sNDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy supplement
Application Number	sNDA 214697 S-001
Priority or Standard	Priority
Submit Date	September 6, 2024
Received Date	September 6, 2024
PDUFA Goal Date	March 6, 2025
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC) / Office of Immunology and Inflammation (OII)
Review Completion Date	March 5, 2025
Established/Proper Name	Epinephrine nasal spray
(Proposed) Trade Name	neffy
Pharmacologic Class	alpha- and beta- adrenergic agonist
Code name	ARS-1
Applicant	ARS Pharmaceuticals Operations, Inc.
Dosage form	Nasal spray
Applicant proposed Dosing Regimen	One spray of neffy 1 mg administered into one nostril. In absence of clinical improvement or if symptoms worsen after initial treatment, administer a second dose of neffy in the same nostril with a new nasal spray starting 5 minutes after the first dose.
Applicant Proposed Indication(s)/Population(s)	For emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 15 kg to less than 30 kg.
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 4 years and older who weigh 15 kg to less than 30 kg.
Recommended Dosing Regimen	Same as Applicant's proposed dosing regimen

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OPQ=Office of Pharmaceutical Quality
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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

AE	adverse event
AUC	area under the concentration-time curve
C_{max}	maximum plasma concentration
CR	clinical response
DBP	diastolic blood pressure
EMA	European Medicines Agency
LLOQ	lower limit of quantification
MAP	mean arterial blood pressure
MedDRA	Medical Dictionary for Regulatory Activities
NAC	nasal allergen challenge
NDA	new drug application
OFC	oral food challenge
OSIS	Office of Study Integrity and Surveillance
PD	pharmacodynamic
PK	pharmacokinetic
PMR	postmarket requirement
PR	pulse rate
PREA	Pediatric Research Equity Act
PT	preferred term
SAE	serious adverse event
SBP	systolic blood pressure
SBP	systolic blood pressure
TBM	to-be-marketed
T_{max}	time to maximum concentration

1. Executive Summary

1.1. Product Introduction

ARS-1 (neffy), epinephrine nasal spray, was first approved on August 9, 2024, as a 2 mg dose for the "emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater." The approval of ARS-1 included a Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR) to "conduct a single-dose, pharmacokinetic and pharmacodynamics study of neffy (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."

ARS Pharmaceuticals (Applicant) now submits a supplement (S-001) to the new drug application (NDA) 214697 for a 1 mg dose to expand the ARS-1 indication to include children ≥4 years of age and weighing 15 to <30 kg. The new ARS-1 indication is for the "emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients 4 years of age and older who weigh 15 kg or greater." The recommended dosages are:

- For patients weighing 30 kg or greater: one spray of neffy 2 mg (0.1 mL)
- For patients weighing 15 kg to less than 30 kg: one spray of neffy 1 mg (0.1 mL)

In absence of clinical improvement or if symptoms worsen after initial treatment, patients may administer a second dose of neffy in the same nostril with a new nasal spray starting 5 minutes after the first dose.

Epinephrine is a direct-acting, nonselective, sympathomimetic, alpha- and beta-adrenergic agonist that acts systemically through vasoconstriction, relaxation of smooth muscle, and increased rate and force of cardiac contractions, leading to decreased mucosal edema, bronchodilation, and increased cardiac output. Epinephrine is the first-line and only life-saving treatment for anaphylaxis. ARS-1 is the first epinephrine product approved for treatment of anaphylaxis that is not administered via injection or intravenous infusion.

ARS-1 contains a [redacted] (b) (4) (n-dodecyl beta-D-maltoside [DDM]) to enhance absorption of epinephrine. The solution is packaged into a nasal spray device; the device is the same as naloxone nasal spray for the treatment of opioid overdose, as well as other approved nasal spray products.

For this supplement, an age limit for patients ≥4 years of age is added as the device is not fit-for-purpose for <4 years of age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action for this supplement is **Approval** of the 1 mg ARS-1 dose for the emergency treatment of type I allergic reactions, including anaphylaxis, in pediatric

patients aged ≥4 years who weigh 15 to <30 kg. The approval is based on extrapolation of the previously demonstrated efficacy of the 2 mg ARS-1 dose for adults who weigh ≥30 kg.

Pediatric extrapolation allows extension of demonstrated efficacy from an adult population to a pediatric population if the disease, drug pharmacology, and expected response to therapy are sufficiently similar between the populations, as outlined in Guidance for Industry- *E11A Pediatric Extrapolation* (December 2024). Given there is a high degree of similarity in anaphylaxis between adult and pediatric subjects, with shared pathophysiology (acute activation of mast cells and/or basophils), disease definition, course of disease, and response to treatment with epinephrine, extrapolation of efficacy from adults to children ≥4 years of age is supported.

Demonstration of substantial evidence of effectiveness for the 2 mg ARS-1 dose in adults was based on establishment of an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and >100 years of use. The bridge was established with pharmacokinetic (PK) bracketing to Adrenalin and EpiPen, as well as supportive hemodynamic pharmacodynamics (PD) results (systolic blood pressure (SBP) and pulse rate (PR) change from baseline), in healthy adults and adults with type 1 allergic diseases, namely allergic rhinitis. Inclusion of pediatric patients ≥30 kg in the initial approval relied on demonstration of similar PK/PD of 2 mg ARS-1 between pediatric subjects ≥30 kg and adults, and extrapolation of efficacy from adults. Details of the supporting data can be found in multidisciplinary reviews dated September 19, 2023, and August 5, 2024.

To support this application, the Applicant completed one single-dose, clinical pharmacology PK/PD trial (EPI 10), with the proposed 1 mg dose, in 21 subjects 4 to 11 years of age, weighing 15 to <30 kg, with a history of systemic (type I) allergies that require epinephrine prescription, but who were not undergoing anaphylaxis. An epinephrine injection product comparator was not included in the trial due to ethical considerations with administration of epinephrine in pediatric subjects not undergoing anaphylaxis. Results from the trial demonstrated that epinephrine exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is similar to pediatric subjects ≥30 kg following 2 mg ARS-1, and approximately 50% higher compared to adults following single-dose administration of 2 mg ARS-1. In addition, a similar hemodynamic PD response (i.e., SBP and PR) was observed between pediatric subjects 15 to <30 kg following 1 mg ARS-1 and pediatric subjects ≥30 kg following 2 mg ARS-1. The SBP response was smaller compared to adults, while the PR response was within the range of adults.

The overall PK/PD similarity between children 15 to <30 kg and children and adults who weigh ≥30 kg supports full extrapolation of efficacy from adults. As a result, substantial evidence of effectiveness has been demonstrated and the recommended regulatory action is approval of the 1 mg ARS-1 dose for children 15 to <30 kg.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Epinephrine is considered 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. Epinephrine was only available by injection (intramuscular or subcutaneous), or intravenously, until the approval of ARS-1 (epinephrine nasal spray) 2 mg for adults and pediatric subjects who weigh ≥30 kg in August 2024. Substantial evidence of effectiveness for ARS-1 was demonstrated in adults based on establishment of an adequate scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and >100 years of use. The bridge was established with pharmacokinetic (PK) bracketing to Adrenalin and EpiPen, as well as supportive hemodynamic pharmacodynamic (PD) results (systolic blood pressure [SBP] and pulse rate [PR] change from baseline), in healthy adults and adults with type 1 allergic diseases, namely allergic rhinitis. Inclusion of pediatric patients ≥30 kg in the initial approval relied on demonstration of similar PK/PD of 2 mg ARS-1 between pediatric subjects ≥30 kg and adults, and extrapolation of efficacy from adults.

Expanding the availability of ARS-1 for the treatment of anaphylaxis for patients ≥4 years of age who weigh 15 to <30 kg may reduce barriers to administration of epinephrine in this patient population. 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 and 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.

To support the efficacy and safety of 1 mg ARS-1 in pediatric patients aged ≥4 years who weigh 15 to <30 kg for the emergency treatment of type I allergic reactions, including anaphylaxis, the Applicant completed one single-arm PK/PD trial (EPI 10) in subjects 4 to 11 years of age with systemic type 1 allergy requiring an epinephrine prescription, but who were not undergoing anaphylaxis. EPI 10 demonstrated PK/PD similarity for 1 mg ARS-1 in pediatric subjects 15 to <30 kg compared to 2 mg ARS-1 in pediatric and adult subjects who weigh ≥30 kg. Given the high degree of similarity in anaphylaxis between adult and pediatric subjects 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 supported. For this supplement, an age limit for patients ≥4 years of age is added as the device is not fit-for-purpose for children <4 years of age.

The safety of 1 mg ARS-1 for pediatric subjects 15 to <30 kg was assessed in EPI 10. No SAEs or discontinuations due to AEs were reported. Adverse events in pediatric subjects 15 to <30 kg included nasal congestion, upper respiratory tract congestion, dry throat, nasal dryness, and paresthesia. Due to the limited sample size and uncontrolled design of the pediatric study, the local safety of 1 mg ARS-1 also relies on extrapolation from adults receiving 2 mg ARS-1 dose. Adverse events observed in adults included nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, and throat irritation. Local safety of multiple doses in adults is limited. Assessment of systemic safety of 1 mg ARS-1 relies on the known safety of the listed epinephrine injection products. The PK for 1 mg ARS-1 in pediatric subjects 15 to < 30 kg was 50% higher compared to adults receiving 2 mg ARS-1, but it is expected to be comparable or lower than EpiPen Jr.; therefore, the safety of the higher PK in children compared to adults is supported from clinical experience EpiPen Jr. 0.15 mg (for 15 to < 30 kg) (NDA 019430) in this population.

Overall, the benefit-risk assessment for 1 mg ARS-1 for patients ≥4 years of age and weighing 15 to <30 kg is favorable and supports approval.

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 for anaphylaxis, primarily due to allergy to foods, drugs, and Hymenoptera venom, among other causes.	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 in this weight range (15 to <30 kg). • Epinephrine nasal spray for adult and pediatric patients who weigh ≥30 kg was approved in August 2024. • Early administration of epinephrine reduces morbidity and mortality from anaphylaxis. Barriers to administration of epinephrine injection for treatment of anaphylaxis include needle phobia.	Epinephrine injection products are safe and effective. There is an unmet need for epinephrine products that are not administered via injection or intravenous infusion in pediatric subjects <30 kg that may increase use and reduce time to administration.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• 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. • Given the 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. • The overall PK/PD comparison results between children 15 to <30 kg who received 1 mg ARS-2 and children and adults who weigh ≥30 kg who received 2 mg ARS-1 support the proposed 1 mg ARS-1 dose in children 15 to <30 kg.	Early administration of epinephrine is the cornerstone of anaphylaxis management. This new route of administration has the potential to address barriers to epinephrine administration by fostering improved compliance and earlier administration compared to epinephrine injection products in children 4 years of age and older and 15 to < 30 kg. Efficacy and safety for pediatric subjects is based on extrapolation from adults given the limitations of the pediatric data. The device is fit-for-purpose for patients ≥4 years of age.
Risk and Risk Management	• The safety of 1 mg ARS-1 for pediatric subjects 15 to <30 kg was assessed in EPI 10. No SAEs or discontinuations due to AEs were reported. Adverse events in pediatric subjects 15 to <30 kg include nasal congestion, upper respiratory tract congestion, dry throat, nasal dryness, and paresthesia. • Due to the limited sample size and uncontrolled design of the pediatric study, the local safety of 1 mg ARS-1 also relies on extrapolation from adults receiving 2 mg ARS-1 dose in adults.	Patients with altered nasal anatomy such as those with nasal polyps or previous surgery were not enrolled in the clinical pharmacology trials. It is unknown whether underlying structural or anatomical nasal conditions would impact absorption of ARS-1. Labeling advises such patients consider use of an alternative route of epinephrine. The program does not demonstrate any safety findings that offset the efficacy findings, particularly

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Adverse events observed in adults include nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, and throat irritation. Local safety of multiple doses in adults is limited. • Systemic safety of ARS-1 for pediatric subjects 15 to <30 kg relies on the known safety profile of epinephrine injection products. The PK for 1 mg ARS-1 in pediatric subjects 15 to < 30 kg was 50% higher compared to adults receiving 2 mg ARS-1, but is expected to be comparable or lower than EpiPen and EpiPen Jr.; therefore, the safety of the higher PK in children compared to adults is supported from clinical experience from EpiPen 0.3 mg (for ≥ 30 kg) and EpiPen Jr. 0.15 mg (for 15 to < 30 kg) (NDA 019430) in this population.	for a product indicated for emergency use that should be administered infrequently. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance. 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 that was issued at the time of approval of ARS-1 (August 2024).

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	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):		
☐	**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: Discussion of need for alternative routes for epinephrine administration at the September 9, 2021, externally led Patient-Focused Drug Development meeting for food allergy.		
	☐	Observational survey studies designed to capture patient experience data		

	X	Other: (Please specify): Public comments at the May 11, 2023 meeting of the Pulmonary-Allergy Drugs Advisory Committee meeting to discuss the original NDA submission	
	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). In a review of International Classification of Diseases, 10th Edition codes from a U.S. National Morality Database (1999 to 2010), 2,458 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).

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. Based on a 2021 National Health Interview Survey it is estimated that approximately 6% of children 0 to 17 years of age are diagnosed with a food allergy (Zablotsky et al. 2023). The potential for anaphylaxis has a large impact on children's quality of life. Due to the fear of anaphylaxis, 25% of parents surveyed relayed they do not send their children to camp, 15% do not go to restaurants, and 10% avoid childcare settings or playdates (Bollinger et al. 2006). Underuse of epinephrine is prevalent in the pediatric population.

2.2. Analysis of Current Treatment Options

Prior to the approval of ARS-1 in August 2024, epinephrine injection was the only approved route of administration for the treatment of anaphylaxis for adult and pediatric patients weighing ≥30 kg. Epinephrine injection is the only route of administration currently approved for the 15 to <30 kg patient population.

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 injection (intramuscular 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). Currently approved epinephrine products for the treatment of anaphylaxis are listed in (Table 2). Epinephrine injection products prescribed for the community setting are generally dispensed as two devices. Dosing can be repeated with severe persistent anaphylaxis, with national and international guidelines recommending dosing every 5 to 15 mins (Sampson et al. 2006). 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

	Body Weight		
Setting	**7.5 to 15 kg**	**15 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 to 0.5 mg

Source: Prescribing information

Table 2. Approved Epinephrine Products

Type of Product **Drug Product** ***(Sponsor)***	**Year of Approval**	**Dosage Strength**	**Approved Population**	**Dosage Form**
Epinephrine nasal spray (home use)				
ARS-1 *(ARS Pharmaceuticals)*	2024	2 mg/spray	4 years and ≥30 kg	Single dose, nasal spray
Autoinjectors (home use)				
EpiPen/EpiPen Jr and authorized generic *(Mylan Specialty LP)*	1987	0.15 mg/injection 0.3 mg/injection	15 to <30 kg ≥30 kg	Single dose, autoinjector
Adrenaclick and authorized generic (*Impax Labs, Inc.)*	2003	0.15 mg/injection 0.3 mg/injection	15 to <30 kg ≥30 kg	Single dose, autoinjector
Auvi-Q *(Kaleo, Inc.)*	2012	0.1 mg/injection 0.15 mg/injection 0.3 mg/injection	7.5 to 15 kg 15 to <30 kg ≥30 kg	Single dose, autoinjector

Type of Product Drug Product *(Sponsor)*	Year of Approval	Dosage Strength	Approved Population	Dosage Form
Generic EpiPen/EpiPen Jr *(Teva)*	2018	0.15 mg/injection 0.3 mg/injection	15 to <30 kg ≥30 kg	Single dose, autoinjector
Prefilled syringe (home use)				
Symjepi *(Adamis Pharms Corp)*	2017	0.3 mg/0.3 mL	≥30 kg	Single dose, prefilled syringe
Vial-syringe (medical setting only)				
Adrenalin and epinephrine injection *(Multiple companies)*	2012	1 mg base/mL	All patients, weight based dosing	Single use and multidose vial

Source: Clinical and clinical pharmacology reviewers

As discussed in the initial review of the NDA 214697 application, 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 intramuscular or subcutaneous doses are based on anecdotal clinical experience.

