Amsterdam, 29 January 2026
EMADOC-1700519818-2691965
Committee for Medicinal Products for Human use (CHMP)

Assessment report

EURneffy

International non-proprietary name: epinephrine

Procedure No. EMA/X/0000248440

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Al Aluminium

API Active Pharmaceutical Ingredient

ASM Active Substance Manufacturer

ASMF Active Substance Master File = Drug Master File

BCS Biopharmaceutics Classification System

BDL Below the limit of detection

BE Bioequivalence

BET Bacterial endotoxin test

BZK Benzalkoium chloride

CEP Certificate of Suitability of the Ph. Eur.

CFU Colony Forming Unit

CMS Concerned Member State

CoA Certificate of Analysis

CRS Chemical reference substance

DDM Dodecylmaltoside

DMF Drug Master File = Active Substance Master File

DSC Differential Scanning Calorimetry

EC European Community

ECD Electrochemical detection

EDMF European Drug Master File

EDTA Edetate Disodium

EDQM European Directorate for the Quality of Medicines

FID Flame ionisation detection

FT-IR Fourrier transmission infra red (spectroscopy)

HPLC High performance liquid chromatography

IPC In-process control test

GC Gas chromatography

HDPE High Density Polyethylene

ICH International Conference on Harmonisation

IR Infra-red

LoA Letter of Access

LOD Loss on Drying

LoD Limit of detection

LoQ Limit of Quantitation

MA Marketing Authorisation

MAH Marketing Authorisation holder

MS Mass spectroscopy

NF National Formulary

NIR Near infra-red

NLT Not less than

NMR Nuclear magnetic resonance

NMT Not more than

PFS Pre-filled syringe

PVC Polyvinyl chloride

PDE Permitted Daily Exposure

Ph.Eur. European Pharmacopoeia

QOS Quality Overall Summary

RH Relative Humidity

RRt Relative retention time

Rt Retention time

RT Room temperature

SPC Summary of Product Characteristics

TAMC Total Aerobic Microbial Count

TGA Thermo-Gravimetric Analysis

TSE Transmissible Spongiform Encephalopathy

TYMC Total Yeasts and Moulds Count

USP United States Pharmacopoeia

UV Ultra violet

XRPD X-ray powder diffraction

WFI Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

ALK-Abelló A/S submitted on 2 February 2025 an extension of the marketing authorisation.

Extension of application to introduce a new strength (1 mg nasal spray, solution) to support an extension of indication in children with a body weight of 15 kg to less than 30 kg.

The RMP version 2.1 has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, point (2)(c) - Extensions of marketing authorisations - Change or addition of a new strength/potency.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P0431/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P0431/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, ALK-Abelló A/S did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek scientific advice for this procedure.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra Co-Rapporteur : Elita Poplavska

The application was received by the EMA on	2 February 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 May 2025

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 May 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to Alk-Abello A/S during the meeting on	19 June 2025
Alk-Abello A/S submitted the responses to the CHMP consolidated List of Questions on	11 September 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 October 2025
The PRAC Rapporteur's Assessment Report was circulated to all PRAC and CHMP members on	15 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	05 November 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to Alk-Abello A/S on	13 November 2025
Alk-Abello A/S submitted the responses to the CHMP List of Outstanding Issues on	19 December 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 January 2026
The CHMP Rapporteurs circulated the Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 January 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to EURneffy on	29 January 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Anaphylaxis is the most severe form of allergic reaction, or hypersensitivity reaction, is almost always

unexpected, and can be life-threatening (Tang-2009[1]). Delay in clinical diagnosis and treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters-2015[2]).

2.1.2. Epidemiology

The incidence of all-cause anaphylaxis in Europe ranges from 1.5 to 7.9 per 100 000 person-years, translating to an approximate 0.3% lifetime risk (Panesar-2013[3]).

2.1.3. Biologic features. Aetiology and pathogenesis

The pathophysiology of anaphylaxis is primarily attributable to antigen-specific immunoglobulin E (IgE) activation and the subsequent activation of mast cells and basophils, ultimately leading to widespread release of histamine and other inflammatory mediators (e.g., cytokines). This histamine release results in generalised vasodilation, elevated heart rate, and increased vascular permeability (Peavy-2008[4]), potentially leading to cardiovascular collapse.

The most common causes of anaphylaxis in children differ from those in adults. Foods are the most common cause of anaphylaxis in childhood, whereas medication and insect sting anaphylaxis are more common in adults. Other less common causes in both children and adults include latex, immunotherapy-related reactions, exercise, cold, or idiopathic.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Anaphylaxis is an acute, severe, systemic allergic reaction that typically develops within minutes to several hours after exposure to a trigger. Clinically, it often begins with skin or mucosal manifestations such as generalised hives, flushing, pruritus, or swelling of the lips, tongue, or uvula. Respiratory compromise is common and may present as dyspnoea, wheeze, bronchospasm, stridor, or hypoxemia, while cardiovascular involvement includes hypotension, collapse, syncope, or other signs of endorgan dysfunction. Gastrointestinal symptoms such as crampy abdominal pain and vomiting may occur, especially after food exposures. Diagnosis is clinical and is confirmed when any one of three criteria are met: an acute onset with skin or mucosal involvement plus respiratory or cardiovascular compromise; rapid involvement of at least two systems (skin, respiratory, cardiovascular, gastrointestinal) after exposure to a likely allergen; or isolated hypotension occurring after exposure to a known allergen, with age specific thresholds in children and systolic pressure <90 mmHg or a ≥30% drop from baseline in adults.

Anaphylaxis progresses rapidly and can be life-threatening without prompt intervention. Although there is no formal staging system, severity is judged by the degree of airway, breathing, and circulatory impairment. Prognosis is generally good when adrenaline is administered early, whereas delayed treatment increases the risk of severe or fatal outcomes. Biphasic reactions can occur hours later, so patients require observation and follow-up. Longer-term management focuses on identifying triggers, educating patients on avoidance, and ensuring access to adrenaline autoinjectors.

[1] Tang Mimi L.K, Osborne N, Allen K. Epidemiology of anaphylaxis. Current Opinion in Allergy and Clinical Immunology. 2009, 9:351-356
[2] Joint Task Force on Practice Parameters, et al, Anaphylaxis-a practice parameter update2015. Ann Allergy Asthma Immunol 115(2015) 341-384 -2015.
[3] Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilo MB, Cardona V, Dubois AEJ, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ & Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy2013; 68: 1353–1361
[4] Peavy RD, Metcalfe DD. Understanding the mechanisms of anaphylaxis. Curr Opin Allergy Clin Immunol. 2008 Aug; 8(4): 310 315.

2.1.5. Management

Adrenaline has been used for over 110 years, with over 60 years use to treat severe allergic reactions, and there has been extensive clinical experience with the use of adrenaline to treat anaphylaxis, severe allergy such as asthma, and shock. The use of adrenaline for the treatment of anaphylaxis was first reported in the 1960s and was based on empiric observation and expert opinion (Simons-2006[5], Upton-2014[6]). Although no prospective, controlled clinical trials have been performed to substantiate the use of adrenaline for treatment of anaphylaxis (Sheikh-2008[7]), one open-label trial using IV administration was conducted to evaluate its use in the treatment of allergic reactions characterised by cardiovascular collapse (Brown-2004[8], Brown-2006[9]).

Current standard care relies on adrenaline autoinjectors for out of hospital use, enabling early intervention to prevent progression to severe or refractory anaphylaxis. Intravenous administration carries risks of overdose and cardiovascular complications and is reserved for life-threatening cases under strict monitoring. Clinical guidelines recommend intramuscular delivery in the thigh (0.01 mg/kg; 0.15 mg for 15–30 kg children), which provides faster systemic absorption than subcutaneous or deltoid injection. Despite effectiveness, challenges remain with needle-based devices, including misuse, needle phobia, and administration errors. Since 2024, EURneffy nasal spray offers a needle free option but is only approved for ≥30 kg patients. Therefore, a therapeutic gap persists for children 15–30 kg who may benefit from a needle free, rapidly administered alternative for treating anaphylaxis.

2.2. About the product

EURneffy (also referred to ARS-1 in this report) is a nasal spray solution which contains the active substance adrenaline (or epinephrine). Adrenaline is a non-selective agonist of all adrenergic receptors, including alpha- and beta-adrenergic receptors. Binding to these receptors triggers a number of actions of sympathetic nerve system. It reduces the vascular permeability induced by histamine that occurs during anaphylaxis, causes bronchial smooth muscle relaxation, and also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

EURneffy (2 mg nasal spray) is indicated in the emergency treatment of allergic reactions (anaphylaxis) due to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis. Treatment is indicated for adults and children with a body weight ≥ 30 kg.

In this procedure, the MAH has applied for a new strength (1 mg nasal spray) intended for children with a body weight of 15 kg to less than 30 kg.

2.3. Type of Application and aspects on development

This application concerns an extension of application for a new strength 1 mg nasal spray solution intended for children with a body weight of 15 kg to less than 30 kg.

[5] Simons FER. Anaphylaxis, killer allergy: Long-term management in the community. J Allergy Clin Immunol. 2006;117:367-77.
[6] Upton J, Vadas P. Potential therapeutic strategies for severe anaphylaxis targeting platelet-activating factor and PAF acetylhydrolas. Current Treatment Options in Allery. 2014;1:232-246.
[7] Sheikh A, Shehata YA, Brown SGA, Simons FER. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock (Review). Cochrane Database of Systematic Reviews. 2008;4:1-17.
[8] Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004; August 371-376.
[9] Brown S, Mullins R. Anaphylaxis: diagnosis and management. MJA Practice Essentials - Allergy. Sept 2006;185(5):283-289.

2.4. Quality aspects

2.4.1. Introduction

The finished product subject of this line extension (LE) is presented as a nasal spray solution in a single container containing 1 mg of epinephrine. Each single-dose container delivers adrenaline (epinephrine) 1 mg in 100 microlitres.

Other ingredients are sodium chloride, dodecylmaltoside, disodium edetate, benzalkonium chloride, sodium metabisulphite (E 223), concentrated hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.

The product is available in Type I glass vials closed with a grey bromobutyl rubber stopper, assembled into a Unit Dose Sprayer (USD) device. The device is a non-pressurised dispenser delivering a single-dose nasal spray.

The currently authorised presentation of EURneffy is a 2 mg nasal spray solution in single dose container. Each single-dose container delivers adrenaline (epinephrine) 2 mg in 100 microlitres.

2.4.2. Active Substance

The information pertaining the active substance is unchanged.

2.4.3. Finished Medicinal Product

The Module 3 sections amended to support this LE are: pharmaceutical development, manufacture, control of the finished product, stability of the finished product and regional information (executed batch records of the finished product). This is acceptable as excipients, container closure system, analytical methods and reference standards are unchanged. Additionally, pharmaceutical development sections regarding the medical device, physicochemical and biological properties are the same as those already approved for 2 mg strength. Moreover, the initial development work was done with the 1 mg strength and was already included in the submission supporting the 2 mg strength application, which was authorised in 2024.

2.4.3.1. Description of the product and pharmaceutical development

EURneffy (adrenaline nasal spray, solution in a single container) is an aqueous solution in a single use nasal spray container.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of dodecylmaltoside (DDM), for which an adequate specification and related analytical tests have been provided. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 3.1.1. of this report.

The formulation of EurNeffty 1 mg nasal spray solution, subject of this LE is qualitative the same as the one of EurNeffy 2 mg nasal spray solution. The amount of the active substance is half of the approved formulation (1 mg rather than 2 mg).

EURneffy (adrenaline nasal spray) was developed for intranasal administration, which is less invasive than the previously approved injection routes.

The same argumentation given in the 2 mg strength application has been provided to justify the use of DDM), benzalkonium chloride and sodium metabisulphite Both quality and safety aspects have been substantiated for the intended paediatric population subject of this line extension (children with a body weight from 15 kg to less than 30 kg). The formulation is considered adequate to support the line extension.

The primary container closure is a 400 µL Type I glass vial, closed with a grey bromobutyl rubber stopper, containing 125 µL of the finished product solution, assembled into a single use, UDS device, which consists of an actuator and a container holder. The same container closure system is used for 1 mg and 2 mg strength. The material of the primary packaging complies with Ph. Eur. and EC requirements. The device is a non-pressurised dispenser delivering a spray containing a unit dose of the product. Each delivered dose contains 100 µL per actuation. The device is packaged into individual single use blisters composed of thermoformable rigid PVC Film and peel open blister lidding. The choice of the primary container closure system has been validated by stability data and is adequate for the intended use of the product.

The applicator is considered suitable for delivery of the medicinal product for children of 4-5 years, as also confirmed in clinical studies.

The information provided on the development of the product is in accordance with the guideline on the pharmaceutical quality of inhalation and nasal drug products (EMEA/CHMP/QWP/49313/2005 Corr.).

The acceptability of formulation (choice of excipients, patient acceptability, dosing device) for the proposed paediatric population has been discussed in line with the guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) and it is considered acceptable.

2.4.3.2. Manufacture of the product and process controls

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of six main stages.

The manufacturing process and associated controls are described in the sufficient detail. Information on in-process tests performed during manufacturing of 1 mg strength is provided. In-process controls (IPCs) are proposed. The same tests and as for 2 mg strength are proposed for 1 mg strength. The IPCS are adequate for this type of manufacturing process and pharmaceutical form.

No process validation data have been provided for the 1 mg strength. However, in consideration of the fact that the 2 mg strength can be considered as representative of the 1 mg strength, both strengths are manufactured with the same standard method, validation data of 2 mg strength manufactured are available, batch data for the commercial 1mg strength have been provided and a process validation scheme is available in the section 3.2.R, it can be concluded that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner and no further data are considered necessary to support the line extension.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of container and device (in house), colour of solution (in house), opalescence of solution (Ph. Eur.), visible particulates (Ph. Eur.), fill weight (Volume, in house), identity (UV and HPLC), adrenaline assay (HPLC), enantiomeric purity (chiral HPLC), DDM assay (HPLC), benzalkonium chloride

assay (UPLC), disodium edetate assay (HPLC), related substances and impurites (HPLC), pH, osmolality (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dose delivered (in house), droplet size distribution of spray (in house), pump delivery (in house), spray pattern (in house), actuation force (in house), particulate matter (Ph. Eur.), and microbial limit testing (TAMC, TYCM, *E. coli, S. aureus, P. aeruginosa, B. Cepacia* complex) (Ph. Eur.).

The finished product specifications are identical to the one approved for the 2 mg strength, with the exception of the assay range, reflecting the different quantity of the active substance. The proposed justification of the specifications is in line with the justification provided for the 2 mg strength. The proposed specifications are suitable for this type of finished product and their justification is considered acceptable. As mentioned above, the analytical methods are the same as the currently approved ones, which were initially developed for the 1 mg strength. This is acceptable.

No new nitrosamine risk assessment or elemental impurities risk assessment has been provided as reference is made to those submitted in the original application for the 2mg strength. This is acceptable as the 2 mg strength is seen as worst case scenario for both risk assessments.

Reference standards used for assay and impurities testing are the same as those used for the 2 mg strength.

Batch analysis results are provided for commercial scale batches of EURneffy 1 mg confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of EURneffy are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. All batches were stored in the inverted orientation which is considered the worst-case storage orientation for the product from a stability perspective.

Samples were tested according to the release specifications with the exception of fill weight, identity, pH and osmolality. The omission of these tests is acceptable as they are not stability indicating. The analytical procedures used are stability indicating.

No significant changes have been observed in the tested parameters under long term and accelerated conditions except for an increase in the opposite enantiomer due to epimerization, and a smaller increase in impurities. Nonetheless, all parameters remained within specification under long term and accelerated storage conditions.

In addition, samples of the finished product were exposed to forced degradation conditions.

ICH photostability studies indicate that the product is photostable when stored in the proposed container.

The MAH conducted further studies at higher temperature and examined the impact of temperature cycling including freezing, in consideration of the fact that users or caregivers would keep the medicine with them in day to day life and this could result in exposing EURneffy to extreme temperatures (e,g. in a hot car during summer, outdoors during winter). Results remained within the specification limits, the quality of the product was demonstrated under these extreme conditions.

Based on the available stability data, the proposed shelf life of 24 months without special storage conditions is acceptable. Furthermore, the proposed labelling instruction "Do not freeze. If accidentally frozen, allow to thaw at least 1 hour prior to use." is acceptable.

2.4.3.5. Adventitious agents

Not applicable.

2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects

The aim of this LE application was to introduce a 1 mg strength of EURneffy for the treatment of paediatric patients weighing 15 kg to less than 30 kg. Information on development, manufacture and control of the finished product supporting the LE has been presented in a satisfactory manner. Most of the information was already provided in support of the for the 2 mg strengths. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.5.2. Ecotoxicity/environmental risk assessment

The MAH submitted an ERA which relies on a previously submitted ERA for a higher strength of EURneffy 2 mg. The maximum daily dose for EURneffy remains the same as in the previous ERA, since the maximum daily dose of EURneffy 1 mg is lower than that considered for the already considered authorised strength, i.e. the worst-case dosing scenario for the maximum dose is unchanged. In contrast, the line extension results in the addition of a new patient population, children weighing 15 kg to less than 30 kg, which increases the assumed prevalence. However, in the previously submitted ERA, a worst-case scenario was assumed, which already included this patient population. Therefore, the calculation of Fpen refined and hence PECSW remain unchanged. As in the previous ERA, the value falls well below the action limit.

Adrenaline PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5.

The previously submitted ERA is acceptable.

Therefore, adrenaline is not expected to pose a risk to the environment.

2.5.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Adrenaline PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5. Further, adrenaline is already used in existing marketed products and no

significant increase in environmental exposure is anticipated with this nasal formulation.

Therefore, adrenaline is not expected to pose a risk to the environment.

2.5.4. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted with this application, which is considered acceptable. Adrenaline is not expected to pose a risk to the environment.

There are no concerns on the non-clinical aspects for this application.

2.6. Clinical aspects

2.6.1. Introduction

To support this extension of application, the MAH submitted the final study results of the phase 1 study EPI 10 which assessed the PK/PD of three doses (0.65 mg, 1 mg, 2 mg) of EURneffy in paediatric allergy subjects. Interim study results were assessed as part of the initial MAA.

The MAH also submitted supportive phase 1 studies (EPI 14, EPI JP01, EPI JP02) and a supportive phase 3 study (EPI J03).

The tabular overview below presents studies that have been included in the Module 5 of this extension of marketing authorisation.

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by Alk-Abello A/S.

Alk-Abello A/S has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD	EPI 10	To assess the PK of three doses of ARS-1 in paediatric allergy subjects. To evaluate the comparative PD response in paediatric allergy subjects	Phase 1, single-dose, single treatment study	ARS-1 0.65 mg ARS-1 1.0 mg ARS-1 2.0 mg	80	Paediatric subjects with Type I allergies	Single dose (1 day)	Completed; CSR
PK/D	EPI 14	To assess the comparative pharmacokinetics of ARS-1 in subjects with normal nasal conditions and with an upper respiratory tract infection (URTI) to evaluate the impact of nasal edema and congestion on the absorption of epinephrine.	Phase 1, single-dose, two-period study	ARS 2.0 mg IN left nostril ARS 2.0 mg IN right nostril	21	Subjects with URTI	1-2 days	Completed; CSR
PK/PD	EPI JP01	To assess the comparative PK after ARS-1, IM adrenaline, and EpiPen in subjects with induced allergic rhinitis. To assess impact of nasal edema and congestion on the absorption of adrenaline following IN and IM administration	Phase 1, partially randomised, four-treatment study	ARS-1 1.0 mg IN Adrenaline 0.3 mg IM EpiPen 0.3 mg	36	Subjects with allergic rhinitis	4 days	Completed CSR
PK/PD	EPI JP02	To assess the comparative bioavailability of adrenaline after administration ARS-1 2.0 mg or Adrenaline 0.3 mg IM in Japanese subjects.	Phase 1, two-period, two-treatment, randomized, crossover study	ARS-1 2.0 mg Adrenaline 0.3 mg IM	13	Healthy subjects	2 days	Completed CSR
Efficacy	EPI JP03	To assess the effect of ARS-1 after administration in patients with symptoms (grade 2 or greater based on anaphylaxis guideline) induced by an oral food challenge	Phase 3, single-period, single-dose study	ARS-1 1.0 mg ARS-1 2.0 mg	15	Subjects with food allergies	1 day	Completed CSR

Abbreviations: CSR, clinical study report; IM, intramuscular; IN, intranasal; PK, pharmacokinetic; SC, subcutaneous

2.6.2. Clinical pharmacology

2.6.2.1. Methods

A method for the determination of epinephrine in buffered human plasma using LC-MS/MS was developed. The validation process, performed in accordance with EMA guidelines, addressed all relevant parameters, including calibration standards, quality control samples, precision, accuracy, dilution integrity, linearity, selectivity in the presence of over-the-counter drugs and metabolites, sensitivity, recovery, matrix factor, matrix effect, reproducibility, and stability. All criteria were met and are considered acceptable. Plasma samples were analysed within the validated conditions. Overall, quality control samples and calibration curve parameters were within acceptable limits in the accepted runs. ISR was acceptable for all the assessments.

The PD surrogates of the adrenaline action were assessed: SBP (systolic blood pressure), DBP (diastolic blood pressure) and PR (pulse rate) using automated cuff.

Pharmacokinetic data analysis

Non-compartmental analysis PK analyses were conducted using conventional software and methods.

2.6.2.2. Pharmacokinetics

2.6.2.2.1. Evaluation and qualification of models

Pharmacologically Based Absorption Model (PBAM)

The MAH submitted a nasal PBAM and simulations for the 1 mg dose in children 15-30kg.

This model incorporates:

- Allometric scaling of systemic pharmacokinetic parameters (clearance and volume of distribution) using fixed exponents of 0.75 and 1.0, respectively.
- Scaling of nasal absorption surface area (SA) based on subject height, which is supported by published literature on nasal physiology and growth-related anatomical changes.
- Verification of model performance using data from the completed study EPI-10, including the 15–20 kg subgroup.

In addition, the MAH performed simulations for paediatrics > 7.5 kg to < 15 kg to evaluate epinephrine exposure in paediatrics aged 6 months to two years.

Table 2: Comparison of observed versus predicted C_{max} and AUC ratios in different paediatric weight groups.

