10\ min}$ (pg*min/mL)	736.2 (112.3)	1446.2 (57.9)	772.3 (114.6)	958.3 (113.0)
$AUC_{0\text{-}20\ min}$ (pg*min/mL)	2685.5 (98.8)	2788.8 (59.4)	1843.8 (111.2)	2452.6 (96.2)
$AUC_{0\text{-}30\ min}$ (pg*min/mL)	5078.4 (83.2)	3791.7 (60.0)	3288.3 (87.3)	4503.4 (87.2)
$AUC_{0\text{-}60\ min}$ (pg*min/mL)	10504.3 (90.9)	6354.3 (60.1)	8559.9 (62.3)	12294.2 (81.0)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 16.
Three subjects each in the Adrenalin 0.3 mg and Adrenalin 0.5 mg arms and one subject in ARS-1 with nasal challenge arm had insufficient number of postdose samples (n <3) collected within 30 min. Two subjects in each in the Adrenalin 0.3 mg, Adrenalin 0.5 mg arm, and the ARS-1 with nasal challenge arm did not have PK data.
[a] median

Table 38. Bioequivalence Assessment, Trial EPI 16

	ARS-1 2 mg with NAC (test) vs. Adrenalin 0.3 mg (reference) GMR (90% CI)	ARS-1 2 mg w/o NAC (test) vs. Adrenalin 0.3 mg (reference) GMR (90% CI)	ARS-1 2 mg with NAC (test) vs. ARS-1 2 mg w/o NAC (reference) GMR (90% CI)
C_{max} (pg/mL)	106.06 (84.32, 133.39)	155.64 (124.36, 194.79)	68.14 (54.69, 84.89)
$AUC_{0\text{-}10\ min}$ (pg*min/mL)	187.04 (134.97, 259.21)	95.32 (69.26, 131.18)	196.23 (143.40, 268.53)
$AUC_{0\text{-}20\ min}$ (pg*min/mL)	150.14 (112.74, 199.94)	144.16 (105.79, 170.26)	104.14 (79.11, 137.10)
$AUC_{0\text{-}30\ min}$ (pg*min/mL)	115.20 (91.05, 145.77)	152.97 (121.52, 192.58)	75.31 (60.10, 94.36)
$AUC_{0\text{-}60\ min}$ (pg*min/mL)	74.66 (61.09, 91.25)	122.16 (100.38, 148.66)	61.12 (50.43, 74.06)

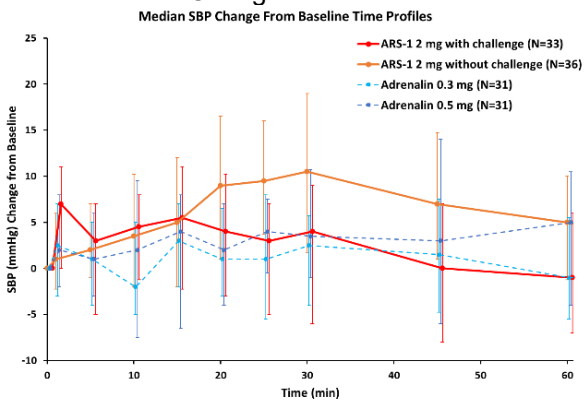
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 16.

PD Results

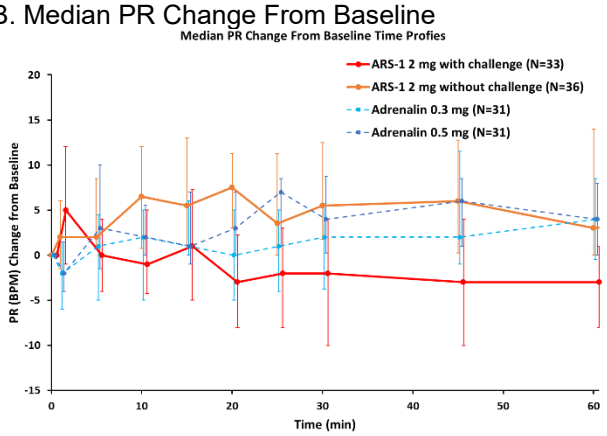
The PD responses are shown in Figure 32. The mean and median of maximum SBP change from baseline within 60 minutes and median T_{max} to reach maximum change are shown in Table 39.

Figure 32. Median PD Responses (SBP, PR, and DBP Changes From Baseline) in Subjects With Allergic Rhinitis, Trial EPI 16

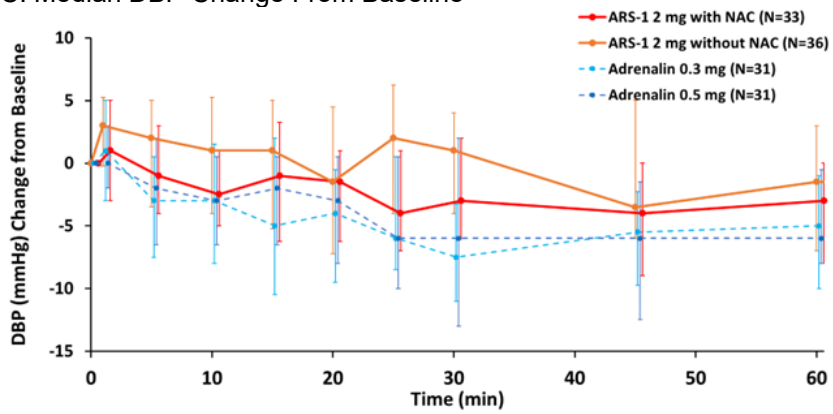
A. Median SBP Change From Baseline



B. Median PR Change From Baseline



C. Median DBP Change From Baseline



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial 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, pharmacodynamic; PK, pharmacokinetic; PR, pulse rate; SBP, systolic blood pressure

Table 39. Maximum SBP Change From Baseline in 60 Minutes in Subjects With Allergic Rhinitis, Trial EPI 16

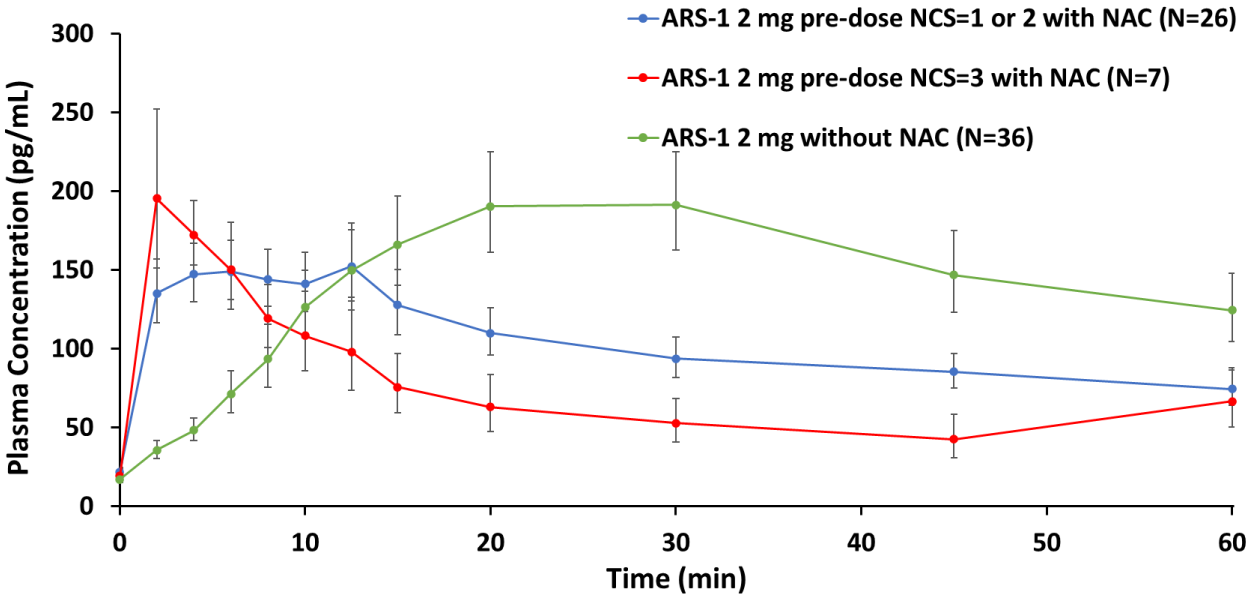
Parameter	ARS-1 Normal (N=36)	ARS-1 Challenge (N=33)	Adrenalin 0.3 mg (N=31)	Adrenalin 0.5 mg (N=31)
Mean (SD) (mmHg)	20 (17)	15 (13)	12 (9)	13 (10)
Median (range) (mmHg)	18 (-24, 88)	13 (-12, 68)	12 (-4, 28)	16 (-19, 32)
Median T_{max} (range) (min)	25 (1, 60)	10 (1, 60)	20 (1, 60)	25 (1, 60)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI16.
Subjects who were included in the PK analysis were included in the PD analysis.
Abbreviations: SBP, systolic blood pressure; Tmax, time to maximum plasma concentration

Subgroup Analyses

As nasal congestion may impact the absorption of ARS-1, a subgroup analysis was performed to evaluate the impact of predose (i.e., pre-ARS-1) nasal congested condition severity based on NCSs on PK of ARS-1, as shown in Figure 33.

Figure 33. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis Under NAC Conditions by Predose NCS Subgroup Analysis in Comparison to Without NAC, Trial EPI 16

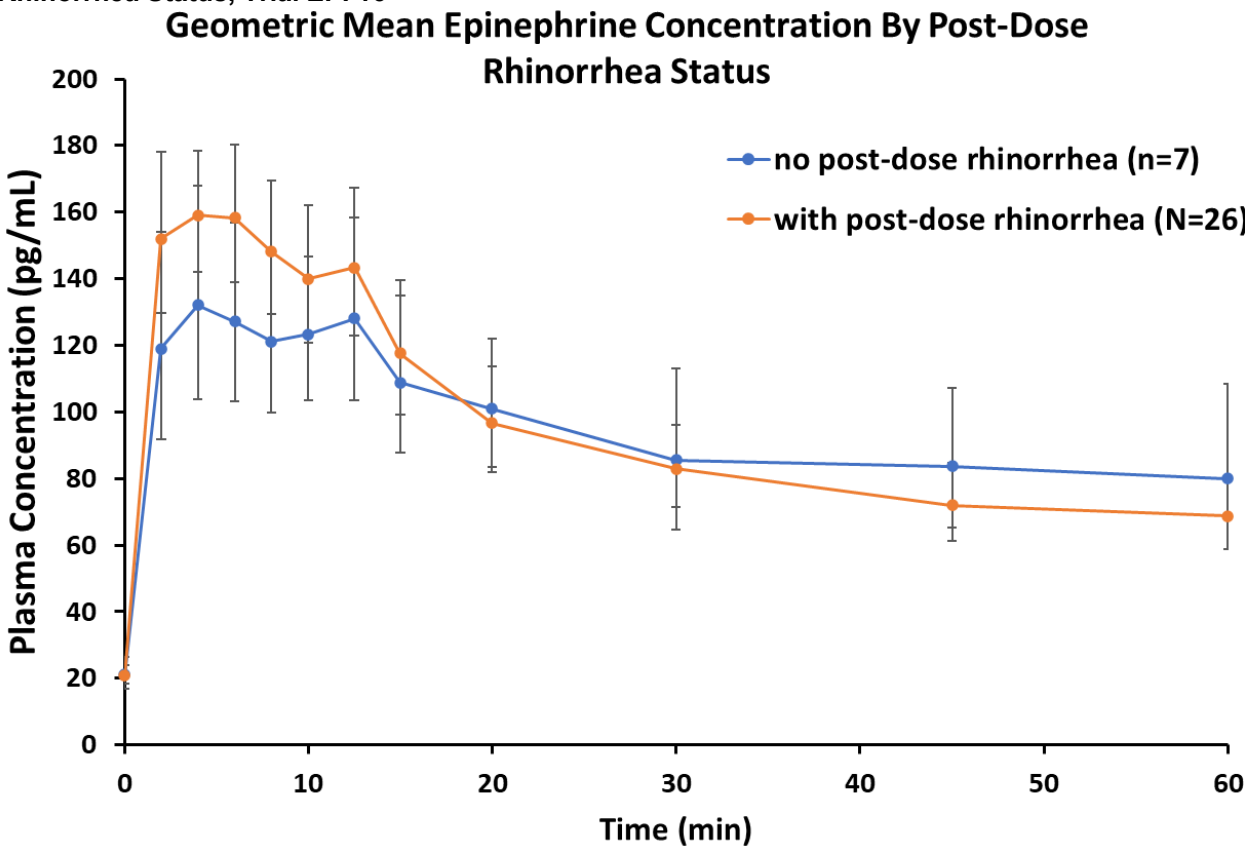


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt and adyn.xpt of Trial EPI 16. Predose refers to prior to ARS-1 administration but after nasal allergen challenge.
Abbreviations: NAC, nasal allergen challenge, NCS, nasal congestion score

It was also noted that most subjects, following NAC but prior to ARS-1 administration, experienced various degrees of rhinorrhea except two subjects. Most subjects had a rhinorrhea score of 1 or 2 before ARS-1 (N=27). Following ARS-1 treatment, only seven subjects did not report any rhinorrhea symptoms, while the rest subjects continued experiencing some degrees of rhinorrhea. As rhinorrhea may impact the continuation of systemic absorption of the drug after delivered to the nasal mucosal membrane, a subgroup analysis was performed to assess

the effect of post-ARS-1 rhinorrhea status on PK, which demonstrated that post-ARS-1 rhinorrhea did not impair epinephrine PK profile as shown in Figure 34.

Figure 34. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis Under Nasal Allergen Challenge Conditions by Post-ARS-1 Rhinorrhea Status, Trial EPI 16



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt and adyn.xpt of Trial EPI 16.

Conclusion

PK

- The epinephrine PK profile demonstrated an initial faster absorption phase followed by a faster decline phase. The geometric mean plasma epinephrine concentrations for ARS-1 under NAC conditions is lower than ARS-1 under normal nasal condition 10 minutes postdose and lower than Adrenalin 0.5 mg and 0.3 mg arms after around 10 and 20 minutes postdose, respectively.
- The PK of epinephrine in subjects with severe nasal congestion (NCS =3) prior to ARS-1 administration had a slightly faster absorption rate followed by a faster decline when comparing to subjects with mild to moderate nasal congestion (NCS =1 or 2).
- The postdose rhinorrhea does not appear to impact the PK of ARS-1 following NAC.

PD

- The median PD responses (median SBP and PR change from baseline) for ARS-1 following NAC is initially higher followed by a decline after around 5 to 15 minutes postdose when compared to ARS-1 without NAC.
- The diastolic blood pressure profile for ARS-1 following NAC is less stable from baseline than ARS-1 under normal nasal condition.
- The median SBP response for ARS-1 with NAC was initially higher than the median SBP response for Adrenalin 0.3 mg through 20 minutes, after which the median SBP response for ARS-1 with NAC became comparable to the Adrenalin 0.3 mg through 60 minutes postdose.
- The median PR response for ARS-1 with NAC was initially higher than Adrenalin 0.3 mg during around first 5 minutes postdose but then was numerically lower than the median PR response for Adrenalin 0.3 mg through the 60 minutes postdose.