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). 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. ARS-1 would be the first available epinephrine for the treatment of anaphylaxis for the 15 to <30 kg population that is not administered by injection.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ARS-1 (2 mg) was approved on August 9, 2024, for the emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh ≥30 kg. The same product, named EURneffy, was approved by the European Medicines Agency (EMA) on June 28, 2024, for the same indication. We refer the reader to two multidisciplinary reviews for the detailed regulatory history of epinephrine and ARS-1 development:

- Multidisciplinary review of the original neffy NDA submission, uploaded to DARRTS on September 19, 2023, that led to a Complete Response action

- Multidisciplinary review of the neffy NDA resubmission, uploaded to DARRTS on August 5, 2024, that led to the approval action

3.2. Summary of Presubmission/Submission Regulatory Activity

The original NDA for ARS-1 triggered the Pediatric Research Equity Act (PREA) as ARS-1 is a new route of administration for epinephrine. 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 the 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 waiver was granted with the approval of ARS-1 on August 9, 2024, and PREA postmarketing requirement (PMR) 4671-1 was established:

> 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 purpose of this supplement is to fulfill the PMR as it contains the remaining data for children 4 to 11 years of age who weighed 15 to <30 kg and received the 1 mg ARS-1 dose.

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

4.1. Office of Study Integrity and Surveillance

An Office of Study Integrity and Surveillance (OSIS) inspection was requested for the new clinical site for EPI 10 at Treasure Valley Medical Research in Boise, Idaho. An inspection was conducted and there were no identifiable concerns for this clinical site regarding reliability of the data or human subject protection for the inspected study, EPI 10. Refer to the Bioequivalence Establishment Inspection Report Review dated January 27, 2025.

A new analytical site was used for EPI 10, which is the same analytical site for EPI 17 (b) (4) . See original NDA review dated September 19, 2023, regarding OSIS inspection results for analytical sites for EPI 10 and EPI 17, and other clinical sites used for EPI 10.

4.2. Product Quality

Epinephrine will be delivered via a single-use nasal spray device which administers one 1 mg in 100 µL in one spray. The proposed 1 mg formulation, which includes a 125 uL overfill and 10% overage, aligns with the approved 2 mg formulation, except for the quantity of the Active Pharmaceutical Ingredient (API). The current manufacturing process, analytical method, drug product specifications, and container closure is maintained from the 2 mg dose. 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. The 24-month proposed expiry is supported and aligns with the 24-month expiry approved for 2 mg ARS-1. The Applicant provided an Environmental Analysis Categorical Exclusion Assessment. Review of the data submitted is adequate for the exclusion justification. See the review by Sara Zimmerman, PhD, for further details.

4.3. Clinical Microbiology

No new microbiology was submitted for this supplement.

4.4. Devices and Companion Diagnostic Issues

No new device information was submitted for this supplement. This indication will be restricted to those ≥ 4 years of age as the device is not fit-for-purpose for pediatric subjects < 4 years of age. The same device is approved without an age restriction for naloxone, indicated for the emergency treatment of known or suspected opioid overdose. Naloxone is known to have a wide therapeutic window with no safety concerns if the targeted pharmacokinetic concentration is overshot. Therefore, even if the device does not properly fit children <4 years

of age, enough drug will be absorbed without safety or efficacy concerns. Epinephrine, for the indication of anaphylaxis, does not have the same efficacy and safety profile as naloxone, and therefore it is necessary to ensure the device can fit into the nostril properly so that proper administration and absorption can occur. Therefore, the device will be limited to the age range for which the device is fit-for-purpose.

5. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted for this supplement.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 3. ARS-1 Supplement-1 Pharmacology Trial

Study Name	Study Design	Objective of the Study	ARS-1	Number of Subjects	Population
EPI 10 Pediatric PK/PD, safety trial	Phase 1, single-dose, single-treatment trial	Assess the PK/PD and safety of three doses of ARS-1 in pediatric allergy subjects ages 4 to 17 years old.	0.65 mg 1 mg 2 mg	0.65 mg 15 to <30 kg n=12 1 mg 15 to <30 kg n=21 1 mg ≥30 kg n=26 2 mg ≥30 kg n=21	Pediatric patients who have type I allergies requiring epinephrine autoinjector prescription

Source: FDA Clinical Reviewer.
Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic.

6.2. Review Strategy

No clinical efficacy trials were conducted to support this supplemental NDA. This review focuses on one pediatric clinical pharmacology and safety trial, EPI 10. The review includes a brief description of the EPI 10 protocol in Section 7, followed by the clinical pharmacology results in Section 8, and safety results in Section 9.

Interim results from the EPI 10 trial, specifically for pediatric subjects ≥30 kg, age range 8 to 17 years, were submitted and analyzed with the original NDA, and supported pediatric approval for patients ≥ 30 kg. This submission includes the completed results for EPI 10. The protocol review and demographics includes the complete results across all age and weight ranges. The clinical pharmacology and safety results, however, focus on children weighing 15 to <30 kg (aged 4 to 11 years) who received the 1 mg ARS-1 dose (the proposed marketed dose) in the EPI 10 trial.

With the original NDA submission, the Applicant included results from trials EPI 03, EPI 04, EPI 07, EPI 12, and JP01 that studied adults receiving a 1 mg ARS-1 dose, but they were not considered pivotal and were not reviewed. Results from these trials were resubmitted with this NDA supplement; however, since they do not inform the efficacy and safety of 1 mg in pediatric subjects 15 to <30 kg, they were similarly not reviewed with this supplement.

The Applicant also conducted and submitted results from additional trials conducted in Japan in adults (JP02) and children (JP03). JP02 compared a single-dose of 2 mg ARS-2 to IM adrenalin in healthy Japanese adults. The trial results did not add new information that was relevant to this pediatric supplement and were not reviewed. JP03 is a single-arm, single-dose trial assessing the efficacy of ARS-1 (1 mg or 2 mg, based on weight) in 15 children with allergic/anaphylaxis symptoms induced by an oral food challenge. JP03 was not reviewed as the trial was small and does not provide clinically meaningful data that inform the efficacy and safety of 1 mg ARS-1 in pediatric subjects 15 to < 30 kg. A summary of the JP03 results can be found in Section 16.4.

7. Pivotal Trial Protocol

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. 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

Trial Dates: July 17, 2020, to January 27, 2023

Trial Sites

- Massachusetts General Hospital, 55 Fruit St, CPZS 533, Boston, MA 02114
- Children's Hospital Colorado, 13 123 East 16th Ave, Aurora, CO 80045
- Institute for Asthma & Allergy, P.C, 2 Wisconsin Circle, Chevy Chase, MD 20815
- University of South Florida, 13801 Bruce B. Downs Blvd, Tampa, FL 33613
- Treasure Valley Medical Research, 1000 North Curtis Road Suite 102, Boise, ID 83706

Trial Report Date: December 15, 2023; Amendment Report Date: January 19, 2024

Trial Design

A phase 1, single-dose trial that assessed the PK/PD of 0.65 mg, 1 mg, and 2 mg ARS-1 doses in pediatric subjects 4 to 17 years of age with type I systemic allergies that require epinephrine prescription. Each subject received one dose of ARS-1 based on body weight. The study included 80 pediatric subjects.

Trial Part 1

- Subjects 15 to <30 kg received a single 0.65 mg/100 µL (with 0.25% or 0.35% DDM) dose of ARS-1 in the left naris.
- Subjects ≥30 kg received a single 1 mg/100 µL (with 0.25% DDM) dose of ARS-1 in the left naris.

Trial Part 2

- Subjects 15 to <30 kg received a single 1 mg/100 µL (with 0.275% DDM) dose of ARS-1 in the left naris.
- Subjects ≥30 kg received a single 2 mg/100 µL (0.275% DDM) dose of ARS-1 in the left naris.

The Applicant first conducted Part 1 to explore dosing and formulations in pediatric subjects. Following Part 1, the Applicant then conducted Part 2 with the to-be-marked formulations to confirm doses (i.e., 1 mg for 15 to less than 30 kg and 2 mg for 30 kg or greater) that are intended for approval in the pediatric population. In the original NDA submission, the Applicant submitted PK/PD data for Part 1 and a portion of Part 2 (16 subjects weighing 30 kg or greater treated with 2 mg and 3 subjects weighing 15 to < 30 kg treated with 1 mg). The PK/PD data for the 16 pediatric subjects treated with 2 mg ARS-1 was reviewed to support the approval of 2 mg during the original NDA review. See Section 16 for more details regarding EPI 10 submission history.

Study Endpoints

Primary Endpoints

PK and PD parameters- see Section 8 for details.

Secondary Endpoint

Safety and tolerability of ARS-1 in pediatric allergy subjects- see Section 9 for details.

Statistical Analysis Plan

Not applicable.

Protocol Amendments

There were four protocol amendments:

- The first amendment, submitted March 24, 2020, took into account the recommendations made by the Agency. 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, considered suggestions from the EMA. Specifically, the EMA disagreed that children were excluded if they had congestion, given that in real life, children may be congested at baseline when receiving intranasal products. Therefore, children were allowed to have baseline congestion, but needed to be off antihistamines 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 and, therefore, increased the number of targeted subjects to enroll (from approximately 60 to 70 subjects).

- The fourth amendment, submitted September 8, 2021, provided additional safety data from the adult trial (2 mg ARS-1) and minor edits to the protocol with no substantive changes.

7.1.2. Study Results

Compliance With Good Clinical Practices

EPI 10 was conducted in accordance with Good Clinical Practice as required by the International Council for Harmonisation 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 16.2 of this review for additional details.

Patient Disposition

For Part 2, of the 21 subjects weighing 15 to <30 kg who received 1 mg ARS-1, 5 were re-enrolled from Part 1 during which they were treated with ARS-1 (0.65 mg). For the 21 subjects weighing 30 kg and above who received 2 mg ARS-1 in Part 2, a total of 12 subjects were re-enrolled from Part 1. In addition, one subject who weighed ≥30 kg initially received 1 mg in Part 1 and was supposed to be re-enrolled to receive 2 mg in Part 2, but actually received 1 mg. The PK of this subject was not included in the Part 2 PK assessment.

Protocol Violations/Deviations

During the trial, there were 165 protocol deviations in 51 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 informed consent form (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 4. For this supplement, the population that was reviewed included the subjects who weighed 15 to <30 kg and received 1 mg ARS-1. This cohort ranged in age from 4 to 11 years old, with a mean age of 8 years. The cohort was predominantly white (71%) and male (62%).

Table 4. EPI 10 Demographics in Subjects Who Received 0.65 mg, 1 mg, and 2 mg ARS-1

Demographic	ARS-1 0.65 mg 15 to <30 kg N=12 n (%)	ARS-1 1 mg 15 to <30 kg N=21 n (%)	ARS-1 1 mg ≥30 kg N=26 n (%)	ARS-1 2 mg ≥30 kg N=21 n (%)
Age (years)				
Mean (SD)	8 (2)	8 (2)	13 (2)	14 (2)
Median	8	8	14	14
Minimum, Maximum	4, 11	4, 11	9, 17	8, 17
Sex				
Male	6 (50)	13 (62)	15 (58)	12 (57)
Female	6 (5)	8 (38)	11 (42)	9 (43)
Race				
White	9 (75)	15 (71)	18 (69)	15 (71)
Black or African American	2 (17)	3 (14)	6 (23)	4 (19)
Asian	1 (8)	1 (5)	2 (8)	1 (5)
Other	0	2 (10)	0	1 (5)
Ethnicity				
Hispanic or Latino	1 (8)	3 (14)	2 (8)	0 (0)
Not Hispanic or Latino	11 (92)	18 (86)	24 (92)	21 (100)

Source: Clinical Review, JMP
Abbreviations: SD, standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No concomitant medications were permitted during this trial. Medications necessary to manage chronic conditions (including hormonal contraceptives), which could not have been discontinued in the opinion of the principal investigator and approved by the Medical Monitor, were allowed. These were unlikely to have resulted in an impact on PKs and safety. Medications included stimulants, inhaled corticosteroids, oral antihistamines, and topical steroids.

Data Quality and Integrity

This submission was appropriately indexed and complete to permit review.

8. Clinical Pharmacology

8.1. Executive Summary

The Applicant submitted a Prior Approval Supplement dated September 6, 2024, in support of neffy (ARS-1) 1 mg for the treatment of type I allergic reactions including anaphylaxis in

pediatric subjects weighing 15 to <30 kg, as well as to fulfill the PREA postmarketing commitment issued in the NDA 214697 approval letter dated August 9th, 2024:

> **4671-1** Conduct a single-dose, pharmacokinetic and pharmacodynamics study of neffy (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.

This supplemental NDA is primarily supported by a single-arm, single-dose PK/PD and safety pediatric study (EPI 10) that evaluated 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg. Of note, the interim study report of EPI 10 with PK/PD data of 2 mg ARS-1 in pediatric subjects weighing ≥30 kg (N=16) was submitted and reviewed in the original NDA submission. In the same submission, some PK/PD data from pediatric subjects weighing 15 to <30 kg who received 1 mg ARS-1 (N=3) were also included. However, as the study was ongoing, the results from this weight group were not reviewed in the original NDA. See Multidisciplinary Review dated September 19, 2023, for details.

In the final EPI 10 study report submitted to this supplement, PK/PD data for 1 mg ARS-1 from 21 pediatric subjects weighing 15 to <30 kg were included. In addition, new PK/PD data following 2 mg ARS-1 from 5 additional subjects weighing ≥30 kg were also included.

The key clinical pharmacology review question for this supplement focuses on the evaluation of EPI 10 PK and PD results from pediatric subjects weighing 15 to <30 kg who received 1 mg ARS-1 compared to the results from adult subjects who received 2 mg ARS-1. In addition, the review team will update the PK/PD results in pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 after including 5 new subjects.

EPI 10 results demonstrated that epinephrine exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is approximately 50% higher than in adults following 2 mg ARS-1 and similar to the systemic epinephrine exposure in pediatric subjects ≥30 kg following 2 mg ARS-1. In addition, a smaller systolic blood pressure (SBP) response was noted for pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 when compared to adult results from EPI 15 and EPI 17, while the PR response in this pediatric population was within the range of adult results from EPI 15 and EPI 17. A similar PD response (including SBP and PR) was observed between pediatric subjects 15 to <30 kg following 1 mg ARS-1 and pediatric subjects ≥30 kg following 2 mg ARS-1.

8.1.1. Recommendation

The Office of Clinical Pharmacology has reviewed the information contained in NDA 214697 and concluded that the epinephrine systemic exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is about 50% higher than in adults following 2 mg ARS-1; and similar to the systemic exposure in pediatric subjects ≥30 kg following 2 mg ARS-1. In addition, a similar PD/vital sign response was observed between pediatric subjects 15 to <30 kg following 1 mg ARS-1 and pediatric subjects ≥30 kg following 2 mg ARS-1. In general, the SBP

response in children is numerically lower than adults; however, the clinical meaning of this observation is unclear. The overall PK/PD comparison results between children 15 to <30 kg and children and adults ≥30 kg support the proposed 1 mg ARS-1 dose in children 15 to <30 kg from the clinical pharmacology perspective. The safety of higher PK in children compared to adults is supported from clinical experience from EpiPen 0.3 mg (for ≥ 30 kg) and EpiPen Jr. 0.15 mg (for 15 to < 30 kg) (NDA 019430) in this population. A comparable or lower systemic exposure following ARS-1 compared to EpiPen and EpiPen Jr. is expected in children for respective body weight groups, based on PK comparison results between pediatric subjects following ARS-1 (EPI 10) and adults following EpiPen (EPI15) and allometric estimate for adults vs. children on EpiPen and EpiPen Jr. The completion of the trial fulfills PREA PMR 4671-1.