	Dose-normalised Cmax ($pg \cdot mL^{-1} \cdot mg^{-1}$)			Dose-normalised AUClast ($pg \cdot h \cdot mL^{-1} \cdot mg^{-1}$)		
Pooled subjects < 6 years old & < 20 kg	**Predicted (N = 1500)**	**Observed (N = 3)**	**Ratio (Pred/ Obs)**	**Predicted (N = 1500)**	**Observed (N = 3)**	**Ratio (Pred/ Obs)**
Mean (SD)	739.6 (341.8)	950.5 (392.0)	0.78	605.5 (251.2)	637.2 (207.6)	0.95
ARS-1 0.65 mg IN (15-30 kg)	**Predicted (N = 1500)**	**Observed (N = 11)**	**Ratio (Pred/ Obs)**	**Predicted (N = 1500)**	**Observed (N = 11)**	**Ratio (Pred/ Obs)**
Mean (SD)	707.9 (321.2)	822.2 (482.6)	0.86	609.8 (246.9)	541.8 (252.6)	1.13
ARS-1 1.0 mg IN (15-30 kg)	**Predicted (N = 1500)**	**Observed (N = 21)**	**Ratio (Pred/ Obs)**	**Predicted (N = 1500)**	**Observed (N = 21)**	**Ratio (Pred/ Obs)**
Mean (SD)	669.1 (315.0)	651.5 (418.3)	1.03	552.5 (234.1)	599.9 (352.2)	0.92
ARS-1 1.0 mg IN (> 30 kg)	**Predicted (N = 1500)**	**Observed (N = 25)**	**Ratio (Pred/ Obs)**	**Predicted (N = 1500)**	**Observed (N = 25)**	**Ratio (Pred/ Obs)**
Mean (SD)	231.2 (100.1)	252.3 (168.1)	0.92	307.1 (126.9)	216.6 (128.9)	1.42
ARS-1 2.0 mg IN (> 30 kg)	**Predicted (N = 1500)**	**Observed (N = 21)**	**Ratio (Pred/ Obs)**	**Predicted (N = 1500)**	**Observed (N = 21)**	**Ratio (Pred/ Obs)**
Mean (SD)	216.4 (96.8)	345.1 (345.4)	0.63	272.7 (118.9)	341.7 (314.2)	0.80

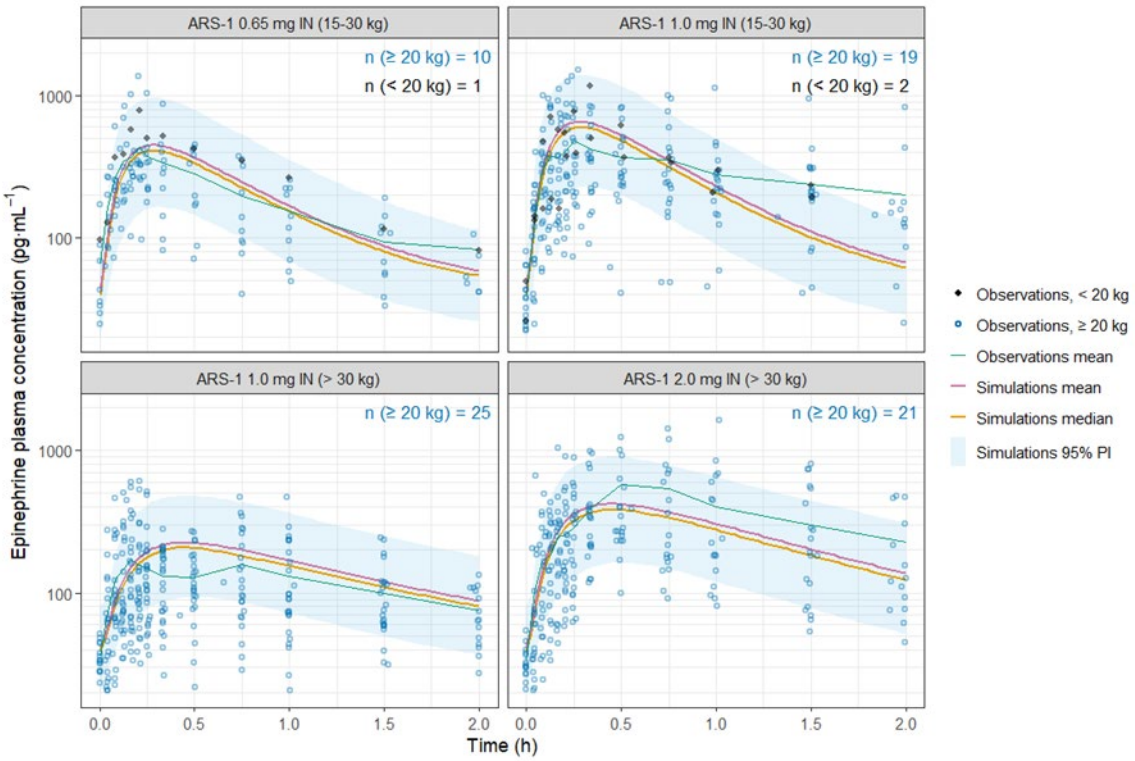

Figure 1: Observed versus predicted epinephrine plasma concentration-time profiles stratified by weight and doses used in the EPI-10 study.

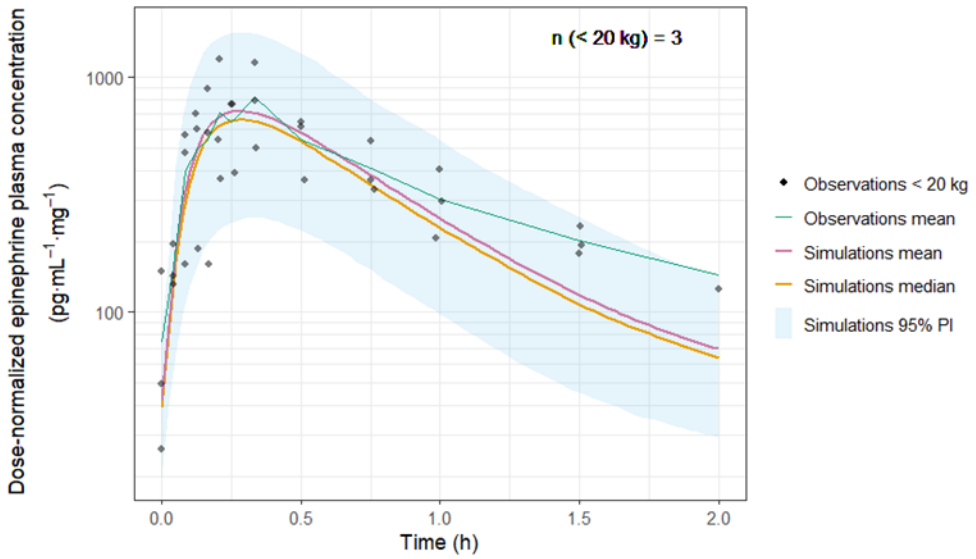

Figure 2: Observed versus predicted epinephrine plasma concentration–time profiles for the lightest patients (<20kg) and youngest patients (<6 years) in the EPI-10 study cohort.

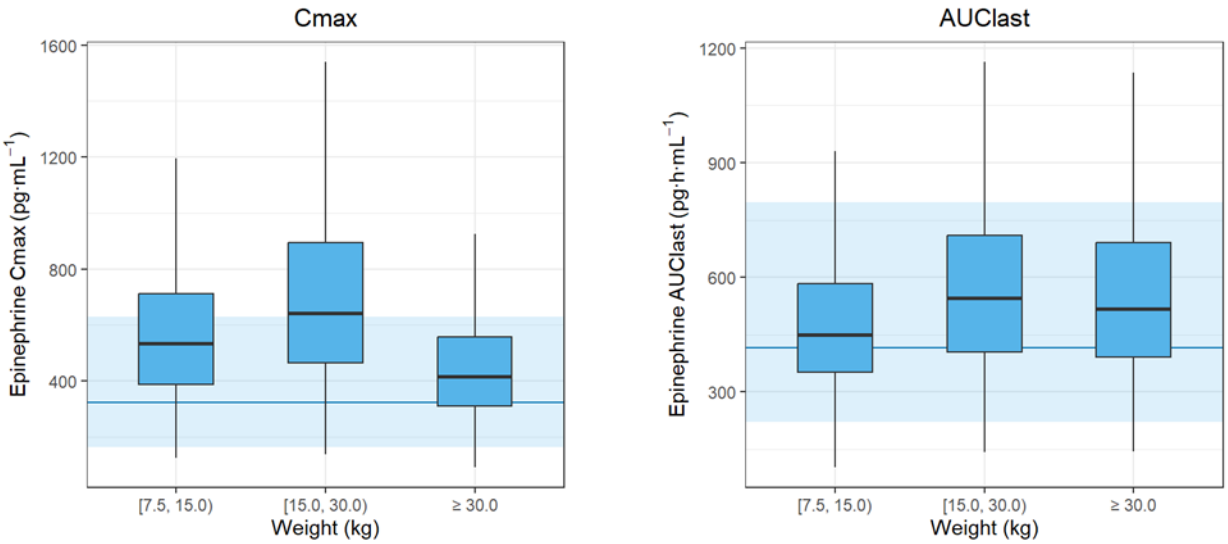

Figure 3: Epinephrine C_{max} and AUC_{last} values, split by weight, following the administration of 0.65mg to paediatrics 7.5-15kg, 1mg to paediatrics 15-30kg, and 2mg to paediatrics >30kg, relative to the adult reference range. The shaded area represents the 5^{th}–95^{th} percentiles range, and the horizontal line represents the median adult value.

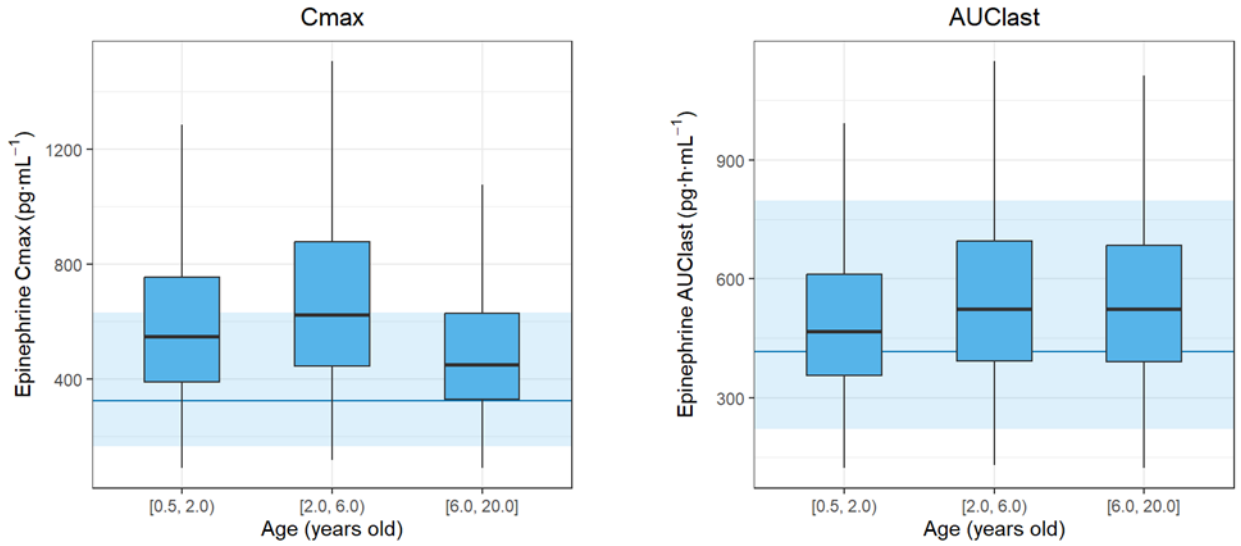

Figure 4: Epinephrine C_{max} and AUC_{last} values, split by age, following the administration of 0.65mg to paediatrics 7.5-15kg, 1mg to paediatrics 15-30kg, and 2mg to paediatrics >30kg, relative to the adult reference range. The shaded area represents the 5th–95th percentiles range, and the horizontal line represents the median adult value.

Population PK model

A fit-for-purpose PopPK model specific to the intranasal administration route was developed. The model incorporates the following key features:

- The model is based on uncorrected plasma concentration data pooled from both adult and paediatric subjects, derived from 5 studies in adult subjects (EPI-03, EPI-04, EPI-07, EPI-15 and EPI-16) and 1 study in paediatric subjects (EPI-10), with a combined total of 255 subjects with 3564 observations to ensure consistency across the dataset.
- A two-compartment distribution model with linear clearance was selected based on the observed PK profiles.
- Systemic PK parameters (clearance and volume of distribution) were scaled using fixed allometric exponents of 0.75 and 1.0, respectively.
- Stratified prediction-corrected visual predictive checks (pcVPCs) were conducted for both adult and paediatric subgroups, with particular focus on the youngest and lowest-weight subjects.

The pcVPV (N=1000) is shown in Figure 5.

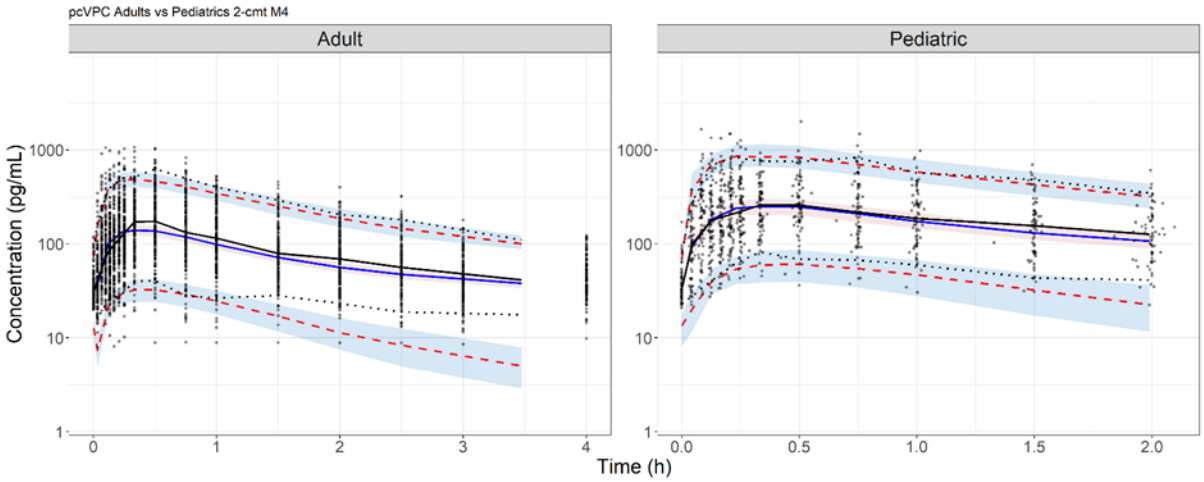

Figure 5: Prediction corrected Visual Predictive Check (pcVPC) plot of the 2-compartment PopPK model stratified by adult vs paediatric subjects.

Observed data are shown as black circles, with the median and 5th-95th percentiles depicted by solid and dotted black lines, respectively. Simulated data are represented by solid and dashed lines: blue for the median and red for the 5th-95th percentiles. Shaded areas indicate the 95% confidence intervals (CIs) around the simulated median (red), and 5th-95th (blue) percentiles.

To assess the potential model bias, the pcVPC for paediatric subjects was further stratified by weight (Figure 6).

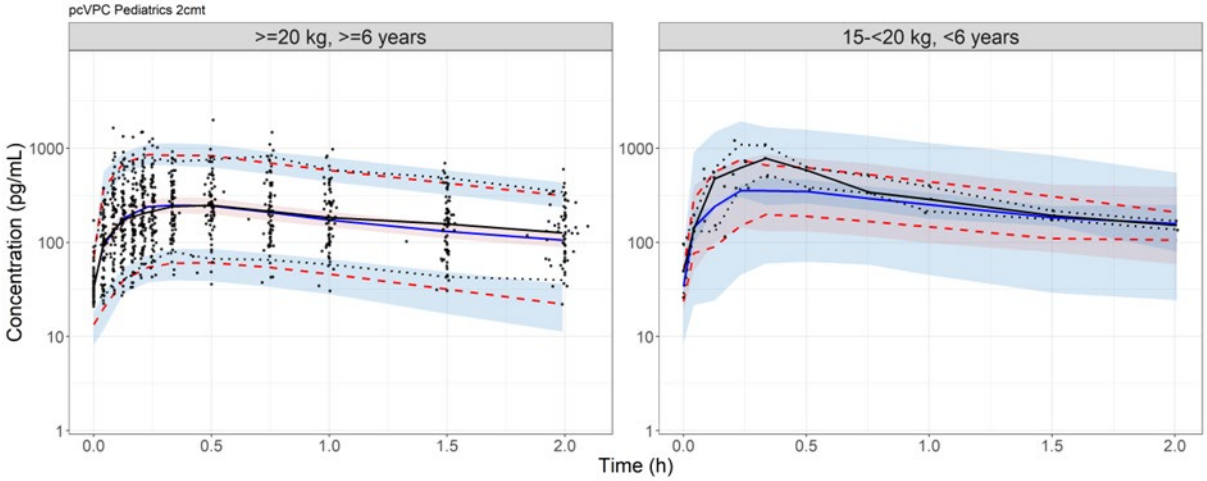

Figure 6: Prediction-corrected Visual Predictive Check (pcVPC) plot of paediatric subjects stratified by body weight ≥ 20 kg or < 20kg

Observed data are shown as black circles, with the median and 5th-95th percentiles depicted by solid and dotted black lines, respectively. Simulated data are represented by solid and dashed lines: blue for the median and red for the 5th-95th percentiles. Shaded areas indicate the 95% confidence intervals (CIs) around the simulated median (red), and 5th-95th (blue) percentiles.

To further support model performance across the paediatric population, dose-normalised, non-binned scatter VPCs stratified by body weight (Figure 7) and age (Figure 8) and overlaid with observed paediatric data were provided.

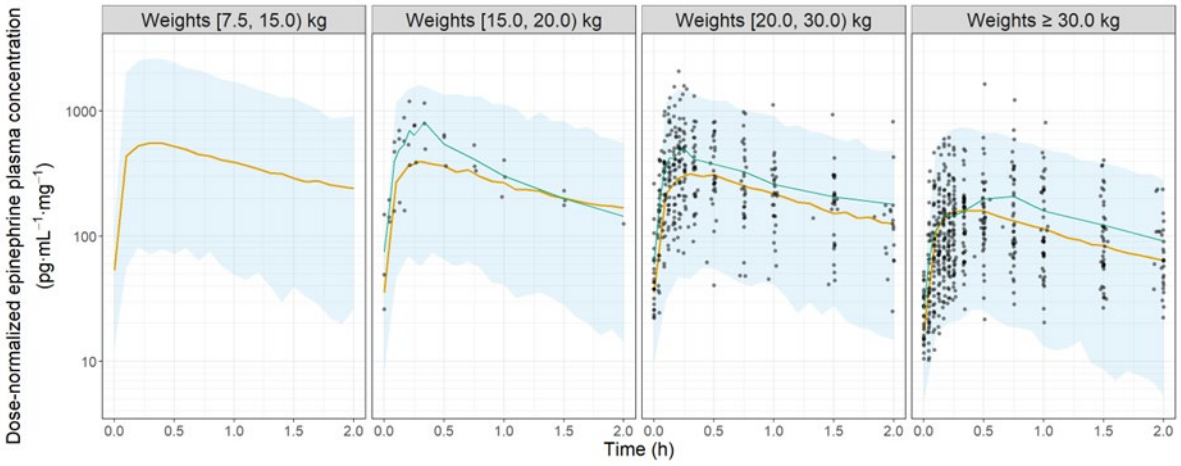

Figure 7: Observed versus predicted adrenaline dose-normalised plasma concentration-time profiles of paediatric subjects stratified by weight.

The green solid line is the mean profile of the observed data from the EPI-10 study; the solid black circles are the observations (Weights [15.0, 20.0) kg, N = 3; Weights [20.0, 30.0) kg, N = 29; Weights ≥ 30 kg, N = 46); the orange solid line is the median profile of the simulations, respectively; the blue shaded area is the 95% prediction interval. **Simulated doses of ARS-1 were assigned according to body weight: i) 0.65 mg for <15 kg children; ii) 1 mg for 15-30 kg children; iii) 2 mg for ≥ 30 kg children**.

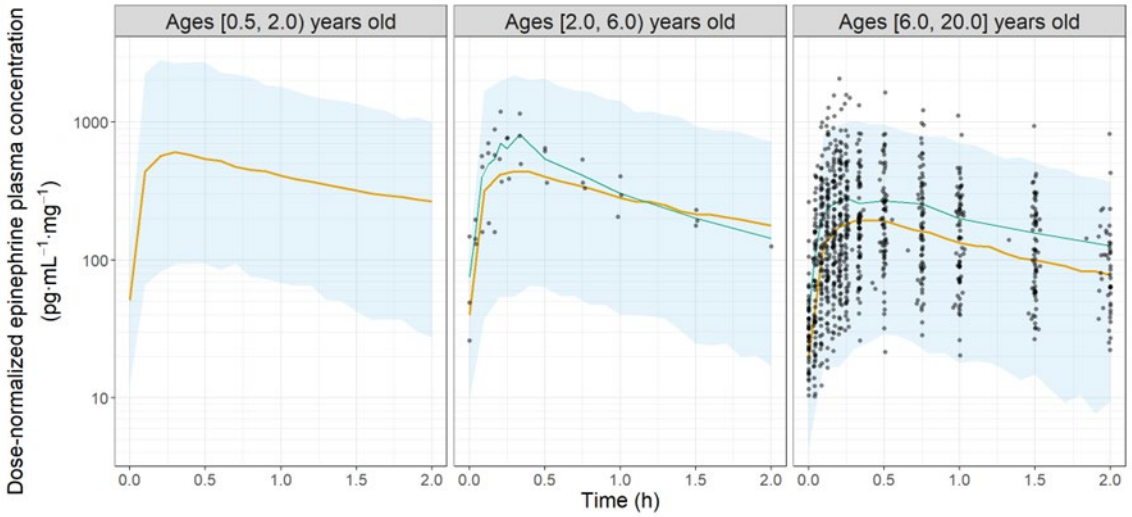

Figure 8: Observed versus predicted adrenaline dose-normalised plasma concentration-time profiles of paediatric subjects stratified by age

The green solid line is the mean profile from the observed data from the EPI-10 study; the solid black circles are the observations (Ages [2.0, 6.0), N = 3; Ages [6.0, 20.0], N = 75); the orange solid line is the median profile of the simulations, respectively; the blue shaded area is the 95% prediction interval. **Simulated doses of ARS-1 were assigned according to body weight: i) 0.65 mg for <15 kg children; ii) 1 mg for 15-30 kg children; iii) 2 mg for ≥ 30 kg children**.

2.6.2.2.2. Absorption

This section summarises the results of the study EPI10 and the supportive study EPI14.

EPI10 - A phase 1 single-period, single-dose study of the pharmacokinetics and pharmacodynamics of adrenaline after administration of intranasal ARS-1 to paediatric subjects with systemic allergies.

This was a phase 1, open-label, single-dose, single treatment pharmacokinetic study that consisted of a screening period and a treatment period. The bioavailability and hemodynamic response of either a 0.65 mg, 1 mg, or 2 mg dose of IN ARS-1, dosed by weight, was assessed in paediatric allergy subjects.

Study Part 1:

- Subjects 15 to <30-kilogram (kg) body weight received a single 0.65 mg/100 microliter (µL) IN dose of ARS-1 in the left nare,
- Subjects 30 kg or greater body weight received a single 1 mg/100 µL IN dose of ARS-1 in the left nare.

Study Part 2:

- Subjects 15 to <30 kg body weight received a single 1 mg/100 µL IN dose of ARS-1 in the left nare,
- Subjects 30 kg or greater body weight received a single 2 mg/100 µL IN dose of ARS-1 in the left nare.

The primary objectives of this study were as follows:

1) to assess the pharmacokinetics of adrenaline after IN administration of 0.65 mg, 1 mg, or 2 mg dose of ARS-1 in paediatric allergy subjects; and

2) to evaluate the PD response based on pulse rate (PR) and BP using an ABPM device after IN administration of 0.65 mg, 1 mg, or 2 mg dose of ARS-1 in paediatric allergy subjects.

Pharmacokinetic Results

This study enrolled 82 paediatric allergy patients aged 4 – 17. Two subjects withdrew prior to dosing and 80 subjects received at least one dose of study medication. Of the 80 subjects that received study medication, a total of 62 were unique subjects. Eighteen (18) subjects that participated in Part 1 of the study were re-screened and reenrolled in Part 2 of the study for a total of 80 administered doses.