15.4.1.3. Trial EPI 17

Trial Type

Phase 1 single-dose self-administration PK trial in healthy subjects

Trial Dates

April 8, 2022, to May 14, 2022

Formulation

- ARS-1 2 mg (Lot: 210928A)
- Adrenalin 0.3 mg (Lot: 36224)

Title

A Two-Period, Two-Treatment, Randomized Crossover Trial of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self- Administration of Epinephrine With Intranasal ARS-1 as compared to IM injection in Subjects with Type I Allergies

Objective

The primary objectives were to assess the comparative bioavailability of epinephrine after self-administration of ARS-1 2 mg IN or trial staff-administered IM injection in subjects who have Type I allergy conditions and to evaluate the comparative PD response based on SBP, DBP and PR using an ABPM device between the two treatment groups.

The secondary objectives were to assess the dosing error rates with ARS-1 after self-administration, the PK of ARS-1 2 mg following significant dosing error by subjects who self-administered, and the safety and tolerability of ARS-1 and Adrenalin.

Trial Design and Method

This was a phase 1, single-dose, two-treatment, two-period, randomized crossover trial in subjects with Type 1 allergies. Subjects were randomized to receive the following treatments in each period:

- A single dose of ARS-1 2 mg IN self-administered into on naris (right or left)
- A single dose of Adrenalin 0.3 mg IM staff-administered int o right thigh

Subject received a training on ARS-1 during the screening period between -28 to -7 days prior to dosing. No additional training, instruction or direct assistance in dosing was provided to subjects at the time of dosing. Prior to self-administration of ARS-1, a scenario was provided to the subjects to pretend they were experiencing a severe allergic reaction and provided the ARS-1 in its secondary blister packaging with Quick Reference Guide (QRG) on the back of the blister, as an end user would carry it without any additional instruction. The subject then proceeded to self-administer ARS-1 without assistance from trial personnel but was permitted to review any product labeling on the device or secondary packaging prior to administration. The subject was only allowed up to 5 minutes to self-administer after the end of scenario given by the trial personnel. If a subject was not able to dose within the 5-minute period, he/she discontinued that treatment. Subjects were video recorded from the time the scenario was given until after dosing. Dosing-related errors for ARS-1 were evaluated.

Subjects were required to remain in a seated position 60 minutes prior to dosing and 120 minutes post dosing. Subjects were encouraged to use the restroom before the trial period but no later than 30 minutes before dosing so that they were sitting relaxed with back supported, legs uncrossed, and upper arm bared (slight recline for comfort is permitted) for at least 20 minutes before PK sampling and start of blood pressure measuring. TNSS was assessed predose in each treatment period. Prior to treatment of ARS-1, only four subjects were noted with NCS =1 at baseline.

PK blood samples for measurement of epinephrine concentrations were collected predose (at -10 and -5 minutes) and serially at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240 and 360 minutes postdose. Actual blood collection times was permitted to vary as follows: 1) ±1 minute for the -10 to 20 minutes samples, 2) ±2 minutes for the 30 to 90 minutes samples, and 3) ±5 minutes for the 120 to 360 minutes samples. Epinephrine plasma concentration data were analyzed using noncompartmental method.

Human plasma samples obtained during the trial were analyzed for epinephrine concentrations using a validated liquid chromatography with tandem mass spectrometry methods [MVI-150-20] at (b) (4) The lower limit of quantification for epinephrine was 11.03 pg/mL.

Pharmacodynamic measurements included SBP, DBP, and PR after each dosing arm using an ABPM device at baseline, predose each treatment period (at -10 and -5 minutes) and at 1, 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes after dosing.

Protocol Deviation

During the trial, there were 42 protocol deviations over 21 subjects (PK or PD sampling not done in necessary window), as shown in Table 40. Samples deviated from predefined window were included in the datasets. As PK and PD samples were collected following an intensive sampling schedule for every 2 to 15 minutes with allowed window between ±1 to ±5 minutes during the first 1 hour postdose, the reported deviation ranging from several seconds to around 5 minutes from predefined sampling collection window in first 1 hour is not expected to have a significant impact on the PK and PD analyses.

Table 40. Protocol Deviations, Trial EPI 17

Subject	Deviation
(b) (6)	Prothrombin Time not done for all subjects at baseline.
	30-minute pulse/blood pressure 7 seconds out of window.
	12.5-minute PK sample not obtained due to AE.
	15-minute PK sample not obtained due to AE.
	-5-minute PK sample 3 minutes out of window due to difficult venipuncture.
	12.5-minute PK sample not obtained due to difficult venipuncture.
	2, 4, 6, 8, 10-minute PK samples not obtained due to AE.
	1-Minute pulse/blood pressure 2 minutes 8 seconds out of window.
	5-Minute pulse/blood pressure 4 minutes 34 seconds out of window.
	10-Minute pulse/blood pressure 2 minutes 34 seconds out of window.
	15-minute pulse/blood pressure 1 minute 11 seconds out of window.
	-10-minute PK sample 1 minute 40 seconds out of widow due to difficult venipuncture.
	-5-minute PK sample 1 minute 27 seconds out of widow due to difficult venipuncture.
	20-minute PK sample 1 minute 4 seconds out of widow due to difficult venipuncture.
	15-minute PK sample not obtained due to difficult venipuncture.
	-10-minute PK sample 3 minutes 4 seconds out of widow due to difficult venipuncture.
	8-minute PK sample not obtained due to difficult venipuncture.
	10-minute PK sample 40 seconds out of widow due to difficult venipuncture.
	20-minute PK sample 1 min 28 seconds out of widow due to difficult venipuncture.
	60-minute PK sample 5 minutes 38 seconds out of widow due to difficult venipuncture.
	15-minute PK sample 1 minute 42 seconds out of widow due to difficult venipuncture.
	-5-minute PK sample 1 minute 7 seconds out of widow due to difficult venipuncture.
	8-minute PK sample not obtained due to difficult venipuncture.
	Pre-dose RR and temperature and 10-minute pre-dose blood pressure and pulse not done
	12.5-minute PK sample 8 seconds out of widow due to difficult venipuncture.
	60-minute pulse/blood pressure 13 seconds out of window.
	10-minute PK sample 4 seconds out of widow due to difficult venipuncture.
	PT not done
	6-minute PK sample 50 seconds out of widow due to difficult venipuncture.
	5-minute pulse/blood pressure 5 minutes 41 seconds out of window.
	5-minute pulse/blood pressure 1 minutes 1 seconds out of window.

Source: CSR EPI 17, Table 14.

Demographic

A total of 45 subjects were enrolled and received at least one dose. Subjects (b) (6) and (b) (6) did not have any PK data for both Period 1 and 2. Subjects (b) (6) and (b) (6) did not have any PK data for Period 2. These four subjects withdrew early from the trial. Subjects ranged in age from 23 to 53 years. Twenty-six subjects (57.8%) were male, and 19 subjects (42.2%) were female. Fourteen subjects (31.1%) were White, 17 subjects (37.8%) were Black or African American, six subjects (13.3%) were Asian, three subject (6.7%) were Native American or Alaska Native, one subject (2.2%) was Hawaiian or Other Pacific Islander; and four subjects (8.9%) were Other.

The baseline age and body weight for EPI 17 is shown in Table 41.

Table 41. Baseline Demographics, Trial EPI 17

	N=45
Age (years)	
Mean (SD)	39.4 (8.48)
Median	40
Minimum, maximum	23, 53
Body Weight (kg)	
Mean (SD)	81.0 (14.4)
Median	80.7
Minimum, maximum	55.8, 112.9

Source: Clinical Pharmacology Reviewer. Based on adls of Trial EPI 17.

The baseline epinephrine concentrations for EPI 17 is shown in Table 42. All subjects had mean baseline concentration (average of -10 and -5 minutes values) <100 pg/mL.

Table 42. Baseline Epinephrine Concentration, Trial EPI 17

	ARS-1 2 mg Self-administration		Adrenalin 0.3 mg Staff Administration	
Time	-10 min (N=42)	-5 min (N=42)	-10 min (N=42)	-5 min (N=42)
Geometric Mean (CV%)	25.2 (55.9)	24.2 (64.4)	28.5 (58.5)	27.7 (57.1)
Median (range)	23.3 (5.5, 93.4)	27.2 (5.5, 89.3)	28.2 (11.4, 83.6)	28.4 (5.5, 105.6)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 17.

PK Endpoints

C_{max}, T_{max}, partial AUCs 10, 20, 30, and 60 minutes postdose (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, and AUC_{0-60})

PD Endpoints

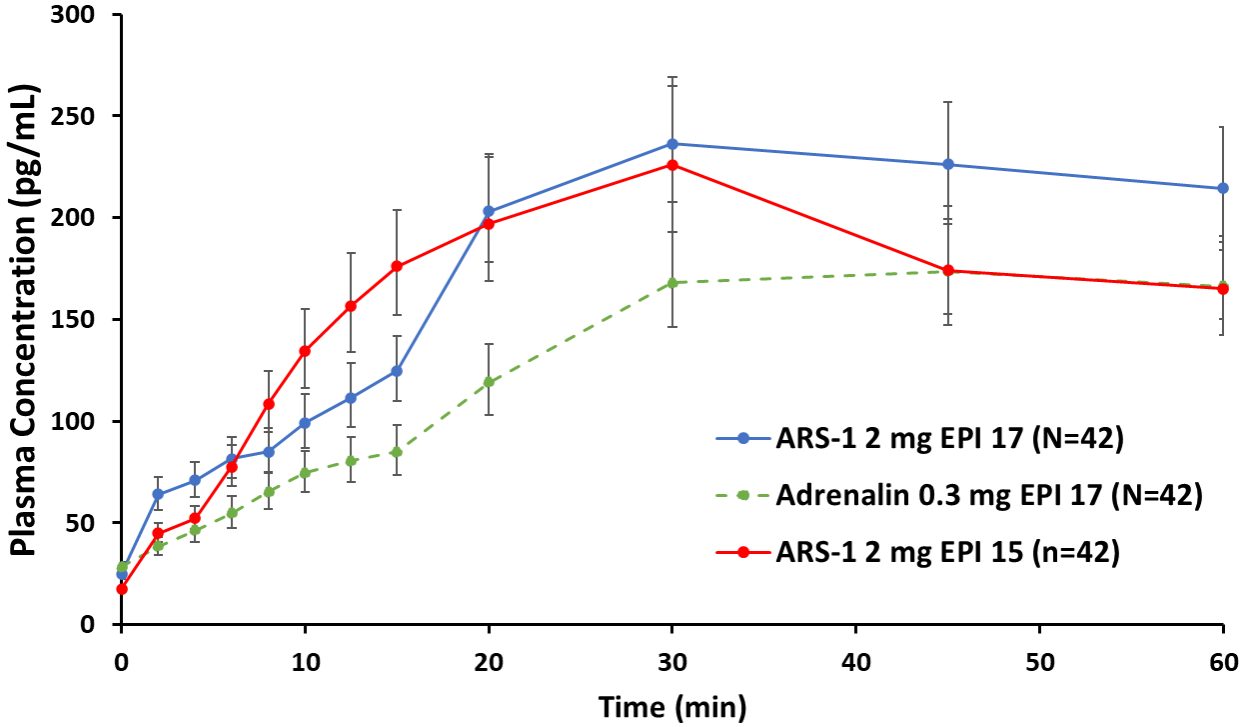
SBP, DBP and PR change from baseline over time, especially within 60 minutes postdose.

Results

PK

The concentration-time profiles for self-administered ARS-1, staff-administered Adrenalin 0.3 mg as well as staff-administered ARS-1 from Trial EPI 15 are shown in Figure 35. Trial EPI 17 did not include a staff-administered ARS-1 arm, so a cross-trial comparison was performed.

Figure 35. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Single Dose of ARS-1 (Self-Administered From EPI 17), Adrenalin 0.3 mg (Staff-Administered From EPI 17) and a Single Dose of ARS-1 (Staff-Administered From EPI 15)



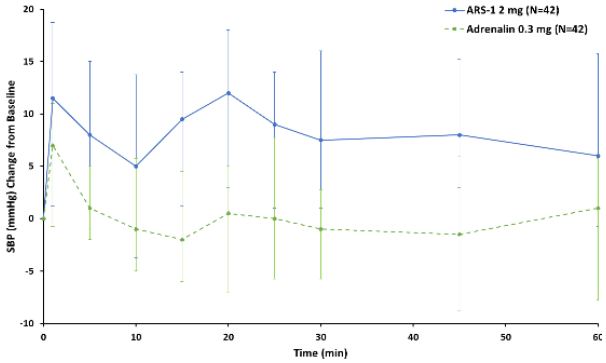
Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Trial EPI 17 and EPI 15.

PD

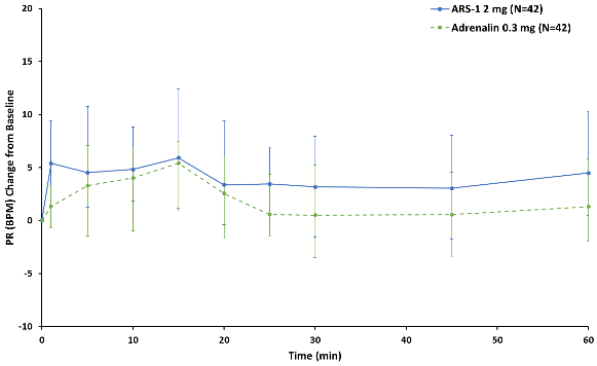
The PD responses for self-administered ARS-1 in comparison to staff-administered Adrenalin is shown in Figure 36.

Figure 36. Median PD Responses (SBP, PR and DBP Change From Baseline) Following a Single Dose of ARS-1 2 mg (Self-Administered) and Adrenalin 0.3 mg (Staff-Administered), Trial EPI 17

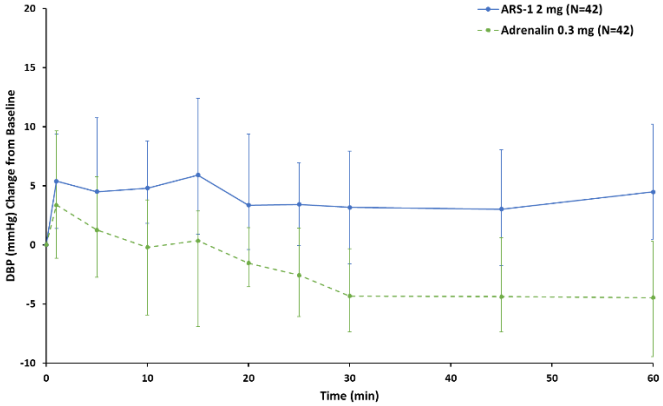
A. Median SBP Change From Baseline



B. Median PR Change From Baseline



C. Median DBP Change From Baseline



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt of Trial EPI 17
Error bars represent the 25% and 75% percentiles of the PD values.

Subgroup Analysis

Subjects who were reported with dosing error when administering ARS-1 to themselves are shown in Table 43.