8.2. Summary of Clinical Pharmacology Assessment

8.2.1. Pharmacology and Clinical Pharmacokinetics

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

8.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed 1 mg ARS-1 to be administered into one nostril for both adult and pediatric patients who weighed 15 to <30 kg; and 2 mg ARS-1 to be administered into one nostril for adult and pediatric patients who weigh ≥30 kg. Technically the 1 mg dose is irrespective of age; however, it is unlikely that an adult would weigh <30 kg (66 lbs).

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 second nasal spray starting 5 minutes after the first dose.

The proposed weight tier regardless of age is the same as the epinephrine listed injection products EpiPen (NDA 019430) and Adrenalin (NDA 204200).

Therapeutic Individualization

Dose adjustment of ARS-1 was proposed to be based on body weight (i.e., 15 to <30 kg and ≥30 kg). The PK following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg is similar to that following 2 mg ARS-1 in pediatric subjects weighing ≥30 kg.

Outstanding Issues

None.

8.3. Comprehensive Clinical Pharmacology Review

8.3.1. General Pharmacology and Pharmacokinetic Characteristics

See the 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 (one dose; interim report of EPI 10).

See NDA resubmission review dated August 9, 2024, regarding PK and PD following two doses of ARS-1 in adults with NAC-induced rhinitis (EPI 18).

8.3.2. Clinical Pharmacology Questions

Is there an update of bioanalytical assay in this pediatric supplement?

A new bioanalytical method (E23 version 00, report MV(C)-179-22) in a new analytical site ((b) (4) was used to analyze the PK samples following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg (N=21). All PK samples following 2 mg ARS-1 in pediatric subjects weighing ≥30 kg (including the 16 subjects reviewed in original NDA and 5 new additional subjects) were also analyzed/re-analyzed using this new method and site. The change of bioanalytical method and analytical site was due to the previous analytical site ((b) (4)) that was used for the interim analysis of EPI 10 running into resource issues. The PK samples that were either new or previously analyzed by (b) (4) were within the long-term stability range (551 days) when analyzed/re-analyzed at the new site. Of note, in the original NDA review, interim PK samples from EPI 10 were analyzed at the same site ((b) (4) as those of adult PK trial EPI 15 with methods (ATM-2394 and ATM-2662 for EPI 10 vs. ATM-2648 and ATM2662 for EPI 15) deemed comparable upon review. Therefore, the cross-study comparison was conducted using EPI 15 data during review of the original NDA. See original NDA review dated September 19, 2023, for more details.

The new analytical site was the same site for analyzing PK samples from adult PK/PD trial EPI 17 (single-dose self-administration PK/PD trial in adult subjects with type 1 allergic reactions) that were also reviewed in the original NDA. OSIS inspection for this site has been requested and reviewed during the original NDA review. See original NDA review dated September 19, 2023, for more details.

Despite using the same analytical site as the adult PK trial EPI 17, this newly developed method was found to be different from that used previously in EPI 17 (E21 version 00, report MV(C)-150-20) in terms of sample preparation, sample volume, and limit of lower quantification (LLOQ). See original NDA review for bioanalytical assay assessment for EPI 17. A cross-validation was performed between E23 version 00 and E21 version 00. Results demonstrated that these two methods were comparable (see Section 16.3 for details). Therefore, the cross-study

comparison between EPI 10 and EPI 17 was supported by the cross-validation results of the bioanalytical assay.

In conclusion, all the pediatric epinephrine PK results for 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg and 2 mg ARS-1 in pediatric subjects weighing ≥30 kg summarized in this review are based on the plasma concentrations measured by the new bioanalytical assay (E23 version 00). The epinephrine PK results from subjects 15 to <30 kg following 1 mg from EPI 10 are compared to the PK results from adults following 2 mg from the self-administration study EPI 17. In addition, comparison is also conducted between pediatric subjects weighing 15 to <30 kg for 1 mg ARS-1 and pediatric subjects weighing ≥30 kg for 2 mg ARS-1 based on the same new bioanalytical assay.

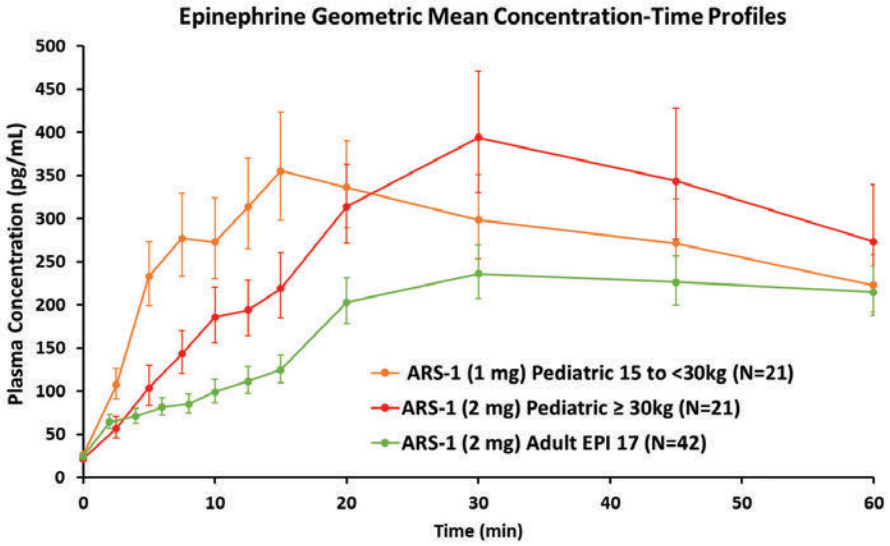
Are the PK/PD results from a single-arm pediatric PK trial sufficient to support the proposed dose of 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg?

The Applicant conducted a single-arm PK/PD trial (EPI 10) in pediatric subjects aged 4 to 17 years with a systemic (type 1) allergic reaction to assess the PK/PD of a single dose of ARS-1. The trial includes two groups divided by weight: 15 to <30 kg (N=21) and ≥30 kg (N=21). The interim report with PK/PD data from 16 subjects with body weight ≥30 kg who received 2 mg ARS-1 was reviewed and supported the approval of ARS-1 in pediatric subjects ≥30 kg. See original NDA review dated September 19, 2023, for details.

PK Results

The new PK data from pediatric subjects weighing 15 to <30 kg who received 1 mg ARS-1 and five new pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 were included in this submission. The geometric mean plasma concentration profiles and PK parameters of these subjects compared to that of adults data from EPI 17 are shown in Figure 1 and Table 5, respectively. The results demonstrate that the epinephrine plasma concentrations following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg were generally higher (geometric mean of maximum plasma concentration [C_{max}] and area under curve [AUC]$_{0\text{-}60min}$ were 57 and 48% higher, respectively) than those of adults following 2 mg ARS-1 within 60 minutes post-dose. The overall geometric mean values of epinephrine C_{max} and $AUC_{0\text{-}60\ min}$ within 60 minutes post-dose were generally comparable between the two pediatric populations, though the time to maximum concentration (T_{max}) was reached earlier in pediatric subjects weighing 15 to <30 kg. Of note, the original review (September 19, 2023, review, table 18) showed that the geometric mean of C_{max} and $AUC_{0\text{-}60min}$ in 16 pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 were 27 and 38% higher, respectively, than those of adults from EPI 15 based on a prior validated bioanalytical assay that was used to analyze samples in this development program (Method ATM-2648 and ATM2662).

Figure 1. Epinephrine Geometric Mean (± Standard Error) Plasma Concentration-Time Profile Following a Single Dose of 1 mg ARS-1 in Pediatric Subjects 15 to <30 kg and a Single Dose of 2 mg ARS-1 in Pediatric Subjects ≥30 kg From EPI 10 vs. a Single Dose of 2 mg ARS-1 in Adult Subjects From EPI 17



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for EPI 10 (submitted September 9, 2024) and EPI 17 (submitted August 19, 2022)

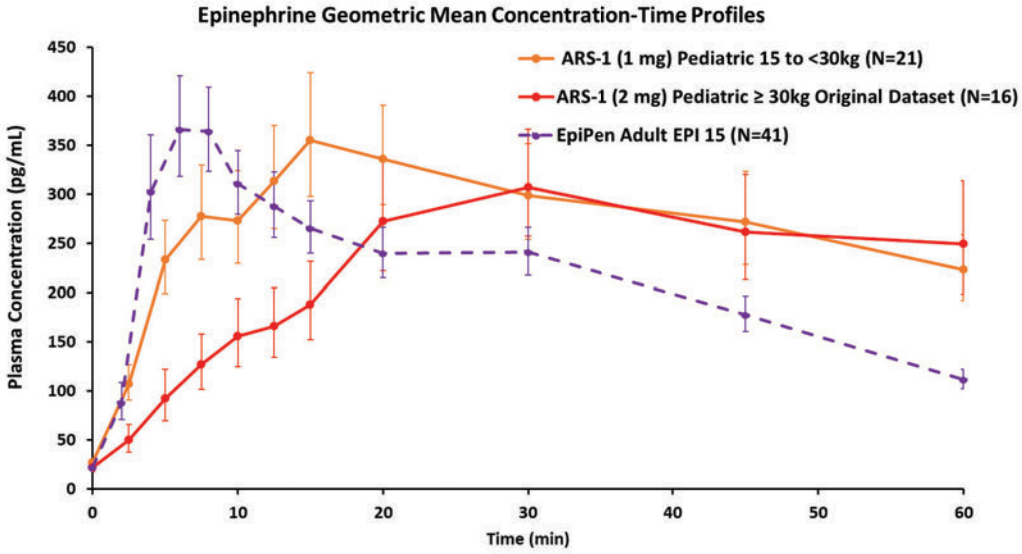
Table 5. PK Parameters Following a Single Dose of 1 mg ARS-1 in Pediatric Subjects 15 to <30 kg and a Single Dose of 2 mg ARS-1 in Pediatric Subjects ≥30 kg From EPI 10 vs. a Single Dose of 2 mg ARS-1 in Adult Subjects From EPI 17

	Geometric Mean (CV%)		
Parameter	Pediatric 15 to <30 kg ARS-1 1 mg N=21	Pediatric ≥30 kg ARS-1 2 mg N=21	Adults From Trial EPI 17 ARS-1 2 mg N=42
C_{max} (pg/mL)	519.8 (84.5)	507.77 (88.8)	331.9 (86.4)
T_{max} (min)[a]	20 (5, 60)	30 (2.5, 120)	30 (6, 240)
AUC_{0-10} (pg*min/mL)	2006.8 (77.8)	1101.4 (94.0)	787.7 (85.4)
AUC_{0-20} (pg*min/mL)	5557.7 (77.9)	3577.1 (76.5)	2317 (86.9)
AUC_{0-30} (pg*min/mL)	9014.4 (72.4)	7561.9 (73.1)	4758.5 (81.3)
AUC_{0-60} (pg*min/mL)	17767.3 (72.1)	18867.9 (84.5)	12029.5 (83.9)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for EPI 10 (submitted September 9, 2024) and EPI 17 (submitted August 19, 2022)
[a] Median (range)
Abbreviations: AUC, area under concentration-time curve; Cmax, maximum plasma concentration; CV, coefficient of variation; Tmax, time to maximum concentration.

Because epinephrine C_{max} and $AUC_{0-60min}$ following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg were approximately 50% higher than those of adults following 2 mg ARS-1, additional comparison was conducted between pediatric subjects following ARS-1 (from EPI 10) and adults following EpiPen (from EPI15) (Figure 2).

Figure 2. Epinephrine Geometric Mean (± Standard Error) Plasma Concentration-Time Profile Following a Single Dose of 1 mg ARS-1 in Pediatric Subjects 15 to <30 kg (New Dataset) and a Single Dose of 2 mg ARS-1 in Pediatric Subjects ≥30 kg (Original Dataset) From EPI 10 vs. a Single Dose of EpiPen in Adult Subjects From EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for EPI 10 (submitted September 9, 2024, for 15 to < 30 kg and submitted August 19, 2022, for ≥ 30 kg) and EPI 15 (submitted August 19, 2022)For an appropriate comparison, the epinephrine PK profiles of ARS-1 (2 mg) in pediatric subjects ≥ 30 kg (N=16, EPI 10) and EpiPen in adults (N=41, EPI 15) were from PK results using the same bioanalytical assay ((b) (4) method) as reviewed from the original submission. The epinephrine PK profile of ARS-1 (1mg) in pediatric subjects 15 to < 30 kg (N=21, EPI10) using the (b) (4) method is displayed only for interest. Refer to Figure 1for dedicated comparison between pediatric subjects 15 to < 30 kg (N=21, EPI 10) on 1 mg ARS-1 and pediatric subjects ≥30 kg (N=21, EPI 10) on 2 mg ARS-1 using the same bioanalytical method (b) (4).

As concluded from the original review of NDA 214697 (Table 18 of original review), the epinephrine concentrations following 2 mg ARS-1 in pediatric subjects ≥ 30 kg is numerically higher than that of adults following 2 mg ARS-1 after 10 minutes post-dose. This observation is 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). However, the epinephrine Cmax and partial AUCs (up to 30 minutes post-dose) values following 2 mg ARS-1 in pediatric subjects ≥ 30 kg is comparable to slightly lower than that of adults following 0.3 mg EpiPen (Table 6). Given the same allometric rationale that epinephrine systemic exposure is expected to be higher in pediatric subjects weighing ≥ 30 kg than that of adults who take the same dose (i.e., 0.3 mg) of EpiPen, the systemic exposure of epinephrine following 2 mg ARS-1 in pediatric subjects weighing ≥ 30 kg is expected to be lower than the same pediatric population on EpiPen (i.e., 0.3 mg). Therefore, the systemic safety of epinephrine following 2 mg ARS-1 in pediatric subjects weighing ≥ 30 kg can be extrapolated from EpiPen.

Table 6. PK Parameters Following a Single Dose of 2 mg ARS-1 in Pediatric Subjects ≥30 kg From EPI 10 (In Original Dataset) vs. a Single Dose of 0.3 mg EpiPen in Adult Subjects From EPI 15

	Geometric Mean (CV%)	
Parameter	Pediatric ≥30 kg ARS-1 2 mg N=16	Adults From Trial EPI 15 EpiPen 0.3 mg N=41
C_{max} (pg/mL)	433 (80)	618 (79)
T_{max} (min)[a]	25 (2.5, 120)	6 (2, 45)
AUC_{0-10} (pg*min/mL)	989 (112)	2979 (98)
AUC_{0-20} (pg*min/mL)	3147 (90)	6007 (77)
AUC_{0-30} (pg*min/mL)	6231 (78)	8759 (67)
AUC_{0-60} (pg*min/mL)	15126 (76)	14772 (56)

Source: Clinical Pharmacology Reviewer. Based on adpc.xpt for EPI 10 and EPI 15 (both submitted August 19, 2022)
[a] Median (range)
For an appropriate comparison, the epinephrine PK profiles of ARS-1 (2 mg) in pediatric subjects ≥ 30 kg (N=16, EPI 10) and EpiPen in adults (N=41, EPI 15) were from PK results using the same bioanalytical assay ((b) (4) method) as reviewed from the original submission.
Abbreviations: AUC, area under concentration-time curve; Cmax, maximum plasma concentration; CV, coefficient of variation; Tmax, time to maximum concentration.

Based on the allometric estimate from review of NDA 201739 S-008/009 dated September 27, 2017[1], epinephrine clearance increases approximately proportional to body weight increase. This estimate supports the reduction of epinephrine dose by half from the pediatric population weighing ≥ 30 kg (median body weight for boys and girls at 18 years of age is about 67 and 56 kg, respectively) to the pediatric population weighing 15 to < 30 kg. Indeed, the PK results from EPI 10 confirmed this allometric scale-based dose adjustment which showed comparable epinephrine systemic exposure between pediatric subjects 15 to <30 kg on 1 mg ARS-1 and pediatric subjects ≥30 kg on 2 mg ARS-1. Of note, the same dose adjustment was approved in pediatric subjects weighing 15 to <30 kg for EpiPen Jr. Although there is a lack of literature reporting a head-to-head comparison of epinephrine PK results between pediatric subjects 15 to <30 kg on EpiPen Jr. and adults on EpiPen, given the same allometric scaling rationale, the epinephrine systemic exposure in pediatric subjects 15 to <30 kg on EpiPen Jr. (i.e., 0.15 mg) is expected to be comparable to children ≥30 kg on EpiPen (i.e., 0.3 mg) and higher than that of adults on EpiPen (i.e., 0.3 mg).