Total doses administered were as follows:

Subjects between 15 and 30 kg (aged 4 to 11 years):

- 12 doses of ARS-1 0.65 mg
- 21 doses of ARS-1 1 mg

Subjects above ⩾30 kg (aged 8 to < 18 years):

- 26 doses of ARS-1 1 mg
- 21 doses of ARS-1 2 mg

It should be noted that, in the 15–<30 kg group receiving 0.65 mg/100 µL IN, one subject was dosed but PK data were not available due to refusal of IV cannulation. Therefore, PK data are available for 11 instead of 12 subjects. Similarly, in the 15–<30 kg group receiving 1 mg IN, another subject was excluded from the PK analysis because all obtained PK data were BLQ and PK data are available for 25 instead of 26 subjects.

Plasma concentrations and noncompartmental analysis

Summary statistics of PK parameters sorted by treatment are presented in Table 3. Summary statistics of epinephrine partial AUCs sorted by treatment are presented in Table 4.

Table 3: Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

Treatment	N	C_{max} (pg/mL) mean (%CV)	t_{max} (min) median (range)	AUC_{0-t} (min*pg/mL) mean (%CV)
15 – 30 kg				
ARS-1 0.65 mg	11	534 (58.7)	12.5 (2.50 – 30.3)	21800 (49.8)
ARS-1 1.0 mg	21	651 (64.2)	20.0 (2.50 – 61.5)	35100 (57.3)
≥ 30 kg				
ARS-1 1.0 mg	25	253 (66.2)	20.1 (7.50 – 122)	14000 (52.9)
ARS-1 2.0 mg	21	690 (100)	29.5 (2.90 – 120)	40200 (92.8)

For the target population (EURneffy 1 mg 15-30 kg), C_{max} geometric mean was 520 and AUC_{0-t} geometric mean was 29 500.

Table 4: Epinephrine Partial AUCs, Sorted by Treatment

Treatment	N	pAUC (min*pg/mL) mean (%CV)					
		AUC 0-2.5min	AUC 0-5min	AUC 0-7.5min	AUC 0-10min	AUC 0-12min	AUC 0-15min
15 – 30 kg							
ARS-1 0.65 mg	11	245 (60.5)	750 (50.2)	1500 (47.3)	2390 (50.0)	3190 (53.9)	4420 (57.6)
ARS-1 1.0 mg	21	210 (48.9)	727 (57.2)	1540 (63.5)	2470 (66.9)	3260 (68.7)	4630 (70.0)
≥ 30 kg							
ARS-1 1.0 mg	25	114 (80.1)	346 (82.6)	681 (82.1)	1080 (82.7)	1410 (83.7)	1870 (83.6)
ARS-1 2.0 mg	21	148 (112)	468 (106)	901 (83.8)	1440 (70.3)	1940 (68.5)	2750 (68.2)
Treatment	**N**	**pAUC (min*pg/mL) mean (%CV)**					
		$AUC_{0-20min}$	**$AUC_{0-30min}$**	**$AUC_{0-45min}$**	**$AUC_{0-60min}$**	**$AUC_{0-90min}$**	**$AUC_{0-118min}$**
15 – 30 kg							
ARS-1 0.65 mg	11	6210 (57.7)	9290 (54.1)	12900 (50.6)	15500 (50.6)	19200 (49.9)	21700 (49.7)
ARS-1 1.0 mg	21	6890 (67.5)	10800 (59.9)	16200 (54.9)	21000 (53.7)	28700 (54.6)	34900 (57.0)
≥ 30 kg							
ARS-1 1.0 mg	25	2560 (77.5)	3860 (62.3)	5960 (51.9)	8080 (52.5)	11400 (54.6)	13800 (53.2)
ARS-1 2.0 mg	21	4400 (66.1)	9350 (72.9)	17800 (89.4)	25100 (92.3)	36300 (82.9)	44500 (86.7)

Comparative Bioavailability

Test/Reference ratios and 90% CIs of the natural log-transformed exposure parameters (C_{max} and partial AUCs) for total epinephrine concentrations comparing the two dose/weight groups of ARS-1 are presented in Table 5.

Table 5: Pairwise Comparison: 1.0 mg IN (15 - 30 kg) vs 0.65 mg IN (15 - 30 kg) Total Epinephrine Systemic Exposure Parameters, Ratios with 90% CI

Calculations Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
Ln(C_{max})	110	72	166
Ln(AUC_{0-t})	153	104	226
Ln($AUC_{0-2.5min}$)	92	62	138
Ln(AUC_{0-5min})	95	65	140
Ln($AUC_{0-7.5min}$)	95	65	139
Ln($AUC_{0-10min}$)	92	62	136
Ln($AUC_{0-12min}$)	90	61	134
Ln($AUC_{0-15min}$)	93	62	138
Ln($AUC_{0-20min}$)	99	67	146
Ln($AUC_{0-30min}$)	108	74	158
Ln($AUC_{0-45min}$)	119	81	175
Ln($AUC_{0-60min}$)	129	88	190
Ln($AUC_{0-90min}$)	143	97	211
Ln($AUC_{0-118min}$)	153	104	225
Reference: 0.65 mg IN (15 - 30 kg)			
Test: 1.0 mg IN (15 - 30 kg)			

The two dose/weight groups of ARS 1: 2.0 mg IN (⩾ 30 kg) vs 1.0 mg IN (⩾ 30 kg) are similarly compared in Table 6.

Table 6: Pairwise Comparison: 2.0 mg IN (≥ 30 kg) vs 1.0 mg IN (≥ 30 kg) Total Epinephrine Systemic Exposure Parameters, Ratios with 90% CI

Calculations Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
Ln(C_{max})	250	174	358
Ln(AUC_{0-t})	224	150	335
Ln($AUC_{0-2.5min}$)	128	89	184
Ln(AUC_{0-5min})	131	86	198
Ln($AUC_{0-7.5min}$)	134	89	202
Ln($AUC_{0-10min}$)	139	93	206
Ln($AUC_{0-12min}$)	145	98	213
Ln($AUC_{0-15min}$)	154	106	224
Ln($AUC_{0-20min}$)	179	127	253
Ln($AUC_{0-30min}$)	234	168	326
Ln($AUC_{0-45min}$)	266	191	371
Ln($AUC_{0-60min}$)	273	194	386
Ln($AUC_{0-90min}$)	278	196	394

Calculations Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(AUC_{0\text{-}118min})$	281	197	400
Reference: 1.0 mg IN (≥ 30 kg)			
Test: 2.0 mg IN (≥ 30 kg)			

The two dose/weight groups of ARS-1: 1.0 mg IN (15 - 30 kg) vs 2.0 mg IN (⩾ 30 kg) are compared in Table 7.

Table 7: Pairwise Comparison: 1.0 mg IN (15 - 30 kg) vs 2.0 mg IN (≥ 30 kg) -- Total Epinephrine Systemic Exposure Parameters, Ratios with 90% CI

Calculations Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(C_{max})$	102	69	151
$Ln(AUC_{0\text{-}t})$	110	71	170
$Ln(AUC_{0\text{-}2.5min})$	167	120	233
$Ln(AUC_{0\text{-}5min})$	189	130	276
$Ln(AUC_{0\text{-}7.5min})$	192	131	281
$Ln(AUC_{0\text{-}10min})$	181	123	265
$Ln(AUC_{0\text{-}12min})$	173	119	253
$Ln(AUC_{0\text{-}15min})$	170	117	248
$Ln(AUC_{0\text{-}20min})$	155	109	221
$Ln(AUC_{0\text{-}30min})$	120	84	171
$Ln(AUC_{0\text{-}45min})$	101	70	145
$Ln(AUC_{0\text{-}60min})$	94	65	137
$Ln(AUC_{0\text{-}90min})$	90	62	131
$Ln(AUC_{0\text{-}118min})$	88	60	130
Reference: 2.0 mg IN (> 30 kg)			
Test: 1.0 mg IN (15 - 30 kg)			

Analysis of Epinephrine tmax Using Truncated Data Collected within 60 Minutes of Administration of ARS-1

The percentage of the subjects within each dose/weight group for whom t_{max} occurred within specific time ranges after administration of ARS-1 is summarised in Table **8**.

Table 8: Percent of Subjects with t_{max} within Specific Time Ranges after Administration of ARS-1

Dose/Weight Group	Time Range of t_{max} (minutes)				
	≤ 20	> 20 to ≤ 30	> 30 to ≤ 45	> 45 to ≤ 60	> 60
	Percent (%) of Subjects				
15 – 30 kg					
ARS-1 0.65 mg	82	9	9	0	0
ARS-1 1.0 mg	57	14	10	14	5
≥ 30 kg					
ARS-1 1.0 mg	48	8	20	20	4
ARS-1 2.0 mg	38	19	19	10	14

EPI 14 - A phase 1, two-treatment, sequential, crossover study of the pharmacokinetics of epinephrine after administration of ARS -1 in subjects with upper respiratory tract infection (infectious rhinitis)

The primary objective of this study was to assess the comparative pharmacokinetics of ARS-1 in subjects with normal nasal conditions and with an upper respiratory tract infection (URTI) to evaluate the impact of nasal oedema and congestion on the absorption of epinephrine.

Pharmacokinetic results

A total of 21 subjects were enrolled, with 16 (76.2%) subjects completing both dosing periods in the study. All 21 subjects received at least one dose of study medication. Five subjects withdrew prematurely (one due to withdrawal by subject, two due to physician decision, and two were lost to follow-up). A total of 38 doses of ARS-1 2.0 mg were administered. The 17 subjects enrolled in both Period 1 and Period 2 received two doses of ARS-1 2.0 mg. The four (4) subjects who withdrew after period 1 received one dose of ARS-1 2.0 mg.

The 21 subjects were male or female between 19 to 55 years of age.

Table 9: Nasal Assessments at Baseline

Baseline Assessment/Score	Number (%) of Subjects
Total Nasal Symptom Score	
5	2 (9.5)
6 - 8	16 (76.2)
>8	3 (14.3)
Congestion Score	
2	16 (76.2)
3	5 (23.8)
Rhinorrhea	
1	1 (4.8)
2	18 (85.7)
3	2 (9.5)

Table 10: Summary Statistics of Epinephrine Pharmacokinetic Parameters by Nasal Condition

Nasal Condition	N	t_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_t (min*pg/mL) mean (%CV)
Normal	16	45.7 (9.90 – 150)	570 (56.1)	64400 (53.4)
URTI	21	45.0 (1.60 – 150)	490 (67.2)	58700 (60.9)

Table 11: Epinephrine Partial AUCs, by Nasal Condition

Nasal Condition	N	pAUC (min*pg/mL) mean (%CV)					
		AUC 0-2min	**AUC 0-4min**	**AUC 0-6min**	**AUC 0-8min**	**AUC 0-10min**	**AUC 0-12.5min**
Normal	16	85.7 (77.2)	225 (85.9)	406 (81.7)	654 (75.2)	982 (70.4)	1460 (66.1)
URTI	21	138 (147)	358 (126)	617 (98.4)	935 (86.3)	1310 (83.0)	1870 (81.7)
Treatment	**N**	**pAUC (min*pg/mL) mean (%CV)**					
		$AUC_{0-15min}$	**$AUC_{0-20min}$**	**$AUC_{0-30min}$**	**$AUC_{0-45min}$**	**$AUC_{0-60min}$**	**$AUC_{0-118min}$**
Normal	16	2010 (66.2)	3210 (70.2)	6040 (72.4)	11300 (62.1)	17200 (58.9)	37400 (60.0)
URTI	21	2450 (81.3)	3680 (79.9)	6210 (76.7)	10800 (76.5)	16000 (77.1)	33200 (66.4)
Treatment	**N**	**pAUC (min*pg/mL) mean (%CV)**					
		$AUC_{0-240min}$	**$AUC_{60-118min}$**	**$AUC_{60-240min}$**			
Normal	16	64400 (53.4)	20200 (73.9)	47200 (62.7)			
URTI	21	58700 (61.0)	17200 (63.9)	42700 (66.0)			

Comparative Bioavailability

Table 12: Comparison of Total Epinephrine C_{max} and pAUCs for URTI vs Normal Nasal Condition

Calculations Using Total Epinephrine Concentrations			
Dependent Variable	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(C_{max})$	78	59	102
$Ln(AUC_{0-t})$	87	66	113
$Ln(AUC_{0-2min})$	122	87	171
$Ln(AUC_{0-4min})$	133	91	194
$Ln(AUC_{0-6min})$	134	92	194
$Ln(AUC_{0-8min})$	125	88	178
$Ln(AUC_{0-10min})$	113	81	157
$Ln(AUC_{0-12.5min})$	107	80	144
$Ln(AUC_{0-15min})$	105	81	137
$Ln(AUC_{0-20min})$	101	79	129
$Ln(AUC_{0-30min})$	93	71	122
$Ln(AUC_{0-45min})$	86	66	112
$Ln(AUC_{0-60min})$	85	65	111
$Ln(AUC_{0-118min})$	83	62	110
$Ln(AUC_{0-240min})$	87	66	113
$Ln(AUC_{60-118min})$	83	59	115
$Ln(AUC_{60-240min})$	90	68	119
Test: URTI Condition			
Reference: Normal Nasal Condition			

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, pAUC = partial AUC, URTI = upper respiratory tract infection.

2.6.2.2.3. Bioavailability

This section summarises the results of the supportive studies EPI JP01 and JP02.

EPI JP01- A phase 1, four-treatment, partially randomised crossover study of the pharmacokinetics of adrenaline after administration of ARS -1 or adrenaline injection in subjects with allergic rhinitis

The primary objectives of this study were as follows: 1) to assess the pharmacokinetics (PK) of adrenaline after administration of ARS-1 1 mg IN in subjects with normal nasal conditions and with induced allergic rhinitis and to evaluate the impact of nasal oedema and congestion on the absorption of adrenaline; and 2) to assess the PK of ARS-1 1 mg IM when administered in subjects under normal conditions to adrenaline injection administered both by IM via needle/syringe and EpiPen. A secondary objective of this study was to evaluate the safety and tolerability of ARS-1 in healthy volunteers.

Thirty-six (36) eligible male or female subjects were enrolled in the Treatment Periods 1 - 4.

At baseline and before ARS-1 dosing in one of the Treatment Periods 1 - 3, no apparent nasal edema and congestion (TNSS score of $\leq$ 2 out of 12 and a congestion score of $\leq$ 1 out of 3) was confirmed. The fourth (4th) treatment period was defined as dosing of ARS-1 after allergy challenge to induce allergic rhinitis symptoms.

Pharmacokinetic results

Plasma Concentrations and Noncompartmental Analysis

Table 13: Summary Statistics of Adrenaline Pharmacokinetic Parameters by Treatment (Primary Population)

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	12.5 (4.00 – 45.0)	364 (62.1)	306	30600 (45.4)	27100
Adrenaline 0.3 mg IM	35	45.0 (4.00 – 60.0)	549 (33.1)	518	56500 (19.7)	55300
EpiPen 0.3 mg	30	10.0 (2.00 – 45.0)	676 (46.6)	608	49400 (23.4)	48100

Table 14: Summary Statistics of Adrenaline Pharmacokinetic Parameters by Treatment (Secondary Population)

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	12.5 (4.00 – 45.0)	364 (62.1)	306	30600 (45.4)	27100
Adrenaline 0.3 mg IM	36	45.0 (4.00 – 60.0)	563 (35.3)	529	56300 (19.6)	55100
EpiPen 0.3 mg	36	6.0 (2.00 – 45.0)	901 (82.6)	729	50200 (22.3)	49000

Table 15: Adrenaline Partial AUCs, Sorted by Treatment (Primary Population)

Treatment	N	pAUC (min*pg/mL)													
		AUC_{0-2min}		AUC_{0-4min}		AUC_{0-6min}		AUC_{0-8min}		$AUC_{0-10min}$		$AUC_{0-12.5min}$		$AUC_{0-15min}$	
		mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	113 (74.2)	91.6	379 (72.4)	307	770 (69.2)	623	1250 (70.1)	1010	1770 (69.3)	1440	2450 (66.4)	2030	3140 (64.4)	2620
Adrenaline 0.3 mg IM	35	109 (72.7)	81.8	417 (76.8)	296	891 (80.4)	628	1380 (77.8)	1000	1860 (74.5)	1390	2450 (71.2)	1890	3040 (68.9)	2390
EpiPen 0.3 mg	30	206 (83.2)	154	819 (63.0)	655	1750 (53.6)	1470	2720 (52.0)	2330	3680 (52.0)	3190	4850 (53.2)	4220	6000 (54.4)	5190

Treatment	N	pAUC (min*pg/mL)									
		$AUC_{0-20min}$		$AUC_{0-30min}$		$AUC_{0-45min}$		$AUC_{0-60min}$		$AUC_{0-120min}$	
		mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	4430 (61.7)	3720	6720 (58.2)	5690	9460 (56.0)	8080	11600 (54.7)	9940	17400 (52.1)	15100
Adrenaline 0.3 mg IM	35	4370 (64.3)	3570	7590 (53.2)	6590	13600 (41.4)	12400	20100 (33.8)	18900	35000 (25.5)	33700
EpiPen 0.3 mg	30	8290 (54.5)	7120	13000 (51.0)	11300	19200 (44.7)	17300	23600 (40.1)	21800	31900 (34.0)	30100

Source: EPI JP01 PK report Appendix Table 4

Table 16: Adrenaline Partial AUCs, Sorted by Treatment (Secondary Population)

Treatment	N	pAUC (min*pg/mL)													
		AUC_{0-2min}		AUC_{0-4min}		AUC_{0-6min}		AUC_{0-8min}		$AUC_{0-10min}$		$AUC_{0-12.5min}$		$AUC_{0-15min}$	
		mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	113 (74.2)	91.6	379 (72.4)	307	770 (69.2)	623	1250 (70.1)	1010	1770 (69.3)	1440	2450 (66.4)	2030	3140 (64.4)	2620
Adrenaline 0.3 mg IM	36	123 (92.7)	86.5	468 (94.3)	313	987 (92.4)	663	1520 (87.4)	1060	2020 (82.5)	1460	2630 (77.1)	1970	3230 (72.9)	2480
EpiPen 0.3 mg	36	468 (175)	219	1590 (149)	902	2950 (125)	1940	4200 (110)	2980	5310 (97.2)	3970	6620 (85.5)	5150	7860 (78.1)	6240

Treatment	N	pAUC (min*pg/mL)									
		$AUC_{0-20min}$		$AUC_{0-30min}$		$AUC_{0-45min}$		$AUC_{0-60min}$		$AUC_{0-120min}$	
		mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
ARS-1 1 mg IN	36	4430 (61.7)	3270	6720 (58.2)	5690	9460 (56.0)	8080	11600 (54.7)	9940	17400 (52.1)	15100
Adrenaline 0.3 mg IM	35	4570 (65.9)	3680	7780 (53.3)	6740	13700 (40.8)	12600	20200 (33.2)	19000	34900 (25.3)	33600
EpiPen 0.3 mg	30	10300 (67.8)	8380	15100 (54.6)	12900	21200 (44.2)	19000	25300 (38.5)	23400	33200 (31.9)	31500

Source: EPI JP01 PK report Appendix Table 4

Comparative Bioavailability

Table 17: Statistical Analysis of the Natural Log-Transformed Pharmacokinetic Parameters of Adrenaline after Administration of ARS-1 1 mg IN, Adrenaline 0.3 mg IM, and EpiPen 0.3 mg (Primary Population)

Test vs. Ref	Dependent Variable	Ratio (%)[a] (Test/Ref)	90% CI [b] Lower	90% CI [b] Upper	p-value[c]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	ln(C_{max})	59.06	49.78	70.06	< 0.0001
	ln(AUC_{0-2min})	110.29	87.18	139.52	0.4894
	ln($AUC_{0-4\ min}$)	102.56	80.00	131.48	0.8655
	ln($AUC_{0-6\ min}$)	98.34	76.43	126.54	0.9121
	ln($AUC_{0-8\ min}$)	99.59	77.93	127.27	0.9778
	ln($AUC_{0-10\ min}$)	103.03	81.49	130.28	0.8322
	ln($AUC_{0-12.5\ min}$)	107.14	85.50	134.25	0.6116
	ln($AUC_{0-15\ min}$)	109.19	87.49	136.27	0.5101
	ln($AUC_{0-20\ min}$)	104.24	84.29	128.91	0.7452
	ln($AUC_{0-30\ min}$)	86.46	71.42	104.67	0.2086
	ln($AUC_{0-45\ min}$)	65.25	55.33	76.95	< 0.0001
	ln($AUC_{0-60\ min}$)	52.90	45.49	61.51	< 0.0001
	ln($AUC_{0-120\ min}$)	45.25	39.33	52.05	< 0.0001
	ln(AUC_{last})	49.39	43.41	56.20	< 0.0001
ARS-1 1 mg IN vs EpiPen 0.3 mg	ln(C_{max})	48.66	40.65	58.26	< 0.0001
	ln(AUC_{0-2min})	59.39	46.32	76.15	0.0009
	ln($AUC_{0-4\ min}$)	44.66	34.35	58.08	< 0.0001
	ln($AUC_{0-6\ min}$)	39.86	30.54	52.03	< 0.0001
	ln($AUC_{0-8\ min}$)	40.65	31.38	52.67	< 0.0001
	ln($AUC_{0-10\ min}$)	42.74	33.37	54.75	< 0.0001
	ln($AUC_{0-12.5\ min}$)	45.65	35.98	57.92	< 0.0001
	ln($AUC_{0-15\ min}$)	47.97	37.97	60.59	< 0.0001
	ln($AUC_{0-20\ min}$)	49.96	39.94	62.49	< 0.0001

Test vs. Ref	Dependent Variable	Ratio (%)[a] (Test/Ref)	90% CI [b] Lower	90% CI [b] Upper	p-value[c]
	ln($AUC_{0\text{-}30\ min}$)	48.25	39.45	59.03	< 0.0001
	ln($AUC_{0\text{-}45\ min}$)	45.04	37.84	53.60	< 0.0001
	ln($AUC_{0\text{-}60\ min}$)	44.34	37.81	51.99	< 0.0001
	ln($AUC_{0\text{-}120\ min}$)	49.25	42.49	57.09	< 0.0001
	ln(AUC_{last})	56.06	48.93	64.23	< 0.0001

[a] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); [b] 90% Confidence Interval; [c] p-value for the difference in the treatment of estimates; Significant difference defined a priori as $p < 0.05$

Table 18: Statistical Analysis of the Natural Log-Transformed Pharmacokinetic Parameters of Adrenaline after Administration of ARS-1 1 mg IN, Adrenaline 0.3 mg IM, and EpiPen 0.3 mg (Secondary Population)

Test vs. Ref	Dependent Variable	Ratio (%)[a] (Test/Ref)	90% CI [b] Lower	90% CI [b] Upper	p-value[c]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	ln(C_{max})	57.80	48.28	69.19	< 0.0001
	ln($AUC_{0\text{-}2min}$)	105.87	79.00	141.89	0.7462
	ln($AUC_{0\text{-}4\ min}$)	98.02	74.79	128.47	0.9024
	ln($AUC_{0\text{-}6\ min}$)	93.94	72.43	121.84	0.6899
	ln($AUC_{0\text{-}8\ min}$)	95.29	74.25	122.29	0.7479
	ln($AUC_{0\text{-}10\ min}$)	98.78	77.93	125.20	0.9312
	ln($AUC_{0\text{-}12.5\ min}$)	103.03	82.18	129.16	0.8266
	ln($AUC_{0\text{-}15\ min}$)	105.34	84.52	131.29	0.6950
	ln($AUC_{0\text{-}20\ min}$)	101.10	81.99	124.65	0.9311
	ln($AUC_{0\text{-}30\ min}$)	84.49	70.13	101.80	0.1363
	ln($AUC_{0\text{-}45\ min}$)	64.26	54.82	75.33	< 0.0001
	ln($AUC_{0\text{-}60\ min}$)	52.35	45.32	60.48	< 0.0001
	ln($AUC_{0\text{-}120\ min}$)	45.05	39.44	51.45	< 0.0001
	ln(AUC_{last})	49.25	43.59	55.65	< 0.0001
ARS-1 1 mg IN vs EpiPen 0.3 mg	ln(C_{max})	41.94	35.04	50.21	< 0.0001
	ln($AUC_{0\text{-}2min}$)	41.88	31.25	56.13	< 0.0001
	ln($AUC_{0\text{-}4\ min}$)	34.04	25.97	44.61	< 0.0001
	ln($AUC_{0\text{-}6\ min}$)	32.18	24.81	41.74	< 0.0001
	ln($AUC_{0\text{-}8\ min}$)	33.82	26.35	43.40	< 0.0001
	ln($AUC_{0\text{-}10\ min}$)	36.28	28.63	45.99	< 0.0001
	ln($AUC_{0\text{-}12.5\ min}$)	39.41	31.44	49.41	< 0.0001
	ln($AUC_{0\text{-}15\ min}$)	41.93	33.64	52.25	< 0.0001
	ln($AUC_{0\text{-}20\ min}$)	44.43	36.03	54.78	< 0.0001
	ln($AUC_{0\text{-}30\ min}$)	44.19	36.68	53.25	< 0.0001
	ln($AUC_{0\text{-}45\ min}$)	42.49	36.25	49.81	< 0.0001
	ln($AUC_{0\text{-}60\ min}$)	42.50	36.79	49.10	< 0.0001
	ln($AUC_{0\text{-}120\ min}$)	48.06	42.08	54.90	< 0.0001
	ln(AUC_{last})	55.44	49.07	62.64	< 0.0001

[a] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref); [b] 90% Confidence Interval; [c] p-value for the difference in the treatment_id estimates; Significant difference defined a priori as $p < 0.05$

EPI JP02 - a phase 1, two-period, two-treatment, randomised, crossover study that consisted of a screening period, baseline period, and an open-label randomised treatment period.