Table 43. ARS-1 Self-Administration Performance Measures

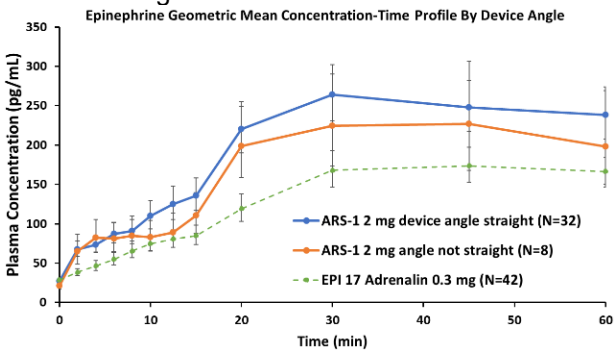
Task/Item	Percentage	Subject No.
Cannot remove from carrying case	0/42 (0%)	
Refuses to dose	0/42 (0%)	
Activates device in or on body part other than nostril	0/42 (5%)	
Prematurely activates without placing in nostril (Sprays outside of nose)	0/42 (0%)	
Attempts to use as injectable	0/42 (2%)	
Attempts to use as injectable	0/42 (2%)	
Does not attempt to press plunger	0/42 (0%)	
Does not press plunger enough to activate spray	0/42 (0%)	
Doses improperly that results in nasal drip	10/42 (23.8%)	(b) (6)
Amount of nozzle insertion		
Just tip	1/42 (2.4%)	
~1/2	8/42 (19.0%)	
~Full	31/42 (73.8%)	
N/A (Hand obstructed clear view)	2/42 (4.8%)	(b) (6)
Sneezes during or after dosing	0/42 (0%)	
Sniffs during or after dosing	29/42 (69.0%)	
Blows nose during or after dosing	0/42 (0%)	
Angle was straight in the nose		
Yes	32/42 (76.2%)	
No	8/42 (19.0%)	(b) (6)
N/A (Hand obstructed clear view)	2/42 (4.8%)	

Source: Module 1.11.3 Clinical Information Amendment dated Feb. 16, 2023

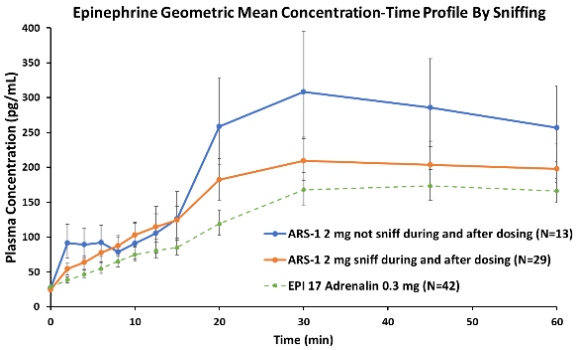
The impact of dosing error on PK is shown in Figure 37.

Figure 37. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Self-Administered Single Dose of ARS-1 2 mg by Administration Issue, Trial EPI 17

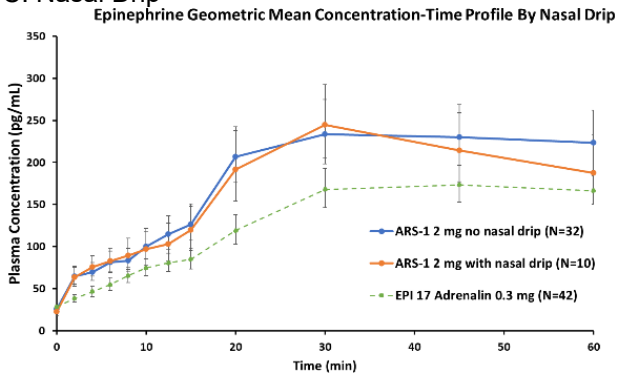
A. Device Angle[a]



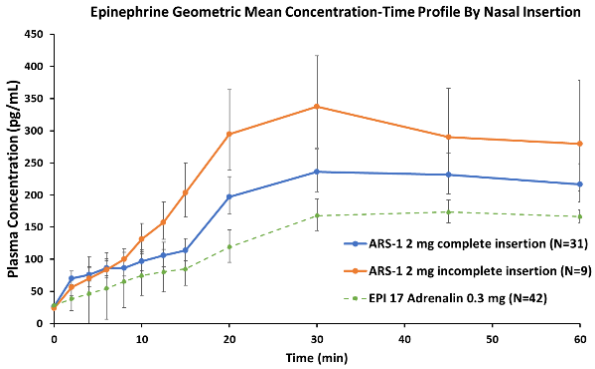
B. Sniffing During and After Dosing



C. Nasal Drip



D. Amount of Nasal Insertiona

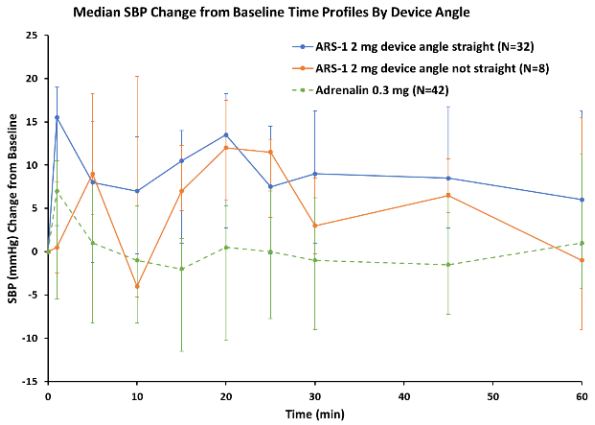


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt and adyh.xpt for Trial EPI 17.
a Two subjects were unable to have the device angle or amount of nasal insertion determined due to subjects' hand obstructing a clear view of dosing based on the CSR. They were excluded in the subgroup analysis. These two subjects had low epinephrine exposures with unclear reason.
Abbreviation: CSR, clinical trial report

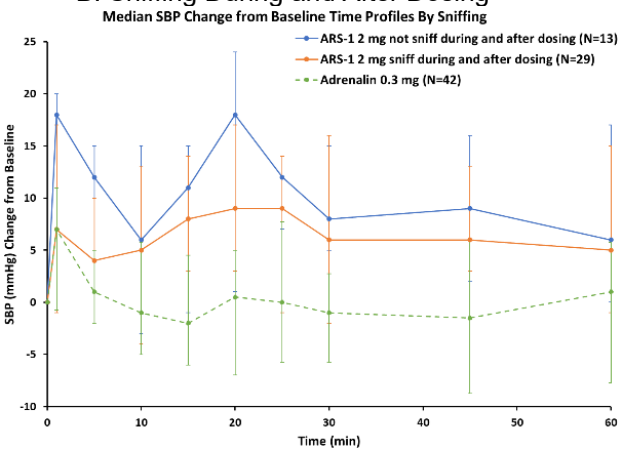
The impact of dosing error on PD (SBP change from baseline) was evaluated, as shown in Figure 38.

Figure 38. Median PD (SBP Change From Baseline) Response Following a Self-Administered a Single Dose of ARS-1 2 mg by Administration Issues (EPI 17)

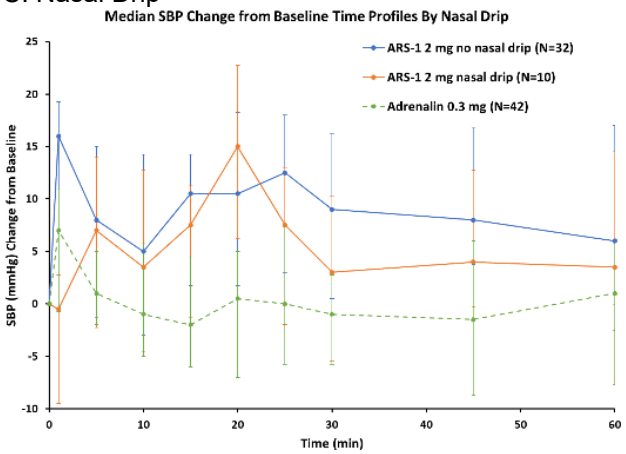
A. Device Angle[a]



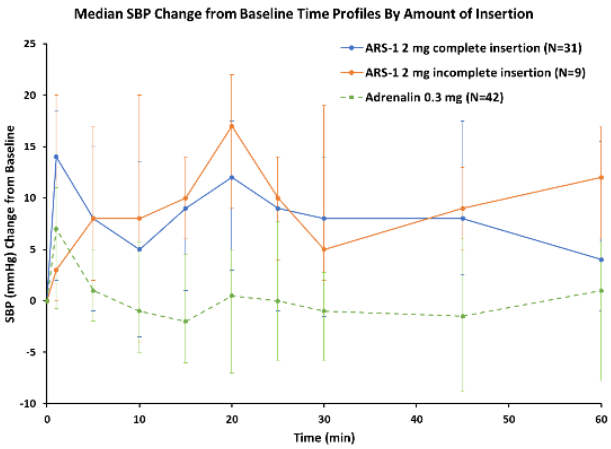
B. Sniffing During and After Dosing



C. Nasal Drip



D. Amount of Nasal Insertiona



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt and adyh.xpt for Trial EPI 17.
Error bars represent the 25% and 75% percentiles of the PD values.
a Two subjects were unable to have the device angle or amount of nasal insertion determined due to subjects' hand obstructing a clear view of dosing based on the CSR. They were excluded in the subgroup analysis. These two subjects had low epinephrine exposures with unclear reason.
Abbreviation: CSR, clinical trial report

Conclusion

PK

- The epinephrine PK profile following self-administration of a single dose ARS-1 2 mg was generally higher than that following staff-administered Adrenalin 0.3 mg.
- Based on the cross-trial comparison between EPI 17 and EPI 15, the PK profiles for ARS-1 were similar between self-administration and staff- administration.
- The subgroup analysis suggested that nasal drip, device insertion angle, and incomplete insertion of nozzle into the nose do not lower the epinephrine PK profile. However, sniffing

lowered the epinephrine PK profile to a certain extent following nasal administration. The overall interpretability of this subgroup analysis may be limited due to small sample size. However, avoiding sniffing during and after administration of ARS-1 is still recommended to be included in the labeling to reduce uncertainties regarding the potential impact on efficacy.

PD

- The PD responses (SBP and PR change from baseline) were greater with self-administered ARS-1 compared to Adrenalin.
- The subgroup analysis suggested that sniffing also lowered epinephrine median PD profile (SBP change from baseline) for ARS-1. The overall interpretability of this subgroup analysis may be limited due to small sample size.

15.4.1.4. Trial EPI 10

Trial Type

Phase 1 single-dose PK trial in pediatric subjects with Type 1 allergies

Trial Dates

July 17, 2020, to March 15, 2021

Formulation

- ARS-1 0.65 mg/0.25% DDM (Lot: 201248A)
- ARS-1 0.65 mg/0.35% DDM (Lot: 202260A)
- ARS-1 1 mg/0.25% DDM (Lot: 201484A)
- ARS-1 1 mg/0.275% DDM (Lot: 211312A)
- ARS-1 2 mg/0.275% DDM (Lot: 210928A)—to-be marketed formulation

Title

A Single-Period, Single-Dose Trial of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Pediatric Subjects with Systemic Allergies (EPI 10)

Objective

The primary objectives were to assess the PK of epinephrine after IN administration of 0.65 mg, 1.0 mg, or 2.0-mg dose of ARS-1 in pediatric allergy subjects and to evaluate the PD response based on PR and BP using an ABPM device after IN administration of 0.65 mg, 1.0 mg, or 2.0-mg dose of ARS-1 in pediatric Type I allergy subjects.

Trial Design

This was a Phase 1, single-dose, single-treatment PK trial in pediatric allergy subjects. Each subject received one dose of ARS-1 based on body weight:

- 15 to <30 kg

– A single dose of 0.65 mg ARS-1 IN in the left naris
– A single dose of 1 mg ARS-1 IN in the left naris

- 30 kg or greater:

– A single dose of 1 mg ARS-1 in the left naris
– A single dose of 2 mg ARS-1 in the left naris

Subjects were dosed with ARS-1 after resting semisupine for at least 30 minutes prior to dosing and remained in a semisupine position with minimal stimulation for 120 minutes after dosing.

PK blood samples for measurement of epinephrine concentrations were collected predose (at -10 and -5 minutes) and serially 2.5, 5, 7.5,10, 12.5, 15, 20, 30, 45, 60, 90, and 120 minutes postdose. Actual blood collection times were permitted to vary as follows: 1) ±1 minute for the -10 to 20 minutes samples, 2) ±2 minutes for the 30 to 90 minutes samples, and 3) ±5 minutes for the 120 minutes sample. Epinephrine plasma concentration data were analyzed using noncompartmental method.

Human plasma samples obtained during the trial were analyzed for epinephrine concentrations using a validated liquid chromatography with tandem mass spectrometry methods (ATM-2394 and ATM-2662) at (b) (4) The lower limit of quantification for epinephrine was 20 pg/mL.

Pharmacodynamic measurements included SBP, DBP, and PR after each dosing arm using an ABPM device at baseline, predose each treatment period (at -10 and -5 minutes) and at 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 minutes after dosing.

Of note, because the trial in children 15 to <30 kg is currently ongoing, this review only covers the results from children ≥30 kg.

Protocol Deviation

As of the interim analysis cutoff date there were 80 protocol deviations over 30 subjects (30 PK samples and 22 PD samples were affected). Samples collected outside windows were included in the datasets. As only up to ~4% samples are affected and intensive sampling with narrow predefined window was adopted during the first hour postdose, the deviations are not expected to have a significant impact on the PK and PD analyses.

A discrepancy was noted between the trial protocol and PK dataset for EPI 10 in terms of body weight groups, as the body weight groups in the dataset are 15 to 30 kg and >30 kg.

Demographic

As of the interim analysis cutoff date, a total of 57 subjects were enrolled in the trial and received at least one dose of the trial drug. Among these subjects, 42 subjects had a body weight 30 kg or greater were treated with ARS-1 1 mg (N=26) or 2 mg (N=16). Of note, 10 subjects who were treated with a 1-mg dose were re-enrolled to receive a 2-mg dose after at least 1 year. One subject (b) (6)) who were planned to be enrolled for 2 mg received 1 mg by incidence. As a result, this subject was actually treated with 1 mg twice separated by 1 year. Overall, there were only 30 unique subjects who weighed ≥30 kg evaluated with either 1 mg or 2 mg of ARS-1 (14 and 6 subjects treated only with 1 mg or 2 mg, respectively, and 10 subjects treated with both 1 mg and 2 mg separated by at least 1 year).

For PK analysis, both PK data following the two treatments of 1 mg from the subject (b) (6) who received the second 1-mg dose by incidence were included. In addition, another subject (b) (6) who weighed ≥30 kg that received a 1-mg dose had all PK samples below the limit of quantification, per Applicant, and was not included in the PK dataset. Thus, only 25 subjects (24 unique subjects) in this dose group were included in the PK analysis.

Subjects weight ≥30 kg ranged in age from 8 to 17 years with a median of 13 years. The baseline demographic of completed subjects is shown in Table 44. Thirty-two subjects (56.1%) were male, and 25 subjects (43.9%) were female. Forty-two subjects (73.7%) were White, ten subjects (17.5%) were Black or African American, and five subjects (8.8%) were Asian. There were two subjects in the 2-mg dosing group who had a body weight ≥30 kg but <33 kg, while the other subjects had a body weight >45 kg.

Table 44. Baseline Demographic of Completed Subjects, Trial EPI 10

	ARS-1 1 mg DDM 0.25% (≥30 kg) (N=25)[a]	ARS-1 2 mg DDM 0.275% (≥30 kg) (N=16)[a]
Age (years)		
Mean (SD)	13.3 (2.2)	14.4 (2.5)
Median (range)	13 (9 to 17)	15 (8 to 17)
Weight (kg)		
Mean (SD)	55.4 (16.5)	56.4 (14.3)
Median (range)	53.2 (31.5 to 94.8)	54.2 (30.8 to 86)

Source: Reviewer's analysis based on adsl.xpt for Trial EPI 10.
a Subject (b) (6) with no PK data was not included.
b 10 subjects were previously treatment 1 mg were re-enrolled to 2 mg after at least 1 year.
Abbreviations: DDM, n-dodecyl-β-D-maltoside; SD, standard deviation

The baseline epinephrine concentration for EPI 10 is shown in Table 45. All subjects except two [one subject each in 2 mg ARS-1 (30 kg or greater) and 0.65 mg of ARS-1 (15 to <30 kg)] had baseline <100 pg/mL.