In conclusion, considering the following information:

1. the observed comparable systemic exposure of epinephrine between pediatric subjects weighing 15 to <30 kg on 1 mg ARS-1 and pediatric subjects weighing ≥30 kg on 2 mg ARS-1;

[1] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8045e01d

2. the observed comparable systemic exposure of epinephrine between pediatric subjects weighing ≥30 kg on 2 mg ARS-1 and adults on 0.3 mg EpiPen; and
3. the expected higher epinephrine exposure in pediatric subjects 15 to <30 kg on 0.15 mg EpiPen Jr. compared to adults on 0.3 mg EpiPen,

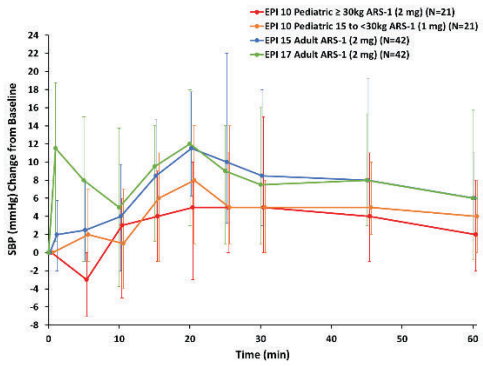
the systemic epinephrine exposure following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg on 1 mg ARS-1 is expected to be lower than the same pediatric population on EpiPen Jr. Therefore, the systemic safety of epinephrine following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg on 1 mg ARS-1 can be extrapolated from EpiPen Jr.

PD Results

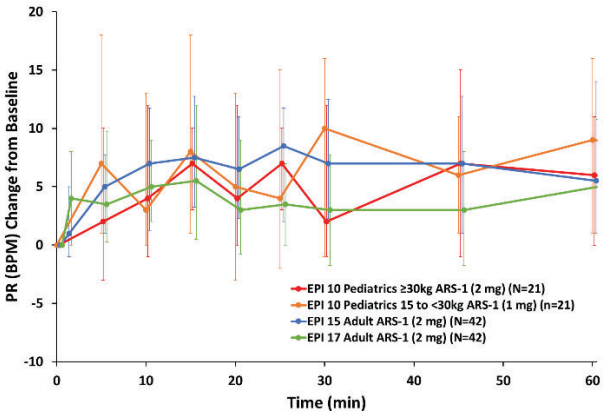
The PD results (SBP, PR, and diastolic blood pressure [DBP] change from baseline) for pediatric subjects from EPI 10 compared to adults from EPI 15 and EPI 17 are shown in Figure 3.

Figure 3. Median PD Responses (SBP, PR, and DBP Change From Baseline) Following a Single Dose of 1 mg ARS-1 in Pediatric Subjects 15 to <30 kg (Orange) and a Single Dose of 2 mg ARS-1 in Pediatric Subjects ≥30 kg (Red) From EPI 10 vs. a Single Dose of 2 mg ARS-1 in Adult Subjects (Green) From EPI 17 and From EPI 15 (Blue)

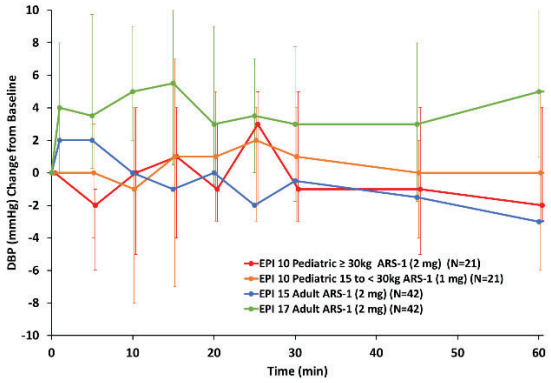
A. Median SBP Change From Baseline



B. Median PR Change From Baseline



C. Median DBP Change From Baseline



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt for EPI 10 (submitted September 9, 2024)
Error bars represent 25% and 75% percentile of the PD values.
Abbreviations: DBP, diastolic blood pressure; PD, pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure.

The PD responses were overall overlapping between pediatric subjects weighing 15 to <30 kg who received 1 mg ARS-1 and pediatric subjects weighing ≥30 kg who received 2 mg ARS-1.

In general, a smaller SBP response was noted for pediatric subjects from both body weight groups when compared to adult results from Trial EPI 15 and EPI 17, while the PR response for pediatric subjects from both body weight groups was within the range of adult results from EPI 15 and EPI 17.

The review team noted minor differences in some PD values reported for a few subjects between the new adxd.xpt dataset in this supplement and the original adxd.xpt dataset

submitted in the original NDA. During the review, the Applicant clarified that additional monitoring and data management review resulted in data correction for PD in three pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 at a single time point each (subject 02-119 at 5 minutes, subject (b) (6) at 120 minutes, and subject (b) (6) at -10 minutes). A sensitivity analysis was performed to evaluate the impact of the correction of the PD dataset and concluded the impact was minimal. See Section 16.3 for more details.

9. Clinical and Evaluation

9.1. Assessment of Efficacy for EPI 10

To support this application, the Applicant completed one single-dose clinical pharmacology PK/PD trial (EPI 10) with the proposed 1 mg dose in 21 pediatric subjects 15 to <30 kg from 4 to 11 years of age with systemic (type I) allergies who require epinephrine prescription, but who were not undergoing anaphylaxis. An epinephrine injection comparator was not included in the trial due to ethical considerations related to administration of epinephrine in pediatric subjects not undergoing anaphylaxis. Results from the trial demonstrated that epinephrine exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is similar to pediatric subjects ≥30 kg following 2 mg ARS-1, and approximately 50% higher compared to adults following 2 mg ARS-1. In addition, a similar PD response (i.e., SBP and PR), was observed between pediatric subjects 15 to <30 kg following 1 mg ARS-1 and pediatric subjects ≥30 kg following 2 mg ARS-1. The SBP response was smaller compared to adults, while the PR response was within the range of adults. The overall PK/PD comparison results between children 15 to <30 kg and children and adults who weigh ≥30 kg support the proposed 1 mg ARS-1 dose in children 15 to <30 kg.

As with the pediatric population ≥30 kg included in the original NDA submission, in considering the pediatric program for pediatric subjects >15 to <30 kg, extrapolation from the adult PK/PD program is necessary given the limitations of the pediatric data. Given there is a high degree of similarity in anaphylaxis between adult and pediatric subjects 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 supported. Therefore, substantial evidence of effectiveness is established based on extrapolation of the evidence that support substantial evidence of effectiveness for 2 mg ARS-1 for adults.

9.2. Review of Safety

9.2.1. Safety Review Approach

The safety of 1 mg ARS-1 for pediatric subjects 15 to <30 kg was assessed in EPI 10 and is the focus of this safety review. Due to the limited sample size and uncontrolled design of the EPI 10, the safety of 1 mg ARS-1 also relies on extrapolation from adults receiving 2 mg ARS-1 dose in adults. Assessment of systemic safety of ARS-1 relies primarily on the known safety of the listed epinephrine injection products since epinephrine exposure is comparable.

9.2.2. Review of the Safety Database

Overall Exposure

Safety support is derived from the 21 pediatric subjects in EPI 10 who weigh 15 to <30 kg and received one dose of 1 mg ARS-1.

Adequacy of the Safety Database

As EPI 10 is an uncontrolled, single-dose trial designed for PK extrapolation, safety conclusions from this trial are limited.

9.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this sNDA were identified.

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 4 hours post dose. Treatment-emergent AEs were events that were not present at baseline, or if present at baseline, worsened in severity after ARS-1 administration. For the EPI 10trial, due to the known mechanism of action of epinephrine, 'blood pressure increased' and 'heart rate increased' were not considered an AEs unless such events required treatment. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.0. The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate.

9.2.4. Safety Results

Deaths

There were no deaths during the trial.

Serious Adverse Events

There were no SAEs in the trial.

Dropouts and/or Discontinuations Due to Adverse Effects

For EPI 10, there were no dropouts or discontinuations due to adverse effects.

Common Adverse Events

The AEs that were reported at highest frequency for the 15 to <30 kg cohort, following administration of one spray of 1 mg ARS-1, include nasal congestion (19%), upper respiratory tract infection (14%), dry throat (10%), nasal dryness (10%), and paresthesia (10%) (Table 7). In general, the AEs reported were numerically higher in the pediatric population of EPI 10 compared to the AEs reported in the adult trials (nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, and throat irritation); however, safety conclusions from EPI 10 are limited due to the small size and single-arm design with no comparator. The majority of AEs were reported as mild.

Table 7. Common Adverse Events by SOC and PT in Subjects 15 to <30 kg Receiving 1 mg ARS-1

System Organ Class Preferred Term	ARS-1 1 mg 15 to <30 kg N=21 n (%)
Any AE	11 (52)
Investigations	1 (5)
Heart rate irregular	1 (5)
Nervous system disorders	2 (10)
Paresthesia	2 (10)
Respiratory, thoracic and mediastinal disorders	9 (43)
Nasal congestion	4 (19)
Upper respiratory tract congestion	3 (14)
Dry throat	2 (10)
Nasal dryness	2 (10)
Nasal discomfort	1 (5)
Nasal pruritus	1 (5)
Oropharyngeal pain	1 (5)
Rhinalgia	1 (5)
Rhinorrhea	1 (5)
Throat irritation	1 (5)
Upper-airway cough syndrome	1 (5)

Source: OCS Analysis Studio, Safety Explorer.
Abbreviations: AE, adverse event.

For comparison, the most common AEs reported with one dose of 2 mg ARS-1 in adults include nasal discomfort (10%), headache (6%), rhinorrhea (3%), dizziness (3%), nausea (3%), throat irritation (2%), and vomiting (2%). The frequency of AEs increase when two doses are administered.

Pediatric subjects (n=21) who weigh ≥30 kg received one nasal dose of 2 mg ARS-1 and common adverse reactions reported in these subjects include nasal discomfort (19%), intranasal paresthesia (19%), rhinorrhea (19%), sneezing (14%), epistaxis (10%), rhinalgia (10%), paresthesia (10%), fatigue (10%), and feeling jittery (10%). Of note, rhinorrhea is reported in

19% of pediatric subjects who weigh 30 kg or greater, which is different than that listed in the original September 19, 2023, review (listed as 14%) due to typographical error.

9.2.5. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The 2 mg dose of ARS-1 has been approved since August 2024 and has been on the market since late September 2024. Postmarketing surveillance has not identified any safety concerns, although there has been limited time on the market. Epinephrine injection products for this weight group, 15 to <30 kg, 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 of 1 mg ARS-1 for pediatric subjects 15 to <30 kg was assessed in EPI 10. There were no deaths or SAEs . Common AEs were mild and generally mirrored those observed in the adult population as expected given the route of administration and mechanism of action. The common AEs that occurred in more than 1 subjects for pediatric subjects (n=21) 15 to < 30 kg who received one nasal dose of 1 mg ARS-1 include nasal congestion (19%), upper respiratory tract congestion (14%), dry throat (10%), nasal dryness (10%), and paresthesia (10%).

Due to the limited sample size and uncontrolled design of the pediatric study, the safety of 1 mg ARS-1 also relies on extrapolation from adults receiving a 2 mg ARS-1 dose. Adverse events observed in adults include nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, and throat irritation. Local safety of multiple doses in adults is limited. Assessment of safety of ARS-1 also relies on the known safety of the listed epinephrine injection. The PK for 1 mg ARS-1 in pediatric subjects 15 to < 30 kg was 50% higher compared to adults receiving 2 mg ARS-1, but is expected to be comparable or lower than EpiPen and EpiPen Jr., therefore the safety of the higher PK in children compared to adults is supported from clinical experience from EpiPen 0.3 mg (for ≥ 30 kg) and EpiPen Jr. 0.15 mg (for 15 to < 30 kg) (NDA 019430) in this population.

9.3. 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 15 to <30 kg,” the Applicant conducted one single-arm PK/PD trial (EPI 10) in the pediatric population to support extrapolation of efficacy and safety from the adult 2 mg ARS-1 trials.

The 2 mg ARS-1 dose in adults was approved based on demonstrating a scientific bridge to approved epinephrine injection products (Adrenalin and EpiPen) via PK bracketing and supportive hemodynamic PD markers (SBP and PR) in four adult trials. 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.

Results from EPI 10 demonstrated that epinephrine exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is similar to pediatric subjects ≥30 kg following 2 mg ARS-1, approximately 50% higher compared to adults following single-dose administration of 2 mg ARS-1, and expected to be comparable or lower than EpiPen Jr. 0.15 mg (for 15 to < 30 kg) (NDA 019430) in this population. In addition, a similar hemodynamic PD response (i.e., SBP and PR) was observed between pediatric subjects 15 to <30 kg following 1 mg ARS-1 and pediatric subjects ≥30 kg following 2 mg ARS-1. The SBP response was smaller compared to adults, while the PR response was within the range of adults. The overall PK/PD similarity between children 15 to <30 kg and children and adults who weigh ≥30 kg supports full extrapolation of efficacy from adults. As a result, substantial evidence of effectiveness has been demonstrated and the recommended regulatory action is approval of the 1 mg ARS-1 dose for children 15 to <30 kg.

The safety of 1 mg ARS-1 for pediatric subjects 15 to <30 kg was assessed in EPI 10. No deaths, SAEs, or discontinuations due to AEs were reported. Adverse events in pediatric subjects 15 to <30 kg include nasal congestion, upper respiratory tract congestion, dry throat, nasal dryness, and paresthesia. Due to the limited sample size and uncontrolled design of the pediatric study, the local safety of 1 mg ARS-1 in pediatric subjects 15 to < 30 kg also relies on extrapolation from adults receiving 2 mg ARS-1 dose. Local adverse events observed in adults include throat irritation, nasal discomfort, and rhinorrhea. Local safety of multiple doses in adults is limited. Assessment of systemic safety of 1 mg ARS-1 in pediatric subjects 15 to < 30 kg relies primarily on the known safety of EpiPen Jr. since epinephrine exposure is expected to be comparable.

The review team has found there to be a favorable benefit-risk assessment, and they recommend Approval of 1 mg ARS-1 “for the emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients aged 4 years and older who weigh 15 to less than 30 kg.”

10. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was held (May 11, 2023) for the NDA review for adults and pediatric subjects ≥30 kg. See original NDA Review from September 19, 2023, for details regarding the Pulmonary-Allergy Drugs Advisory Committee (PADAC). For this supplement, the review team did not identify any additional issues that would benefit from discussion at an Advisory Committee meeting.

11. Pediatrics

The following PREA PMR (PMR 4671-1) was issued upon approval of the NDA.

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.

Draft Protocol: Complete

Final Protocol: Complete

Study Complete: Complete

Final Report Submission: November 2024

The completion of EPI 10fulfills the PREA PMR and a fulfillment letter will be sent upon approval of this supplement.