The bioavailability of a single dose of IN ARS-1 (2.0 mg epinephrine) was compared to a single dose of IM injection (0.3 mg epinephrine). Each dose was separated by a 24-hour wash-out period.

Eligible male or female were 13 healthy Japanese subjects, aged 29 to 54 years of age.

Pharmacokinetic Results

Table 19: Summary Statistics of Epinephrine Pharmacokinetic Parameters – 0 – 360 Minutes

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_{total} (min*pg/mL) mean (%CV)
ARS-1 2.0 mg	12	20.0 (15.0 – 120.0)	814 (105.67)	56782 (79.6)
Epinephrine IM 0.3 mg	12	45.0 (15.0 – 360.0)	268 (31.5)	30644 (36.4)
ARS-1 2.0 mg without Subject 3010*	11	20.0 (15.0 – 120.0)	583 (56.5)	45573 (53.2)

Table 20: Summary Statistics of Epinephrine Pharmacokinetic Parameters – 0 – 60 Minutes

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_{0-60} (min*pg/mL) mean (%CV)
ARS-1 2.0 mg	12	20.0 (15.0 – 30.0)	800 (108.7)	23780 (107)
Epinephrine IM 0.3 mg	12	37.5 (15.0 – 61.0)	266 (32.5)	9870 (34.8)

Table 21: Epinephrine Partial AUCs, by Treatment

Treatment	N	pAUC (min*pg/mL)						
		AUC_{0-2min}	AUC_{0-4min}	AUC_{0-6min}	AUC_{0-8min}	$AUC_{0-10min}$	$AUC_{0-12.5min}$	$AUC_{0-15min}$
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	12	47 (57.5)	145 (76.6)	313 (109.1)	572 (127.8)	981 (138.5)	1703 (135.3)	2860 (117.4)
Epinephrine IM 0.3 mg	12	46 (56.0)	110 (49.7)	208 (60.9)	337 (67.9)	481 (63.8)	683 (57.2)	946 (53.5)
Treatment	**N**	**pAUC (min*pg/mL)**						
		$AUC_{0-20min}$	$AUC_{0-30min}$	$AUC_{0-45min}$	$AUC_{0-60min}$	$AUC_{0-120min}$	$AUC_{0-360min}$	$AUC_{60-360min}$
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	12	6011 (108.0)	125877 (114.5)	19560 (112.6)	23779 (107.0)	34284 (90.4)	57097 (78.8)	33318 (80.0)
Epinephrine IM 0.3 mg	12	1622 (52.5)	3477 (43.4)	6740 (36.4)	9870 (34.8)	18425 (38.9)	30987 (35.0)	21116 (39.4)

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.1.2

Table 22: Statistical Analysis of the Pharmacokinetic Parameters after Administration of ARS-1 2.0 mg IN and IM Epinephrine 0.3 mg IM

Test vs Ref	Dependent Variable	ln-transformed Geometric Mean [a]		Ratio (%) [b] (Test/Ref)	90% CI [c]		p-value [d]	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 2.0 mg vs Epinephrine 0.3 mg IM	$C_{max0-60}$	581.739	247.269	235.3	155.27	356.47	0.0044	60.1
	$C_{max0-360}$	612.583	251.940	243.1	169.83	348.12	0.0014	50.9
	AUC_{0-1}	46654.972	29222.720	159.7	128.96	197.65	0.0030	29.1
	AUC_{0-2}	40.772	38.685	105.4	73.94	150.24	0.7919	50.2
	AUC_{0-4}	115.731	93.475	123.8	86.54	177.14	0.2997	49.9
	AUC_{0-6}	219.466	168.565	130.1	84.86	199.53	0.2981	65.8
	AUC_{0-8}	370.273	266.624	138.9	87.52	220.36	0.2322	72.2
	AUC_{0-10}	608.286	387.046	157.2	96.45	256.09	0.1255	77.4
	$AUC_{0-12.5}$	1071.079	564.833	189.6	108.32	331.98	0.0632	92.9
	AUC_{0-15}	1906.491	808.115	235.9	136.58	407.50	0.0142	89.9
	AUC_{0-20}	4161.102	1419.615	293.1	174.05	493.62	0.0043	79.0
	AUC_{0-30}	8880.202	3163.942	280.7	182.11	432.56	0.0018	63.0
	AUC_{0-45}	14261.760	6263.853	227.7	159.50	325.02	0.0022	50.4
	AUC_{0-60}	17963.008	9215.311	194.9	143.66	264.48	0.0031	42.5
	AUC_{0-120}	27942.759	17197.231	162.5	136.65	193.20	0.0006	23.4
	AUC_{0-360}	47084.138	29651.116	158.8	127.81	197.29	0.0036	29.6
	$AUC6_{0-360}$	26483.003	20128.321	131.6	96.19	179.96	0.1427	43.7

a = ln-transformed Geometric Mean based on Least Squares Mean; b = Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref); c = 90% Confidence Interval; d = p-value for the difference in the treatment id estimates; Significant difference defined *a priori* as $p < 0.05$
Test: ARS-1 2.0 mg; Reference: Epinephrine 0.3 mg IM
Source EPI JP02 PK Report Appendix 16.1.13, Table 14.2.1.1

Categorisation of Subjects by T_{max} Time Category

Table 23: Distribution of Subjects by T_{max} Time Category

T_{max} Category	Subjects in Each Category n(%)	
	ARS-1 2.0 mg (n = 12)	Epinephrine 0.3 mg IM (n = 12)
≤ 10 minutes	0 (0)	0 (0)
> 10 to ≤ 20 minutes	8 (66.7)	2 (16.7)
> 20 to ≤ 30 minutes	2 (16.7)	3 (25.0)
> 30 to ≤ 45 minutes	0 (0)	3 (25.0)
≥ 60 minutes	2 (16.7)	4 (33.3)

Integrated Pharmacokinetic-Pharmacodynamic Analysis

Pharmacokinetic parameters were calculated for adrenaline, as appropriate, from raw drug concentration data after reconciliation of the PK data file with the clinical data from Studies EPI 03, EPI 04, EPI 07, EPI 15, and EPI 16. Summaries of concentration time data included only subjects with evaluable concentration time profiles.

Table 24: Summary Statistics of Total Adrenaline Pharmacokinetic Parameters: Once-Dosed Treatments

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			Mean(%CV)	Geo.mean	Mean (%CV)	Geo.mean
ARS-1 1.0 mg IN	99	21 (2 - 150)	276 (68.7)	222	25900 (52.1)	22800
ARS-1 2.0 mg IN	78	20.5 (2 - 150)	485 (70.6)	361	40900 (67.5)	32600
Adrenaline 0.3 mg IM	178	45 (3.9 -360)	277 (65.4)	234	27900 (38.7)	26100
EpiPen 0.3 mg	77	10 (2 - 45)	581 (75.6)	447	31600 (39.3)	29200
Adrenaline 0.5 mg IM	123	45 (4 -360)	399 (65.5)	335	43700 (34)	41300
Adrenaline 0.3 mg SC	35	45 (4 -180)	246 (61.6)	214	30200 (34.9)	28400

Source: Integrated analysis Tables 39, 42, 45, 47, 48, 49

Table 25: Summary Statistics of Total Adrenaline Pharmacokinetic Parameters: Twice-Dosed Treatments

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			Mean(%CV)	Geo.mean	Mean (%CV)	Geo.mean
ARS-1 1.0 mg twice (L/R)	35	30 (10 - 60)	474 (76.2)	370	42800 (63.7)	36000
ARS-1 1.0 mg twice (L/L)	7	21 (15 - 60)	544 (109)	337	34400 (79.2)	25900
ARS-1 2.0 mg twice (L/R)	39	30 (6 - 150)	1000 (93.1)	706	86000 (77)	66700
ARS-1 2.0 mg twice (R/R)	39	30 (4 - 150)	992 (75.3)	729	86500(60.5)	69900
Adrenaline 0.3 mg IM twice	70	45 (6 - 180)	436 (48.8)	386	47500(32.6)	45300
EpiPen 0.3 mg twice	78	20 (4 - 360)	754 (64.7)	630	55000(47.9)	49900

Source: Integrated analysis Tables 40, 41, 43, 44, 46, 50

Table 26: Adrenaline Partial AUCs, Once Dosed Treatments

Treatment	N	pAUC (min*pg/mL)													
		AUC_{0-2min}		AUC_{0-4min}		AUC_{0-6min}		AUC_{0-8min}		$AUC_{0-10min}$		$AUC_{0-12.5min}$		$AUC_{0-15min}$	
		Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean
ARS-1 1.0 mg IN	99	66.2 (86.2)	52.1	178 (93.7)	136	324 (94.3)	243	505 (97.5)	371	741 (94.3)	553	1090 (89.4)	831	1440 (87.8)	1100
ARS-1 2.0 mg IN	78	74.3 (90.8)	56.4	193 (99.7)	143	370 (97.9)	272	649 (100)	460	1010 (98.9)	719	1590 (90.2)	1140	2230 (87.5)	1600
Adrenaline 0.3 mg IM	178	83 (107)	61.4	250 (120)	170	480 (122)	311	717 (114)	462	949 (105)	627	1230 (96.6)	843	1500 (92.3)	1050
EpiPen 0.3 mg	77	206 (191)	96.1	716 (143)	378	1420 (111)	810	2150 (98.9)	1300	2830 (91.7)	1820	3600 (85.1)	2460	4300 (80.6)	3040
Adrenaline 0.5 mg IM	123	83.2 (130)	57.9	266 (144)	169	523 (147)	320	790 (141)	484	1080 (133)	681	1450 (124)	957	1810 (117)	1220
Adrenaline 0.3 mg SC	35	52.4 (81.6)	40.2	129 (84.5)	96.1	232 (84.2)	170	357 (88.2)	254	511 (86.7)	370	731 (85)	534	939 (85.3)	686

Treatment	N	PAUC (min*pg/mL)													
		$AUC_{0-20min}$		$AUC_{0-30min}$		$AUC_{0-45min}$		$AUC_{0-60min}$		AUC_{0-118}		AUC_{0-240}		AUC_{60-240}	
		Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean
ARS-1 1.0 mg	99	2240 (82.8)	1770	4220 (74.5)	3430	6980 (70.1)	5740	9180 (66.9)	7610	15000 (60.8)	12600	20900 (56.5)	18000	11700 (63.3)	9800
ARS-1 2.0 mg	78	3610 (84)	2640	6640 (77.3)	4980	11000 (75.8)	8140	14600 (75.9)	10700	24100 (75.8)	17900	34500 (71.7)	26700	19900 (81.7)	15000
Adrenaline 0.3 mg IM	178	2090 (86.1)	1520	3550 (72.5)	2790	6290 (60.7)	5260	9060 (55.1)	7820	15300 (46.7)	13800	21400 (42.5)	19700	12300 (44.8)	11300
EpiPen 0.3 mg	77	5640 (73.3)	4240	8410 (62.1)	6840	12000 (52.8)	10200	14400 (49)	12500	19200 (43.7)	17300	25200 (38.8)	23200	10800 (43.1)	9930
Adrenaline 0.5 mg IM	123	2590 (104)	1840	4710 (84.6)	3610	8860 (68)	7250	13300 (59.7)	11300	23900 (47.6)	21400	34100 (39.8)	31500	20800 (42.8)	19100
Adrenaline 0.3 mg SC	35	1360 (83.5)	1020	2590 (86)	2020	5080 (77.2)	4180	7690 (62)	6640	14800 (43)	13600	22300 (38.7)	20700	14600 (40.8)	13300

Source: Integrated analysis Tables 39, 42, 45, 47, 48, 49

Table 27: Adrenaline Partial AUCs, Twice Dosed Treatments

Treatment	N	pAUC (min*pg/mL)													
		AUC_{0-2min}		AUC_{0-4min}		AUC_{0-6min}		AUC_{0-8min}		$AUC_{0-10min}$		$AUC_{0-12.5min}$		$AUC_{0-15min}$	
		Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean
ARS-1 1.0 mg twice (L/R)	35	56.8 (48.3)	50.5	144 (49.2)	128	249 (48.3)	223	380 (47.1)	342	618 (46.7)	560	1050 (58.2)	920	1520 (61.7)	1320
ARS-1 1.0 mg twice (L/L)	7	39.2 (39.6)	36.3	89.6 (41.3)	81.4	140 (44.5)	125	194 (47.8)	171	307 (58.6)	261	564 (73.9)	452	881 (73.3)	695
ARS-1 2.0 mg twice (L/R)	39	90.4 (97.5)	66.2	274 (164)	168	548 (186)	318	882 (165)	529	1290 (140)	816	2050 (120)	1320	2970 (106)	1950
ARS-1 2.0 mg twice (R/R)	39	78 (118)	58.2	261 (230)	148	476 (231)	258	690 (179)	413	988 (142)	625	1680 (106)	1110	2730 (95.5)	1800
Adrenaline 0.3 mg IM twice	70	80.5 (76)	62.3	232 (82.9)	169	438 (88.5)	306	675 (93.6)	457	989 (89.9)	688	1450 (87.4)	1030	1860 (86.7)	1330
EpiPen 0.3 mg twice	78	170 (169)	89.8	612 (130)	335	1250 (116)	694	1890 (108)	1090	2510 (98.9)	1570	3400 (91.6)	2260	4500 (87.6)	3120

Treatment	N	PAUC (min*pg/mL)													
		$AUC_{0-20min}$		$AUC_{0-30min}$		$AUC_{0-45min}$		$AUC_{0-60min}$		AUC_{0-118}		AUC_{0-240}		AUC_{60-240}	
		Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean	Mean (%CV)	Geo. mean
ARS-1 1.0 mg twice (L/R)	35	2850 (66.9)	2440	6490 (73.2)	5360	11800 (73.5)	9490	16000 (73.1)	12700	25800 (72.7)	20500	34700 (68.4)	28300	18700 (73.3)	15100
ARS-1 1.0 mg twice (L/L)	7	2090 (94.6)	1470	6150 (122)	3630	11500 (116)	6940	15100 (104)	9470	22400 (88.9)	15400	28700 (80.6)	21200	13600 (73.6)	10700
ARS-1 2.0 mg twice (L/R)	39	5430 (98.7)	3630	12100 (105)	8020	22000 (97.3)	15000	30300 (91.7)	21000	50800 (90.2)	35800	71900 (82.8)	54400	41600 (88.8)	31300
ARS-1 2.0 mg twice (R/R)	39	5610 (93.7)	3650	12300 (88.2)	8310	22500 (81.7)	15700	31200 (79.4)	22100	52200 (71.2)	39300	74500 (63.6)	58900	43300 (66.7)	33900
Adrenaline 0.3 mg IM twice	70	2750 (83)	2040	5190 (70.5)	4150	9610 (59.4)	8160	14100 (52.1)	12400	24500 (40.1)	22500	34600 (34.8)	32700	20500 (37)	19300
EpiPen 0.3 mg twice	78	6930 (77.2)	5210	11700 (62.7)	9510	18300 (53.5)	15700	23600 (48.4)	20800	33400 (44.8)	30200	44100 (49.1)	39900	20600 (76.2)	17400

Source: Integrated analysis Tables 40, 41, 43, 44, 46, 50

2.6.2.2.4. Distribution

Distribution of the adrenaline is well documented in the literature. No additional studies were performed by the MAH.

2.6.2.2.5. Elimination

The elimination of adrenaline is well described in the literature. No studies analysing the elimination parameters have been conducted.

2.6.2.2.6. Dose proportionality and time dependencies

Dose proportionality

Table 28: Summary Statistics of Total Adrenaline Pharmacokinetic Parameters: Once-Dosed Treatments

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			Mean(%CV)	Geo.mean	Mean (%CV)	Geo.mean
ARS-1 1.0 mg IN	99	21 (2 - 150)	276 (68.7)	222	25900 (52.1)	22800
ARS-1 2.0 mg IN	78	20.5 (2 - 150)	485 (70.6)	361	40900 (67.5)	32600
Adrenaline 0.3 mg IM	178	45 (3.9 -360)	277 (65.4)	234	27900 (38.7)	26100
EpiPen 0.3 mg	77	10 (2 - 45)	581 (75.6)	447	31600 (39.3)	29200
Adrenaline 0.5 mg IM	123	45 (4 -360)	399 (65.5)	335	43700 (34)	41300
Adrenaline 0.3 mg SC	35	45 (4 -180)	246 (61.6)	214	30200 (34.9)	28400

Source: Integrated analysis Tables 39, 42, 45, 47, 48, 49

The results from different studies with ARS-1 indicate a dose-dependent increase in systemic exposure after EURneffy administration. In the case of single administration, increasing the dose from 1.0 mg to 2.0 mg leads to a rise in mean C_{max} from 276 to 485 pg/mL and in mean AUC_{last} from 22,800 to 32,600 min·pg/mL, with no change in t_{max} (approximately 21 minutes). These findings support linear pharmacokinetics following single intranasal administration.

Time dependencies

Table 29: Summary Statistics of Total Adrenaline Pharmacokinetic Parameters: Twice-Dosed Treatments

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL)		AUC_{last} (min*pg/mL)	
			Mean(%CV)	Geo.mean	Mean (%CV)	Geo.mean
ARS-1 1.0 mg twice (L/R)	35	30 (10 - 60)	474 (76.2)	370	42800 (63.7)	36000
ARS-1 1.0 mg twice (L/L)	7	21 (15 - 60)	544 (109)	337	34400 (79.2)	25900
ARS-1 2.0 mg twice (L/R)	39	30 (6 - 150)	1000 (93.1)	706	86000 (77)	66700
ARS-1 2.0 mg twice (R/R)	39	30 (4 - 150)	992 (75.3)	729	86500(60.5)	69900
Adrenaline 0.3 mg IM twice	70	45 (6 - 180)	436 (48.8)	386	47500(32.6)	45300
EpiPen 0.3 mg twice	78	20 (4 - 360)	754 (64.7)	630	55000(47.9)	49900

Source: Integrated analysis Tables 40, 41, 43, 44, 46, 50

Data from repeat-dose administration, similarly to single dosing, also demonstrate a dose-dependent increase in systemic exposure following administration of EURneffy. Following administration to different nostrils (L/R) or to the same nostril twice (R/R), the systemic levels of adrenaline increase with the administered dose. Mean C_{max} increases from 474 pg/mL with 1 mg (L/R) to 992 pg/mL with 2

mg (R/R), while AUC_{last} rises from 36,000 to 69,900 min·pg/mL. This indicates a relationship between administered dose and systemic exposure, under varying intranasal delivery conditions.

2.6.2.2.7. Intra- and inter-individual variability

Inter-individual variability is reflected by the %CV values provided for both C_{max} and AUC_{last} across different treatments. The values of inter-individual variability range from moderate to high across studies. For ARS-1 1 mg single dose, %CV for C_{max} is 66.2% and for AUC_{last} is 57.3%. For ARS-1 2.0 mg single dose, %CV increases slightly to 100% (C_{max}) and 92.8% (AUC_{last}). Repeat dosing tends to show even higher variability, with %CV for C_{max} reaching up to 109% in some subgroups (e.g., ARS-1 1 mg twice L/L). This suggests high inter-individual variability, particularly with repeated intranasal administration.

2.6.2.2.8. Pharmacokinetics in the target population

The PK of intranasal adrenaline was not studied in the paediatric population with anaphylaxis, as appropriate studies are not feasible for ethical and organisational reasons. Instead, PD surrogates are used as measures of adrenaline action. This approach was agreed upon in the previous application and is applicable to the paediatric population weighing 15–30 kg.

Therapeutic window

Plasma concentration of adrenaline 100 pg/mL is generally considered as a threshold for pharmacodynamic activity. Although no minimum concentration has been clearly established in guidelines, this threshold could be accepted in comparative pharmacokinetic assessments. As in clinical practice, treatment guidelines recommend waiting approximately 5–10 minutes for a clinical response before administering a repeat dose of adrenaline, the time required to reach the 100 pg/mL threshold is crucial to predict therapeutic utility of adrenaline products.

Data presented in the integrated analyses show that EURneffy 1 mg administered intranasally reaches the 100 pg/mL threshold with a median time of 9.28 minutes, while the 2 mg dose achieves this in 6.32 minutes. These values are comparable to those observed after IM administration of adrenaline 0.3 mg (7.85 min) and somewhat slower than the EpiPen 0.3 mg autoinjector (2.39 min), but it still remains within the acceptable window. It is important to note that the time above the 100 pg/mL threshold is prolonged after EURneffy dosing (111 minutes after a single 2 mg dose and up to 226 minutes after repeat administration), which could play protective role in bi-phasic anaphylaxis.

2.6.2.2.9. Special populations

Ethnic factors

In the initial MAA, the influence of ethnic factor on the PK of adrenaline was studies in popPK modelling.

The analysis showed that Japanese subjects presented higher systemic exposure to adrenaline after IM and EpiPen administration, with relative bioavailability (F) values of 2.3 and 2.17, respectively, compared to US subjects. This difference is probably a result of the lower body weight and leaner muscle mass, that affects drug absorption. In contrast, intranasal ARS-1 showed similar bioavailability (F = 1.0) across ethnicities. Once ethnicity-specific F is accounted for, body weight becomes the primary covariate influencing clearance and volume parameters.

Weight

Effect of body weight and BMI was analysed as part of the EPI 10 study.