Table 45. Baseline Epinephrine Concentration, Trial EPI 10

	ARS-1 1 mg DDM 0.25% (≥30 kg) (N=25)	ARS-1 2 mg DDM 0.275% (≥30 kg) (N=16)
Geometric mean (CV%)	21.4 (54.5)	21.9 (196.8)
Median (range)	27.6 (10, 51.5)	23.1 (10, 336)

Source: Reviewer's analysis based on adpc.xpt for Trial EPI 10.
Abbreviations: DDM, n-dodecyl-β-D-maltoside

PK Endpoints

C_{max}, T_{max}, partial AUCs 10, 20, 30, and 60 minutes postdose (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, and AUC_{0-60})

PD Endpoints

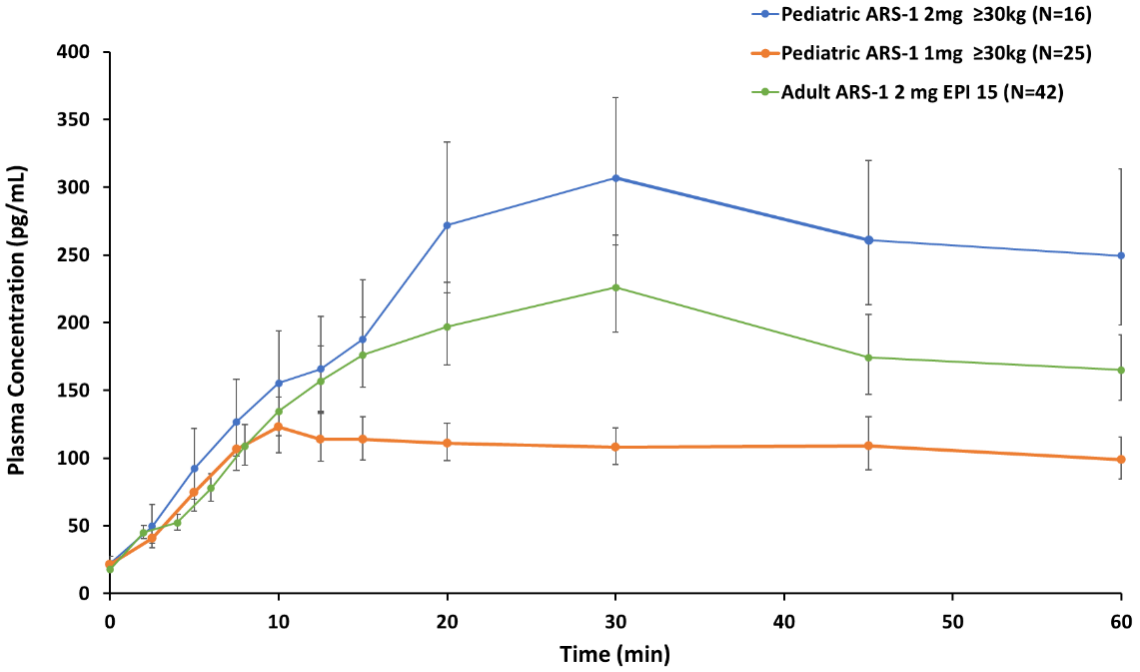
SBP, DBP and PR change from baseline over time, especially within 60 minutes postdose.

Results

PK

The PK profiles of pediatric subjects with body weight ≥30 kg who received 1 or 2 mg of ARS-1 in comparison to that of adults from EPI 15 are shown in Figure 39. The PK parameters were reported in Table 46. The epinephrine PK distribution relative to adult reference range is compared in Table 47.

Figure 39. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥30 kg in Trial EPI 10 and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Trial EPI 15



Source: Reviewer's analysis based on adsl.xpt for Trial EPI 10 and EPI 15.

Table 46. PK Parameters Following a Single Dose ARS-1 in Pediatric Subjects Weighing ≥30 kg

	Geometric Mean (CV%)	
	ARS-1 2 mg DDM 0.275% (N=16)	**ARS-1 1 mg DDM 0.25% (N=25)**
C_{max} (pg/mL)	433.1 (79.5)	203.3 (78.0)
T_{max} (min) [a]	25	20
AUC_{0-10} (pg*min/mL)	988.5 (111.7)	795.5 (96.1)
AUC_{0-20} (pg*min/mL)	3147.4 (89.9)	1996.5 (81.4)
AUC_{0-30} (pg*min/mL)	6230.5 (78.3)	3202.1 (70.6)
AUC_{0-60} (pg*min/mL)	15125.6 (75.6)	6883.4 (68.6)

Source: Reviewer's analysis based on adsl.xpt for Trial EPI 10.
a median
Abbreviations: AUC, area under the curve; DDM, n-dodecyl-β-D-maltoside

Table 47. Distribution of Epinephrine PK Relative to Adult Reference Range

		Reference: 5th to 95th Range of Geometric Mean	Number (%) of Pediatric Subjects		
Dose Group	**PK Parameters**	**Adult ARS-1 2 mg (EPI 15)**	**Lower**	**Within**	**Higher**
2 mg, 30 kg or greater (N=16)	C_{max} (pg/mL)	67.2 to 1190.5	0 (0%)	15 (93.8%)	1 (6.2%)
	AUC_{0-10} (pg*min/mL)	210.9 to 3504.4	0 (0%)	15 (93.8%)	1 (6.2%)
	AUC_{0-20} (pg*min/mL)	542.9 to 13502.3	0 (0%)	16 (100%)	0 (0%)
	AUC_{0-30} (pg*min/mL)	853.2 to 21343.3	0 (0%)	15 (93.8%)	1 (6.2%)
	AUC_{0-60} (pg*min/mL)	2014.3 to 41885.1	0 (0%)	14 (87.5%)	2 (12.5%)

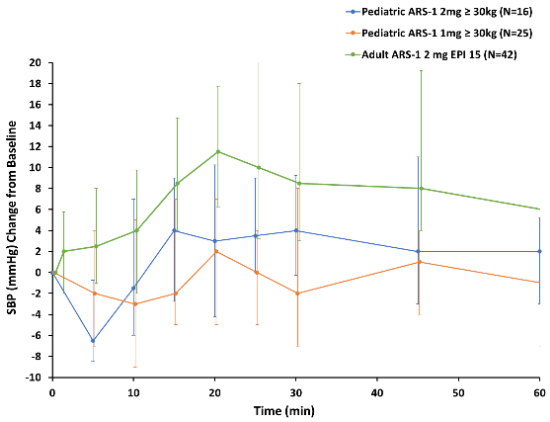
Source: Reviewer's analysis based on adpc.xpt for Trial EPI 10 and Trial EPI 15

PD

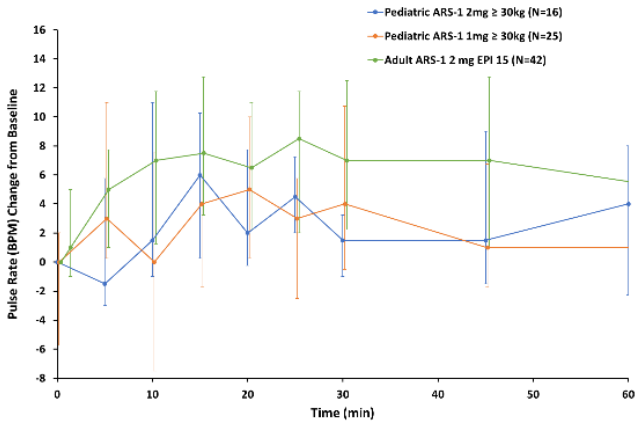
The PD responses in pediatric subjects in comparison to adults from EPI 15 is shown in Figure 40.

Figure 40. Median PD Responses (SBP, PR and DBP Change From Baseline) Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥30 kg From Trial EPI 10 and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Trial EPI 15

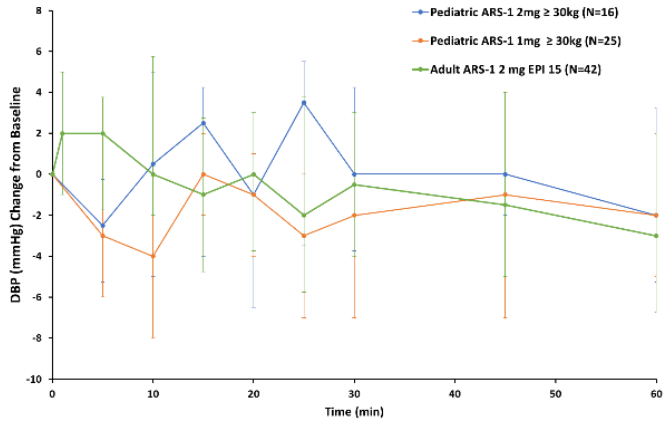
A. Median SBP Change From Baseline



B. Median PR Change From Baseline



C. Median DBP Change From Baseline

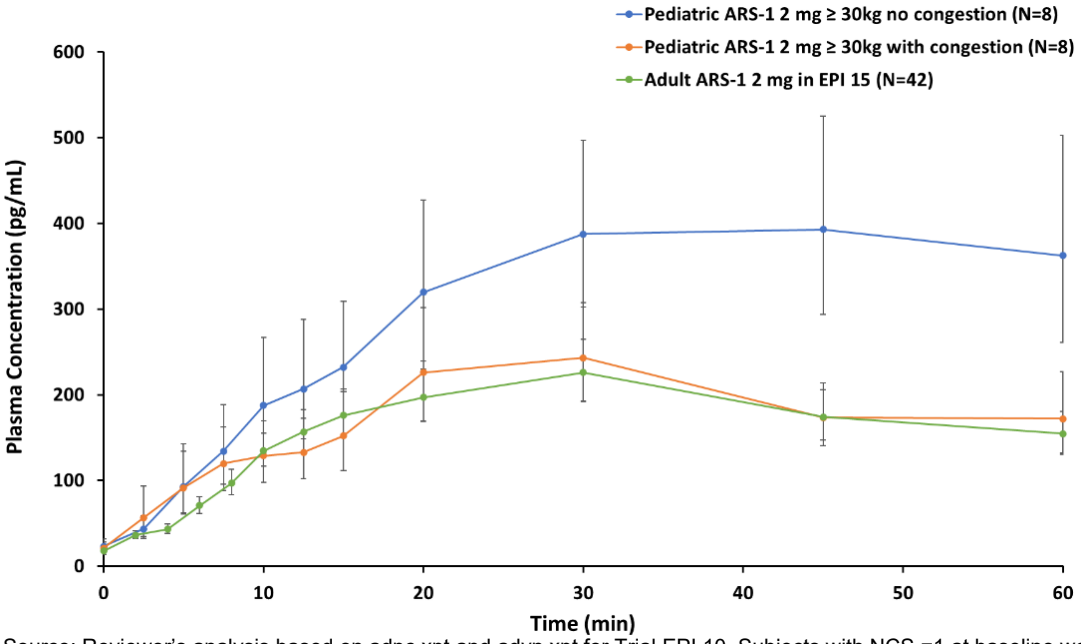


Source: Reviewer's analysis based on adxd.xpt for Trial EPI 10 and Trial EPI 15
Error bars represent the 25% and 75% percentiles of the PD values.

Subgroup Analysis

In 2 mg of ARS-1 group, half of pediatric subjects (N=8) had baseline NCS =1, while others had baseline NCS =0. The impact of baseline nasal congestion on PK and PD is shown in Figure 41 and Figure 42, respectively.

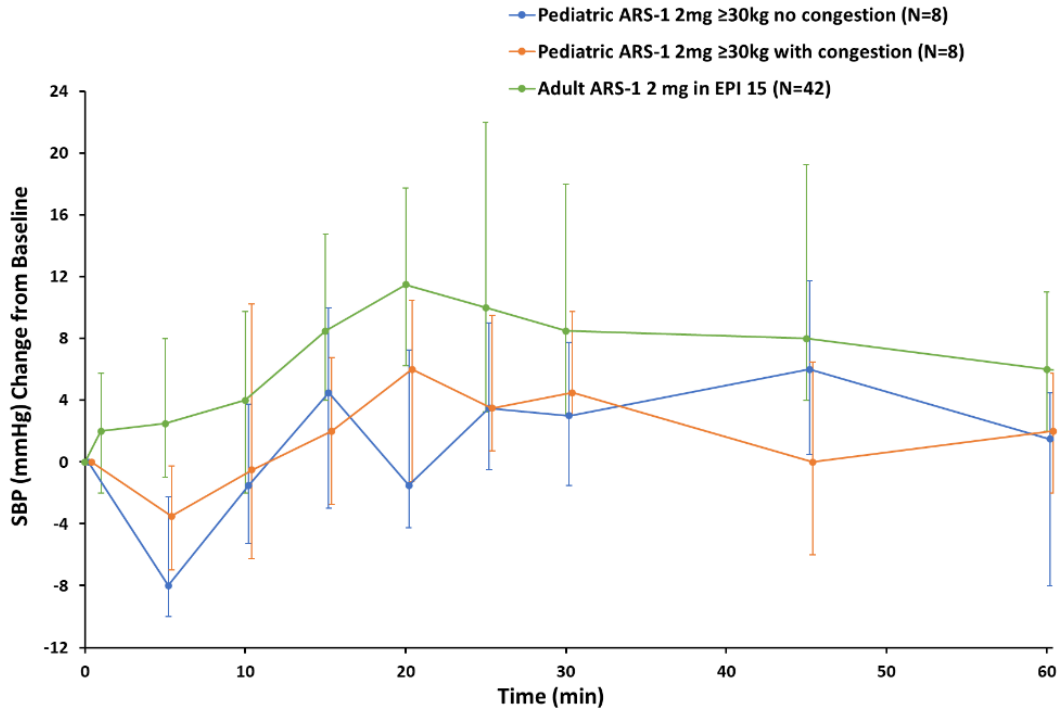
Figure 41. Epinephrine Geometric Mean (±Standard Error) Concentration of ARS-1 2 mg in Pediatric Subjects Weighing 30 kg or Greater by Nasal Congestion in Trial EPI 10 vs. a Single Dose of ARS-1 2 mg in Adults in Trial EPI 15



Source: Reviewer's analysis based on adpc.xpt and adyn.xpt for Trial EPI 10. Subjects with NCS =1 at baseline were (b) (6) (b) (6)

Abbreviation: NCS, nasal congestion score

Figure 42. Median PD Response (SBP Change From Baseline) Following a Single Dose of ARS-1 2 mg in Pediatric Subjects Weighing 30 kg or Greater by Nasal Congestion in EPI 10 vs. a Single Dose of ARS-1 2 mg in Adults in EPI 15



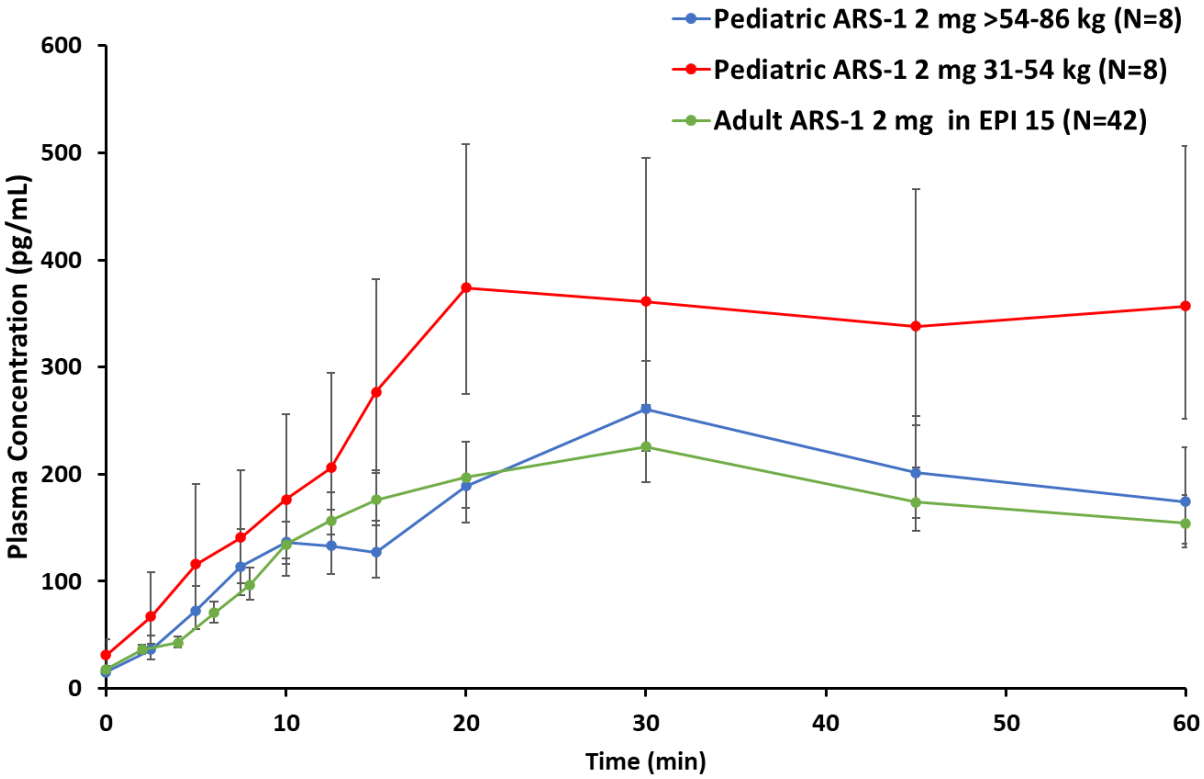
Source: Reviewer's analysis based on adxd.xpt and adyn.xpt for Trial EPI 10. Subjects with NCS =1 at baseline were (b) (6) (b) (6)

Error bars represent the 25% and 75% percentiles of the PD values.