12. Labeling Recommendations

12.1. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
HIGHLIGHTS	ADVERSE REACTIONS: The Applicant proposed to change [redacted] (b) (4) The Agency changed the adverse reaction incidence in HL back to ≥2% to reflect and be consistent with Section 6 of the FPI. Refer to Information Request dated February 11, 2025. The listing of adverse reactions was revised consistent with changes in Section 6 of the FPI, for which the listing of adverse reaction was based on decreasing order of frequency for one dose of neffy 2 mg. Lastly, the adverse reactions for adults and pediatric patients are listed separately because of different adverse reaction incidence rates for each subgroup.
1 INDICATIONS AND USAGE	Indications should include age groups to provide clear and consistent communication to HCPs about the indicated population for which FDA grants approval. Epinephrine injection for this indication previously has not included an age group as the drug is dosed based on weight. The Applicant proposed an indication statement that specified the weight (i.e., 15 kg or greater) of the indicated pediatric population but did not include age. The indication statement was revised to include the age group of the pediatric patients (i.e., aged 4 years and older) in addition to weight solely to highlight that the device is not fit-for-purpose for patients less than 4 years and older. *neffy is indicated for emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients aged 4 years and older who weigh 15 kg or greater.*

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
2 DOSAGE AND ADMINISTRATION	**2.1 Recommended Dosage** The recommended dosage of neffy is based on weight and the information was revised from text to a tabular format to improve readability. **2.2 Administration Instructions** The Applicant proposed (b) (4)
6 ADVERSE REACTIONS	The (b) (4) (b) (4) was proposed by the Applicant. The Division reverted to the originally approved safety labeling and added a separate adverse reactions section for pediatric patients aged 4 years and older and 15 to <30 kg. (b) (4) The adult adverse reactions in Table 2 were revised to list the adverse reactions in decreasing order of frequency for one dose of neffy 2 mg consistent with the adverse reactions for pediatric patients that were based on one dose of neffy (1 mg and 2 mg). The revised decreasing order of frequency for one dose of neffy 2 mg was added to the ADVERSE REACTIONS section of Highlights.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	**8.4 Pediatric Use** The pediatric use statement was updated to specify the pediatric population by age and weight. The evidence to support use of neffy in pediatric patients was revised to convey extrapolation from clinical pharmacology studies in adults, and pediatric data from a clinical pharmacology study in pediatric patients aged 4 years and older who weigh 15 kg or greater (Study 5).

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
12 CLINICAL PHARMACOLOGY	**12.2 Pharmacodynamics** The language for systolic blood pressure (SBP) and pulse rate (PR) in pediatric patients was updated to reflect the results from Study 5. The median change in SBP from baseline was lower in pediatric patients compared to adults who received neffy 2 mg, and the median change in PR from baseline in pediatric patients was within the range of adults who received neffy 2 mg. **12.3 Pharmacokinetics** The language for pharmacokinetic information in pediatric patients was updated based on the results from Study 5. The geometric mean plasma epinephrine concentration time profiles for the two pediatric weight groups (i.e., neffy 1 mg for pediatric patients who weigh 15 kg to <30 kg and neffy 2 mg for pediatric patients who weight ≥30 kg) were higher than adults who received neffy 2 mg.
14 CLINICAL STUDIES	This section is omitted from the PI because clinical efficacy studies were not conducted for neffy.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	**3 DOSAGE FORMS AND STRENGTHS and 16 HOW SUPPLIED/STORAGE AND HANDLING** Format revisions for clarity and to improve readability

13. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

14. Postmarketing Requirements and Commitment

No new PMR or postmarketing commitments (PMCs) will be issued with this supplement.

This supplement fulfills the following PREA PMR.

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.

Draft Protocol: Complete

Final Protocol: Complete

Study Complete: Complete

Final Report Submission: November 2024

A letter of fulfillment will be sent upon approval of this supplement.

Postmarketing Commitment (PMC)

A PMC study was issued at the time of NDA approval.

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: December 2024

Final Protocol Submission: February 2025

Study Completion: February 2026

Final Report Submission: June 2026

15. Associate Director for Therapeutic Review (Clinical) Comments

Anaphylaxis is a severe allergic reaction that is rapid in onset and can progress rapidly, in rare cases, to death. Anaphylaxis usually occurs immediately after exposure to an allergen, in sensitized persons, or after exposure to a direct mast cell activator, but it can be idiopathic.

Fatal anaphylaxis most frequently occurs within 30-60 minutes of onset. Epinephrine is the first-line treatment for anaphylaxis, and early administration is critical for successful outcomes. Up to 10% of anaphylaxis cases require administration of a second dose of an epinephrine injection product; up to 2% of anaphylaxis cases, when including anaphylaxis in the medical setting, may progress to refractory anaphylaxis requiring additional epinephrine and resuscitation treatments. Administration of epinephrine injection products is frequently delayed after onset of anaphylaxis for a number of reasons, including lack of recognition of anaphylaxis, lack of available epinephrine, and needle phobia. As a result, as discussed by patients and caregivers at an externally led Patient-Focused Drug Development meeting for food allergy on September 9, 2021, and at the public hearing for the May 11, 2023, Pulmonary-Allergy Drugs Advisory Committee to discuss the original ARS-1 NDA submission, there is a need for needleless epinephrine products administered by alternative routes of administration, including for young children with food allergy.

ARS-1 (neffy), epinephrine nasal spray, was approved on August 9, 2024, as a 2 mg dose for the "emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater." Demonstration of substantial evidence of effectiveness for the 2 mg ARS-1 dose in adults was based on establishment of an adequate scientific bridge (PK/PD) to approved epinephrine injection products (Adrenalin and EpiPen) via the 505(b)(2) pathway, relying on the demonstrated efficacy of epinephrine injection products from case series, expert opinion, and >100 years of use. ARS-1 is the first epinephrine product approved for the treatment of anaphylaxis that is not administered by injection or intravenously.

The approval of ARS-1 included a Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR), 4671-1, to "conduct a single-dose, pharmacokinetic and pharmacodynamics study of neffy (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." Studies in children <4 years of age were waived due to the nasal spray device not being fit-for-purpose for children in this age group. ARS Pharmaceuticals (Applicant) now submits a supplemental new drug application for a 1 mg ARS-1 dose to expand the ARS-1 indication to include children ≥4 years of age and weighing 15 to <30 kg. The new ARS-1 indication is for the "emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients 4 years of age and older who weigh 15 kg or greater." The recommended dosages are:

- For patients weighing 30 kg or greater: one spray of neffy 2 mg (0.1 mL)
- For patients weighing 15 kg to less than 30 kg: one spray of neffy 1 mg (0.1 mL)

In absence of clinical improvement or if symptoms worsen after initial treatment, patients may administer a second dose of neffy in the same nostril with a new nasal spray starting 5 minutes after the first dose.

The clinical development program for ARS-1 in subjects 15 to <30 kg consisted of one single-arm, single-dose, PK/PD and safety pediatric study (EPI 10) that evaluated 1 mg ARS-1 in 21 pediatric subjects weighing 15 to <30 kg. EPI 10 results demonstrated that epinephrine

exposure in pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 is approximately 50% higher than in adults following administration of 2 mg ARS-1, and is similar to the systemic epinephrine exposure in pediatric subjects ≥30 kg following administration of 2 mg ARS-1. In addition, a smaller systolic blood pressure (SBP) response was noted for pediatric subjects 15 to <30 kg following single-dose administration of 1 mg ARS-1 when compared to adult results from EPI 15 and EPI 17, while the PR response in this pediatric population was within the range of adult results from EPI 15 and EPI 17. A similar PD response (including SBP and PR) was observed between pediatric subjects 15 to <30 kg following administration of 1 mg ARS-1 and pediatric subjects ≥30 kg following administration of 2 mg ARS-1. The comparative PK/PD results from EPI 10 support efficacy of ARS-1 in pediatric patients 15 to <30 kg.

Assessment of the systemic safety of ARS-1 relies on the known safety of the listed epinephrine injection products. The systemic epinephrine exposure following administration of 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg is expected to be lower than in the same pediatric population treated with EpiPen Jr. Therefore, the systemic safety of epinephrine following 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg on 1 mg ARS-1 can be extrapolated from EpiPen Jr. and is included in labeling. Local safety was assessed in the small population studied in EPI 10; adverse reactions included nasal congestion, upper respiratory tract infection, dry throat, nasal dryness, and paresthesia. No local safety data is available for the pediatric population 15 to <30 kg when receiving repeat doses of ARS-1. Although the study population in EPI 10 was small, based on available safety data from EPI 10 and extrapolation of local safety data from adults, the safety profile of ARS-1 in pediatric subjects 15 to <30 kg is acceptable, particularly for a product intended for emergency use that should be used infrequently.

Postmarketing Requirement/Commitment

The EPI 10 trial and results were discussed at the February 4, 2025, meeting of the Pediatric Review Committee (PeRC). The PeRC agreed that this product has been adequately assessed in children 4 to 11 years of age (15 to less than 30 kg) and that PMR 4671-1 should be considered fulfilled.

A clinical efficacy trial in patients with anaphylaxis was not conducted in the ARS-1 development program due to feasibility concerns. Similarly, the PK/PD trials in the ARS-1 development program, including EPI 10, were not conducted in patients with anaphylaxis. As a result, there is an ongoing PMC study:

> 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.

The study is planned for completion by February 2026, with final report submission by June 2026.

Inspection

An Office of Study Integrity and Surveillance (OSIS) inspection was requested for a new clinical site for the EPI 10 trial at Treasure Valley Medical Research in Boise, Idaho. The inspection was conducted and there were no identifiable concerns regarding reliability of the data or human subject protection for the inspected study, EPI 10.

Product Quality

The Office of Pharmaceutical Quality completed a review of the chemistry, manufacturing and controls data included with this submission and recommended approval of this sNDA. OPMA/Facility review noted that no additional facility assessment was needed.

Labeling

Labeling was reviewed by the Division of Medical Policy Programs and the Office of Prescription Drug Promotion and was found to be acceptable. Labeling was also reviewed by the Division of Medication Error Prevention and Analysis I in the Office of Surveillance and Epidemiology to determine if final labeling is acceptable from a medication error perspective; labeling was determined to be acceptable with no recommendations for revisions.

Benefit/Risk Assessment and Recommendation

Overall, the findings from EPI 10 demonstrate a favorable benefit-risk assessment. I agree with the recommendation of the review team for **approval** of this supplement. Approval of ARS-1 for children ≥ 4 years of age and weighing 15 to <30 kg provides another option for children for the treatment of anaphylaxis that has the potential to improve compliance and timeliness of treatment of anaphylaxis episodes.

16. Appendices

16.1. References

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): EPI10

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32		
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)

16.3. OCP Appendices (technical documents supporting OCP recommendations)

16.3.1. Individual Trial Review

16.3.1.1. *EPI 10*

History

The trial consists of two parts. In Part 1, subjects weighing 15 to <30 kg and ≥30 kg received a single dose of ARS-1 (0.65 mg with 0.25% or 0.35% DDM) and ARS-1 (1 mg with 0.25% DDM), respectively. In Part 2, subjects weighing 15 to <30 kg and ≥30 kg received a single dose of ARS-1 (1 mg with 0.275% DDM) (to be marketed [TBM]) and ARS-1 (2 mg with 0.275% DDM) (approved), respectively. The TBM ARS-1 (1 mg) and marketed formulation ARS-1 (2 mg) was assessed in Part 2 of the study, while Part 1 explored different doses in each weight group.

At the interim analysis, Part 2 was ongoing. The interim study report that was submitted to original NDA included all PK/PD data from Part 1 and a portion of Part 2: 16 subjects weighing ≥30 kg receiving 2 mg ARS-1 and 3 subjects weighing 15 to <30 kg receiving 1 mg ARS-1.

As PK/PD assessment for pediatric subjects (15 to <30 kg) following 1 mg ARS-1 in Part 2 was ongoing at the time of interim report submission, the PK/PD data was not reviewed for subjects weighing 15 to <30 kg in original NDA review.

In the final report of EPI 10, a total of 21 subjects weighing 15 to <30 kg received 1 mg ARS-1 were included in the PK/PD assessment. There are also PK/PD data from 5 new subjects weighing ≥30 kg following 2 mg ARS-1 in addition to the 16 subjects that were reviewed in the original NDA review dated September 19, 2023.

In the interim report, all PK samples were analyzed by (b) (4) (method ATM-2394 and ATM-2662). However, in the final report, all PK samples from Part 2 were analyzed/re-analyzed by (b) (4) (E23 version 00, report MV(C)-179-20), while PK samples from Part 1 were not re-analyzed with the new method. The previous bioanalytical site was the same as the site used for adults in EPI 15 and two methods were deemed comparable. See original NDA review dated September 19, 2023. The new bioanalytical site was the same as that used for adults in EPI 17, and the new method for EPI 10 (E23 version 00) was cross validated with that used for EPI 17 (E21 version 00). See Section 16.3.2 for more details.

In addition, minor corrections were made in the new dataset for PD values of a single timepoint from three pediatric subjects weighing ≥30 kg treated with 2 mg ARS-1 after additional monitoring and data management review.

This review focuses on PK/PD results for pediatric subjects weighing 15 to <30 kg as well as updated PK/PD results for pediatric subjects weighing ≥30 kg who received 2 mg ARS-1 with the new bioanalytical method and including data from five new subjects.

Title: A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Pediatric Subjects with Systemic Allergies (EPI 10)

Trial Type: Phase 1 single-dose PK trial in pediatric subjects with type 1 allergies

Trial Date: July 17, 2020, to January 27, 2023

Formulation

Part 1

- ARS-1 (1 mg) (with 0.25% DDM) (Lot: 201484A and 190932A)
- ARS-1 (0.65 mg) (with 0.25% DDM) (Lot: 201248A)
- ARS-1 (0.65 mg) (with 0.35% DDM) (Lot: 202260A) (only used in one subject)

Part 2

- ARS-1 (1 mg) (with 0.275% DDM) (Lot: 211312A and 211681A) ----**to be marketed (TBM)**
- ARS-1 (2 mg) (with 0.275% DDM) (Lot: 210928A) (used in 5 new subjects weighing 30 kg and above)--- **approved product**

Study Design and Method

See Section 7 and original NDA Review dated September 19, 2023.

PK and PD Endpoints

See original NDA Review dated September 19, 2023.

Protocol Deviation

See original NDA Review dated September 19, 2023, for protocol deviations as of the interim analysis cutoff date.

In the final clinical study report (CSR) of EPI 10, the Applicant reported a total of 165 protocol deviations over 51 subjects. Among 21 pediatric subjects (15 to <30 kg) who received a single dose of 1 mg ARS-1 TBM product, 19 subjects were reported with protocol deviations. However, most of the deviations were not related to PK and PD assessments. Only five subjects had one or two instances of PK or PD sampling time out of specified window. The sampling times that were affected were 12.5 minutes or later post-dose. The deviation did not impact PK and PD assessment of this dose group. The affected sampling time was not excluded from the

analysis, as an intensive PK sampling time was adopted during the first 30 minutes, with a 2.5-minute interval between each sampling time during the first 15 minutes post-dose and 5- to 10-minute intervals between each sampling time during 15 minutes to 30 minutes post-dose. The deviation observed after 60 minutes is not expected to affect PK assessment within 60 minutes post-dose.

Among the five new subjects (≥30 kg) who received a single dose of 2 mg ARS-1, two subjects did not have PK samples collected after 20 to 30 minutes due to difficulties encountered during blood sample collection (subject (b) (6)'s vein blood flow was blocked after 20 minutes-post dose, while subject (b) (6)'s vein clotted after 30 minutes).

Demographics

A total of 80 pediatric subjects were enrolled in EPI 10, which included 18 subjects who were re-enrolled to participate in both Part 1 and Part 2, with at least 6 months or greater between two enrollments.

For 21 subjects weighing 15 to <30 kg who received 1 mg ARS-1 (TBM) in Part 2, 5 subjects were re-enrolled from Part 1 during which they were treated with 0.65 mg ARS-1. For the 21 subjects weighing 30 kg and above who received 2 mg ARS-1 in Part 2, a total of 12 subjects were re-enrolled from Part 1. In addition, one subject ((b) (6)) who weighed ≥30 kg initially received 1 mg in Part 1 and was supposed to be re-enrolled to receive 2 mg in Part 2 but actually received 1 mg again. The PK of this subject was not included in the Part 2 PK assessment.