Table 30: Effect of Body Weight and BMI on Epinephrine C_{max} and AUC_{0-t} (EPI10)

Dose/Weight Group	Ln(AUC_{0-t})		Ln(C_{max})	
	Slope	P value	Slope	P value
15 – 30 kg				
ARS-1 0.65 mg	-0.09967	0.073	-0.06005	0.258
ARS-1 1.0 mg	-0.005444	0.898	-0.03579	0.452
≥ 30 kg				
ARS-1 1.0 mg	0.002257	0.765	-0.0005800	0.947
ARS-1 2.0 mg	-0.005374	0.755	-0.01659	0.196

Source: EPI 10 PK Report, In-Text Table 72

The original POP PK model (POP PK Model Report) was updated to include data from the EURneffy 2 mg clinical trials, as well as to extrapolate results from IM adrenaline injection 0.3 mg and EpiPen 0.3 mg in adults to paediatric subjects. For children 15 - 30 kg, the comparison was made to once or twice dosing of ARS-1 1 mg, EpiPen 0.3mg, or Epinephrine 0.3 mg IM. This update has been provided during previous EURneffy (2mg) application.

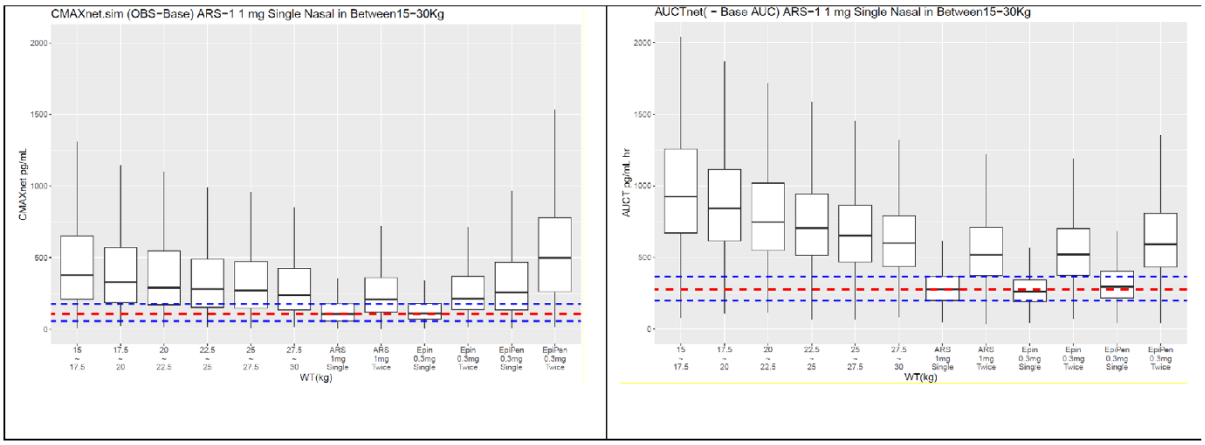

Figure 9: Simulation of C_{max}, AUC for Paediatric Population: ARS-1 1 mg once C_{max} net and AUC (15 - 30 kg)

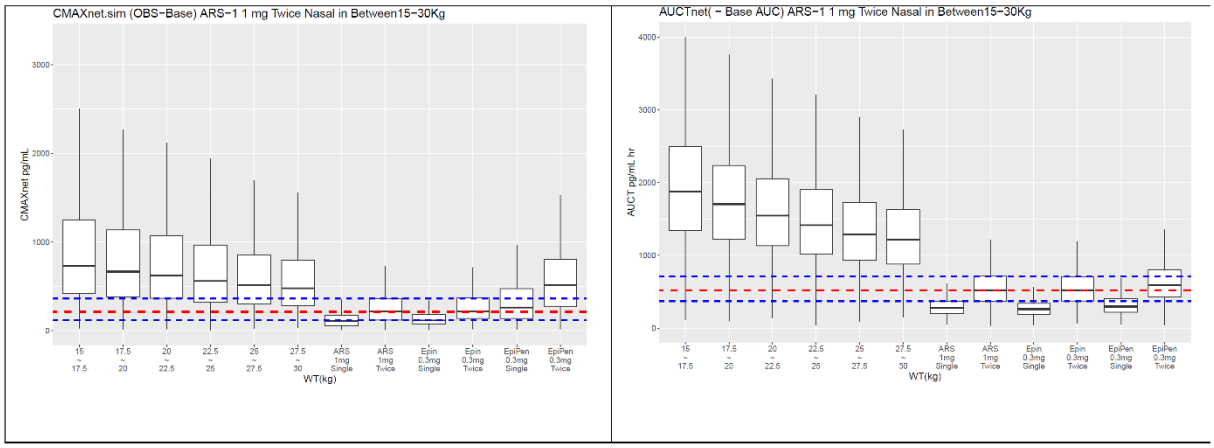

Figure 10: Simulation of C_{max}, AUC for Paediatric Population: ARS-1 1 mg twice C_{max} net and AUC (15 - 30 kg)

Figures below provide simulated C_{max} and total AUC versus body weight in paediatric subjects (⩾ 30 kg) dosed with 1 mg and 2 mg adrenaline dosed or EURneffy, both once and twice. Extrapolations for body weight and age were conducted for EURneffy 1 mg, EURneffy 2 mg, IM adrenaline injection 0.3 mg ("Epin" in figures) and EpiPen 0.3 mg. In the EPI 10 study the mean C_{max} for paediatric patients ⩾ 30 kg was 540 pg/mL, which is similar to results predicted in the POP PK analysis.

Simulations to compare the predicted exposures from IM adrenaline injection and EpiPen were conducted to compare exposures in paediatric subjects to that obtained from EURneffy. These simulations assessed both EURneffy 1 mg in children 15 kg to < 30 kg and EURneffy 2 mg in children and adolescents ⩾ 30 kg by both weight and age.

Table 31: Linear Regression of Ln(Cmax) and Ln($AUC_{0-240min}$) vs Body Weight (kg) for Total and Baseline Corrected Adrenaline, Sorted by Treatment

Treatment	Co-variate: Body Weight							
	Dependent Variable							
	Ln(C_{max})				Ln($AUC_{0-240min}$)			
	Adrenaline				Adrenaline			
	Baseline Corrected		Total		Baseline Corrected		Total	
	P value	Slope	P value	Slope	P value	Slope	P value	Slope
ARS-1 2.0 mg IN	0.187	-0.01194	0.200	-0.01052	0.918	0.0009762	0.977	0.0002129
ARS-1 2.0 mg IN twice (L/R)	0.498	-0.009521	0.512	-0.008777	0.687	-0.005257	0.751	-0.003722
ARS-1 2.0 mg IN twice (R/R)	0.585	-0.006426	0.566	-0.006591	0.204	-0.01424	0.187	-0.01352
Adrenaline 0.3 mg IM	0.022	-0.009371	0.014	-0.009016	0.098	-0.005750	0.039	-0.005274
Adrenaline 0.3 mg IM twice (L/R)	0.037	-0.01237	0.041	-0.01145	0.030	-0.009724	0.036	-0.008087
EpiPen 0.3 mg	0.942	0.0005607	0.989	0.0001057	0.129	-0.008272	0.071	-0.007702
EpiPen 0.3 mg twice (L/R)	0.025	-0.01358	0.021	-0.01329	0.268	-0.005487	0.249	-0.004955

Table 32: Linear Regression of Ln(C_{max}) and Ln($AUC_{0-240min}$) vs BMI (kg/m^2) for Total and Baseline Corrected Epinephrine, Sorted by Treatment

Co-variate: BMI								
	Dependent							
	Ln(C_{max})				Ln($AUC_{0-240min}$)			
	Epinephrine				Epinephrine			
	Total		Baseline Corrected		Total		Baseline Corrected	
Treatment	P value	Slope	P value	Slope	P value	Slope	P value	Slope
ARS-1 1.0 mg IN	0.227	0.03030	0.153	0.03957	0.587	0.01134	0.199	0.03628
ARS-1 1.0 mg IN twice (L/L)	0.806	0.02954	0.803	0.03091	0.764	0.02920	0.725	0.03890
ARS-1 1.0 mg IN twice (L/R)	0.673	-0.01824	0.601	-0.02382	0.275	-0.04201	0.156	-0.07668
ARS-1 2.0 mg IN	0.421	0.02358	0.400	0.02717	0.074	0.04590	0.043	0.06709
ARS-1 2.0 mg IN twice (L/R)	0.368	0.03844	0.363	0.04073	0.492	0.02566	0.487	0.02891
ARS-1 2.0 mg IN twice (R/R)	0.831	0.009083	0.806	0.01072	0.689	-0.01539	0.734	-0.01428
Epinephrine 0.3 mg IM	0.077	-0.02548	0.159	-0.02259	0.362	-0.009175	0.753	0.004292
Epinephrine 0.3 mg IM twice (L/R)	0.112	-0.03884	0.108	-0.04162	0.160	-0.02374	0.156	-0.02775
Epinephrine 0.3 mg SC	0.023	-0.06479	0.041	-0.06985	0.093	-0.03739	0.225	-0.04408
Epinephrine 0.5 mg IM	0.516	0.01240	0.409	0.01713	0.826	0.002858	0.600	0.008460
EpiPen 0.3 mg	0.289	0.02703	0.248	0.03084	0.769	0.004368	0.591	0.01018
EpiPen 0.3 mg twice (L/R)	0.959	0.001050	0.992	0.0002147	0.386	0.01300	0.443	0.01333

2.6.2.2.10. Pharmacokinetic interaction studies

No dedicated pharmacokinetic interaction studies with adrenaline have been conducted. Available literature data indicate that adrenaline is not metabolised by cytochrome P450 enzymes, that reduces the potential for PK interactions with drugs affecting this pathway. As adrenaline undergoes rapid and intense metabolism via MAO and COMT, the risk of clinically relevant pharmacokinetic interactions is considered low. Given its use in emergency settings and the brief duration of exposure, PK interaction studies are not deemed necessary.

2.6.2.2.11. Exposure relevant for safety evaluation

Table 33: Study Subject Drug Exposure by Cumulative Dose Safety Population – EURneffy Treatments

EURneffy				
0.65 mg (N=12) n(%)	1 mg (N = 21) n(%)	1 mg (N = 200) n(%)	2 mg[1] (N=2877) n(%)	4 mg[2] (N=85) n(%)
15 to < 30 kg		≥ 30 kg		
12 (100.0)	21 (100.0)	200 (100.0)	277 (100.0)	85 (100.0)

N = unique subjects per treatment received

[1] ***EURneffy*** 2 mg dose includes subjects that received a single 2 mg dose and subjects that received two 1 mg doses spaced 10 minutes apart.

[2] ***EURneffy*** 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.

Source: ISS, Table 2

Table 34: Study Subject Drug Exposure by Cumulative Dose Safety Population – Injection Treatments

Epinephrine						
IM			SC	EpiPen		Symjepi
0.3 mg (n = 233) n(%)	0.5 mg (n = 127) n(%)	0.6 mg[1] (n = 113) n(%)	0.3 mg (n = 35) n(%)	0.3 mg (n = 122) n(%)	0.6 mg[2] (n = 78) n(%))	0.3 mg (N=36) n(%)
233 (100.0)	127 (100.0)	113 (100.0)	35 (100.0)	122 (100.0)	78 (100.0)	36 (100.0)

N = unique subjects per treatment received

[1] Epinephrine IM 0.6 mg includes subjects that received two 0.3 mg doses spaced 10 minutes apart.

[2] EpiPen 0.6 mg includes subjects that received two 0.3 mg doses spaced 10 minutes apart.

Source: ISS, Table 3

2.6.2.3. Pharmacodynamics

- ***Mechanism of action***

Adrenaline is a nonselective agonist of all adrenergic receptors, including alpha- and beta-adrenergic receptors. Binding to these receptors triggers a number of actions of sympathetic nerve system.

Through its action on alpha-adrenergic receptors, adrenaline lessens histamine induced vasodilation. Adrenaline also reduces the vascular permeability induced by histamine that occurs during anaphylaxis.

Adrenaline, through its action on beta-adrenergic receptors in bronchial smooth muscle, causes bronchial smooth muscle relaxation.

Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

- ***Primary pharmacology***

EPI 10

A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Adrenaline After Administration of Intranasal ARS-1 to Paediatric Subjects with Systemic Allergies

Pharmacodynamic Measurements

Pharmacodynamic measurements included PR and BP (systolic and diastolic pressure) using an ABPM device. Pulse rate and BP measurements were taken at baseline, pre-dose (twice at approximately -10 min and -5 min before dosing) and at 5 (± 2 min), 10 (± 2 min), 15 (± 2 min), 20 (± 2 min), 25 (± 2 min), 30 (± 2 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes after dosing. Pharmacodynamic data were expressed as (1) observed measurement (raw data) and (2) change from baseline.

The following pharmacodynamic parameters were calculated: E_{max}, t_{Emax}, $AUEC_{0\text{-}xmin}$ (Area under the effect time curve from time zero to x min post dose, where x = 5, 10, 15, 20, 25, 30, 45, and 60 min), $AUEC_{last}$.

Pharmacodynamic results

Table 35: Pharmacodynamic Parameters for SBP Change from Baseline

Treatment	N	E_{max} (mmHg) Mean (%CV)	t_{Emax} (min) median (range)	AUEC min*mmHg									
				AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-90	AUEC 0-118
				Mean (%CV)									
15 – 30 kg													
ARS-1 0.65 mg	12	12.3 (43.5)	30.5 (10.0 – 120)	3.65 (357)	19.5 (208)	42.2 (153)	64.1 (128)	85.2 (113)	111 (104)	188 (101)	227 (98.4)	236 (119)	255 (169)
ARS-1 1.0 mg	21	13.4 (44.6)	20.0 (11.0 – 122)	5.88 (338)	13.8 (380)	35.3 (235)	72.1 (147)	111 (116)	140 (109)	215 (104)	284 (109)	396 (112)	644 (100)
≥ 30 kg													
ARS-1 1.0 mg	26	7.81 (97.7)	30.0 (5.00 – 124)	-1.79 (-947)	-8.36 (-647)	-10.8 (-830)	-6.67 (-1710)	-5.65 (-2420)	-6.67 (-2450)	-5.12 (-4910)	-16.5 (-2150)	-61.8 (-968)	-97.5 (-816)
ARS-1 2.0 mg	21	12.2 (67.4)	25.0 (14.0 – 90.0)	-7.52 (-217)	-12.3 (-382)	-0.936 (-8660)	14.4 (846)	37.3 (439)	66.4 (307)	149 (205)	207 (193)	246 (256)	223 (366)

Source: EPI 10 PK Report, In-Text Tables 26, 27, 28, and 29

Table 36: Pharmacodynamic Parameters for DBP Change from Baseline

Treatment	N	E_{max} (mmHg) Mean (%CV)	t_{Emax} (min) median (range)	AUEC min*mmHg									
				AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-90	AUEC 0-118
				Mean (%CV)									
15 – 30 kg													
ARS-1 0.65 mg	12	9.50 (111)	28.0 (5.00 – 120)	-1.08 (-2090)	-1.42 (-5200)	0.536 (23100)	-4.58 (-3500)	-11.0 (-1780)	-10.7 (-2220)	-26.3 (-1370)	-68.2 (-671)	-146 (-475)	-178 (-542)
ARS-1 1.0 mg	21	7.00 (97.9)	15.0 (4.00 – 117)	0.112 (19200)	-9.66 (-620)	-15.7 (-626)	-14.7 (-909)	-13.0 (-1270)	-14.3 (-1380)	-29.0 (-969)	-47.1 (-791)	-76.7 (-746)	120 (472)
≥ 30 kg													
ARS-1 1.0 mg	26	4.54 (110)	17.5 (4.00 – 121)	-3.59 (-458)	-16.6 (-283)	-23.9 (-307)	-25.3 (-342)	-38.5 (-266)	-54.7 (-235)	-101 (-202)	-154 (-183)	-261 (-180)	-348 (-186)
ARS-1 2.0 mg	21	8.67 (108)	25.0 (9.00 – 120)	-6.79 (-219)	-15.2 (-252)	-17.0 (-358)	-18.5 (-451)	-15.6 (-640)	-11.0 (-1120)	-21.3 (-932)	-27.3 (-1000)	-50.8 (-885)	-114 (-512)

Source: EPI 10 PK Report, In-Text Tables 38, 39, 40, and 41

Table 37: Pharmacodynamic Parameters for PR Change from Baseline

Treatment	N	E_{max} (mmHg) Mean (%CV)	t_{Emax} (min) median (range)	AUEC min*mmHg									
				AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-90	AUEC 0-118
				Mean (%CV)									
15 – 30 kg													
ARS-1 0.65 mg	12	15.7 (118)	15.0 (5.00 – 91.0)	9.51 (345)	32.1 (316)	57.9 (276)	74.4 (272)	78.2 (313)	76.9 (370)	26.1 (1520)	-17.4 (-3080)	-129 (-706)	-328 (-390)
ARS-1 1.0 mg	21	18.5 (63.5)	25.0 (4.00 – 120)	17.1 (186)	45.3 (168)	87.6 (145)	126 (139)	162 (134)	201 (130)	316 (121)	447 (118)	654 (126)	806 (142)
≥ 30 kg													
ARS-1 1.0 mg	26	13.8 (73.0)	20.0 (5.00 – 124)	0.772 (3520)	9.81 (751)	32.1 (364)	54.5 (280)	71.8 (243)	85.7 (237)	115 (263)	149 (260)	204 (266)	256 (281)
ARS-1 2.0 mg	21	16.9 (64.1)	44.0 (5.00 – 120)	9.52 (223)	35.4 (159)	65.9 (138)	104 (123)	143 (119)	179 (119)	297 (129)	420 (132)	619 (130)	756 (131)

Source: EPI 10 PK Report, In-Text Tables 50, 51, 52, and 53

Least Squares Analysis

Statistical analysis of the change from baseline pharmacodynamic parameters E_{max} and partial AUECs was conducted to compare the 2 dose/weight groups of ARS-1: 0.65 mg IN (15 - 30 kg) vs 1 mg IN (15 - 30 kg).

Systolic Blood Pressure

Table 38: Pairwise Comparison of ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg): Least Squares Mean Difference for Change from Baseline SBP Parameters

ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg):					
Variable	**Unit**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	mmHg	-1.13	-4.66	2.39	0.590
$AUEC_{0\text{-}5min}$	min*mmHg	-2.23	-13.1	8.66	0.731
$AUEC_{0\text{-}10min}$	min*mmHg	5.70	-24.1	35.5	0.748
$AUEC_{0\text{-}15min}$	min*mmHg	6.91	-40.4	54.2	0.806
$AUEC_{0\text{-}20min}$	min*mmHg	-8.02	-68.2	52.2	0.823
$AUEC_{0\text{-}25min}$	min*mmHg	-26.0	-98.7	46.7	0.549
$AUEC_{0\text{-}30min}$	min*mmHg	-29.1	-115	57.0	0.570
$AUEC_{0\text{-}45min}$	min*mmHg	-27.2	-158	104	0.727
$AUEC_{0\text{-}60min}$	min*mmHg	-57.1	-230	115	0.579
$AUEC_{0\text{-}90min}$	min*mmHg	-160	-402	81.9	0.271
$AUEC_{0\text{-}118min}$	min*mmHg	-389	-787	8.93	0.107

Source: EPI 10 PK Report, In-Text Table 30

Table 39: Pairwise Comparison of ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg): Least Squares Mean Values with 90% CI for Change from Baseline SBP Parameters

Variable	**Units**	**ARS-1 Dose/Weight Group**					
		0.65 mg IN (15 - 30 kg)			**1.0 mg IN (15 - 30 kg)**		
		LS Mean	**Lower 90% CI**	**Upper 90% CI**	**LS Mean**	**Lower 90% CI**	**Upper 90% CI**
E_{max}	mmHg	12.3	9.44	15.1	13.4	11.3	15.5
$AUEC_{0\text{-}5min}$	min*mmHg	3.65	-5.04	12.3	5.88	-0.692	12.4
$AUEC_{0\text{-}10min}$	min*mmHg	19.5	-4.29	43.3	13.8	-4.18	31.8
$AUEC_{0\text{-}15min}$	min*mmHg	42.2	4.51	80.0	35.3	6.82	63.9
$AUEC_{0\text{-}20min}$	min*mmHg	64.1	16.1	112	72.1	35.8	108
$AUEC_{0\text{-}25min}$	min*mmHg	85.2	27.2	143	111	67.4	155
$AUEC_{0\text{-}30min}$	min*mmHg	111	42.3	180	140	88.2	192
$AUEC_{0\text{-}45min}$	min*mmHg	188	83.7	292	215	136	294
$AUEC_{0\text{-}60min}$	min*mmHg	227	89.3	365	284	180	388
$AUEC_{0\text{-}90min}$	min*mmHg	236	43.6	429	396	250	542
$AUEC_{0\text{-}118min}$	min*mmHg	255	-32.3	543	644	369	920

Source: EPI 10 PK Report, In-Text Table 31

Diastolic Blood Pressure

Table 40: Pairwise Comparison of ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg): Least Squares Mean Difference for Change from Baseline DBP Parameters

ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg)					
Variable	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	mmHg	2.50	-2.63	7.63	0.415
$AUEC_{0\text{-}5min}$	min*mmHg	-1.19	-14.6	12.2	0.881
$AUEC_{0\text{-}10min}$	min*mmHg	8.24	-31.8	48.2	0.729
$AUEC_{0\text{-}15min}$	min*mmHg	16.3	-50.1	82.6	0.680
$AUEC_{0\text{-}20min}$	min*mmHg	10.1	-78.6	98.8	0.848
$AUEC_{0\text{-}25min}$	min*mmHg	1.97	-107	110	0.976
$AUEC_{0\text{-}30min}$	min*mmHg	3.61	-127	134	0.963
$AUEC_{0\text{-}45min}$	min*mmHg	2.77	-188	194	0.981
$AUEC_{0\text{-}60min}$	min*mmHg	-21.1	-270	227	0.886
$AUEC_{0\text{-}90min}$	min*mmHg	-69.0	-448	310	0.759
$AUEC_{0\text{-}118min}$	min*mmHg	-298	-861	264	0.372

Source: EPI 10 PK Report, In-Text Table 42

Table 41: Pairwise Comparison of ARS-1 0.65 mg vs ARS-1 1.0 mg (15 - 30 kg): Least Squares Mean Values with 90% CI for Change from Baseline DBP Parameters

Change From Baseline Diastolic Blood Pressure (mmHg)							
Variable	**Units**	**ARS-1 Dose/Weight Group**					
		0.65 mg IN (15 - 30 kg)			**1.0 mg IN (15 - 30 kg)**		
		LS Mean	**Lower 90% CI**	**Upper 90% CI**	**LS Mean**	**Lower 90% CI**	**Upper 90% CI**
E_{max}	mmHg	9.50	5.41	13.6	7.00	3.91	10.1
$AUEC_{0\text{-}5min}$	min*mmHg	-1.08	-11.8	9.61	0.112	-7.96	8.19
$AUEC_{0\text{-}10min}$	min*mmHg	-1.42	-33.3	30.5	-9.66	-33.8	14.5
$AUEC_{0\text{-}15min}$	min*mmHg	0.536	-52.4	53.5	-15.7	-55.8	24.3
$AUEC_{0\text{-}20min}$	min*mmHg	-4.58	-75.3	66.1	-14.7	-68.1	38.8
$AUEC_{0\text{-}25min}$	min*mmHg	-11.0	-97.6	75.5	-13.0	-78.4	52.4
$AUEC_{0\text{-}30min}$	min*mmHg	-10.7	-115	93.5	-14.3	-93.1	64.4
$AUEC_{0\text{-}45min}$	min*mmHg	-26.3	-179	126	-29.0	-144	86.3
$AUEC_{0\text{-}60min}$	min*mmHg	-68.2	-266	130	-47.1	-197	103
$AUEC_{0\text{-}90min}$	min*mmHg	-146	-448	156	-76.7	-305	152
$AUEC_{0\text{-}118min}$	min*mmHg	-178	-584	228	120	-269	509