Abbreviation: NCS, nasal congestion score

The impact of body weight on PK of ARS-1 2 mg is shown in Figure 43.

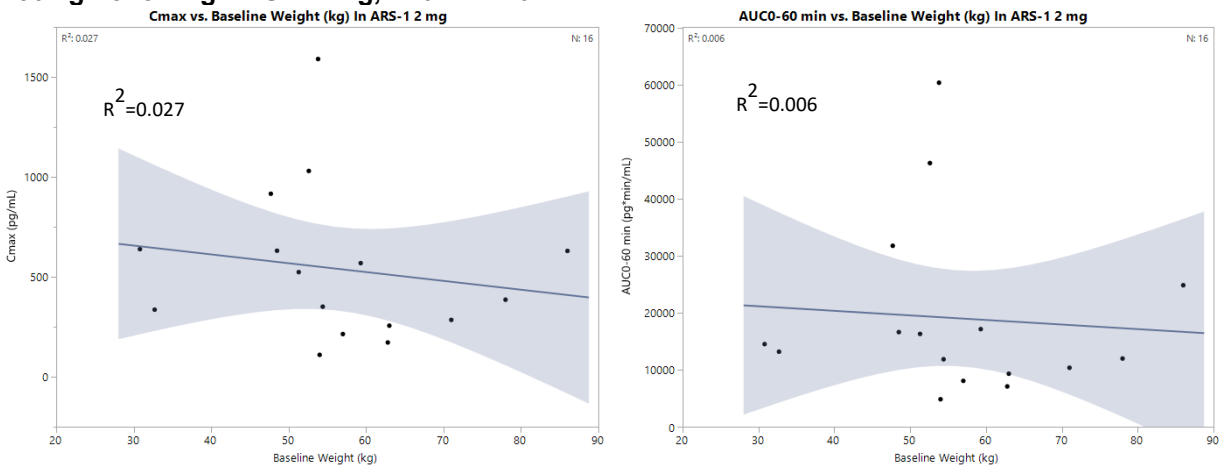
Figure 43. Geometric Mean (±Standard Error) Epinephrine Concentration of ARS-1 2 mg in Pediatric Subjects Weighing 30 kg or Greater by Body Weight in Trial EPI 10 vs. Adult, Trial EPI 15



Source: Reviewer's analysis based on adpc.xpt for Trial EPI 10

The observed C_{max} and $AUC_{0\text{-}60min}$ versus baseline body weight in pediatric subjects receiving ARS-1 2 mg is shown in Figure 44.

Figure 44. Observed Cmax and AUC0-60 min vs. Baseline Body Weight in Pediatric Subjects ≥30 kg Following ARS-1 2 mg, Trial EPI 10



Source: Reviewer's analysis based on adpc.xpt and adsl.xpt for Trial EPI 10.Blue Line: linear regression line; Shade: 95% confidence interval. The three subjects with C_{max} and $AUC_{0\text{-}60\ min}$ outside 95% confidence intervals were Subject (b) (6) and (b) (6)

A linear regression model demonstrates a weak relationship between the body weight and epinephrine C_{max}/$AUC_{0\text{-}60\ min}$ in the studied pediatric population.

Conclusion

PK

- Pediatric subjects ≥30 kg following 2 mg ARS-1 have similar to slightly higher epinephrine PK profiles compared to that of adults.
- Nasal congestion also appears to be associated with lower epinephrine concentrations following ARS-1 administration. The pediatric PK profiles of 2 mg ARS-1 with baseline NCS =1 is similar to that of adults with same dose.

PD

- The pediatric SBP and PR responses are slightly lower compared to adults.
- Following a single dose of ARS-1 2 mg, pediatric subjects with baseline NCS =1 had similar SBP response compared to that of subjects whose baseline NCS =0.

15.4.2. Bioanalytical Assay Review

The bioanalytical methods used for evaluating plasma epinephrine PK samples in Trial EPI 15, EPI 16, EPI 17 and EPI 10 are shown in Table 48. Two different methods were used to evaluate samples from EPI 15 and EPI 10. A cross validation was performed between methods ATM-2648 and ATM-2662 used in EPI 15, while the change between ATM-2394 and ATM-2648 are deemed minor and no cross-validation is needed. Therefore, method ATM-2394 and ATM-2662 used in EPI 10 are considered comparable given that cross-validation has been conducted between ATM-2648 and ATM-2662.

Table 48. Summary of Bioanalytical Methods for Each Trial

Trial	Bioanalytical Method
EPI 15	ATM-2648, ATM-2662
EPI 16	ATM-2662
EPI 17	(b) (4) 0058-22
EPI 10	ATM-2394, ATM-2662

Source: reviewer generated table.

A request for Biopharmaceutical Inspection for both analytical and clinical sites for Trial EPI 15, 17 and 10 was submitted to OSIS dated Sep. 22, 2022. Data from these studies were determined reliable. See inspection details in Section 4.

The initial validated Liquid chromatography- with tandem mass spectrometry (LC-MS-MS) method was ATM-2220 from (b) (4) This method was modified to ATM-2394, ATM-2648 and ATM-2662 and were used to assess PK samples from Trials EPI 15, EPI 16, and EPI 10. The lifecycle of the bioanalytical methods in (b) (4) is shown in Table 49.

Table 49. Summary of Life Cycle Information of Bioanalytical Methods Developed in (b) (4)

Report	DCN_ 1004490	DCN_ 1004490_am4	DCN_ 1004490_am9	DCN_ 1004490_am10	Trial EPI 15 (DCN_5029768)	Trial EPI 16 (DCN_5035445)	Trial EPI 10 (DCN_4010308)
Release year	Feb. 1, 2017	July 9, 2018	July 14 2022	July 15, 2022	August 2022	August 1, 2022	July 19, 2022
Validation type	Original method	Partial validation	Partial Validation	Partial Validation	N/A	N/A	N/A
Method ID	ATM-2220	ATM-2394	ATM-2648	ATM-2662	ATM-2648 and ATM-2662	ATM-2662	ATM-2394 and ATM-2662
CRO	(b) (4)						
Bioanalytical method	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS	LC-MS-MS
Matrix	Acidified K2-EDTA human plasma (every 40 mL of plasma, 2 mL HCl solution added) This acidification process introduced a 5.00% dilution of the samples	Acidified K2-EDTA human plasma (every 40 mL of plasma, 2 mL HCl solution added) This acidification process introduced a 5.00% dilution of the samples	Acidified K2-EDTA human plasma (every 40 mL of plasma, 2 mL HCl solution added)	Acidified K2-EDTA human plasma (every 40 mL of plasma, 2 mL HCl solution added)	Acidified K2-EDTA human plasma	Acidified K2-EDTA human plasma	Acidified K2-EDTA human plasma
Analyte	Epinephrine	Epinephrine	Epinephrine	Epinephrine	Epinephrine	Epinephrine	Epinephrine

Report	DCN_ 1004490	DCN_ 1004490_am4	DCN_ 1004490_am9	DCN_ 1004490_am10	Trial EPI 15 (DCN_5029768)	Trial EPI 16 (DCN_5035445)	Trial EPI 10 (DCN_4010308)
Stock reference & lot (expiry)	Epinephrine Bitartrate 55 and 80 mcg/mL in Hydrochloric Acid Solution (0.1 N in water) (expiry: 86 days for 55 mcg/mL and 54 days for 80 mcg/mL refrigerated 1 to 11°C)	Epinephrine Bitartrate 55 mcg/mL and 80 mcg/mL in Hydrochloric Acid Solution (0.1 N in water) (expiry: 86 days for 55 mcg/mL and 54 days for 80 mcg/mL refrigerated)	Epinephrine bitartrate 55 mcg/mL in HCl 0.1 N in water Epinephrine-D6 40 mcg/mL in HCl 0.1 N in water (expiration: 5 weeks)	Epinephrine bitartrate 55 mcg/mL in HCl 0.1 N in water Epinephrine-D6 40 mcg/mL in HCl 0.1 N in water (expiration: 5 weeks)	Epinephrine bitartrate 55 mcg/mL in HCl 0.1 N in water (expiry: 54 days) Epinephrine-D6 40 mcg/mL in HCl 0.1 N in water (expiry: 86 days) Epinephrine-D6 40 mcg/mL in 0.1% formic acid (expiry:11 days)	Epinephrine bitartrate 55 mcg/mL in HCl 0.1 N in water (expiry: 54 days) Epinephrine-D6 40 mcg/mL in HCl 0.1 N in water (expiry: 86 days)	Epinephrine Bitartrate 55 mcg/mL and 27.5 mcg/mL in Hydrochloric Acid Solution (0.1 N in Water) (expiry: 86 days for 55 mcg/mL and 54 days for 27.5 mcg/mL) Epinephrine-D6 40 mcg/mL in HCl 0.1 N in water (expiry: 86 days)
Calibration range (LLOQ-ULOQ)	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL	20.0 to 4000 pg/mL
Matrix/Trial population	---	---	---	---	Healthy subject plasma	Rhinitis subjects plasma	Pediatric Type 1 allergy subjects plasma
Change from original method		Change the extraction reagent to accommodate sample analysis for very high dose nasal spray or oral administration Add new platform Sciex API 4000	Change in chromatographic method, column, and gradient settings from ATM-2394	Change in extraction procedure, extraction reagents, reconstitution solvent, column, mobile phases, gradient parameters, and ions monitored and new platform (Sciex API 4000)	New stock solution	--	New concentration of stock solution

Source: Reviewer-generated table based on Applicant's method validation and bioanalytical reports

For Trial EPI 17, a new method from a different laboratory [redacted] was used to evaluate the plasma epinephrine concentrations. The life cycle summary for this method is summarized in Table 50.

Table 50. Summary of Life Cycle Information of Bioanalytical Methods Developed in [redacted]

Report	MV(C)-150-20	Trial EPI 17 0058-22
Release year	March 17, 2021	June 20, 2022
Validation type	Method Validation	N/A
Method ID	MV(C)-150-20	MV(C)-150-20
CRO	[redacted]	[redacted]
Bioanalytical method	LC-MS/MS	LC-MS/MS
Matrix	Bufferized human plasma	Bufferized human plasma
Analyte	Epinephrine	Epinephrine
Stock reference & lot (expiry)	Epinephrine (1014300000.000 pg/mL) in 0.1 M Hydrochloric acid solution (stable for 36 days within 2-8°C) Epinephrine-d6 (100000.000 ng/mL) in Methanol: 1.0 M Hydrochloric Acid Solution (95:5, v/v) Solution (stable for 36 days at 2-8°C)	Epinephrine into 0.1M Hydrochloric Acid solution (v/v) Epinephrine-d6 in Methanol: 1.0 M Hydrochloric Acid Solution (95:5, v/v) Solution (expiry: prepared 4/4/2022 and stable for 36 days at 2-8°C, trial completed on 6/7/2022)
Calibration range (LLOQ-ULOQ)	11.030 pg/mL to 1509.278 pg/mL	11.030 pg/mL to 1509.278 pg/mL
Matrix/Trial population	---	Healthy subjects plasma
Change from original method	---	

Source: Reviewer-generated table based on Applicant's method validation and bioanalytical reports

The method validations and partial validations for all methods used in [redacted] are summarized in Table 51 for ATM-2220, Table 52 for ATM-2394, Table 53 and Table 55 for ATM-2648, and Table 54 for ATM-2662.

Table 51. Method ATM-2220 Validation

Bioanalytical method validation report name, amendments, and hyperlinks	Determination of Epinephrine in Human Acidified K2-EDTA Plasma by LC-MS-MS Validation of the Analytical Method
Method description	The method was validated for a range of 20.0 to 4000 pg/mL based on the analysis of 0.250 mL of human acidified plasma. Human acidified plasma containing epinephrine and the internal standard, epinephrine-D6, was extracted using solid-phase extraction (SPE) and derivatized then was analyzed by a Sciex API 4000 LC-MS-MS equipped with an HPLC column. Quantitation was performed using a weighted $1/x^2$ linear least squares regression analysis generated from calibration standards prepared on the day of extraction.