In the original NDA review, 11 re-enrolled subjects who weighed ≥30 kg were identified (including Subject (b) (6)). In this review, 2 additional subjects who weighed ≥30 kg (b) (6) and (b) (6)) were also found to be re-enrolled from 1 mg and 0.65 mg treatment, respectively. Subject (b) (6) was one of the 5 new subjects whose PK was not available at the time of original NDA review, while Subject (b) (6) had PK data available at original NDA review but was not identified initially as this subject participated in Part 1 of the trial and was in the body weight group of 15 to <30 kg and was treated with 0.65 mg. PK/PD data from pediatric subjects 15 to <30 kg was not reviewed in the original NDA, as the study was ongoing for this body weight group during the review.

The baseline body weight and age of pediatric subjects weighing 15 to <30 kg and ≥30 kg who received 1 mg ARS-1 and 2 mg ARS-1 in Part 2, respectively, were included in the PK analysis shown in Table 8.

Table 8. Baseline Characteristics for Pediatric Subjects (15 to <30 kg) Receiving 1 mg ARS-1 and Pediatric Subjects (≥30 kg) Receiving 2 mg ARS-1 in EPI 10

Characteristic	ARS-1 1 mg 15 to <30 kg N=21	ARS-1 2 mg ≥30 kg N=21
Age, years		
Mean (SD)	7.8 (1.8)	14.1 (2.4)
Median (range)	8 (4, 11)	14 (8, 17)
Body weight, kg		
Mean (SD)	25.3 (3.5)	54.1 (13.5)
Median (range)	26.2 (18.5, 29.9)	53.8 (30.8, 86)

Source: Clinical Pharmacology Review. Based on adsl.xpt and adpc.xpt for EPI 10 (submitted September 9, 2024)
Abbreviations: SD, standard deviation.

Results

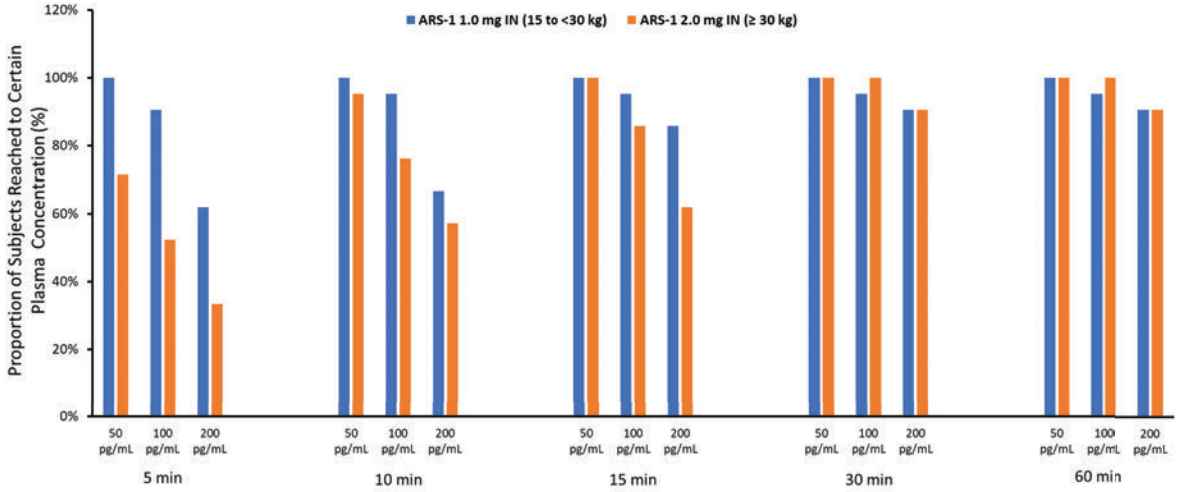
PK in Pediatric Subjects 15 to <30 kg

ARS-1 (1 mg)

See Figure 1 in Section 8.3.2 for geometric mean epinephrine plasma concentration-time profile and PK parameters for pediatric subjects (15 to <30 kg) following a single dose of 1 mg ARS-1 in comparison to adult PK following 2 mg ARS-1 from EPI 17.

The proportion of subjects weighing 15 to <30 kg receiving 1 mg ARS-1 and pediatric subjects weighing ≥30 kg receiving 2 mg ARS-1 who achieved 50 pg/mL, 100 pg/mL, and 200 pg/mL at timepoints within 60 minutes is shown in Figure 4. In general, a higher proportion of pediatric subjects weighing 15 to 30 kg receiving 1 mg ARS-1 achieved these threshold concentrations earlier than pediatric subjects weighing ≥30 kg within 5 to 15 minutes post-dose. The proportional comparison result is consistent with the PK profile comparison result (Figure 1).

Figure 4. Proportion of Subjects With Epinephrine Concentration Reaching 50, 100, 200 pg/mL or Greater by Time Following a Single Dose of 1 mg ARS-1 For Pediatric Subjects 15 to <30 kg and 2 mg ARS-1 for Pediatric Subjects ≥30 kg From EPI 10



Source: Clinical Pharmacology Review. Based on adpc.xpt for EPI 10 (submitted September 9, 2024)

The epinephrine PK distribution in pediatrics (15 to <30 kg) who received 1 mg ARS-1 is shown in Table 9. The majority of pediatric subjects had PK parameters within the 5th to 95th percentile of adult reference. For some partial AUCs, 19 to 48% of children had higher values than the 95th percentile of adult reference values.

Table 9. Distribution of Epinephrine PK Parameters of Pediatrics (15 to <30 kg) Receiving 1 mg ARS-1 Relative to Adult Reference Range (EPI 17)

		Pediatric Subjects n (%)		
PK Parameters	Reference: 5th to 95th Range of Geometric Mean Adult ARS-1 (2 mg) in EPI 17	Lower	Within	Higher
C_{max} (pg/mL)	90.4 to 950.7	0 (0)	15 (71.4)	6 (28.6)
AUC_{0-10} (pg*min/mL)	224.8 to 2137.7	0 (0)	11 (52.4)	10 (47.6)
AUC_{0-20} (pg*min/mL)	579.8 to 8011.1	0 (0)	15 (71.4)	6 (28.6)
AUC_{0-30} (pg*min/mL)	1061.7 to 14895.9	0 (0)	15 (71.4)	6 (28.6)
AUC_{0-60} (pg*min/mL)	2744.2 to 33475.6	0 (0)	17 (81.0)	4 (19.0)

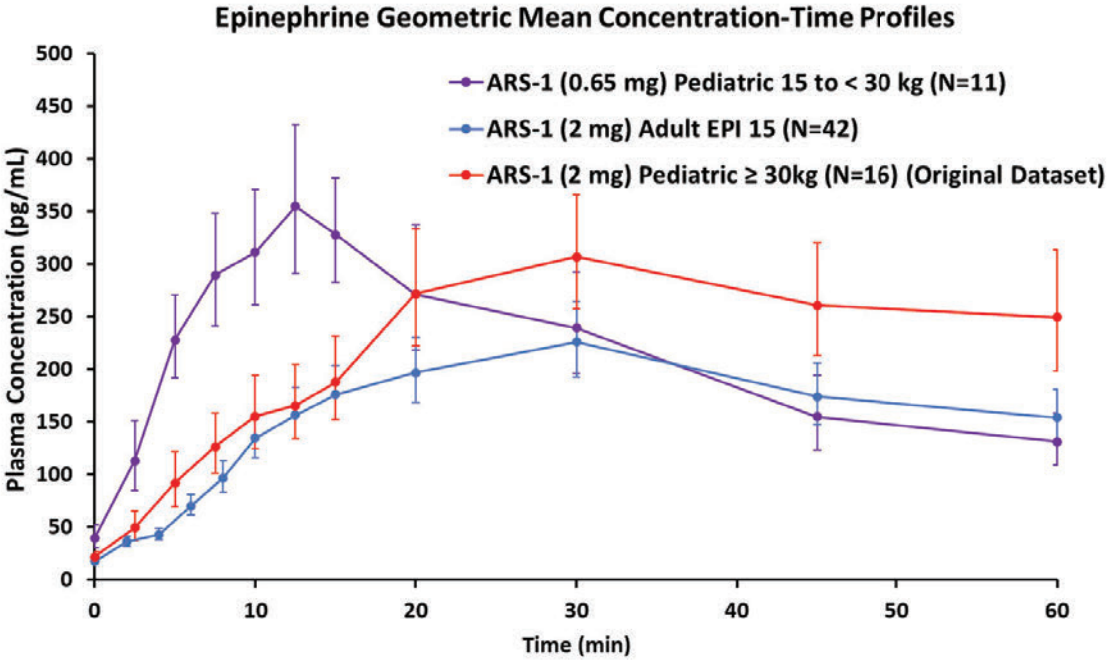
Source: Reviewer's analysis based on adpc.xpt for EPI 10 (submitted September 9, 2024) and EPI 17 (submitted August 19, 2022).
Abbreviations: AUC, area under concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic.

ARS-1 (0.65 mg)

ARS-1 (0.65 mg) with non-to-be-marketed formulation was also explored for this body weight group in Part 1. As the PK from this dose group was not re-analyzed with the new method, the PK profile of this group in comparison to adult PK following 2 mg ARS-1 from EPI 15 (with comparable bioanalytical method) and PK results from pediatric subjects (≥30 kg) following 2

mg ARS-1 using the original dataset (with original bioanalytical method) is shown in Figure 5. The PK profile of 0.65 mg ARS-1 in pediatric subjects weighing 15 to <30 kg was initially the highest within 20 minutes post-dose but fell below 2 mg ARS-1 in pediatric subjects weighing ≥30 kg as well as below adults after around 40 minutes post-dose. The results of 0.65 mg appeared less sustained compared to 1 mg ARS-1 in this weight group. It is unclear whether the epinephrine PK profile following the 0.65 mg dose is impacted by a different formulation.

Figure 5. Epinephrine Geometric Mean (±SE) Concentration-Time Profile of 0.65 mg ARS-1 in Pediatric Subjects Weighing 15 to <30 kg Compared to 2 mg ARS-1 in Pediatric Subjects Weighing ≥30 kg (Original Dataset) From EPI 10 and 2 mg ARS-1 in Adults From EPI 15

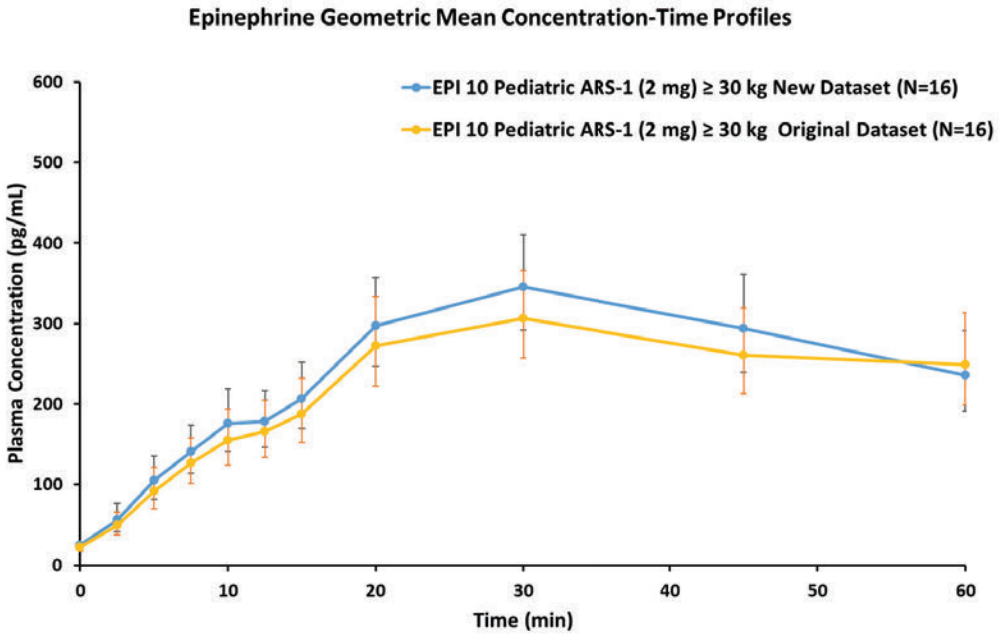


Source: Clinical Pharmacology Review. Based on adpc.xpt for EPI 10 (submitted August 19, 2022, and September 9, 2024) and EPI 17 (submitted August 19, 2022)
Abbreviations: SE, standard error.

Sensitivity Analysis (Interim vs. Final report) for 2 mg ARS-1 PK

As the bioanalytical method was updated for pediatric subjects (≥30 kg) treated with 2 mg ARS-1 in the final report, the PK profiles of 2 mg ARS-1 were compared between original and new datasets excluding new subjects, as shown in Figure 6.

Figure 6. Epinephrine Geometric Mean (±SE) Concentration – Time Profile For 2 mg ARS-1 in Pediatric Subjects Weighing ≥30 kg Using New Dataset vs. Original Dataset for 16 Subjects From EPI 10 Reviewed in Original NDA Review



Source: Clinical Pharmacology Review. Based on adpc.xpt for EPI 10 (submitted August 19, 2022 and September 9, 2024).
Abbreviations: SE, standard error.

Only a slight difference in PK profiles was noted between the two bioanalytical methods based on the same PK samples. Nevertheless, the review team adopted the most conservative approach; the PK comparison between children and adults is guided by the same bioanalytical assay, as shown in Table 10.

Table 10. PK Dataset and Bioanalytical Methods Used to Support Analysis of 1 mg ARS-1 in Pediatric Subjects Weighing 15 to <30 kg and 2 mg ARS-1 in Pediatric Subjects Weighing ≥30 kg in Comparison to Adults (EPI 15 and EPI 17)

Comparison Pair	Pediatric Dataset	Pediatric Bioanalytical Assay	Adult/Pediatric Dataset	Adult Bioanalytical Assay
Children 15 to <30 kg (1 mg) vs. adults	All 21 children 15 to <30 kg	E23, version 00 ((b) (4))	42 adults from EPI 17	E21 version 00 ((b) (6))
Children ≥30 kg (2 mg) vs. adults (original review)	16 children ≥30 kg	Method ATM-2648 and ATM2662 ((b) (6))	42 adults from EPI 15	Method ATM-2648 and ATM2662 ((b) (6))
Children ≥30 kg (2 mg) vs. adults (this review)	21 children ≥30 kg	E23, version 00 ((b) (6))	42 adults from EPI 17	E21, version 00 ((b) (6))
Children 15 to <30 kg (1 mg) vs. children ≥30 kg (2 mg)	All 21 children 15 to <30 kg	E23, version 00 ((b) (6))	All 21 children ≥30 kg	E23, version 00 ((b) (6))

Source: clinical pharmacology reviewer generated table.
Abbreviations: PK, pharmacokinetic.

Pharmacodynamics

ARS-1 (1 mg) PD results

See Section 8.3.2 for PD comparison results for pediatric subjects (15 to <30 kg) following a single dose of 1 mg ARS-1 in comparison to adult PK following 2 mg ARS-1 from EPI 17.

Cross-study PD comparison with EPI 15 and EPI 17

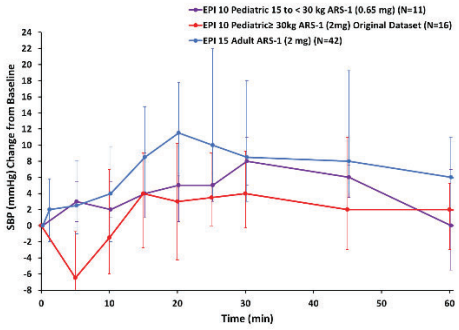
See Figure 4 for the PD responses of 1 mg ARS-1 in pediatric subjects weighing 15 to <30 kg and 2 mg ARS-1 in pediatric subjects weighing ≥30 kg compared with adult results from both EPI 15 and EPI 17.

ARS-1 (0.65 mg) PD results

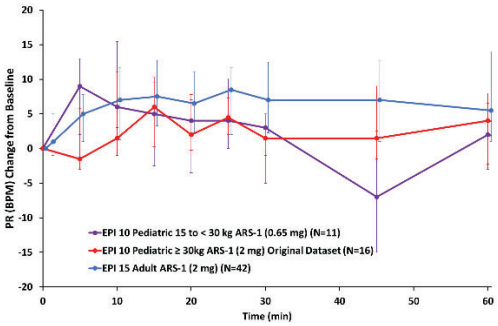
The PD responses for 0.65 mg ARS-1 in pediatric subjects weighing 15 to <30 kg in comparison to pediatric subjects weighing ≥30 kg following 2 mg ARS-1 as well as adult PD results following 2 mg ARS-1 from EPI 15 are shown in Figure 7. For consistency, the same comparing populations/studies for Figure 5 were used in Figure 7.