Source: EPI 10 PK Report, In-Text Table 43

Pulse Rate

Table 42: Pairwise Comparison of 0.65 mg IN (15 - 30 kg) vs 1.0 mg IN (15 - 30 kg): Least Squares Mean Difference for Change from Baseline Pulse Rate Parameters

Change from Baseline Pulse Rate (bpm) ARS-1 Dose/Weight Groups 0.65 mg IN (15 - 30 kg) vs 1.0 mg IN (15 - 30 kg)					
Variable	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	mmHg	-2.86	-11.7	6.03	0.590
$AUEC_{0\text{-}5min}$	min*mmHg	-7.63	-27.4	12.1	0.517
$AUEC_{0\text{-}10min}$	min*mmHg	-13.1	-65.8	39.5	0.675
$AUEC_{0\text{-}15min}$	min*mmHg	-29.8	-115	56.0	0.560
$AUEC_{0\text{-}20min}$	min*mmHg	-51.7	-166	62.2	0.447
$AUEC_{0\text{-}25min}$	min*mmHg	-84.1	-224	55.4	0.315
$AUEC_{0\text{-}30min}$	min*mmHg	-124	-289	41.3	0.213
$AUEC_{0\text{-}45min}$	min*mmHg	-290	-528	-51.7	0.0475
$AUEC_{0\text{-}60min}$	min*mmHg	-464	-790	-138	0.0219
$AUEC_{0\text{-}90min}$	min*mmHg	-783	-1310	-259	0.0166
$AUEC_{0\text{-}118min}$	min*mmHg	-1130	-2010	-264	0.0358

Source: EPI 10 PK Report, In-Text Table 54

Table 43: Pairwise Comparison of 0.65 mg IN (15 - 30 kg) vs 1.0 mg IN (15 - 30 kg): Least Squares Mean Values with 90% CI for Change from Baseline Pulse Rate Parameters

Change From Baseline Pulse Rate (bpm)							
		ARS-1 Dose/Weight Group					
		0.65 mg IN (15-30 kg)			1.0 mg IN (15-30 kg)		
Variable	**Units**	**LS Mean**	**Lower 90% CI**	**Upper 90% CI**	**LS Mean**	**Lower 90% CI**	**Upper 90% CI**
E_{max}	mmHg	15.7	8.58	22.8	18.5	13.2	23.9
$AUEC_{0\text{-}5min}$	min*mmHg	9.51	-6.23	25.3	17.1	5.24	29.0
$AUEC_{0\text{-}10min}$	min*mmHg	32.1	-9.89	74.1	45.3	13.5	77.0
$AUEC_{0\text{-}15min}$	min*mmHg	57.9	-10.5	126	87.6	36.0	139
$AUEC_{0\text{-}20min}$	min*mmHg	74.4	-16.4	165	126	57.5	195
$AUEC_{0\text{-}25min}$	min*mmHg	78.2	-33.2	189	162	78.1	246
$AUEC_{0\text{-}30min}$	min*mmHg	76.9	-54.9	209	201	101	301
$AUEC_{0\text{-}45min}$	min*mmHg	26.1	-164	216	316	172	460
$AUEC_{0\text{-}60min}$	min*mmHg	-17.4	-277	243	447	250	643
$AUEC_{0\text{-}90min}$	min*mmHg	-129	-547	289	654	338	970
$AUEC_{0\text{-}118min}$	min*mmHg	-328	-957	300	806	204	1410

Source: EPI 10 PK Report, In-Text Table 55

EPI 14

A Two-Treatment, Sequential, Crossover Study of the Pharmacokinetics of Epinephrine After Administration of ARS -1 in Subjects with Upper Respiratory Tract Infection (Infectious Rhinitis)

Pharmacodynamic Measurements

Pharmacodynamics measurements included BP and PR. Assessments were conducted at baseline, pre-dose (twice after at least 20 minutes in a sitting position, at least 5 minutes apart, with back supported, legs uncrossed, and upper arm bared, slight recline for comfort is permitted), at 5 (± 2 min), 10 (± 2 min), 15 (± 2 min), 20 (± 2 min), 25 (± 2 min), 30 (± 2 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes post dosing. Automated and appropriately calibrated blood pressure monitoring equipment with the capability of printing the results were used to ensure accuracy and consistency of assessments. Actual reading times by hour/minutes/seconds were recorded.

The following PD parameters were calculated for change from baseline SBP, DPB, and HR: Emax, tEmax, AUEC0-xmin (where x was every post-dose time point through 60 min in the PK analysis (i.e., 5, 10, 15, 20, 25, 30, 45, and 60 min), AUEClast.

Pharmacodynamic Results

Table 44: Pharmacodynamic Parameters for SBP Change from Baseline

Nasal Condition	N	E_{max} (mmHg) Mean (%CV)	t_{Emax} (min) median (range)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					$AUEC_{0-2}$	$AUEC_{0-4}$	$AUEC_{0-6}$	$AUEC_{0-8}$	$AUEC_{0-10}$	$AUEC_{0-12.5}$	$AUEC_{0-15}$	$AUEC_{0-20}$	$AUEC_{0-30}$
					Mean (%CV)								
URTI	21	20.9 (64.1)	45.1 (10.2 90.6)	1880 (80.3)	1.38 (204)	5.50 (204)	12.1 (201)	19.5 (185)	27.9 (165)	40.5 (150)	56.9 (146)	97.9 (137)	193 (114)
Normal	16	19.9 (61.8)	45.2 (0.00 – 106)	2060 (89.4)	0.488 (444)	1.95 (444)	4.18 (457)	5.04 (643)	4.51 (1220)	8.53 (983)	20.4 (521)	60.2 (247)	162 (162)

Nasal Condition	N	$AUEC_{0-45}$	$AUEC_{0-60}$	$AUEC_{0-118}$	$AUEC_{60-118}$
		Mean (%CV)			
URTI	21	357 (94.3)	518 (90.3)	1040 (78.0)	522 (74.6)
Normal	16	347 (132)	537 (116)	1040 (105)	500 (101)

Source: EPI 14 PK Report, Table 16 and Table 17

Table 45: Pharmacodynamic Parameters for DBP Change from Baseline

Nasal Condition	N	E_{max} (mmHg) Mean (%CV)	t_{Emax} (min) median (range)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					$AUEC_{0-2}$	$AUEC_{0-4}$	$AUEC_{0-6}$	$AUEC_{0-8}$	$AUEC_{0-10}$	$AUEC_{0-12.5}$	$AUEC_{0-15}$	$AUEC_{0-20}$	$AUEC_{0-30}$
					Mean (%CV)								
URTI	21	11.7 (67.3)	30.1 (0.00 – 120)	266 (460)	0.300 (873)	1.20 (871)	2.91 (776)	5.93 (555)	10.2 (407)	12.5 (403)	5.05 (1120)	-10.3 (-849)	-15.8 (-944)
Normal	16	12.1 (81.8)	24.7 (0.00 – 91.0)	279 (535)	1.03 (223)	4.13 (223)	8.78 (227)	11.7 (258)	11.9 (345)	11.0 (537)	10.7 (767)	21.1 (623)	51.6 (452)

Nasal Condition	N	$AUEC_{0-45}$	$AUEC_{0-60}$	$AUEC_{0-118}$	$AUEC_{60-118}$
		Mean (%CV)			
URTI	21	-25.2 (-1040)	-4.47 (-8090)	179 (361)	183 (213)
Normal	16	90.7 (370)	126 (364)	213 (354)	87.0 (384)

Source: EPI 14 PK Report, Table 23 and Table 24

Table 46: Pharmacodynamic Parameters for HR Change from Baseline

Nasal Condition	N	E_{max} (bpm) Mean (%CV)	t_{Emax} (min) median (range)	$AUEC_{last}$ (min*bpm) (Mean (%CV)	AUEC min*bpm								
					AUEC 0-2	AUEC 0-4	AUEC 0-6	AUEC 0-8	AUEC 0-10	AUEC 0-12.5	AUEC 0-15	AUEC 0-20	AUEC 0-30
					Mean (%CV)								
URTI	21	17.2 (55.5)	25.4 (5.10 88.1)	1560 (84.3)	2.24 (171)	8.96 (171)	19.6 (170)	30.9 (160)	41.7 (152)	56.1 (142)	73.3 (129)	113 (111)	197 (98.8)
Normal	16	16.4 (50.2)	30.4 (5.00 – 106)	1820 (82.3)	2.07 (104)	8.29 (104)	18.2 (104)	29.3 (99.9)	40.9 (100)	55.7 (106)	70.5 (109)	99.2 (109)	168 (96.5)

Nasal Condition	N	AUEC 0-45	AUEC 0-60	AUEC 0-118	AUEC 60-118
		Mean (%CV)			
URTI	21	303 (104)	407 (106)	665 (124)	258 (167)
Normal	16	300 (85.8)	413 (94.3)	754 (115)	340 (156)

Source: EPI 14 PK Report, Table 30 and Table 31

Least Squares Analysis

Table 47: Change from Baseline Systolic Blood Pressure: LS Mean Difference Comparing Normal Nasal - URTI Condition

Change from Baseline Systolic Blood Pressure (mmHg): Normal Nasal - URTI					
Dependent	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	mmHg	-0.751	-6.94	5.44	0.836
$AUEC_{0\text{-}2min}$	min*mmHg	-0.629	-1.57	0.307	0.257
$AUEC_{0\text{-}4min}$	min*mmHg	-2.52	-6.26	1.23	0.257
$AUEC_{0\text{-}6min}$	min*mmHg	-5.54	-13.6	2.48	0.245
$AUEC_{0\text{-}8min}$	min*mmHg	-10.3	-21.5	0.942	0.129
$AUEC_{0\text{-}10min}$	min*mmHg	-18.2	-36.0	-0.379	0.0936
$AUEC_{0\text{-}12.5min}$	min*mmHg	-26.0	-54.4	2.31	0.128
$AUEC_{0\text{-}15min}$	min*mmHg	-29.2	-66.2	7.80	0.187
$AUEC_{0\text{-}20min}$	min*mmHg	-29.0	-83.0	25.0	0.363
$AUEC_{0\text{-}30min}$	min*mmHg	-24.1	-131	82.7	0.700
$AUEC_{0\text{-}45min}$	min*mmHg	-0.365	-175	174	0.997
$AUEC_{0\text{-}60min}$	min*mmHg	38.7	-187	264	0.769
$AUEC_{0\text{-}118min}$	min*mmHg	24.7	-413	462	0.923
$AUEC_{0\text{-}t}$	min*mmHg	211	-679	1100	0.687

Source: EPI 14 PK Report, Table 18

Table 48: Change from Baseline Diastolic Blood Pressure: LS Mean Difference Comparing Normal Nasal - URTI Condition

Change from Baseline Diastolic Blood Pressure: Normal Nasal- URTI					
Dependent	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	mmHg	0.780	-3.58	5.14	0.759
$AUEC_{0\text{-}2min}$	min*mmHg	0.714	-0.623	2.05	0.367
$AUEC_{0\text{-}4min}$	min*mmHg	2.85	-2.49	8.20	0.368
$AUEC_{0\text{-}6min}$	min*mmHg	5.66	-5.74	17.1	0.401

Change from Baseline Diastolic Blood Pressure: Normal Nasal- URTI					
Dependent	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
$AUEC_{0\text{-}8min}$	min*mmHg	4.99	-10.8	20.8	0.591
$AUEC_{0\text{-}10min}$	min*mmHg	-0.103	-19.3	19.1	0.993
$AUEC_{0\text{-}12.5min}$	min*mmHg	-4.59	-28.8	19.6	0.745
$AUEC_{0\text{-}15min}$	min*mmHg	2.41	-27.9	32.7	0.892
$AUEC_{0\text{-}20min}$	min*mmHg	27.6	-19.7	74.9	0.325
$AUEC_{0\text{-}30min}$	min*mmHg	59.5	-29.8	149	0.263
$AUEC_{0\text{-}45min}$	min*mmHg	111	-46.2	268	0.237
$AUEC_{0\text{-}60min}$	min*mmHg	127	-94.6	348	0.334
$AUEC_{0\text{-}118min}$	min*mmHg	39.6	-317	396	0.849
$AUEC_{0\text{-}t}$	min*mmHg	29.0	-686	744	0.945

Source: EPI 14 PK Report, Table 25

Table 49: Change from Baseline Heart Rate: LS Mean Difference Comparing Normal Nasal - URTI Condition

Change from Baseline Heart Rate: Normal Nasal - URTI					
Dependent	**Units**	**LS Mean Difference**	**Lower 90% CI**	**Upper 90% CI**	**P Value**
E_{max}	bpm	-0.716	-4.23	2.79	0.728
$AUEC_{0\text{-}2min}$	min*bpm	-0.0997	-1.59	1.40	0.909
$AUEC_{0\text{-}4min}$	min*bpm	-0.386	-6.36	5.59	0.912
$AUEC_{0\text{-}6min}$	min*bpm	-0.809	-13.8	12.2	0.915
$AUEC_{0\text{-}8min}$	min*bpm	-0.517	-19.9	18.9	0.964
$AUEC_{0\text{-}10min}$	min*bpm	0.937	-23.9	25.8	0.949
$AUEC_{0\text{-}12.5min}$	min*bpm	2.32	-28.3	32.9	0.897
$AUEC_{0\text{-}15min}$	min*bpm	0.593	-34.8	36.0	0.977
$AUEC_{0\text{-}20min}$	min*bpm	-10.1	-56.0	35.8	0.707
$AUEC_{0\text{-}30min}$	min*bpm	-24.7	-87.1	37.8	0.501
$AUEC_{0\text{-}45min}$	min*bpm	-5.08	-107	96.6	0.932
$AUEC_{0\text{-}60min}$	min*bpm	4.62	-143	152	0.957
$AUEC_{0\text{-}118min}$	min*bpm	105	-193	403	0.547
$AUEC_{0\text{-}t}$	min*bpm	254	-321	829	0.453

Source: EPI 14 PK Report, Table 32

EPI JP01:

A Four-Treatment, Partially Randomised Crossover Study of the Pharmacokinetics of Adrenaline After Administration of ARS -1 or Adrenaline Injection in Subjects with Allergic Rhinitis

Pharmacodynamic Measurements

Pharmacodynamic data for systolic blood pressure [SBP], diastolic blood pressure [DPB], and pulse rate or heart rate [HR] are expressed as (1) observed measurement (raw data) and (2) change from baseline (ΔBaseline), where ΔBaseline = Value (at each time) – Value (baseline or predose). For SBP, DPB, and HR, the baseline was based on the mean of the two predose measurements (-10 min and -5 min). If only one of these planned measurements was available, the single reported value was used as the Value(predose).

Pharmacodynamic Results

Standard vital signs (blood pressure, pulse rate, respiratory rate, and temperature) were assessed prior to dosing, and at the 5 (± 2 min), 10 (± 2 min), 15 (± 5 min), 30 (± 5 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hour time points after dosing.

Pharmacodynamic Parameters

Table 50: Pharmacodynamic Parameters for SBP Change from Baseline (Primary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} mmHg Mean (%CV)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg IN	36	17.5 (5.00 – 240)	14.7 (46.5)	1120 (147)	18.0 (105)	52.1 (94.5)	87.8 (88.5)	131 (82.1)	177 (77.6)	216 (78.5)	321 (79.0)	410 (79.2)	630 (88.1)
Adrenaline 0.3 mg IM	35	25.0 (0.00 - 240)	7.57 (58.7)	-10.3 (-15100)	2.79 (525)	4.86 (761)	2.93 (1750)	2.71 (2300)	5.14 (1510)	5.79 (1650)	8.36 (1980)	20.1 (1210)	3.43 (16200)
EpiPen 0.3 mg	30	22.5 (5.00 - 360)	11.9 (50.1)	372 (403)	14.5 (121)	43.1 (111)	68.3 (109)	89.8 (115)	114 (118)	135 (121)	177 (132)	219 (138)	298 (185)

Source: EPI JP01 PK report Appendix Table 12, Table 15

Table 51: Pharmacodynamic Parameters for SBP Change from Baseline (Secondary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} mmHg Mean (%CV)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg IN	36	17.5 (5.00 – 240)	14.7 (46.5)	1120 (147)	18.0 (105)	52.1 (94.5)	87.8 (88.5)	131 (82.1)	177 (77.6)	216 (78.5)	321 (79.0)	410 (79.2)	630 (88.1)
Adrenaline 0.3 mg IM	36	22.5 (0.00 - 240)	8.25 (72.5)	55.8 (2840)	4.93 (392)	10.4 (474)	10.7 (643)	12.5 (681)	17.0 (614)	19.7 (637)	26.4 (742)	41.2 (658)	34.1 (1690)
EpiPen 0.3 mg	36	15.0 (5.00 - 360)	13.8 (64.6)	186 (873)	21.1 (125)	57.6 (109)	86.9 (104)	111 (107)	133 (110)	151 (115)	181 (134)	202 (152)	214 (276)

Source: EPI JP01 PK report Appendix Table 12, Table 15

Table 52: Pharmacodynamic Parameters for DBP Change from Baseline (Primary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} mmHg Mean (%CV)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg IN	36	25.0 (0.00 – 240)	7.28 (55.1)	33.2 (2960)	7.85 (155)	18.0 (173)	24.9 (204)	31.6 (225)	38.3 (231	45.9 (237)	65.9 (256)	72.8 (299)	51.5 (811)
Adrenaline 0.3 mg IM	35	15.0 (0.00 – 360)	3.46 (118)	-1070 (-125)	-3.79 (-248)	-15.8 (-162)	-31.4 (-132)	-49.5 (-120)	-73.0 (-102)	-104 (-86.8)	-198 (-73.5)	-281 (-76.3)	-558 (-91.6)
EpiPen 0.3 mg	30	15.0 (0.00 240)	2.83 (117)	-1410 (-87.0)	-9.25 (-145)	-31.3 (-114)	-55.0 (-101)	-78.4 (-95.6)	-102 (-90.5)	-129 (-84.2)	-224 (-71.3)	-315 (-66.3)	-580 (-66.8)

Source: EPI JP01 PK report Appendix Table 11, Table 14

Table 53: Pharmacodynamic Parameters for DBP Change from Baseline (Secondary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} mmHg Mean (%CV)	$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg	36	25.0 (0.00 - 240)	7.28 (55.1)	33.2 (2960)	7.85 (155)	18.0 (173)	24.9 (204)	31.6 (225)	38.3 (231)	45.9 (237)	65.9 (256)	72.8 (299)	51.5 (811)
Adrenaline 0.3 mg IM	36	12.5 (0.00 - 360)	3.36 (121)	-1100 (-120)	-3.82 (-242)	-16.5 (-155)	-33.1 (-127)	-51.9 (-116)	-75.8 (-99.7)	-107 (-84.8)	-201 (-72.0)	-285 (-74.6)	-568 (-89.4)
EpiPen 0.3 mg	30	10.0 (0.00 - 240)	3.03 (112)	-1390 (-96.8)	-7.57 (-184)	-27.4 (-127)	-50.1 (-106)	-73.4 (-97.3)	-97.9 (-89.5)	-125 (-83.1)	-218 (-70.5)	-309 (-65.6)	-585 (-70.7)

Source: EPI JP01 PK report Appendix Table 11, Table 14

Table 54: Pharmacodynamic Parameters for PR Change from Baseline (Primary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} bpm Mean (%CV)	$AUEC_{last}$ (min*bpm) (Mean (%CV)	AUEC min*beats/min								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg IN	36	15.0 (5.00 - 360)	14.5 (34.0)	2040 (63.0)	18.3 (80.8)	58.3 (64.6)	107 (51.4)	151 (45.5)	185 (42.6)	218 (40.8)	320 (41.8)	418 (45.1)	841 (48.5)
Adrenaline 0.3 mg IM	35	60.0 (5.00 - 360)	16.7 (31.8)	2680 (47.6)	11.4 (104)	39.6 (85.6)	69.4 (81.8)	95.4 (83.9)	127 (79.9)	167 (71.8)	321 (56.9)	504 (48.2)	1190 (40.3)
EpiPen 0.3 mg	30	30.0 (5.00 - 360)	16.2 (45.4)	2520 (62.7)	23.1 (51.3)	67.3 (51.0)	110 (55.9)	148 (60.9)	187 (63.1)	240 (61.8)	411 (57.1)	567 (53.2)	1140 (46.0)

Source: EPI JP01 PK report Appendix Table 13, Table 16

Table 55: Pharmacodynamic Parameters for PR Change from Baseline (Secondary Population)

Treatment	n	t_{Emax} (min) Median (range)	E_{max} bpm Mean (%CV)	$AUEC_{last}$ (min*bpm) (Mean (%CV)	AUEC min*beats/min								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 1.0 mg	36	15 (5.00 - 360)	14.5 (34.0)	2040 (63.0)	18.3 (80.8)	58.3 (64.6)	107 (51.4)	151 (45.5)	185 (42.6)	218 (40.8)	320 (41.8)	418 (45.1)	841 (48.5)
Adrenaline 0.3 mg IM	36	60.0 (5.00 - 360)	16.8 (31.6)	2720 (46.9)	12.7 (110)	42.5 (88.5)	72.7 (81.7)	99.0 (82.6)	131 (78.6)	172 (70.7)	325 (55.9)	508 (47.4)	1190 (39.6)
EpiPen 0.3 mg	36	30.0 (5.00 - 360)	16.8 (41.5)	2430 (65.5)	25.5 (53.1)	73.1 (51.4)	117 (54.1)	157 (58.1)	198 (60.1)	251 (58.7)	420 (53.6)	572 (49.8)	1120 (45.5)

Source: EPI JP01 PK report Appendix Table 13, Table 16

Least Squares Analysis

Systolic Blood Pressure

Table 56: Statistical Analysis of SBP Parameters, by Treatment (Primary population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	14.7	7.50	7.17	5.15	9.18	< 0.0001
	$AUEC_{0-5}$	18.0	2.71	15.3	9.78	20.77	< 0.0001
	$AUEC_{0-10}$	52.1	4.51	47.6	32.04	63.10	< 0.0001
	$AUEC_{0-15}$	87.8	2.07	85.7	60.31	111.10	< 0.0001
	$AUEC_{0-20}$	131	1.46	130	94.80	164.22	< 0.0001
	$AUEC_{0-25}$	177	3.38	173	128.65	217.77	< 0.0001
	$AUEC_{0-30}$	216	3.54	212	157.60	266.85	< 0.0001
	$AUEC_{0-45}$	321	5.32	316	234.30	397.83	< 0.0001
	$AUEC_{0-60}$	410	16.6	394	287.88	499.69	< 0.0001
	$AUEC_{0-120}$	630	-0.436	630	438.33	821.57	< 0.0001
	$AUEC_{0-last}$	1120	-12.3	1140	588.09	1682.30	0.0010
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	14.7	12.2	2.48	0.36	4.60	0.0551
	$AUEC_{0-5}$	18.0	15.6	2.41	-3.39	8.21	0.4902
	$AUEC_{0-10}$	52.1	45.3	6.76	-9.59	23.12	0.4924
	$AUEC_{0-15}$	87.8	71.0	16.8	-9.85	43.49	0.2964
	$AUEC_{0-20}$	131	93.6	37.3	0.91	73.76	0.0920
	$AUEC_{0-25}$	177	119	58.0	11.26	104.75	0.0425
	$AUEC_{0-30}$	216	141	75.0	17.75	132.33	0.0325
	$AUEC_{0-45}$	321	187	135	48.73	220.37	0.0111
	$AUEC_{0-60}$	410	230	181	69.42	292.09	0.0087
	$AUEC_{0-120}$	630	308	321	119.37	523.50	0.0101
	$AUEC_{0-last}$	1120	441	682	105.59	1258.85	0.0527