Materials used for calibration curve, QCs & concentration	Epinephrine Bitartrate (United States Pharmacopeia, Inc. Lot: P1L152) Epinephrine-D6 (b) (4) Lot: I-360) Matrix source: Human K2-EDTA Plasma (b) (4) Human K2-EDTA Hemolyzed Plasma (b) (4) Human K2-EDTA Lipemic Plasma (b) (4) Human K2-EDTA Whole Blood (b) (4) Acidified plasma used in this method was prepared as follows: for every 40.0 mL of blank plasma, 2.00 mL of hydrochloric acid solution (2.4 N in water) was added. This acidification process introduced a 5.00% dilution of the samples. Calibration standards were prepared at 20.0, 40.0, 80.0, 200, 800, 2000, 3600, and 4000 pg/mL of epinephrine in human acidified plasma on the day of each extraction and aliquoted at 0.250 mL QC samples were prepared in human acidified plasma at 20, 60, 400, 3200 and 20000 pg/mL		
Validated assay range	20.0 to 4000 pg/mL		
Minimum required dilutions (MRDs)	N/A		
Regression model & weighting	weighted $1/x^2$ linear least squares regression		
Validation parameters	Method validation summary		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	DCN1004490 Table 1
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.5% to 3.6%	DCN1004490 Table 1
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.7%	DCN1004490 Table 1
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 **QCs**:	-4% to 6.5%	DCN1004490 Table 3
	Interbatch %CV QCs: Product A	≤7.3%	DCN1004490 Table 3

Selectivity & matrix effect	**Selectivity**: Six different (individual, nonpooled) lots of blank acidified plasma were fortified at the concentration of the LLOQ standard and extracted to examine the effect of variation in matrix. Assay selectivity was first assessed in Run 1. All samples were rejected for extraction error as the excipient volume of a common plasma spiking solution exceeded 5% during the samples' preparation. The experiment was repeated in Run 3 using a different procedure but Lots 1 and 2 failed to meet the acceptance criterion. These lots were repeated in Run 4 in duplicate and both replicates passed **Matrix effect** (reported as matrix factor) was evaluated in six different (individual, nonpooled) lots at high (3600 pg/mL) and low levels (40 pg/mL). Matrix effect was first assessed in Run 3; however, results were greater than 15.0% for the six lots for both levels. The experiment was repeated in Run 4 using a different procedure which allowed for better mixing of all samples. Matrix factor was greater than 1.20 for several samples. When IS-normalized matrix factor is evaluated, all values are within 0.800 and 1.20. **Recovery:** extraction recovery was evaluated in triplicate at low, medium, and high levels. Recovery was first assessed in Run 3; however, results were greater than the 20% recommendation for the internal standard. The experiment was repeated in Run 4 using a different procedure which allowed for better mixing of the postextraction spiked samples	DCN1004490 Table 8, 9 and 10
Interference & specificity	**Specificity:** Six different (individual, nonpooled) lots of blank acidified plasma were analyzed to identify any interference at the retention time of epinephrine or the internal standard. Detection specificity met the acceptance criteria Two solutions of common medications were tested for possible interference with epinephrine or the internal standard. One solution contained acetaminophen, acetylsalicylic acid, brompheniramine, caffeine, cetirizine, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, famotidine, ibuprofen, ketoprofen, loratadine, naproxen, omeprazole, phenylephrine, pseudoephedrine, ranitidine, salicylic acid, and triprolidine (approximately 10 µg/mL each). The second solution contained drospirenone, ethinyl estradiol, levonorgestrel, medroxyprogesterone acetate, norgestimate, and norethindrone (approximately 10 µg/mL each). Each solution was injected in triplicate. The experiment met the acceptance criteria.	
Hemolysis effect	Hemolytic effect was assessed in one lot at both low (40 pg/mL) and high (3600 pg/mL) level with matrix factor ranged from 0.89 to 1.25	DCN1004490 Table 9
Lipemic effect	Lipemic effect was assessed in one lot at both low (40 pg/mL) and high (3600 pg/mL) level with matrix factor ranged from 0.939 to 1.25	DCN1004490 Table 9
Dilution linearity & hook effect	Six replicates of the dilution QC level were diluted 10X prior to analysis. Intrarun precision and accuracy must be within 15.0%	DCN1004490 Page 10

Bench-top/process stability	Epinephrine Extracted from Human Acidified K2-EDTA Plasma was stable for 24 hours at benchtop on ice with 1° C Epinephrine Extracted from Human Acidified K2-EDTA Plasma was stable for 76 hours at 4° C	DCN1004490 Table 4 and 6
Freeze-Thaw stability	Epinephrine Extracted from Human Acidified K2-EDTA Plasma was stable for 5 Freeze and thaw cycles	DCN1004490 Table 5
Long-term storage	Epinephrine extract was stable at -70° C for 551 days	DCN1004490_am3
Parallelism	Not applicable	
Carry over	The matrix blank sample following the ULOQ standard is used to assess carryover. This method met the criteria for carryover	

Source: Reviewer-generated table based on method validation report of ATM-2220

Table 52. Partial Validation for Method ATM-2394

Bioanalytical method validation report name and hyperlink	Partial Validation of the Analytical Method (DCN: 1004490_am4) (ATM-2394)		
Changes in method	Change the extraction reagent to accommodate sample analysis for very high dose nasal spray or oral administration; Add new platform Sciex API 4000		
New validated assay range if any	N/A		
Validation parameters	Cross-validation performance		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-3.3% to 2.3%	DCN 104490_am4 Table 22
	Cumulative precision (%CV) from LLOQ to ULOQ	≤8.2%	DCN 104490_am4 Table 22
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 24 QCs (4 levels of QC, 6 replicates per level)	1.7% to 5.5%	DCN 104490_am4 Table 23
	Interbatch %CV	≤6.7%	DCN 1004490_am4 Table 23
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters	Recovery: Recovery was first assessed in Run 13; however, results were greater than the 20% recommendation for the analyte. The experiment was repeated in Run 14 using a different procedure which prepared the pre-extraction spiked samples in a more similar way to the postextraction spiked samples. (CV%>20% for both epinephrine and epinephrine-D6 at all levels) Matrix Effect: Matrix effect was first assessed in Run 13; however, since the technique was edited for recovery, which uses the same solutions, matrix effect was repeated in Run 14. Matrix factor was less than 0.800 and greater than 1.20 for several samples. When IS-normalized matrix		

	factor is evaluated, all values are within 0.800 and 1.20. Assay selectivity: Six different (individual, nonpooled) lots of blank acidified plasma were fortified at the concentration of the LLOQ standard and extracted to examine the effect of variation in matrix. (LLOQ: bias -6% to 2%, Table 26) Specificity: Six different (individual, nonpooled) lots of blank acidified plasma were analyzed to identify any interference at the retention time of epinephrine or the internal standard. Detection specificity met the acceptance criteria. Carryover effect: The matrix blank sample following the ULOQ standard is used to assess carryover. This method met the criteria for carryover.		

Source: Reviewer-generated table based on method validation for ATM-2394

Table 53. Partial Validation for Method ATM-2648

Bioanalytical method validation report name and hyperlink	Partial Validation of the Analytical Method (DCN: 1004490_am9) Method ATM-2648		
Changes in method	Change in chromatographic method, including included the following: column and gradient settings modifications to ATM-2394.		
New validated assay range if any	N/A		
Validation parameters	Cross-validation performance A&P was evaluated in Run 1, 3, and 4. (Run 1 was rejected due to extraction error).		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-2.5 to 1.6%	DCN 1004490 Table 46
	Cumulative precision (%CV) from LLOQ to ULOQ	≤9.6%	DCN 1004490 Table 46
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 24 QCs (4 levels: LLOQ, L, M, HQC and 6 replicates per level)	-3.3 to 7.5%	DCN 1004490 Table 48
	Interbatch %CV	≤16.7%	DCN 1004490 Table 48
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters	Recovery: CV% were below 20% for both epinephrine and epinephrine-D6 at all three levels Matrix Effect: For epinephrine, matrix factor was greater than 1.20 for all low-level samples and one high level		

	sample. For epinephrine-D6, matrix factor was greater than 1.20 for some low-level samples and one high level sample. IS-normalized matrix factor for Lot HMN648633, HMN648635, HMN648636 and hemolytic lot HMN482053 at low level were still above the recommendation at 1.27, 1.34, 1.27, and 1.22, respectively. Assay selectivity: Six different (individual, nonpooled) lots of blank acidified plasma were fortified at the concentration of the LLOQ standard and extracted to examine the effect of variation in matrix. Assay selectivity was attempted in Run 1; however, the QC mediums used in the run were deactivated for extraction error, and the run was rejected. Assay selectivity was attempted in Run 4, but Lot 3 and Lot 5 failed to meet acceptance criterion. Lot 3 and Lot 5 were repeated in duplicate in Run 5. However, Standard A was deactivated for Dixon outlier. Selectivity samples, prepared at the same concentration as Standard A, were deactivated for extrapolated values, and the experiment was rejected. Lot 3 and Lot 5 were further repeated in duplicate in Run 6, but low or no peak responses for epinephrine were produced for the selectivity samples, and the experiment was rejected after determining there was an extraction error. Lot 3 and Lot 5 were repeated in Run 7 in duplicate and met the acceptance criterion. LLOQ (% bias: -11.5% to 24.5%) Specificity: Six different (individual, nonpooled) lots of blank human acidified K2-EDTA plasma were analyzed to identify any interference at the retention time of epinephrine or the internal standard. Detection specificity was attempted in Run 1; however, the QC mediums used in the run were deactivated for extraction error and the run was rejected. Detection specificity was successfully repeated in Run 4 and met the acceptance criteria. Carryover effect: IS peak response at the retention time of the IS that was 14.21% (acceptable ≤5.0%) of the mean of the nonzero internal standard responses for the run.		

Source: Reviewer-generated table based on method validation for ATM-2648

Table 54. Partial Validation for Method ATM-2662 and Cross-Validation With ATM-2648

Bioanalytical method validation report name and hyperlink	Partial Validation of the Analytical Method (DCN: 1004490_am10) (Method ATM-2662)		
Changes in method	Change in extraction procedure, extraction reagents, reconstitution solvent, column, mobile phases, gradient parameters, and ions monitored; New platform used (Sciex API 4000 versus previous Sciex API 5000)		
New validated assay range if any	N/A		
Validation parameters	Cross-validation performance A&P was attempted in Run 8, 9, 11, 14, 16, 19, 20, 22, 23, 25, 26, 27, 28 but rejected for various reasons (extraction error, insufficient acceptable standard, unacceptable QCs). Accepted A&P run: 10, 18, 21 (partial validation for new platform), 24, 30, 39.		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-19.5% to 1.8% (accepted and rejected run 8-24, 38) -4.5% to 4.5% (accepted and rejected run 25-34, 39)	DCN 1004490 Table 58 (accepted and rejected run 8-24, 38) Table 59 (accepted and rejected run 25-34, 39)
	Cumulative precision (%CV) from LLOQ to ULOQ	≤96.9% (accepted and rejected run 8-24, 38)[a] ≤6.1% (accepted and rejected run 25-34, 39)	DCN 1004490 Table 58 (accepted and rejected run 8-24, 38) DCN 1004490 Table 59 (accepted and rejected run 25-34, 39)
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 24 QCs (4 levels of QC with 6 replicates for each level)	-0.9% to 10.2% (run 8, 10, 18, 24) -0.2% to 5.7% (run 27, 30, 39)	DCN 1004490 Table 60 (run 8, 10, 18, 24) Table 61 (Run 27, 30, 39)
	Interbatch %CV	≤10.6% (Run 8, 10, 18, 24) ≤6.6% (run 27, 30, 39)	DCN 1004490 Table 60 (Run 8, 10, 18, 24)

			Table 61 (Run 27, 30, 39)
Cross-validation	Numbers of spiked or incurred samples analyzed and result (cross-validation between ATM-2648 and ATM-2662)	50 samples that were previously analyzed by ATM-2648 were used 70.3% of repeated samples concentration had deviation ≤ ±20% from mean concentration of original analysis. Six samples from each QC level (high, medium, and low): %Bias: 5 to 8.3% and %CV ≤3.8%	Bioanalytical Report 5025436 Table 9 and 10
List other parameters	Extract stability was established 192 hours at 4° C Recovery: Run 15/38: Recovery was outside of this recommendation for epinephrine and epinephrine-D6 for the high-level samples (CV%79.5% and 79.63% for epinephrine and epinephrine-D6 at high dose level). When the IS-normalized values are considered (peak area ratio of analyte to internal standard), recovery differences are ≤20.0%. Run 33/34 (partial validation for complexing solution): Recover for epinephrine and epinephrine-D6 was outside recommended criteria (CV%>20% at 800 and 3600 pg/mL). When the IS-normalized values are considered (peak area ratio of analyte to internal standard), recovery differences are ≤20.0% Matrix effect: Run 15: For epinephrine and epinephrine-D6, matrix factor was lower than 0.800 for one low and one high level sample. Run 33: for epinephrine and epinephrine-D6, matrix factor was greater than 1.20 for most low level plasma lots. When IS-normalized matrix factor is evaluated for epinephrine and		

	epinephrine-D6, all values are within 0.800 and 1.20 Selectivity: Run 12: Six different (individual, nonpooled) lots of blank plasma were fortified at the concentration of the LLOQ standard and extracted to examine the effect of variation in matrix (% bias: -12% to 7%). Run 29/31/33/34: %bias: -26% to 18.5%. At least 90% of the lots tested met the acceptance criterion.		

a Results included failed runs.
Source: Reviewer-generated table based on method validation for ATM-2662

The assay performances in Trials EPI 15, EPI 16, and EPI 10 are shown in Table 55, Table 56, and Table 57, respectively.

Table 55. Method Performance, Trial EPI 15

Method performance in trial EPI 15 Method ATM-2662 and ATM-2648		
Assay passing rate	(including incurred sample reanalysis (ISR)): 54 of 84 runs are accepted (64%) 18 runs were required at least one restart and 85 runs were required at least one reinjection	DCN 5029768 Table 1
Standard curve performance	Cumulative bias range:-1.3% to 0.5% Cumulative precision: ≤5% CV	DCN 5029768 Table 3
QC performance	Cumulative bias range: -5.3% to 10.6% Cumulative precision: ≤11.1% CV	DCN 5029768 Table 4
Method reproducibility	Incurred sample reanalysis was performed in 7% of trial samples (320 samples out of 4605 total samples in ISR) and 75% of samples met the prespecified criteria.	DCN 5029768 Table 8
Trial sample analysis/ stability	Samples were stored at -70° C for 264 days and was within the established stability range.	

Source: Reviewer-generated table based on bioanalytical report for EPI 15

Table 56. Method Performance, Trial EPI 16

Method Performance, Trial EPI 16 Method ATM-2662		
Assay passing rate	(including incurred sample reanalysis (ISR)): 39 out of 49 runs were accepted (80%) Run 50 and 51 contained samples that were overacidified at the time of collection. Both runs were information purpose only and did not meet acceptance criteria and will not appear in Individual Run Report. Fourteen (14) of the forty-nine (49) total runs within this trial required at least one restart or reinjection.	DCN 5035445 Table 1
Standard curve performance	Cumulative bias range:-1.5% to 1.9% Cumulative precision: ≤4.3% CV	DCN 5035445 Table 2
QC performance	Cumulative bias range: -0.3% to 11.9% Cumulative precision: ≤7.2% CV	DCN 5035445 Table 4
Method reproducibility	ISR was performed in 7% of trial samples (182 samples out of 2478 total samples in ISR) and 86% of samples met the prespecified criteria	DCN 5035445 Table 8
Trial sample analysis/ stability	Samples were stored up to 106 days and was within the established stability range.	

Source: Reviewer-generated table based on bioanalytical report for EPI 16

Table 57. Method Performance, Trial EPI 10

Method Performance, Trial EPI 10 Method ATM-2394 and ATM-2662		
Assay passing rate	(including incurred sample reanalysis (ISR)): 16 out of 19 runs were accepted (84.2%)	DCN 4010308 Table 1
Standard curve performance	Cumulative bias range:- 2.3% to 2.3% Cumulative precision: ≤4.4% CV	DCN 4010308 Table 2
QC performance	Cumulative bias range: -6.3% to -2.5% (Table 5); -6.3% to 14% (Table 4) Cumulative precision: ≤7.7% CV (Table 5); ≤106.1% (Table 4)	DCN 4010308 Table 4 (outlier included) Table 5 (outlier excluded)
Method reproducibility	ISR was performed in 10% of trial samples (78 samples out of 795 total samples in ISR) and 93.6% of samples met the prespecified criteria Incurred sample reproducibility (ISR) for epinephrine was evaluated for clinical samples using ATM-2394, Original and ATM-2662, Validation.	DCN 4010308 Table 8
Trial sample analysis/ stability	Sample was stored and analyzed within the established stability range.	