Figure 7. Median PD Responses (SBP, PR, and DBP Change From Baseline) Following a Single Dose of 0.65 mg ARS-1 in Pediatric Subjects (15 to <30 kg) (Purple) and a Single Dose of 2 mg ARS-1 in Pediatric Subjects (≥30 kg) (Red) Based on Original Dataset From EPI 10 vs. a Single Dose of 2 mg ARS-1 in Adults From EPI 15 (Blue)

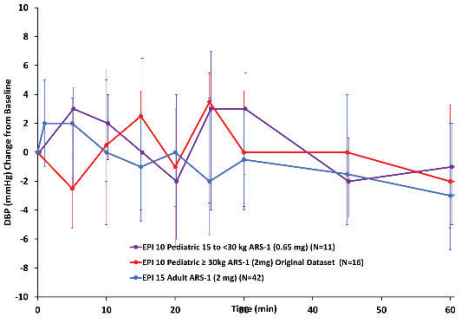
A. SBP Response



B. PR Response



C. DBP Response



Source: Clinical Pharmacology Review. Based on adxd.xpt for EPI 10 (submitted August 22, 2022 and September 9, 2024) and adxd.xpt for EPI 15 (submitted August 19, 2022)
Error bars represent the 25% and 75% percentile of PD values.
Abbreviations: DBP, diastolic blood pressure; PD, pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure.

The PD responses of 0.65 mg ARS-1 in pediatric subjects weighing 15 to <30 kg was also similar compared to 2 mg ARS-1 in pediatric subjects weighing ≥30 kg.

Conclusion

Pharmacokinetics

Children 15 to <30 kg following 1 mg ARS-1 compared to adults

The epinephrine PK profile and systemic exposure following 1 mg ARS-1 in pediatric subjects (15 to <30 kg) are higher than that of adults from EPI 17 with comparable bioanalytical methods. The geometric mean of C_{max} and $AUC_{0\text{-}60min}$ following 1 mg ARS-1 in pediatric subjects (15 to <30 kg) were 57 and 48% higher, respectively, than those of adults following 2 mg ARS-1 within 60 minutes post-dose.

Children ≥30 kg following 2 mg ARS-1 compared to adults

The PK profile following 2 mg ARS-1 in pediatric subjects (≥30 kg) with the new dataset and new subjects is higher than that of adults from EPI 17 that was evaluated with a comparable bioanalytical method. The cross-study comparison conclusion with adult PK data remains the same as the original NDA review dated September 19, 2023, despite using a new bioanalytical method and adding new subjects.

In the original NDA review, the geometric mean of C_{max} and $AUC_{0\text{-}60min}$ in 16 pediatric subjects weighing ≥30 kg following 2 mg ARS-1 were 27 and 38% higher, respectively, than those of adults from EPI 15. In this review, the geometric mean of C_{max} and $AUC_{0\text{-}60min}$ using a new bioanalytical method in 21 pediatric subjects (including 5 new subjects) weighing 30 kg following ARS-1 (2 mg) were 53 and 57% higher, respectively, than those of adults from EPI 17 using a comparable bioanalytical method.

Children 15 to <30 kg following 1 mg ARS-1 compared to children ≥30 kg following 2 mg ARS-1

The overall geometric mean values of epinephrine C_{max} and $AUC_{0\text{-}60\ min}$ within 60 minutes post-dose are generally comparable between two pediatric populations, although T_{max} was reached earlier in pediatric subjects weighing 15 to <30 kg (median 20 minutes in children 15 to <30 kg with 1 mg vs. median 30 minutes in children ≥30 kg with 2 mg).

Pharmacodynamics:

Children (15 to <30 kg following 1 mg ARS-1 and ≥30 kg following 2 mg ARS-1) compared to adults

The SBP response from pediatric subjects in both body weight groups is lower than adult SBP response from trials EPI 15 and EPI 17 (2 mg). The DBP response of 1 mg ARS-1 from pediatric subjects in both body weight groups is comparable to adult DBP response from EPI 15 (2 mg). The PR response of 1 mg ARS-1 from pediatric subjects in both body weight groups is within the range of adult PR response from EPI 15 and EPI 17 (2 mg).

Children 15 to <30 kg following 1 mg ARS-1 compared to children ≥30 kg following 2 mg ARS-1

The PD responses between the two pediatric groups were similar overall.

16.3.1.2. *Trial EPI-JP03*

Title: A Phase III Study Evaluating Efficacy and Safety of Adrenaline of ARS-1 in Patients with Food Allergies

Trial Type: Open-label efficacy trial

Trial Date: July 18, 2023, to August 31, 2023

Formulation

- ARS-1 (1 mg) (lot: 230194)
- ARS-1 (2 mg) (Lot: 230211)

Study Design and Method

See Section 16.4.

PD Endpoints

PD (SBP, DBP, and PR) was collected at Day 1 pre-oral food challenge (OFC), baseline (after OFC with clinical response and before ARS-1 dosing), 5, 10, 15, 30, 60, 90, and 120 minutes post-dose, and Day 2.

Demographics

The baseline age and body weight for subjects participated in the study is shown in Table 11. All subjects were Japanese.

Table 11. Summary of Baseline Age and Body Weight Range

Characteristic	ARS-1 1 mg N=6	ARS-1 2 mg N=9
Age, years	6 to 11	8 to 17
Body weight, kg	15.7 to 28.6	30.1 to 54.3

Source: CSR EPI-JP03, Listing 16.2.4.1.

Results

After OFC when clinical response (CR) was induced, the median PR values of SBP, DBP, PR and mean arterial pressure (MAP) was increased slightly compared to before OFC, as shown in Table 12.

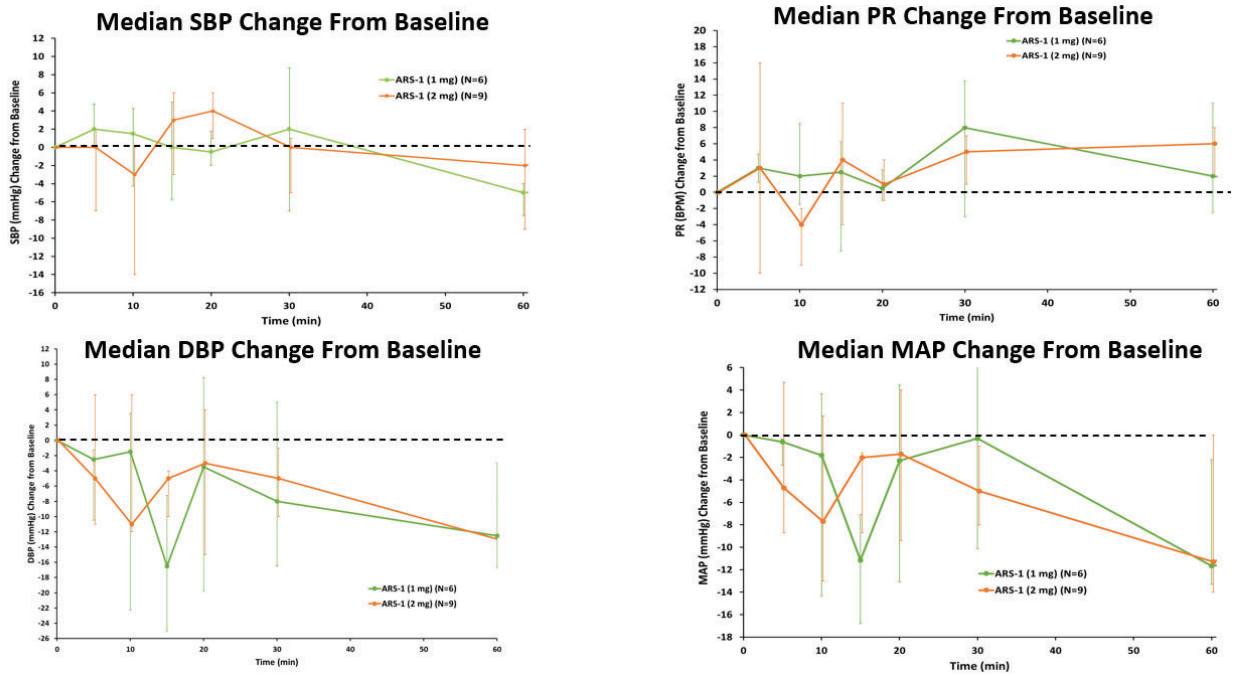
Table 12. Median (Range) PD Change at CR From Pre-OFC

ARS-1 Formulation	SBP Change (mmHg)	DBP Change (mmHg)	PR Change (bpm)	MAP Change (mmHg)
1 mg (N=6)	6 (-1, 15)	6.5 (-5, 17)	0.5 (-14, 42)	4.8 (-0.7, 16.3)
2 mg (N=9)	3 (-10, 39)	5 (-1, 34)	5 (-15, 16)	3.7 (0, 35.7)

Source: Clinical Pharmacology Reviewer. Based on adxd.xpt dataset for EPI-JP03.
Abbreviations: CR, clinical response; DBP, diastolic blood pressure; OFC; oral food challenge; PD; pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure; MAP, mean arterial pressure.

After administration of ARS-1, SBP and PR were increased from baseline at CR (after OFC), while DBP and MAP were decreased from baseline at CR, as shown in Figure 8.

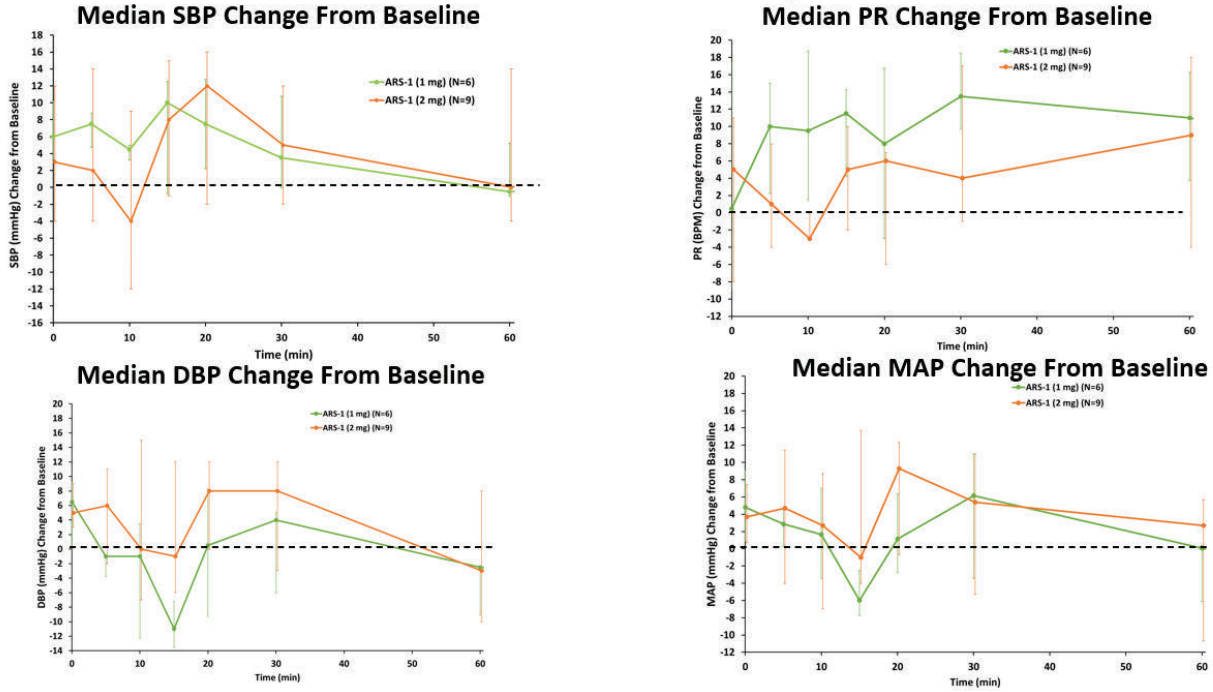
Figure 8. Median PD Response (SBP, PR, DBP, and MAP Change From Baseline) Following ARS-1 Administration (Baseline is at CR at Time 0)



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt dataset for EPI-JP03. Time 0 is at CR after OFC and when ARS-1 was administered.
Error bars represent the 25% and 75% percentile of PD values.
Abbreviations: CR, clinical response; DBP, diastolic blood pressure; OFC; oral food challenge; PD; pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure; MAP, mean arterial pressure.

When using pre-OFC PD values as baseline, SBP, PR, DBP, and MAP all increased from baseline (pre-OFC value) following ARS-1 administration, as shown in Figure 9. The differences of PD responses between Figure 8 and Figure 9 were likely due to the increased PD after OFC (Table 12).

Figure 9. Median PD Response (SBP, PR, DBP, and MAP Change From Baseline) Following ARS-1 Administration (Baseline is Pre-OFC, Time 0 is at CR After OFC)



Source: Clinical Pharmacology Reviewer. Based on adxd.xpt dataset for EPI-JP03. Time 0 is at CR after OFC and when ARS-1 was administered.
Error bars represent the 25% and 75% percentile of PD values.
Abbreviations: CR, clinical response; DBP, diastolic blood pressure; OFC; oral food challenge; PD; pharmacodynamic; PR, pulse rate; SBP, systolic blood pressure; MAP, mean arterial pressure.

Conclusion

After OFC and prior to ARS-1 administration, a general increase of vital signs was observed in children. Following administration of ARS-1 at CR, SBP, and PR further increased. However, a temporary decrease in these PD responses at 10 to 15 minutes post-dose was noted. The reason was unclear. The PD responses were overall overlapping between 1 mg and 2 mg groups.

Of note, additional alternative treatments were provided to 8 patients beyond 15 minutes post ARS-1, which include medications such as beta 2 agonist via nebulization that can impact vital signs.[2] In addition, one subject (01-061) from the 2 mg group received beta 2 agonist via nebulization within 15 minutes post-ARS-1. Therefore, the interpretation of PD responses from this trial is further limited by allowed concomitant medications.

[2] Clinical Pharmacology Review of NDA 205636 Albuterol Sulfate (ProAir RespiClick) by Dr. Yunzhao Ren

16.3.2. Bioanalytical Assay Review

The Applicant indicated that the PK samples from EPI 10 Part 2 were transferred from the previous analytical site ([redacted]) to a new site [redacted]), which included all PK samples from 2 mg ARS-1 in the pediatric group weighing ≥30 kg (5 new subjects + 16 subjects that were previously reviewed in original NDA) and from 1 mg ARS-1 in the pediatric group weighing 15 to <30 kg (N=21).

The new bioanalytical site has been previously used to analyze PK samples from adult PK/PD EPI 17. See original NDA review dated September 19, 2023, for bioanalytical methods summary and OSIS inspection results for this analytical site. However, in order to accommodate pediatric samples with smaller sample volume, the bioanalytical method for EPI 17 was modified by [redacted] to evaluate pediatric samples. The modified method was found to be different from methods used for EPI 17 as well as previous methods from [redacted] (Method ATM-2394 and 2662) used to analyze 16 pediatric subjects PK samples from the 2 mg ARS-1 group, in terms of sample volume, calibration range and [redacted] (sodium metabisulfite for E23 and hydrochloric acid for E21). The summary of methods difference among these bioanalytical methods is shown in Table 13.