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: Source: EPI JP01 PK report Appendix Table 24

Table 57: Statistical Analysis of SBP Parameters, by Treatment (Secondary population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	14.7	8.25	6.42	3.92	8.91	< 0.0001
	$AUEC_{0-5}$	18.0	4.93	13.1	6.32	19.80	0.0019
	$AUEC_{0-10}$	52.1	10.4	41.7	23.90	59.43	0.0002
	$AUEC_{0-15}$	87.8	10.7	77.1	49.01	105.16	< 0.0001
	$AUEC_{0-20}$	131	12.5	118	80.42	156.52	< 0.0001
	$AUEC_{0-25}$	177	17.0	160	111.04	208.13	< 0.0001
	$AUEC_{0-30}$	216	19.7	196	136.84	255.24	< 0.0001
	$AUEC_{0-45}$	321	26.4	295	206.85	383.15	< 0.0001
	$AUEC_{0-60}$	410	41.2	369	255.34	483.00	< 0.0001
	$AUEC_{0-120}$	630	34.1	595	391.76	799.07	< 0.0001
	$AUEC_{0-last}$	1120	55.8	1070	493.74	1640.42	0.0028
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	14.7	13.8	0.861	-1.63	3.36	0.5669
	$AUEC_{0-5}$	18.0	21.1	-3.13	-9.86	3.61	0.4421
	$AUEC_{0-10}$	52.1	57.6	-5.49	-23.25	12.28	0.6082
	$AUEC_{0-15}$	87.8	86.9	0.833	-27.24	28.91	0.9607
	$AUEC_{0-20}$	131	111	20.3	-17.77	58.33	0.3773
	$AUEC_{0-25}$	177	133	43.5	-5.07	92.02	0.1400
	$AUEC_{0-30}$	216	151	64.3	5.10	123.51	0.0745
	$AUEC_{0-45}$	321	181	141	52.40	228.71	0.0098
	$AUEC_{0-60}$	410	202	208	94.43	322.09	0.0033
	$AUEC_{0-120}$	630	214	415	211.69	619.00	0.0011
	$AUEC_{0-last}$	1120	186	937	363.67	1510.35	0.0082

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: EPI JP01 PK report Appendix Table 24

Diastolic Blood Pressure

Table 58: Statistical Analysis of DBP Parameters, by Treatment (Primary Population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	7.28	3.46	3.81	2.43	5.20	< 0.0001
	$AUEC_{0-5}$	7.85	-3.94	11.8	7.60	15.97	< 0.0001
	$AUEC_{0-10}$	18.0	-16.3	34.2	23.29	45.19	< 0.0001
	$AUEC_{0-15}$	24.9	-32.1	57.0	39.21	74.87	< 0.0001
	$AUEC_{0-20}$	31.6	-50.4	82.0	57.31	106.64	< 0.0001
	$AUEC_{0-25}$	38.3	-74.3	113	82.55	142.69	< 0.0001
	$AUEC_{0-30}$	45.9	-106	151	115.36	187.59	< 0.0001
	$AUEC_{0-45}$	65.9	-200	265	210.72	320.13	< 0.0001
	$AUEC_{0-60}$	72.8	-283	356	284.79	426.71	< 0.0001
	$AUEC_{0-120}$	51.5	-560	612	469.95	753.72	< 0.0001
	$AUEC_{0-last}$	33.2	-1070	1100	711.15	1497.68	< 0.0001
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	7.28	2.94	4.34	2.88	5.80	< 0.0001
	$AUEC_{0-5}$	7.85	-8.96	16.8	12.40	21.21	< 0.0001
	$AUEC_{0-10}$	18.0	-30.8	48.7	37.23	60.27	< 0.0001
	$AUEC_{0-15}$	24.9	-54.5	79.4	60.69	98.20	< 0.0001
	$AUEC_{0-20}$	31.6	-77.4	109	83.01	134.89	< 0.0001
	$AUEC_{0-25}$	38.3	-99.9	138	106.57	169.86	< 0.0001
	$AUEC_{0-30}$	45.9	-126	172	134.09	210.07	< 0.0001
	$AUEC_{0-45}$	65.9	-219	285	227.60	342.80	< 0.0001
	$AUEC_{0-60}$	72.8	-309	382	306.66	456.35	< 0.0001
	$AUEC_{0-120}$	51.5	-568	619	469.56	769.28	< 0.0001
	$AUEC_{0-last}$	33.2	-1350	1390	970.73	1800.50	< 0.0001

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: EPI JP01 PK report Appendix Table 23

Table 59: Statistical Analysis of DBP Parameters, by Treatment (Secondary Population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	7.28	3.36	3.92	2.55	5.28	< 0.0001
	$AUEC_{0-5}$	7.85	-3.82	11.7	7.48	15.86	< 0.0001
	$AUEC_{0-10}$	18.0	-16.5	34.4	23.65	45.24	< 0.0001
	$AUEC_{0-15}$	24.9	-33.1	58.1	40.49	75.62	< 0.0001
	$AUEC_{0-20}$	31.6	-51.9	83.5	59.13	107.82	< 0.0001
	$AUEC_{0-25}$	38.3	-75.8	114	84.53	143.67	< 0.0001
	$AUEC_{0-30}$	45.9	-107	153	117.39	188.03	< 0.0001
	$AUEC_{0-45}$	65.9	-201	267	212.67	320.66	< 0.0001
	$AUEC_{0-60}$	72.8	-285	358	286.51	428.49	< 0.0001

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
	$AUEC_{0-120}$	51.5	-568	620	473.97	765.20	< 0.0001
	$AUEC_{0-last}$	33.2	-1110	1140	735.18	1543.98	< 0.0001
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	7.28	3.03	4.25	2.89	5.61	< 0.0001
	$AUEC_{0-5}$	7.85	-7.57	15.4	11.23	19.61	< 0.0001
	$AUEC_{0-10}$	18.0	-27.4	45.4	34.62	56.21	< 0.0001
	$AUEC_{0-15}$	24.9	-50.1	75.0	57.43	92.57	< 0.0001
	$AUEC_{0-20}$	31.6	-73.4	105	80.65	129.35	< 0.0001
	$AUEC_{0-25}$	38.3	-97.9	136	106.68	165.82	< 0.0001
	$AUEC_{0-30}$	45.9	-125	171	135.44	206.09	< 0.0001
	$AUEC_{0-45}$	65.9	-218	284	229.89	337.89	< 0.0001
	$AUEC_{0-60}$	72.8	-309	382	311.02	453.00	< 0.0001
	$AUEC_{0-120}$	51.5	-585	636	490.56	781.80	< 0.0001
	$AUEC_{0-last}$	33.2	-1390	1420	1020.11	1828.91	< 0.0001

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: EPI JP01 PK report Appendix Table 23

Pulse Rate

Table 60: Statistical Analysis of PR Parameters, by Treatment (Primary population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	14.5	16.7	-2.17	-3.97	-0.37	0.0487
	$AUEC_{0-5}$	18.3	11.6	6.64	2.75	10.53	0.0060
	$AUEC_{0-10}$	58.3	40.2	18.1	7.34	28.85	0.0066
	$AUEC_{0-15}$	107	70.1	36.6	18.79	54.41	0.0011
	$AUEC_{0-20}$	151	96.2	54.8	29.92	79.64	0.0005
	$AUEC_{0-25}$	185	128	56.9	25.91	87.86	0.0032
	$AUEC_{0-30}$	218	168	50.2	12.96	87.39	0.0279
	$AUEC_{0-45}$	320	321	-0.782	-59.85	58.29	0.9824
	$AUEC_{0-60}$	418	504	-85.5	-162.55	-8.50	0.0685
	$AUEC_{0-120}$	841	1190	-345	-496.54	-193.65	0.0003
	$AUEC_{0-last}$	2040	2690	-653	-1057.51	-249.23	0.0090
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	14.5	16.3	-1.77	-3.68	0.13	0.1250
	$AUEC_{0-5}$	18.3	23.9	-5.68	-9.80	-1.56	0.0247
	$AUEC_{0-10}$	58.3	69.1	-10.8	-22.19	0.56	0.1175
	$AUEC_{0-15}$	107	112	-4.86	-23.69	13.97	0.6678

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
	$AUEC_{0-20}$	151	149	1.50	-24.78	27.78	0.9245
	$AUEC_{0-25}$	185	189	-4.39	-37.13	28.35	0.8235
	$AUEC_{0-30}$	218	242	-24.3	-63.62	15.06	0.3067
	$AUEC_{0-45}$	320	414	-94.0	-156.41	-31.61	0.0145
	$AUEC_{0-60}$	418	566	-148	-229.45	-66.62	0.0035
	$AUEC_{0-120}$	841	1130	-291	-451.01	-130.90	0.0035
	$AUEC_{0-last}$	2040	2500	-463	-890.51	-35.04	0.0757

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: EPI JP01 PK report Appendix Table 25

Table 61: Statistical Analysis of PR Parameters, by Treatment (Secondary Population)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1 mg IN vs Adrenaline 0.3 mg IM	E_{max}	14.5	16.8	-2.33	-4.09	-0.57	0.0304
	$AUEC_{0-5}$	18.3	12.7	5.56	1.04	10.07	0.0442
	$AUEC_{0-10}$	58.3	42.5	15.8	4.25	27.27	0.0255
	$AUEC_{0-15}$	107	72.7	34.0	15.86	52.06	0.0026
	$AUEC_{0-20}$	151	99.0	51.9	26.89	77.00	0.0009
	$AUEC_{0-25}$	185	131	53.8	22.52	84.98	0.0055
	$AUEC_{0-30}$	218	172	46.3	8.96	83.68	0.0425
	$AUEC_{0-45}$	320	325	-5.35	-63.00	52.30	0.8775
	$AUEC_{0-60}$	418	508	-89.7	-164.98	-14.47	0.0508
	$AUEC_{0-120}$	841	1190	-353	-500.81	-204.47	0.0002
	$AUEC_{0-last}$	2040	2720	-681	-1072.81	-289.13	0.0050
ARS-1 1 mg IN vs EpiPen 0.3 mg	E_{max}	14.5	16.8	-2.25	-4.01	-0.49	0.0366
	$AUEC_{0-5}$	18.3	25.5	-7.22	-11.74	-2.70	0.0096
	$AUEC_{0-10}$	58.3	73.1	-14.8	-26.30	-3.28	0.0357
	$AUEC_{0-15}$	107	117	-10.4	-28.51	7.68	0.3406
	$AUEC_{0-20}$	151	157	-5.83	-30.89	19.22	0.6991
	$AUEC_{0-25}$	185	198	-13.2	-44.42	18.03	0.4835
	$AUEC_{0-30}$	218	251	-32.8	-70.21	4.51	0.1472
	$AUEC_{0-45}$	320	420	-99.5	-157.16	-41.86	0.0053
	$AUEC_{0-60}$	418	572	-154	-229.14	-78.63	0.0011
	$AUEC_{0-120}$	841	1120	-279	-427.06	-130.72	0.0025
	$AUEC_{0-last}$	2040	2430	-391	-782.40	1.29	0.1011

[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$
Source: EPI JP01 PK report Appendix Table 25

Study JP 02

This was a phase 1, two-period, two-treatment, randomised, crossover study that consisted of a screening period, baseline period, and an open-label randomized treatment period. The bioavailability

of a single dose of IN ARS-1 (2.0 mg epinephrine) was compared to a single dose of IM injection (0.3 mg epinephrine).

Pharmacodynamic Measurements

Pharmacodynamic measurements included SBP, DBP, and PR using an ABPM device on Day 0 through Day 1. Blood pressure and PR measurements were taken at baseline, at -10 (± 2 min) and -5 (± 2 min) minutes prior to dosing, and at 1 (±1 min), 5 (± 2 min), 10 (± 2 min), 15 (± 2 min), 20 (± 2 min), 25 (± 2 min), 30 (± 2 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes after dosing in each treatment period. Actual reading time by hour/minutes/seconds were recorded.

The following PD parameters were calculated for change from baseline SBP, DPB, and heart rate (HR): $E_{max0\text{-}60}$, $E_{max0\text{-}120}$, $T_{Emax0\text{-}60}$, $T_{Emax0\text{-}120}$, $AUEC_{0\text{-}xmin}$ (where x = 5, 10, 15, 20, 25, 30, 45, and 60 minutes), $AUEC_{0\text{-}120min}$, $AUEC_{last}$.

Pharmacodynamic Results

Pharmacodynamic measurements included SBP, DBP, and PR using an ABPM device on Day 0 through Day 1. Blood pressure and PR measurements were taken at baseline, at -10 (± 2 min) and -5 (± 2 min) minutes prior to dosing, and at 1 (± 1 min), 5 (± 2 min), 10 (± 2 min), 15 (± 2 min), 20 (± 2 min), 25 (± 2 min), 30 (± 2 min), 45 (± 5 min), 60 (± 5 min), 90 (± 5 min), and 120 (± 5 min) minutes after dosing in each treatment period.

Table 62: Pharmacodynamic Parameters for SBP Change from Baseline

Treatment	N	t_{Emax} (min) median (range)		E_{max} (mmHg) Mean (%CV)		$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg Mean (%CV)								
		0-60 min	0-120 min	0-60 min	0-120 min		$AUEC_{0\text{-}5}$	$AUEC_{0\text{-}10}$	$AUEC_{0\text{-}15}$	$AUEC_{0\text{-}20}$	$AUEC_{0\text{-}25}$	$AUEC_{0\text{-}30}$	$AUEC_{0\text{-}45}$	$AUEC_{0\text{-}60}$	$AUEC_{0\text{-}120}$
ARS-1 2.0 mg	12	25 (1-25)	25 (0-25)	27 (42.1)	27 (42.1)	1080 (1070.3)	34 (99.6)	103 (60.2)	189 (59.1)	284 (59.8)	385 (56.8)	485 (55.3)	707 (62.7)	860 (66.6)	1074 (95.5)
ARS-1 2.0 mg without 3010*	11	NC	25 (1-55)	NC	25 (30.3)	NC	NC								
Epinephrine IM 0.3 mg	12	25 (1-25)	25 (0-25)	-	8 (68.0)	40 (1070.3)	-3 (-719.8)	-8 (-562.4)	-20 (-348.7)	-33 (-267.5)	-29 (-387.9)	-30 (-486.6)	-26 (-929.3)	-29 (-1095.0)	429 (152.9)

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.3.2 and 14.2.3.2-1; NC not calculated

Table 63: Pharmacodynamic Parameters for DBP Change from Baseline

Treatment	N	t_{Emax} (min) median (range)		E_{max} (mmHg) Mean (%CV)		$AUEC_{last}$ (min*mmHg) (Mean (%CV)	AUEC min*mmHg Mean (%CV)								
		0-60 min	0-120 min	0-60 min	0-120 min		$AUEC_{0\text{-}5}$	$AUEC_{0\text{-}10}$	$AUEC_{0\text{-}15}$	$AUEC_{0\text{-}20}$	$AUEC_{0\text{-}25}$	$AUEC_{0\text{-}30}$	$AUEC_{0\text{-}45}$	$AUEC_{0\text{-}60}$	$AUEC_{0\text{-}120}$
ARS-1 2.0 mg	12	12 (0-12)	22 (0-22)	8 (61.1)	8 (59.4)	189 (146.7)	17 (105.7)	31 (101.2)	28 (126.9)	32 (148.7)	42 (166.4)	46 (205.1)	38 (434.2)	20 (1191.6)	317 (202.4)
ARS-1 2.0 mg without 3010*	11	NC	18 (1-85)	NC	8 (63.1)	NC	NC								
Epinephrine IM 0.3 mg	12	1 (0-1)	3 (0-3)	4 (91.3)	5 (83.4)	-49 (-426.6)	4 (379.8)	-4 (-651.9)	-22 (-177.6)	-46 (-118.1)	-60 (-110.4)	-73 (-109.9)	-136 (-94.5)	-215 (-96.2)	308 (N/A)

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.5.2 and 14.2.5.2-1; NC = not calculated

Table 64: Pharmacodynamic Parameters for PR Change from Baseline

Treatment	N	t_{Emax} (min) median (range)		E_{max} (bpm) Mean (%CV)		$AUEC_{last}$ (min*bpm) (Mean (%CV)	AUEC min*bpm Mean (%CV)								
		0-60 min	0-120 min	0-60 min	0-120 min		AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
ARS-1 2.0 mg	12	16 (1-16)	16 (1-16)	20 (44.4)	20 (40.7)	1141 (70.6)	24 (134.4)	84 (88.1)	148 (79.6)	213 (70.0)	278 (64.3)	341 (62.3)	514 (62.4)	683 (63.7)	1241 (67.3)
ARS-1 2.0 mg without 3010*	11	NC	13 (1-85)	NC	19 (41.1)	NC	NC								
Epinephrine IM 0.3 mg	12	25 (0-25)	27 (5-27)	12 (63.1)	13 (61.3)	565 (89.2)	4 (489.3)	24 (191.0)	46 (153.4)	68 (128.8)	93 (117.4)	125 (107.8)	217 (109.7)	328 (99.3)	802 (52.4)

Source: Appendix 16.1.13, Table 14.2.7.2 and 14.2.7.2-1; NC not calculated

Least Squares Analysis

Table 65: Statistical Analysis of the Pharmacodynamic Parameters of SBP by Treatment

Test vs Ref	Dependent Variable	LS Mean [a]		Diff [b]	90% CI [c]		p-value[d]
		Test	Ref		Lower	Upper	
ARS-1 2.0 mg IN vs Epinephrine 0.3 mg IM	$E_{max0-60}$	27	7	20.2	13.91	26.42	< 0.0001
	$E_{max0-120}$	27	8	19.3	12.92	25.74	< 0.0001
	$AUEC_{0-t}$	1080	40	1010.3	535.05	1485.47	0.0019
	$AUEC_{0ti-5}$	34	-3	37.8	20.5	55.61	0.0036
	$AUEC_{0-10}$	103	-8	111.4	70.96	151.87	0.0007
	$AUEC_{0-15}$	189	-20	209.2	140.41	278.06	< 0.0001
	$AUEC_{0-20}$	284	-33	316.5	220.71	412.20	0.0002
	$AUEC_{0-25}$	385	-29	413.6	295.64	531.61	0.0001
	$AUEC_{0-30}$	485	-30	515.5	358.17	672.86	0.0002
	$AUEC_{0-45}$	707	-26	732.7	483.39	982.09	< 0.0001
	$AUEC_{0-60}$	860	-29	889.5	575.49	1203.44	0.0001
	$AUEC_{0-120}$	1074	429	NE	NE	NE	NE

a = Least Squares Mean for the Test Treatment (Test) and the Reference Treatment (Ref); b = Difference = LS Mean (Test) – LS Mean (Ref); c = 90% Confidence Interval; d = p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.3.1

Table 66: Statistical Analysis of the Pharmacodynamic Parameters of DBP by Treatment

Test vs Ref	Dependent Variable	LS Mean [a]		Diff [b]	90% CI [c]		p-value[d]
		Test	Ref		Lower	Upper	
ARS-1 2.0 mg IN vs Epinephrine 0.3 mg IM	$E_{max0-60}$	8	4	4.1	2.72	5.44	0.0004
	$E_{max0-120}$	8	5	3.8	2.33	5.34	0.0012
	$AUEC_{0-t}$	189	-49	244.8	72.34	417.31	0.0251
	$AUEC_{0ti-5}$	17	4	13.7	5.30	22.11	0.0152
	$AUEC_{0-10}$	31	-4	35.0	17.01	53.04	0.0035
	$AUEC_{0-15}$	28	-22	50.0	24.63	75.29	0.0032
	$AUEC_{0-20}$	32	-46	78.1	39.81	116.44	0.0046
	$AUEC_{0-25}$	42	-60	102.1	55.45	148.72	0.0031
	$AUEC_{0-30}$	46	-73	118.4	62.08	174.69	0.0039
	$AUEC_{0-45}$	38	-136	174.3	73.56	274.99	0.0113
	$AUEC_{0-60}$	20	-215	234.3	75.08	393.47	0.0245
	$AUEC_{0-120}$	317	308	NE	NE	NE	NE

a – Least Squares Mean for the Test Treatment (Test) and the Reference Treatment (Ref); b – Difference – LS Mean (Test) – LS Mean (Ref); c = 90% Confidence Interval; d = p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.5.1

Table 67: Statistical Analysis of the Pharmacodynamic Parameters of PR by Treatment

Test vs Ref	Dependent Variable	LS Mean [a]		Diff [b]	90% CI [c]		p-value[d]
		Test	Ref		Lower	Upper	
ARS-1 2.0 mg IN vs Epinephrine 0.3 mg IM	$E_{max0-60}$	20	12	8.1	2.72	13.45	0.0221
	$E_{max0-120}$	20	13	7.4	1.83	13.01	0.0338
	$AUEC_{0-t}$	1141	565	575.7	99.97	1051.45	0.0505
	$AUEC_{0ti-5}$	24	4	20.4	4.02	36.82	0.0484
	$AUEC_{0-10}$	84	24	59.8	25.93	93.71	0.0102
	$AUEC_{0-15}$	148	46	102.5	48.92	155.98	0.0066
	$AUEC_{0-20}$	213	68	145.0	70.10	219.95	0.0062
	$AUEC_{0-25}$	278	93	184.9	89.85	279.90	0.0061
	$AUEC_{0-30}$	341	125	215.8	100.09	331.46	0.0076
	$AUEC_{0-45}$	514	217	296.8	98.12	495.52	0.0229
	$AUEC_{0-60}$	683	683	354.6	72.42	636.87	0.0467
	$AUEC_{0-120}$	1241	802	690.3	-460.22	1840.85	0.2931

a = Least Squares Mean for the Test Treatment (Test) and the Reference Treatment (Ref); b = Difference = LS Mean (Test) – LS Mean (Ref); c – 90% Confidence Interval; d – p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Source: EPI JP02 PK Report Appendix 16.1.13, Table 14.2.7.1

EPI JP03

A Phase 3 Study Evaluating Efficacy and Safety of Epinephrine of ARS-1 in Patients with Food Allergies

The EPI JP03 study was conducted in Japan for the purpose of regulatory submission in Japan. The primary objective was to assess the efficacy of ARS-1 after administration in patients with symptoms (Grade 2 or greater based on Anaphylaxis Guideline) induced by an oral food challenge (OFC).

The secondary objectives were as follows: 1) to assess the safety and tolerability of ARS-1 in patients with symptoms (Grade 2 or greater based on Anaphylaxis Guideline) induced by OFC and 2) to evaluate the pharmacodynamic (PD) response to ARS-1.