Source: Reviewer-generated table based on bioanalytical report for EPI 16

The method validation and assay performances in EPI 17 is reported in Table 58.

Table 58. Method Validation and Assay Performance, Trial EPI 17

Bioanalytical method validation report name, amendments, and hyperlinks	Determination of Epinephrine in Bufferized Human Plasma (K2EDTA) BY LC-MS/MS (AB SCIEX API 6500) Method: MV(C)-150-20
Method description	The concentrations of epinephrine in bufferized human plasma were determined using selective, reproducible, precise, and accurate LC-MS/MS method using epinephrine-d6 as an internal standard. Epinephrine and epinephrine-d6 (ISTD) were extracted from bufferized human plasma by solid-phase extraction method. Plasma sample treated with prechilled 0.5% Formic acid in Acetonitrile (v/v) solution were centrifuged. The supernatant was transferred into Agilent Captiva NDLIPIDS cartridge, wait for 10 minutes, and then applied full pressure, and collected in collection tubes. Thereafter, 100mM Ammonium dihydrogen phosphate buffer pH 10.0 solution was added to the collected samples. The samples were further extracted using Agilent BondElut PBA SPE cartridge (100 mg/3mL) conditioned with Acetonitrile followed by Elution solution and 100mM Ammonium dihydrogen phosphate buffer pH 10.0 solution. The cartridge was then washed with washing solution and the contents were eluted with

<table>
<tr><td>Materials used for calibration curve, QCs & concentration</td><td>The drug stock solution used for preparation of calibration curve standards & quality control samples were prepared using 0.1 M Hydrochloric acid solution (v/v). Further the stock dilutions and spiking solutions were prepared using 0.01 M Hydrochloric acid solution (v/v). The following material were used:
Epinephrine (Lot: 1-PYL-3-1, expiry: Jan 13, 2022)
Epinephrine-d6 (Lot: FN05061904; expiry: Aug 31, 2023)

Table 59. Plasma Lots Used in Bioanalysis
<table>
<tr><th rowspan="2">Description</th><th rowspan="2">Batch No.*</th><th rowspan="2">Received Date</th><th colspan="2">Any interference at the retention time of</th></tr>
<tr><th>Epinephrine</th><th>Epinephrine-d6 (ISTD)</th></tr>
<tr><td>Normal Plasma</td><td>HMN464446</td><td rowspan="3">21 September 2020</td><td>NI</td><td>NI</td></tr>
<tr><td>Normal Plasma</td><td>HMN464449</td><td>NI</td><td>NI</td></tr>
<tr><td>Normal Plasma</td><td>HMN464442</td><td>NI</td><td>NI</td></tr>
<tr><td>Normal Plasma</td><td>HMN359100</td><td>19 March 2020</td><td>NI</td><td>NI</td></tr>
<tr><td>Normal Plasma</td><td>HMN351732</td><td>10 March 2020</td><td>NI</td><td>NI</td></tr>
<tr><td>Normal Plasma</td><td>HMN464456</td><td>21 September 2020</td><td>NI</td><td>3.0 %</td></tr>
<tr><td>Hemolysed Plasma</td><td>HMN464446 (Degree of hemolysis is 5%)</td><td rowspan="2">Prepared in-house**</td><td>NI</td><td>NI</td></tr>
<tr><td>Hemolysed Plasma</td><td>HMN464456 (Degree of hemolysis is 5%)</td><td>NI</td><td>NI</td></tr>
<tr><td>Lipemic Plasma</td><td>BC20009LP-1</td><td rowspan="2">21 September 2020</td><td>NI</td><td>NI</td></tr>
<tr><td>Lipemic Plasma</td><td>BC20009LP-2</td><td>NI</td><td>NI</td></tr>
</table>
NI = no interference
**Hemolysed plasma was prepared by spiking previously frozen whole blood (having lot number R537744 received on date: 16 December 2019) into blank human plasma in the ratio of 5% of total hemolysed plasma volume i.e., 100 mL of hemolysed plasma will contain 5mL of whole blood and 95mL of blank human plasma

Stock solution:
Epinephrine (1014300000.000 pg/mL) in 0.1 M Hydrochloric acid solution (stable for 36 days within 2-8°C, Table 15a)
Epinephrine-d6 (100000.000 ng/mL) Methanol: 1.0 M Hydrochloric Acid Solution (95:5, v/v) Solution (stable for 36 days at 2-8°C, Table 15d)

Calibration standards were prepared at 11.030 22.061 74.782 226.614 755.379 1127.431 1358.351 and 1509.278 pg/mL

Quality controls were prepared at 11.030, 32.574, 80.629, 503.933, and 1145.303 pg/mL.</td></tr>
<tr><td>Validated assay range</td><td>11.030 pg/mL to 1509.278 pg/m</td></tr>
<tr><td>Minimum required dilutions (MRDs)</td><td>N/A</td></tr>
<tr><td>Regression model & weighting</td><td>linear regression analysis with a weighting factor of 1/concentration^2.</td></tr>
</table>

Validation parameters	Method validation summary		Source location (hyperlinked)
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	MV(C)-150-20 Table 2a
	Cumulative accuracy (%bias) from LLOQ to ULOQ	5.7% to 8.2%	MV(C)-150-20 Table 2a
	Cumulative precision (%CV) from LLOQ to ULOQ	≤3.6%	MV(C)-150-20 Table 2a
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs:	-6.4 to 0.8%	MV(C)-150-20 Table 7
	Interbatch %CV QCs:	≤7.5%	MV(C)-150-20 Table 7
Selectivity & matrix effect	LLOQ: bias CV 7.5% Matrix effect was evaluated in 10 lots at HQC (1145.303 pg/mL) and LQC (32.574 pg/mL) with bias -3.3% and -10.6%, respectively and CV% 4.2% and 4.1%, respectively Recovery for epinephrine and epinephrine-63 were determined at LQC (32.574 pg/mL), MQC (503.99 pg/mL) and HQC (1145.303 pg/mL) with CV <5%		MV(C)-150-20 Table 7 MV(C)-150-20 Table 12b
Interference & specificity	The precision and accuracy of epinephrine in presence of co administered (concomitant) drugs/ OTC drugs have been evaluated with LQC (32.574 pg/mL). Precision were ≤15% and accuracy are within 85% to 115% of nominal.		MV(C)-150-20 Table 5b
Hemolysis effect	Two hemolytic lots were evaluated with HQC (1145.303 pg/mL) and LQC (32.574 pg/mL). All samples had values within ±15% value of all QCs		MV(C)-150-20 Table 12b
Lipemic effect	Two lipemic lots were evaluated with HQC (1145.303 pg/mL). 14 out of 16 samples (87%) had values within ±15% value of all QCs		MV(C)-150-20 Table 12b
Dilution linearity & hook effect	Dilution Integrity of epinephrine was determined by evaluating precision and accuracy of six individual samples of DQC, diluted at 1/5th and 1/10th dilutions from each aliquot with interference-free pooled blank human plasma having same anticoagulant.		MV(C)-150-20 Table 8b
Bench-top/process stability	Low (32.574pg/mL) and high QC (1145.303 pg/mL) samples were stable after 17 hours on ice-cold water bath (bias: 3.2% to -4.5%, respectively; CV ≤8.3%) Low (32.574pg/mL) and high QC (1145.303 pg/mL) samples were stable after 195 hours in auto sampler at 5±3°C. (bias: -2.4% and -7.3%, respectively, CV ≤9.1%) Wet extract was table at room temperature for 2 hours (bias:		MV(C)-150-20 Table 17, 19 and 20
Freeze-thaw stability	Low (32.574pg/mL) and high QC (1145.303 pg/mL) samples were stable after 5 freeze-thaw cycle (bias 0.1% and -8.4% respectively; CV ≤5.5%		MV(C)-150-20 Table 18

Long-term storage	Long-term stability of analyte in bufferized human plasma for 405 days at -25±10°C & -70±10°C	MV(C)-150-20 (Addendum-II)
Parallelism	Not evaluated	
Carry over	Carry-over experiment was performed by injecting the following sequence: 1) Extracted blank plasma 2) Extracted high sample 3) Extracted blank plasma 4) Extracted high sample 5) Extracted blank plasma 6) Extracted blank plasma 7) Extracted low sample In above mentioned sequence, after 1st and 2nd injection of extracted high sample no carry-over was observed at the retention time of epinephrine and epinephrine-d6 (ISTD).	
Method Performance, Trial EPI 17		
Assay passing rate	(including incurred sample reanalysis (ISR)): 28 of 33 runs are accepted	0058-22 Table 1
Standard curve performance	Cumulative bias range: -8.6% to 5.4% Cumulative precision: ≤3.6% CV	0058-22 Table 2
QC performance	Cumulative bias range: -2.5% to 4.5% Cumulative precision: ≤5% CV	0058-22 Table 3a and 3b
Method reproducibility	Incurred sample reanalysis was performed in 8.5% of trial samples (135/1587 samples) and 90.4% of samples met the prespecified criteria.	0058-22 Table 9
Trial sample analysis/ stability	Samples were stored up to 61 days at -70±10°C and within the established stability range.	

Source: Reviewer-generated table based on bioanalytical report for EPI 17

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA ASSESSMENT AND EVALUATION

Application Number*:	214697
Supporting Document Number/s:	1
CDER Receipt Date:	8/19/2022
Applicant:	ARS Pharmaceuticals Inc.
Product:	Neffy® (ARS-1)
Pharmacologic Class:	α- and β-adrenergic receptors agonist
Indication:	Type 1 (b) (4) reactions, including anaphylaxis
Therapeutic area:	Allergy and Immunology
Clinical Review Division:	Division of Pulmonology, Allergy and Critical Care (DPACC)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Xiaochun Chen, PhD
Team Leader:	Carol Galvis, PhD
Project Manager:	Ji Hyun LaRose, PharmD
Purpose of Review:	Other
If “Other”:	Safety Assessment of Extractables and Leachables Studies
Alternative Assays:	None
Reviewer Completion Date:	June 2, 2023

Template Version: Sep 11, 2020

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

ARS Pharmaceuticals Inc. submitted a 505(b)(2) New Drug Application (NDA) on August 19, 2022, for Neffy® 2 mg (ARS-1), an epinephrine nasal spray proposed for the treatment of Type I allergic reactions including anaphylaxis in adults and children 30 kg or greater. The sponsor is relying in part on the previous findings submitted in NDA 204200 and NDA 019430 for the reference listed drugs (RLD), Adrenalin® and EpiPen® (epinephrine) Injections, respectively to support the current NDA application. The extractables and leachables study reports were submitted on August 19, 2022.

Epinephrine (adrenaline), the drug substance (DS), is a white to practically white, odorless, microcrystalline powder or granules, (b) (4) (b) (4)

Neffy® drug product (DP) is a (b) (4) solution filled into a unit dose 400 µL Type (b) (4) glass vial and closed with a (b) (4) rubber stopper. This primary CCS contains a formulation of (b) (4) mg/mL epinephrine (active pharmaceutical ingredient, API) in 125 µL of solution ((b) (4) mg/mL dodecylmaltoside [DDM], (b) (4) mg/mL benzalkonium chloride, (b) (4) mg/mL (b) (4) (b) (4) (b) (4) mg/mL sodium chloride and (b) (4) mg/mL sodium metabisulfite (b) (4) designed for intranasal (IN) spray. To account for the known (b) (4) with other epinephrine products, this solution includes a (b) (4) This primary CCS is assembled into a commercially available (b) (4), a Unit Dose Sprayer (UDS) device, that will deliver 100 µL of ARS-1 solution per actuation. The overfill of 125 µL is included to achieve the 100 µL spray volume per actuation.

There is no extractable and leachable study report or toxicity assessment submitted by the sponsor for the (b) (4) (b) (4) that is manufactured by (b) (4) The safety information supporting this DMF has been reviewed previously and considered adequate (refer to DMF review dated 2/23/2015). This DMF has been referenced 93 times since 1985 and been used to support the approval of 6 NDAs and 6 ANDAs since 1985. The most recent approval was for NON-RESPONSIVE under NDA NON-RESPONSIVE The same (b) (4) is used to store the DS for subsequent manufacturing of (b) (4) the final DP. No manufacturing changes have been reported by (b) (4) based on annual reports submitted since (b) (4) Considering the long history of this referenced DS in supporting marketing approval of 12 epinephrine injections or mist, the absence of safety reports directly related to the use of this (b) (4) for DS storage, and the nature of the proposed single IN administration, this (b) (4) is not considered a safety issue regarding potential leachables exposure. Further, the safety

of this (b) (4) in direct contact with the DS was previously reviewed under the DMF. Therefore, this review will only focus on the forced extraction and leachable study reports of the critical components from the primary CCS used in the DP manufacture processes, i.e., (b) (4) stoppers and glass vials.

1.2 Brief Discussion of Nonclinical Findings

The safety evaluation consisted of 1) an extractables study with the (b) (4) stoppers and glass vials, and 2) a leachables study with ARS-1 samples stored at accelerated conditions (50°C) for 3 months.

The above extractable and leachable studies were performed/analyzed under presumably the worst-case scenario when the total fill volume of 125 µL DS is sprayed. In general, any organic (nonmetal) compound with expected patient exposure below the Qualification Threshold (QT) of 5 µg/day for compounds lacking genotoxic potential and irritant potential or Safety Concern Threshold (SCT) of 0.15 µg/day for compounds with genotoxic potential as recommended by Product Quality Research Institute (PQRI) is considered qualified for safety.

The sponsor determined the analytical evaluation threshold (AET) based on one spray per day although the proposed labeling does imply situations when two sprays may be needed "*if symptoms continue to progress after approximately* (b) (4) *minutes* (b) (4) (b) (4) For the most common situation when only one spray was applied, the AET was determined to be (b) (4) µg/container based on EQ 1. Based on this, extractable and leachable study protocols were designed so that the analytical thresholds (AT) were above the limit of quantification (LOQ) for each assay. For detected organic extractable and compounds, only extractables and leachables with concentrations above the AT level were reported.

(b) (4)

Since the DP in each container is for single use, for patients receiving two sprays, they could be exposed to 2 times the level of leachables identified from one container. However, the potential safety concern is considered low based on the list of extractables and leachables identified for one spray (reviewed below) and additional reasons as below:

- The DP is mainly for single IN use during emergency. Highly frequent use during one's lifetime is not expected.
- The glass vial (b) (4) and the (b) (4) stopper (Aptar Pharma, France) have a long marketing history in US. Predominantly, they are used as the primary CCS for injections that could have higher safety requirement than IN products in general. In brief,
  1. DMF (b) (4) for glass vials has been referenced 2192 times in DARRTS since 1959 and been used to support the approval of many NDAs and ANDAs. The most recent one was for ANDA (b) (4) approved for (b) (4) an injection on (b) (4)

2. DMF [redacted] and DMF [redacted] stoppers have been referenced 2388 and 2855 times in DARRTS since 1947, respectively. Both DMFs have been used to support the approval of many NDAs and ANDAs. For DMF [redacted] the most recent one was for ANDA [redacted] approved for [redacted] an injection on [redacted] For DMF [redacted] the most recent one was for ANDA [redacted] approved for [redacted], an injection on [redacted] Both DMFs have been used to support the approval of ANDA-[redacted] an inhalant on [redacted].

- The absence of safety report directly related to the use of [redacted] stoppers and glass vials supplied from these two manufacturers.