Table 13. Summary of Bioanalytical Method Differences Across New and Original Methods Used for EPI 10 vs. Method Used for Adult EPI 17

Variable	Original Method for EPI 10 (Method ATM-2394 and ATM-2662)	Modified Method for EPI 10 (Method E23, Version 00)	Method for EPI 17 (Method E21, Version 00)
Validation report	Report	Report MV(C)-179-22 and Addendum-I	Report MV(C)-150-20 and Addendum-I & II
Analytical site	[redacted]	[redacted]	[redacted]
Method type	LC-MS/MS		
Matrix	Bufferized human plasma		
Analyte	Epinephrine		
[redacted]	Hydrochloric acid ([redacted]	Hydrochloric acid ([redacted]	Sodium metabisulfite [redacted]
Sample volume (mL)	0.25	0.375	0.75
Calibration range (pg/mL)	20.0 to 4000	20.079 to 1499.3	11.030 to 1509.278
LLOQ (pg/mL)	20	20.079	11.030
QC range (pg/mL)	20, 60, 400, and 3200	20.2, 57.5, 77.8, 507.0 and 1220.7	10.5, 25.4, 63.0, 492.0 and 1135.1
Long-term stability in acidified human plasma	551 days	741 days	405 days

Source: compiled by clinical pharmacology Reviewer.
Abbreviations: LC, liquid chromatography; MS, mass spectrometry; LLOQ, lower limit of quantification; QC, quality control.

In order to support the cross-study comparison between adults and pediatric PK, a cross validation was performed between the new bioanalytical method for pediatric PK samples (Method E23, version 00) and the method used for adult PK samples from EPI 17 (Method E21,

version 00). The cross validation was carried out to evaluate two sets of quality control samples prepared using respective sample stabilizers (sodium metabisulfite for E23 and hydrochloric acid for E21) with various concentrations: low quality control (LQC), lower medium quality control (LMQC), medium quality control (MOC) and high quality control (HQC) against one calibration curve prepared with E23 method. The result is shown in Table 14.

Table 14. Cross Validation of Bioanalytical Method E23 Version 00 and Method E21 Version 00

Batch/Run	Epinephrine in human plasma (pg/mL)							
	Quality control samples Id							
	Method SOP no. E23 version 00				Method SOP no. E21 version 00			
	HQC	MQC	LMQC	LQC	HQC	MQC	LMQC	LQC
Cross validation experiment	1138.357	461.224	77.267	61.650	1196.645	459.032	77.480	34.666
	1152.896	447.805	78.570	58.323	1199.121	469.284	75.664	35.391
	1137.970	427.466	78.697	58.930	1146.867	451.655	79.534	34.162
	1182.359	438.450	74.326	58.209	1150.667	463.797	79.729	35.483
	1150.614	442.745	76.029	58.360	1162.982	464.557	79.174	36.505
	1137.436	432.604	77.765	56.158	1181.442	471.164	81.346	35.625
Mean	1149.9387	441.7157	77.1090	58.6050	1172.9540	463.2482	78.8212	35.3053
SD ±	17.28572	11.96206	1.67470	1.76985	22.78027	7.11735	1.97980	0.81194
Precision (% CV)	1.5	2.7	2.2	3.0	1.9	1.5	2.5	2.3
Nominal value	1157.399	454.279	78.742	59.678	1141.800	456.720	77.642	33.056
Accuracy (%)	99.4	97.2	97.9	98.2	102.7	101.4	101.5	106.8
n	6	6	6	6	6	6	6	6

Source: Table 04, Report MV(C)-179-22 (A-I) (submitted under NDA 214697 on October 21, 2024)
Abbreviations: CV, coefficient of variation; HQC, high quality control; MQC, medium quality control; LMQC, lower medium quality control; LQC, low quality control; SOP, standard operating procedure.

Using the calibration curve prepared with method E23 version 00, the analysis results for replicates of quality control (QC) prepared with different methods had acceptable precision and accuracy at each level. Therefore, the new bioanalytical method (E23, version 00) for pediatric samples is deemed comparable to the method for EPI 17 (E21, version 00).

The method validation summary for the new bioanalytical method (E23, version 00) and in-study performance in EPI 10 are shown in Table 15. The method validation and assay performance were in line with the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022).

Table 15. Method Validation Summary for E23 Version 00 and In-Study Performance for EPI 10 Part 2

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Method E23 Version 00 MV(C)-179-22 MV(C)-179-22 Addendum-I**		
Method description	Epinephrine and Epinephrine-d6 (ISTD) were extracted from human plasma by solid phase extraction method. Samples treated with 0.5 M Sodium metabisulfite solution (w/v) and pre-chilled 0.5% Formic acid in Acetonitrile: Methanol (90:10) solution (v/v) were centrifuged. The supernatant was transferred into (b) (4) cartridges, applied full pressure, and collected in collection tubes. Thereafter, 100 mM Ammonium dihydrogen phosphate buffer pH 10.0 (±0.1) solution was added to the collected samples. The samples were further extracted using (b) (4) cartridges (100mg/3mL) which were conditioned with Acetonitrile followed by Elution solution and 100mM Ammonium dihydrogen phosphate buffer pH 10.0 (±0.1) solution. The cartridges were then washed with Washing solutions & water and the contents were eluted with Elution solution. Thereafter, the contents were dried at ~35°C under nitrogen gas and reconstituted with reconstitution solution and vortexed. Samples were then transferred for analysis and centrifuged prior to loading in autosampler.		
Materials used for calibration curve & concentration	The calibration curve standards were prepared from the reference standard of epinephrine bitartrate (Lot No. R093E0) with concentration of 1004892868.073 pg/mL. The stock was prepared using 1.0 M Hydrochloric Acid solution (v/v). Stock dilution and spiking solutions for calibration standards were prepared using 0.2M acetic acid in water solution(v/v).		
Validated assay range	20.079 pg/mL to 1499.300 pg/mL		
Material used for QCs & concentration	The quality control samples were prepared from the reference standard of epinephrine bitartrate (Lot No. R093E0) with a separate stock having a concentration of 1004892868.073 pg/mL. The stock was prepared using 1.0 M Hydrochloric Acid solution (v/v). Stock dilution and spiking solutions for quality control samples were prepared using 0.2M acetic acid in water solution(v/v).		
Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	N/A		
Regression model & weighting	1/concentration²		
Validation Parameters	**Method Validation Summary**		**Source Location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 07a Report MV(C)-179-22
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.4% to 2.5%	Table 07a Report MV(C)-179-22

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Method E23 Version 00 MV(C)-179-22 MV(C)-179-22 Addendum-I**		
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.8%	Table 07a Report MV(C)-179-22
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs: HQC: 1155.627 pg/mL MQC: 453.584 pg/mL LMQC: 78.621 pg/mL LQC: 60.145 pg/mL LOQQC: 20.079 pg/mL	-2.8% to 3.5%	Table 08 Report MV(C)-179-22
	Inter-batch %CV QCs:	≤5.8%	Table 08 Report MV(C)-179-22
	Total Error (TE) QCs:	N/A	
Selectivity & matrix effect	Selectivity and Matrix Effect: Ten batches of bufferized blank human plasma containing K2EDTA as an anticoagulant (six normal, two hemolysed and two lipemic) were evaluated for selectivity experiment [Bufferized with 5% of 2.4 N Hydrochloric acid solution (v/v) after thawing]. One Blank sample of each lot was processed along with one set of calibration curve standards and two sets each of batch evaluation QCs (HQC, MQC and LQC samples. Batch evaluation QCs were found within acceptance criteria (i.e. At least (b) (4) % of total QCs and at least (b) (4) % QCs per level were (b) (4) % of the nominal value). No significant interference was observed at the retention times of Epinephrine and Epinephrine-d6 (ISTD) in any of the bufferized blank human plasma batches. Matrix Effect 01 failed for blank matrix sr. no. 9 (BLPL09) at LQC and HQC level. Therefore, Matrix Effect 02 was repeated for BLPL09 and the results were accepted		Table 3b Report MV(C)-179-22
Interference & specificity	Number of total lots tested: 15 Co-administered drugs / OTC drugs. Range of observed % Accuracy: 3.7% to 6.4% and %Precision ≤3.5%		Table 5a and 6b Report MV(C)-179-22
Hemolysis effect	Two lots were tested. HQC: Accuracy: 3.0% to 3.3%; Precision: ≤1.3% LQC: Accuracy: 0.1% to 1.1%; Precision: ≤3.1%		Table 13c Report MV(C)-179-22
Lipemic effect	Two lots were tested. HQC: Accuracy: -11.0% to 13.7%; Precision: ≤12.9% LQC: Accuracy: 15.0 % to 4.8%; Precision: ≤3.7%		Table 13c Report MV(C)-179-22

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	**Method E23 Version 00 MV(C)-179-22 MV(C)-179-22 Addendum-I**	
	Matrix Effect 01 failed for blank matrix sr. no. 9 (BLPL09) at LQC and HQC level. Therefore, Matrix Effect 02 was repeated for BLPL09 and the results were accepted	
Dilution linearity & hook effect	Highest concentration tested: 4471.773 pg/mL Diluted 5 times: Observed % Accuracy: 10.5% and %Precision: 1.4% Diluted 10 times: Observed % Accuracy 2.7% and %Precision: 1.0%	Table 9b Report MV(C)-179-22
Bench-top/process stability	18.0 hours in an ice-cold water bath HQC: Accuracy 4.7%; Precision 2.0% LQC: Accuracy 2.5%; Precision 2.5%	Table 20 Report MV(C)-179-22
Freeze-Thaw stability	5 cycles at -70 ± 10°C temperature HQC: Accuracy 5.2%; Precision 2.2% LQC: Accuracy 5.8%; Precision 4.2%	Table 19 Report MV(C)-179-22
Long-term storage	Epinephrine at -70° C was stable for 741 days.	Table 3 Report MV(C)-179-22 Addendum-I
Parallelism	N/A	
Carry over	The chromatographic system was tested to evaluate the possibility of carry-over. Before performing the carry-over experiment, a system performance experiment was performed and after obtaining its results within acceptance criteria; 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 significant carry-over was observed at the retention time of Epinephrine and Epinephrine-D6 (ISTD). Hence chromatographic system was in appropriate order.	
Method performance in study EPI 10 Part 2, Report 0045-22		
Assay passing rate	A total of 14 runs (100% accepted)	Table 1 Report 0045-22
Standard curve performance	Cumulative bias range: -2.5 to 2.9% Cumulative precision: ≤4.8% CV	Table 2 Report 0045-22
QC performance	Cumulative bias range: -3.8 to 1.7% Cumulative precision: ≤6% CV	Table 3 Report 0045-22
Method reproducibility	Incurred sample reanalysis was performed in 10.2% (59/578) of study samples and 96.6% (57/59) of samples met the pre-specified criteria	Table 7 Report 0045-22

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	Method E23 Version 00 MV(C)-179-22 MV(C)-179-22 Addendum-I
Study sample analysis/ stability	Samples were stored at -70° C for up to 517 days from first day of sample collection to completion of study analysis (October 5, 2021, to March 6, 2023). Samples were stored within the long-term stability range.

Source: Compiled by Clinical Pharmacology Reviewer based on Clinical Information Amendment submitted dated Oct. 21, 2024.

16.4. JP03: A Phase III Study Evaluating Efficacy and Safety of Adrenalin of ARS-1 in Patients With Food Allergies

The Applicant included results from a clinical trial conducted in Japan, JPN03, in pediatric subjects ≥ 15 kg undergoing oral food challenges (OFC) and who developed acute allergic reactions. This trial does not contribute to substantial evidence of effectiveness due to the small size, uncontrolled design, and endpoints. However, as no clinical trial has been conducted, topline results are summarized here. This trial was not conducted under an investigational new drug (IND)

Trial Design

A single-arm, single-dose trial was conducted in Japan to assess the efficacy and safety of ARS-1 (1 mg or 2 mg based on weight) in pediatric patients ≥ 15 kg administered as treatment for an acute allergic reaction induced by OFC (≥ grade 2 based on Japanese anaphylaxis guidelines)[3]. If symptoms remained unchanged or worsened and the investigator determined that alternative treatment was clinically necessary, patients received standard treatment (the specific treatments were not specified). Timing of onset of symptoms, administration of ARS-1, resolution of symptoms, along with physical exam and vitals were performed. The study enrolled 15 patients with food allergies that ranged from 6 to 17 years of age. Nine subjects received 2 mg ARS-1 and six subjects received 1 mg ARS-1. Subjects were monitored for 2 hours post-OFC and then returned the next day for follow-up.

Primary Endpoint

The primary endpoint was the change from baseline of the main symptom (improvement rate) or final assessment before alternative treatment until 15 minutes after dosing. “Main symptom” referred to the symptom (gastrointestinal, respiratory, or cardiovascular symptoms) induced by the OFC that is ≥ grade 2 per the Anaphylaxis Guideline. If symptoms with the same grade were observed in multiple organs, the main symptoms were specified according to the following order: cardiovascular symptoms > respiratory symptoms > gastrointestinal symptoms.

[3] Ebisawa M. Anaphylaxis Guidelines 2022. Japanese Society of Allergology, Anaphylaxis Countermeasures Committee. https://www.jsaweb.jp/uploads/files/Web_AnaGL_2022_0914.pdf

Improvement was defined as a decrease in the grade of each organ symptom by 1 or more compared to the pre-dose grade.

Secondary Endpoints

- Proportion of patients who did not require alternative treatment
- Grade of each organ symptom at each time point
- Total grade of each organ symptom at each time point
- Time to resolution by organ symptoms

Efficacy Results

Primary

Per the Applicant, all 15 patients responded to ARS-1 with a clinically meaningful reduction of symptoms.

Five of the six patients who received 1 mg ARS-1 improved at least one grade. Six of the nine patients who received 2 mg ARS-1 improved at least one grade. While four patients did not improve by ≥1 Grade by 15 minutes post dose, all four did demonstrate clinically meaningful improvement by the first assessment. The definition of clinically meaningful was not specified. None of these four subjects required additional epinephrine treatment.

Secondary

Proportion of patients not requiring alternative treatment

No patient required additional epinephrine treatment within 15 minutes of ARS-1 administration. One patient received a beta-2 agonist to treat respiratory symptoms, which was given within 15 minutes of ARS-1 administration.

Additional alternative treatments were provided to 8 patients beyond 15 minutes post ARS-1. These include levocetirizine, beta-2 agonist via nebulizer, mast cell stabilizer, hydrocortisone sodium succinate, oxygen, and cooling.

One patient demonstrated a biphasic reaction at 2 hours and 45 minutes and did require additional epinephrine treatment.

Grade of each organ symptom at each time point

All organ systems , decreased within 5 minutes of ARS-1 administration, except cardiovascular symptoms as there is no Grade 1 for this system.

Time to resolution by organ symptoms

Across all organ systems, the median time to symptoms resolution from Grade 2 to Grade 0 was 16 minutes.

Safety

Ten subjects experienced at least one AE. There were no SAEs. The most common AEs not induced by the acute allergic reaction include tremors and nasal mucosal disorder. Other AEs that were considered treatment related and occurred in one subject included intranasal hypoesthesia, nasal crusting, nasal discomfort, oropharyngeal pain, pharyngeal hypoesthesia, rhinalgia, gastrointestinal disorder, hypoesthesia oral, chills, pain, and tachycardia. Overall, the safety profile from JP03 is consistent with the known safety profile in adults and pediatric subjects ≥ 30 kg and pediatric subjects 15 to ≥ 30 kg.

Conclusions

Although this is the first clinical scenario in which ARS-1 was evaluated, conclusions regarding efficacy and safety from the trial are limited given the uncontrolled design, the size, and endpoints. The primary endpoint was change from baseline in main symptom at 15 minutes. Per the Applicant, all 15 subjects had a clinically meaningful improvement; however, the definition of clinically meaningful was not specified and there was no rationale provided for limiting the assessment to 15 minutes post-dose. Although no one required a second dose of epinephrine at 15 minutes, it is unclear why eight patients received alternative treatments beyond 15 minutes and whether these treatments altered the clinical course in which a second dose of epinephrine may have been needed beyond the 15-minute timepoint.

Overall, JP03 was a small, uncontrolled trial that does not provide clinically meaningful data to inform the efficacy and safety of 1 mg ARS-1 in pediatric subjects 15 to < 30 kg.

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