Therefore, the current assessment will be based on one spray although estimated exposures for two sprays are listed when possible.

In brief, extractables were only found from [redacted] stoppers, including 21 SVOCs and 18 NVOCs that are normally seen in rubber stoppers. For elements, the Guideline for Elemental Impurities (ICH Q3D, 2014) was followed for safety assessment. Three elements, i.e., [redacted], were detected and the levels were below the inhaled Permitted Daily Exposures (PDEs) listed in ICH Q3D.

In the follow up 3-month leachables study under an accelerated condition and the worst-case scenario (inverted orientation), no organic leachables were detected above the ATs for each assay. Seven elements, i.e., [redacted] were detected and the levels were below the PDEs listed in ICH Q3D.

Overall, it appears that there is no safety concern from the exposure to potential leachables from the [redacted] stoppers and glass vials.

2 Drug Information

2.1 Drug

Code Name(s): ARS-1

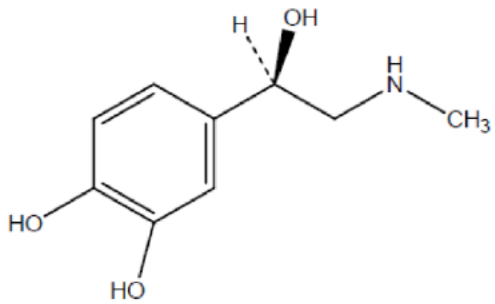
CAS Registry Number(s): 51-43-4

Generic Name: L-Epinephrine

Chemical Name: 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-; (-)-3,4-Dihydroxy- [(methylamino)methyl]benzyl alcohol

Molecular Formula/Molecular Weight: $C_9H_{13}NO_3$ / 183.20 g/mol

Structure or Biochemical Description:



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2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 139091 for ARS-1
- DMF (b) (4) for the DS
- DMF (b) (4) for Intravail® A3 (DDM)
- DMF (b) (4)
- DMF (b) (4)
- DMF (b) (4) for glassware containers

Statements of the right to reference to these DMFs were provided by letter of authorization (LOA) in the NDA.

2.3 Drug Formulation

The DP is provided as a liquid formulation ((b) (4) mg L-Epinephrine in 125 µL) intended for nasal spray. The composition of the DP is described in Table 1 (excerpted from the sponsor's submission).

Table 1. Composition of Epinephrine Nasal Spray, 2 mg

Ingredients	Quality Standard	Quantity/mL	Quantity % w/v	Quantity/100 µL Spray Volume*
L-Epinephrine	USP/Ph Eur	(b) (4)		
Dodecylmaltoside (DDM)	Internal Standard	2.75 mg	0.275	0.275 mg
Benzalkonium Chloride	USP/NF/Ph Eur	(b) (4)		
Sodium Chloride	USP/Ph Eur			
Disodium Edetate	USP/Ph Eur			
Sodium Metabisulfite***	USP/NF/Ph Eur			
Water for Injection (WFI)	USP/Ph Eur			
Hydrochloric Acid	USP/NF/Ph Eur			
Sodium Hydroxide	USP/NF/Ph Eur			

Definition: Adj. = Adjust; (b) (4) NA = Not applicable
* an overfill of 125 µL is included to achieve a 100 µL spray volume.
** Target drug product potency is (b) (4) % of label claim.
*** Sodium metabisulfite is (b) (4)
USP = United States Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; NF = National Formulary; qs = quantum sufficient

2.4 Comments on Novel Excipients

There are no novel excipients present in the drug product formulation. Excipients are within the ranges that are found in the inactive ingredient database for FDA-approved nasal spray products.

2.5 Comments on Extractables and Leachables Studies

The CCS for Neffy® 2mg consists of Type (b) (4) glass (b) (4) vials (400 µL) sealed by a (b) (4) rubber stopper. The vial/stopper is held within the nasal actuator and container holder (Table 2, excerpted from the sponsor's submission). The (b) (4) vial holder protects the DP (b) (4) Nasal actuator and

container holder components are both manufactured by Aptar Pharma, France (Aptar) and [redacted] The UDS device is secondary packaged into individual single use blisters composed of [redacted] and [redacted] Because the UDS is designed for single use (100 µL dose spray) and the vial/stopper CCS provides [redacted] only [redacted] stoppers and glass vials are considered critical components for controlled extraction studies and leachables studies.

Table 2. Primary Container Closure System Components for DP

Component	Description	Manufacturer	Product Code	DMF#
Vial	[redacted]			
Closure				
Vial holder				
Spray pump				

Extractable Studies

Methods:

The sponsor provided extractables study protocol for [redacted] stoppers and glass vials (Study Report # SGS-EL-07-ARS-20-024). The methods used in these studies consists of a set of forced extraction experiments followed by subsequent analyses of the extracts by GC/MS for semi volatile organic compounds (SVOCs), by headspace (HS)-GC/MS for volatile organic compounds (VOCs), by LC/MS for non-volatile organic compounds (NVOCs), and by inductively coupled plasma (ICP)/MS or optical emission (OES) for elemental analysis.

The surface areas of the [redacted] stoppers and glass vials are estimated to be 1.3 cm^2 and 7.9 cm^2, respectively. The recommended surface area-to-volume ratio (SAN) is at least 1.25 cm^2/mL for elastomeric closures and 3 cm^2/mL for other small, molded items per ISO 10993-12. Based on the proposed dose, the extraction volume and number of test articles for extraction were calculated so that the analytical threshold was above the LOQ for the method. The extractions were conducted according to Table 3 for GC/MS and LC/MS (excerpted from the sponsor's submission).

Table 3. Extraction Plan

Description	Quantity	Extraction Solution	Extraction Volume (mL)	Temp (°C)	Time (hours)	Extraction Technique
[redacted] Stoppers	30	0.1 HCl	30	50	72	Incubation with agitation
		IPA				
Glass Vials	10	0.1 HCl	25			

For GC/MS and LC/MS, the LOQ was [redacted] µg/mL. The extraction volume, the concentration factor (C), and the number of test articles extracted (F) were selected so that the AT calculated based on EQ 2 below is above the LOQ. For example, for [redacted] stoppers, the extraction volume was 30 mL, C was 7, and F was 30. The AT was [redacted]

[redacted]

For (HS)-GC/MS, the LOQ was [redacted] µg/HS vial. Two glass vials [redacted] g) and eight [redacted] stoppers ([redacted] g) were weighed into individual 20 ml headspace vials (HS) vials. For one spray a day, one glass vial and one stopper will be used. The AT was [redacted] µg/glass vial and [redacted] (= [redacted] µg/stopper, respectively. Both ATs were above the AET of [redacted] µg/container. Therefore, this assay is insufficient in identifying extractables for the DP under the proposed use. Since the AT for the follow-up leachable study of VOCs is acceptable, the insufficient assay condition for (HS)-GC/MS in the extractable study is not considered an issue.

For element analysis, only HCl samples were analyzed and were diluted 1:10 first by 3% nitric acid and 2% HCl before the analysis. For SVOCs, both HCl samples and isopropanol (IPA) samples were analyzed; the HCl samples were extracted by methylene chloride (DCM, v/v: 1/2) before the analysis. For NVOCs, both HCl samples and IPA samples were analyzed; the HCl samples were dried and reconstituted with methanol before analysis. For VOCs, 2 glass vials and 8 [redacted] stoppers were placed into individual HS vials and heated at 80 ºC for 30 minutes and analyzed by (HS)-GC/MS.

Results:

VOCs: There were no VOCs detected above the AT of [redacted] µg/glass vial or [redacted] µg/stopper. However, since both ATs were above the AET for the DP, the potential VOCs as extractables for further monitoring is not fully explored.

SVOCs: No extractables were identified from the HCl extracts for glass vials and [redacted] stoppers. From the IPA extract for the [redacted] stoppers, 64 extractables

including 21 compounds (Table 4) with known structures and 43 compounds with unknown structures were identified above the AET of (b) (4) µg/container. These 21 compounds are various derivates or (b) (4) (b) (4) These are normally found in rubber stoppers. The total concentration for all detected compounds and all unknown compounds was (b) (4) µg/stopper and (b) (4) µg/stopper, respectively.

Table 4. GC-FID/MS Results for the (b) (4) Stoppers in IPA Extracts

Compound	Concentration in IPA extract (µg/mL)[a]	Concentration in each stopper (µg/stopper)[b]	Amount /day (µg/day)		AET (µg/day)
			1 spray[c]	2 sprays[d]	
(b) (4)					(b) (4)

: This dose is based off the worst case when all 125 uL filled DP was taken after one spray.

[d]: This dose is based off the worst case when all 125 uL filled DP was taken after two sprays.

NVOCs: No extractables were mentioned form the HCl extracts for glass vials and (b) (4) stoppers. From the IPA extracts for the (b) (4) stoppers, 18 extractables were identified above the AET of (b) (4) µg/container (Table 5). These compounds are (b) (4) (b) (4) (b) (4) a common impurity of (b) (4) used in food packaging); (b) (4)

Table 5. LC/MS Results for the (b) (4) Stoppers in IPA Extracts

Compound	Concentration in IPA extract	Concentration in each stopper	Amount /day (µg/day)		AET (µg/day)
			1 spray[c]	2 sprays[d]	

	(ug/mL)[a]	(ug/stopper)[b]			

(b) (4)

(b) (4)

(b) (4)

[c]: This dose is based off the worst case when all 125 uL filled DP was taken after one spray.

[d]: This dose is based off the worst case when all 125 uL filled DP was taken after two sprays.

Element: One element from glass vials and two elements from (b) (4) stoppers were detected above (b) (4) ng/mL (Table 6). These are all below the inhalation PDEs listed in ICH Q3D (2015).

Table 6. ICP-MS Elemental Results for Extractable Samples in 0.1 N HCl

Sample	Element	Concentration (ng/mL) a	Concentration in each part (ng/part)	Amount /day (ng/day)		ICH Q3D Control Inhalation PDE, ng/day
				1 spray[d]	2 sprays[e]	
Glass Vial	(b) (4)					
(b) (4) Stoppers						

[a]: Concentration as injected into the instrument.

(b) (4)

[d]: This dose is based off the worst case when all 125 uL filled DP was taken after one spray.

[e]: This dose is based off the worst case when all 125 uL filled DP was taken after two sprays.

Final list of potential Leachable Compounds

The sponsor did not specifically mention the final list of compounds for monitoring in the follow-up leachables studies. It is believed that all the above SVOCs (known and unknown structures) and NVOCs, and all Class 1, 2A, 2B and 3 elements listed in ICH Q3D were selected.

Leachable Studies:

The leachables studies evaluated extractables from critical components that has leaching potential from the primary CCS into the DP. The extractable studies described above guided the leachable studies.

Methods:

According to eCTD Section 3.2.P.8.3, Neffy® 2 mg DP registration batches #210928, #210929, and #210930 are undergoing stability study under ICH recommended storage conditions (25°C/60% RH for 24 months) and accelerated storage conditions (40°C/75% RH for 6 months). In addition, the registration batches were stored at 50 ± 2°C for 3 months to demonstrate high temperature stability (i.e., replicating extreme temperatures inside a car). Registration batches were filled into glass vials sealed with a (b) (4) rubber stopper used in the UDS device. Samples were stored in an inverted orientation representing the worst-case condition.

For the leachables study, samples stored at 50°C for 3 months were analyzed to accurately determine the levels of leachables potentially exposed to patients.

For GC/MS and LC/MS, the LOQ was (b) (4) µg/mL. The fill volume was 125 µl (worst case scenario). The C and F were selected so that the AT calculated based on EQ 2 below is above the LOQ. For example, for (b) (4) stoppers, the C was (b) (4) and F was (b) (4) The AT was (b) (4) µg/mL.

(b) (4)

For (HS)-GC/MS, the LOQ was (b) (4) µg/HS vial according to extractable study report (# SGS-EL-07-ARS-20-024R.01, Section 4.3). In the leachable study, two mL of each sample was transferred to individual 20 mL HS vials (# SGS-EL-07-ARS-21-078R-3M). The estimated AT was (b) (4) µg/mL. This is close to the AT of (b) (4) µg/mL claimed by the sponsor (leachable study report # SGS-EL-07-ARS-21-078R-3M, pg 5). This assay condition is considered acceptable since any VOC with concentration above (b) (4) µg/mL will be considered above the AET of (b) (4) µg/container for safety justification.

For element analysis, samples were diluted 1:20 first by 3% nitric acid and 2% HCl before the analysis.

Results:

No VOCs, SVOCs, or NVOCs were detected above (b) (4) µg/mL.

For elements, ICP-MS analysis detected seven elements above the LOQ. The highest level for each element was listed in Table 7. All the elements were below the ICH Q3D control limits.

Table 7. ICP-MS Elemental Results for Leachable Samples

Element	Concentration (ng/mL) [a]	Concentration in each container (ng/mL) [b]	Amount /day (ng/day)		ICH Q3D Control
			1 spray[c]	2 sprays[d]	Inhalation PDE, ng/day
(b) (4)					

[a]: Highest concentration among the 3 lots as injected into the instrument.

(b) (4)

[c]: This dose is based off the worst case when all 125 uL filled DP was taken after one spray.

[d]: This dose is based off the worst case when all 125 uL filled DP was taken after two sprays.

3 Studies Submitted

3.1 Studies Reviewed

- SGS-EL-07-ARS-20-024: Study protocol for the evaluation of extractables (screening) profile on vials and stoppers for epinephrine nasal spray
- SGS-EL-07-ARS-20-024R.01: Evaluation of extractables profile (screening) on vials and stoppers for epinephrine nasal spray
- SGS-EL-07-ARS-21-078.01: Study protocol for the evaluation of leachables profile on vials and stoppers for epinephrine nasal spray new formulation
- SGS-EL-07-ARS-21-078R-3M: Evaluation of leachables profile on vials and stoppers for epinephrine nasal spray new formulation

11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of potential leachables from glass vials and (b) (4) stoppers, the primary CCS for Neffy® 2 mg based on data submitted by the sponsor and other available information. The sponsor is seeking approval for the DP at a nominal dose of 2 mg ARS-1 to be delivered via a single IN spray. In certain circumstances, a 2nd spray may be needed approximately (b) (4) minutes after the 1st spray. However, the submitted extractables and leachables study reports were based on one spray only. Considering the intended emergency use and the long-standing safety records for the glass vials (since 1959) and (b) (4) stoppers (since 1947) used in

many products approved by the FDA including several approvals in 2023, the assessment only for single IN spray is accepted.

A total of 64 SVOCs and 18 NVOCs were identified as extractables above the AET of (b) (4) µg/day after forced extractions. Although no VOCs were identified as extractables by (HS)-GC/MS, the ATs for this assay for glass vials and (b) (4) stoppers were about 7 times and 1 time higher than the AET, respectively. Therefore, it is possible that some VOCs might not have been identified for evaluation. For elements, (b) (4) from the glass vial, and (b) (4) from (b) (4) stoppers were detected and the levels were below the inhalation PDEs listed in ICH Q3D (2015).

For leachable study, all assay conditions were acceptable. In particular, the AT for VOCs was lower than the AET of (b) (4) µg/container. Therefore, the conclusion of no SVOCs, NVOCs, or VOCs identified for safety evaluation is valid. In addition, total seven elements were detected. The estimated levels of exposure were below PDEs as specified in ICH Q3D (2015).

Overall, there appear to be no nonclinical safety concerns from any leachables from the primary CCS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOCHUN CHEN
06/02/2023 09:50:31 AM

CAROL M GALVIS
06/02/2023 01:52:08 PM
I concur.