Pharmacodynamic Results

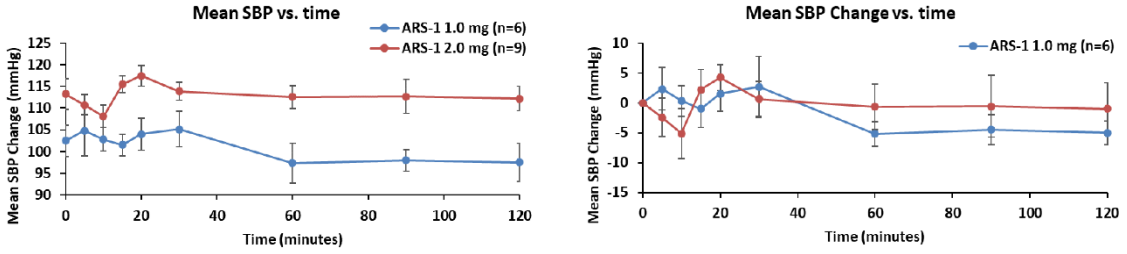

Figure 11: Mean SBP and SBP Change Over Time, by Treatment

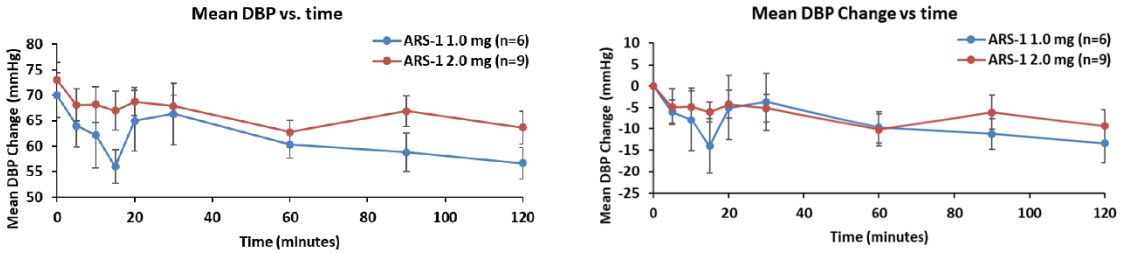

Figure 12: Mean DBP and DBP Change Over Time, by Treatment

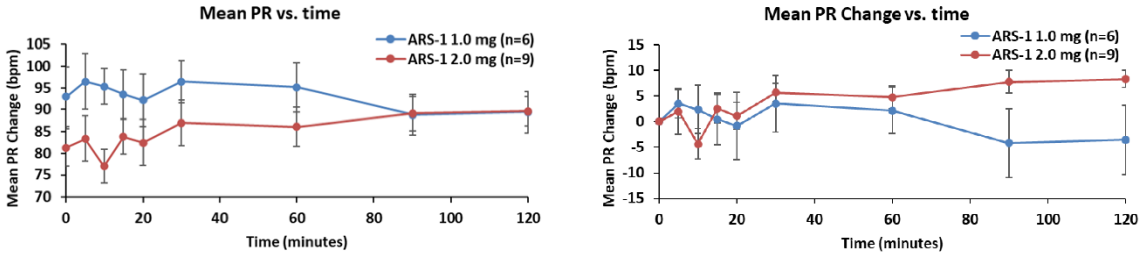

Figure 13: Mean PR and PR Change Over Time, by Treatment

Mean baseline SBP was higher in ARS-1 2 mg group relative to ARS-1 1 mg group, while mean baseline PR was higher in ARS-1 1 mg group relative to the ARS-1 2.0 mg groups. These findings are most likely attributable to age-related physiological difference. There was an initial decrease in DBP in both dose groups resulting from the ß2 mediated vasodilation. As expected, the initial decrease in DBP modulated the initial increase of SBP.

- ***Secondary pharmacology***

No specific study assessing secondary pharmacology of epinephrine has been performed.

- ***Pharmacodynamic interactions with other medicinal products or substances***

Pharmacodynamic interaction studies have not been conducted with ARS-1. Available information on adrenaline pharmacodynamic interactions based on the published literature and its extensive clinical use is considered sufficient.

- ***Genetic differences in PD response***

Variability in response to adrenaline may result from genetic polymorphisms in genes encoding a β1- and β2-adrenergic receptors, α2B-adrenergic receptors, the COMT enzyme or MAO. These variants may influence cardiovascular, metabolic, or vascular sensitivity to adrenaline.

Despite these known genetic differences, they do not affect current clinical recommendations regarding adrenaline use because in emergency situations, such as anaphylaxis or cardiac arrest, where adrenaline is administered as first-line and life-saving therapy, genetic variability is not clinically relevant and do not affect standard dosing or administration recommendations.

2.6.2.4. Pharmacokinetics-Pharmacodynamics (PK/PD)

- ***Relationship between plasma concentration and effect and safety***

Table 68: Calculated Parameters for E_{max} Model: Change from Baseline Systolic Blood Pressure and Heart Rate

PD Measurement	Pooled Data	E_{max}	EC_{50}	E_{max} CV%	EC_{50} CV%
PD Model ΔSBP	ARS-1 IN	34.5	154	6.79	24.9
	Adrenaline IM	18.4	127	11.0	37.2
	EpiPen	25.3	110	9.82	51.5
PD Model ΔHeart Rate	ARS-1 IN	32.1	233	6.37	19.5
	Adrenaline IM	20.5	138	9.17	29.6
	EpiPen	21.3	105	9.21	49.7

Abbreviations: CV = coefficient of variance, EC_{50} = adrenaline concentration producing half the E_{max} effect; E_{max} = maximum effect, IM = intramuscular, IN = intranasal, PD = pharmacodynamic, SBP = systolic blood pressure
Source: ARS-1 Integrated 1 mg 2 mg PK-PD Report Version 1.1, Table 276

Table 69: Calculated Parameters for Emax Model: Change from Baseline Diastolic Blood Pressure

PD Measurement	Pooled Data	E_{max}	EC_{50}	E_{max} CV%	EC_{50} CV%
PD Model ΔSBP	ARS-1 IN	34.5	154	6.79	24.9
	Adrenaline IM	18.4	127	11.0	37.2
	EpiPen	25.3	110	9.82	51.5
PD Model ΔHeart Rate	ARS-1 IN	32.1	233	6.37	19.5
	Adrenaline IM	20.5	138	9.17	29.6
	EpiPen	21.3	105	9.21	49.7

Abbreviations: CV = coefficient of variance, EC_{50} = adrenaline concentration producing half the E_{max} effect; E_{max} = maximum effect, IM = intramuscular, IN = intranasal, PD = pharmacodynamic, SBP = systolic blood pressure
Source: ARS-1 Integrated 1 mg 2 mg PK-PD Report Version 1.1, Table 276

PD Measurement: ΔDBP Model				
Pooled Data	E_{max}	EC_{50}	E_{max} CV%	EC_{50} CV%
ARS-1 IN	10.6	0.000480	6.51	2450000
Adrenaline IM	5.71	1.11	12.7	2370
EpiPen	6.91	0.0151	15.0	335000

Abbreviations: CV = coefficient of variance, DBP = diastolic blood pressure EC_{50} = adrenaline concentration producing half the E_{max} effect; E_{max} = maximum effect, IM = intramuscular, IN = intranasal, PD = pharmacodynamic
Source: ARS-1 Integrated 1 mg 2 mg PK-PD Report Version 1.1, Table 277

No new E-R analysis has been provided. The analyses originate from the previous application.

The exposure–response (E–R) analysis demonstrates a relationship between systemic epinephrine exposure (C_{max}) and PD effects on SBP and HR. ARS-1 showed stronger PD responses compared to intramuscular epinephrine and EpiPen. The Emax model confirms that the PD effects of ARS-1 (both SBP and HR) are positively correlated with systemic exposure up to approximately 1000 pg/mL, beyond which a plateau is observed. ARS-1 was more effective than IM epinephrine and EpiPen in increasing SBP and HR. In contrast, DBP effects were inconsistent and variable, especially for ARS-1, likely reflecting competing adrenergic receptor effects (β_2-mediated vasodilation vs. α-mediated vasoconstriction).

2.6.3. Discussion on clinical pharmacology

This extension of application introduces a new strength: 1 mg for the paediatric population weighing 15–30 kg. This corresponds to half the previously approved dose of 2 mg for adults and children weighing over 30 kg. The clinical documentation submitted included both studies presented in the previous application and new data (EPI 10, JP03). Additionally, studies EPI 14, JP01, and JP02 were presented, which evaluated the impact of infection and repeat dosing on the PK and PD of EURneffy. These studies were already included in the previous application and confirm the lack of significant impact of infectious rhinitis (EPI 14) and allergic rhinitis (JP01) on the PK and PD of EURneffy.

Pharmacokinetics

In study EPI 10, EURneffy was used in the paediatric population in children weighing 15–30 kg at single doses of 0.65 mg and 1 mg, and at doses of 1 mg and 2 mg in children weighing over 30 kg. The lower age limit in the inclusion criteria was 4 years. EURneffy 2 mg in subjects ≥30 kg achieved systemic exposure (C_{max} 690 pg/mL; AUC_{0-t} 40200 min·pg/mL) comparable with EURneffy 1 mg in the 15–30 kg group, (C_{max} 651 pg/mL and AUC_{0-t} of 35100), with slower absorption (median T_{max} 29.5 vs. 20.0 min). Comparative analyses showed that EURneffy 1 mg in lighter children provides systemic

exposure comparable to EURneffy 2 mg in heavier children (30 kg). These findings support the use of 1 mg in children 15–30 kg from a pharmacokinetic standpoint, as the exposure is comparable to the dosing regimen of 2 mg for patients ≥30 kg.

However, in the group weighing 15–30 kg and receiving 1 mg of EURneffy —i.e., consistent with the proposed indication—two enrolled children were 4 years old, three were 6 years old, and the remaining participants were older. Additionally, in EPI 10, in the 1 mg (15–30 kg) group, only two children had a body weight below 20 kg (18.5 and 19.8 kg), and the mean and median body weight was approximately 25 kg. Therefore, the number of children under 6 years of age included in the study was small. The limited number of subjects under 20 kg represented a gap in data for the youngest and smallest children.

A similar situation occurred in study JP03, where EURNeffy was administered at a dose of 1 mg in the group of children weighing 15–30 kg and 2 mg in those weighing more than 30 kg. The lower age limit for children was 4 years (as an inclusion criterion), but the children finally enrolled were 6 years old. In the 15–30 kg group, the average body weight was approximately 20 kg (median around 18 kg); three of six children were 6 years old, and four had a body weight below 20 kg.

In the popPK modeling presented during the initial marketing authorisation application, there was an increased exposure (C_{max} and AUC) in children below 30 kg body weight, particularly in the 15–20 kg subgroup. Although, these values are comparable to those observed with the 2 mg dose in subjects weighing approximately 30 kg, there is the lack of real-world data in the population below 20 kg (EPI 10 and JP03). Moreover, the modelling data are limited to children aged 4 years and older. According to WHO population data, a body weight of 15 kg corresponds approximately to the 50^{th}–85^{th} percentile for a 2.5–3-year-old, the 50^{th} percentile for a 3.5-year-old, and around the 15^{th} percentile for a 4-year-old. Therefore, the proposed indication defining 15 kg as the minimum body weight implicitly allowed the use of the drug in the young children, for whom no data are available.

To address this concern, the MAH provided an updated nasal PBAM and simulations for the 1 mg dose in children 15–30 kg, stating that EPI-10 aligns with prior models and that recruitment below 4 years was not feasible. This response was acknowledged but only partially addressed the issue. The PBAM reduced uncertainty and was appropriate mechanistically, but its verification was largely internal. Model fit to EPI-10 was acceptable: dose-normalised Pred/Obs ratios for C_{max} and AUC_{last} are 0.63–1.42 and are well centered in the target group (1 mg, 15–30 kg: C_{max} 1.03; AUC_{last} 0.92). However, the <20 kg/<6 y stratum was based on n=3 and the model showed minor bias in ≥30 kg cohorts, so uncertainty remained greatest near 15–<20 kg.

Empirical data remained sparse below 20 kg and in <6-year-olds; EPI-10 contained no subjects between 15 and 18.5 kg and only a few aged 4–6 years. Therefore, the MAH was asked to provide PopPK simulations to support the use of the 1 mg strength in children 15–<30 kg.

As requested, the MAH provided an updated PopPK analysis (including EPI-10), with a 2-compartment model, fixed allometric exponents (CL 0.75; V 1.0), and stratified pcVPCs. This addressed the main limitation identified, where reliance on PBAM alone was considered not sufficient. Overall, the model qualification was acceptable: the adult vs paediatric pcVPC showed that the model broadly captures the observed median and variability, and the paediatric pcVPC stratified by weight/age supports adequate description across paediatric strata, including the lowest-weight/youngest subgroup.

On the basis of the updated PopPK model and simulations, the proposed 1 mg dose in paediatric patients with body weight 15–<30 kg is acceptable.

However, although the model is adequate to simulate exposure in younger children, which may be supporting the full extrapolation approach starting from 2 years, an appropriate age device has not

been developed yet. As mentioned in the quality part, the applicator is considered suitable for delivery of the medicinal product for children of 4-5 years. Therefore, it has not been demonstrated that the device will be suitable for patient below 4 years of age. It is to be noted that an appropriate age device in children from 6 months to 4 years is planned to be developed as agreed in the PIP. Therefore, the MAH agreed to revise the initially proposed indication to include the age cut-off of 4 years with the weight limit of 15 kg or more: *EURneffy is indicated in the emergency treatment of allergic reactions (anaphylaxis) due to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis. Treatment is indicated for adults and children aged 4 years and over with a body weight of 15 kg or more.*

Consequently, the recommended initial dose in children aged 4 years and over weighing 15 kg to less than 30 kg is a single nasal administration of 1 mg adrenaline. A maximum of 2 mg (two doses of 1 mg adrenaline) for children aged 4 years or more weighing 15 kg to less than 30 kg may be given unless instructed by a medical professional to give additional doses. Section 4.2 of the SmPC and package leaflet have been updated accordingly.

In the EPI 14 study, the impact of upper respiratory tract infection (URTI) on the PK of EURneffy was studied. The key study findings showed that while URTI slightly reduced C_{max} (570 pg/mL vs. 490 pg/mL) and AUC_{0-t} (64400 vs. 58700 min·pg/mL), t_{max} remained comparable (45.7 min vs. 45.0 min). The differences can be considered not clinically significant. Early absorption (within the first 20 minutes) was slightly faster under URTI. The comparative bioavailability analysis confirmed that URTI did not significantly affect epinephrine pharmacokinetics. Overall, the study supports the use of EURneffy during URTI.

Pharmacodynamics

The PD results were presented in the EPI 10, EPI 14, JP01, JP02, and JP03 studies, as well as in the integrated PK-PD summary.

In EPI 10, the comparison between results in the 1 mg dose (15-30 kg subjects) and 2 mg dose (>30 kg subjects), showed that the increase in systolic blood pressure was similar between the two groups. The mean maximum change in SBP (Emax) was 13.4 mmHg in the 1 mg group and 12.2 mmHg in the 2 mg group, with the similar corresponding area under the effect curve to 60 minutes ($AUEC_{0-60}$). These values demonstrate a comparable magnitude and duration of response. Heart rate responses were also similar across the two groups. The maximum increase in HR was 18.5 bpm in the 1 mg group and 16.9 bpm in the 2 mg group. The total exposure to heart rate change over 60 minutes was similar between groups. ARS-1 did not have a consistent effect on DBP.

In summary, the pharmacodynamic profiles of the 1 mg dose in children weighing 15–30 kg and the 2 mg dose in children and adults weighing ≥30 kg were comparable. The observed differences in E_{max} and AUEC values were small and not clinically relevant. High inter-individual variability was observed in many PD parameters, with coefficients of variation often exceeding 60% and, in some cases, nearing or exceeding 100%. This suggests substantial heterogeneity in individual responses.

The consistency, magnitude, and duration of the 0.65 mg dose of ARS-1 were less robust than with 1 mg. The 1 mg dose provided a more stable and sustained PD response across all parameters with lower variability in children weighing 15–30 kg. When compared with the 2 mg dose in the ≥30 kg group, 0.65 mg showed comparable peak responses in some endpoints (SBP, HR), but with higher variability and less consistent effect over time. In conclusion, the 1 mg dose performed better than 0.65 mg dose in terms of PD response in children 15–30 kg. The 1 mg dose provides the more consistent and clinically appropriate PD profile for the lower-weight group. The 0.65 mg dose may be subtherapeutic for some patients and may be considered less optimal.

The presence of nasal congestion (EPI 14) did not change the PD response.

In the JP03 study, the resolution of anaphylactic symptoms was also similar across doses.

2.6.4. Conclusions on clinical pharmacology

In conclusion, the proposed dose of 1 mg in children with a body weight between 15–<30 kg has been demonstrated based on PK/PD data. However, in absence of an age-appropriate device for children under 4 years of age, the initially proposed indication has been revised to include a cut-off age of 4 years with the weight-based criterion of ≥ 15 kg. Consequently, the sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated. The package leaflet and the risk management plan (version 2.3) were also updated accordingly.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dose response study has been conducted. Dose justification is described in the PK/PD section.

2.6.5.2. Main study

EPI JP03 - a phase 3 study evaluating efficacy and safety of adrenaline of ARS-1 in patients with food allergies

Methods

This was a phase 3, single-period, single-dose study that consisted of a screening period and an open-label treatment period. The efficacy and safety of a single dose of ARS-1 (1.0 mg or 2.0 mg adrenaline) in patients with symptoms (grade 2 or greater based on anaphylaxis guideline) induced by an oral food challenge (OFC) was assessed. This study included 15 allergy patients aged 6 – 17.

- **Study Participants**

Main inclusion criteria

For a subject to have been eligible for this study, he or she must have met all following criteria:

1. Was a patient between the ages of 4 and 55 years, inclusive, at the time of obtaining informed consent.

2. Had body weight 15 kg or higher at the time of pre-OFC exam on Day 1.

3. Was scheduled for an inpatient OFC.

4. Was willing and able to provide written informed consent prior to participating in the study. In the case of minors (<18 years old), ascent could be obtained from his/her legal representative, and as much as possible from the patient himself/herself.

After OFC was initiated:

1. Was a food allergy patient who elicited OFC induced symptoms of Grade 2 or higher gastrointestinal, respiratory, or circulatory symptoms according to the Anaphylaxis Guideline.

Main exclusion criteria

Subjects must not have met any of the following exclusion criteria to be eligible for enrollment.

1. A history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the PI or sub-PI, would jeopardise the safety of the patient or impact the validity of the study results.

2. Prior nasal fractures, severe nasal injuries, history of nasal disorders, any nasal conditions that could interfere with nasal spray administration, abuse of nasal decongestants, or sleep apnoea.

3. Used nasal drugs within 14 days from Day 1.

4. Any clinically significant medical condition or physical exam (PE) finding as deemed inappropriate by the PI or sub-PI.

- **Treatments**

Patients who were eligible for the OFC were admitted to the investigational site on Day 1. An OFC was performer according to the Guidance to Oral Food Challenge 2020 (Ebisawa-2020). Foods that were determined or suspected to be as causative allergen were divided into single doses or multiple doses and were recorded. If food was taken in divided portions, the date and time of each intake and the amount of each intake was recorded as per below:

• Name of food consumed (i.e., chicken egg, wheat, milk, peanut, cashew nut, walnut, soba, etc.)

• Ingestion time: Time when food intake started

• Amount of intake: Actual amount taken

• Current intake status of ingested foods (complete removal/low or moderate intake when possible)

When clinical symptoms (skin/mucosa, digestive organs, respiratory organs, circulatory organs, nerves) were induced by the OFC, the PI or sub-PI graded the symptoms according to the Anaphylaxis Guideline. If more than one symptom occurred in each organ, the most severe symptom grade was used. Once Grade 2 or higher occurred in either gastrointestinal, respiratory, or cardiovascular symptoms (clinical reaction [CR]), study drug was administered as below. If the defined symptoms did not occur, the study was completed without administering study drug.

• Patients 15 to <30-kilogram (kg) body weight received a single 1.0 mg/100 µL dose of ARS-1 in the nare.

• Patients 30 kg or greater body weight received a single 2.0 mg/100 µL dose of ARS-1 in the nare.

If anaphylactic symptoms remained unchanged or worsened and the PI or sub-PI determined that alternative treatment was clinically necessary, patients received standard treatment. The time and the treatment were recorded. All the observation and examinations were continued, even if alternative treatment was provided. Pharmacodynamic measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) using a device such as an automated blood pressure monitoring (ABPM) device. Pharmacodynamic assessments were conducted per the schedule of events (SOE). Safety assessments included vital signs, oxygen saturation, (adverse events) AEs, ECG, and nasal mucosa findings. Concomitant medications were recorded. Safety assessments were performed according to the SOE.

Each patient participated in the study for up to 122 days, which comprised a max of 120-day screening period and a 1-night confinement period for dosing.

- **Objectives**

The primary objective of this study was to assess the effect of ARS-1 after administration in patients with symptoms (grade 2 or greater based on anaphylaxis guideline) induced by an OFC.

The secondary objectives were to assess the safety and tolerability of ARS-1 in patients with symptoms (grade 2 or greater based on anaphylaxis guideline) induced by OFC after administration of ARS-1 and to evaluate the pharmacodynamic (PD) response to ARS-1.

- **Outcomes/endpoints**

The primary endpoint was the change from baseline in main symptom (improvement rate) at 15 minutes 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 or greater per the Anaphylaxis Guideline. If symptoms with the same grade were observed in multiple organs, the main symptoms were specified according to the order of cardiovascular symptoms > respiratory symptoms > gastrointestinal symptoms. Improvement was defined as a decrease in the grade of each organ symptom by 1 or more compared to that of before dosing.

Secondary endpoints included the following:

• Proportion of patients who did not require alternative treatment.

• Grade of each organ symptom at each timepoint.

• Total grade of each organ symptom at each timepoint.

• Time to resolution by organ symptoms.

- **Sample size**

The study population sample size consisted of 15 eligible patients who elicited oral food challenge induced symptoms of grade 2 or greater per the anaphylaxis guideline.

- **Randomisation and Blinding (masking)**

The study consisted of a single-period, single-dose study of a screening period and an open-label treatment period.

- **Statistical methods**

The primary endpoint was the change from baseline of the main symptom (improvement rate) and its CI at 15 minutes or final assessment before alternative treatment until 15 minutes after dosing. Patients had a confirmed diagnosis of a food allergy that elicited symptoms of either Grade 2 or higher gastrointestinal, respiratory, or circulatory symptoms according to the Anaphylaxis Guideline. Based on the Anaphylaxis Guideline, the following assessments were made:

• Improvement rate and its 95% CI was calculated by treatment group (2 mg+1 mg, 2 mg, 1 mg).

Secondary Endpoint Analysis

• Proportion of patients who did not require alternative treatment: proportion of patients who did not require alternative treatment and its 95% CI were calculated by treatment group (2 mg+1 mg, 2 mg, 1 mg).

• Grade of each organ symptom at each time point: grade of each organ symptom at each time point was tabulated by treatment group (2 mg+1 mg, 2 mg, 1 mg).

• Total grade of each organ symptom at each time point: total grade of each organ symptom at each time point was tabulated by treatment group (2 mg+1 mg, 2 mg, 1 mg).

• Time to resolution by organ symptoms: time to resolution by organ symptoms was calculated descriptive statistics by treatment group (2 mg+1 mg, 2 mg, 1 mg).

Results

- **Participant flow**

A total of 15 subjects were enrolled, with 15 (100.0%) subjects completing the study. All 15 subjects received at least one dose of study medication.

- **Recruitment**

Study period 18 July 2023 – 31 August 2023

- **Conduct of the study**

The study was initiated under protocol version 2.0 (08 June 2023). There were no changes to the planned analysis.

Protocol deviation occurred during the conduct of the study: the pre-OFC blood sample was not collected for one subject.

- **Baseline data**

ARS-1 1.0 mg

Subjects receiving ARS-1 1.0 mg ranged in age from 6 to 11 years. One subject (16.7%) was male, and 5 subjects (83.3%) were female. All subjects (100.0%) were Asian and not Hispanic or Latino.

ARS-1 2.0 mg

Subjects receiving ARS-1 2.0 mg ranged in age from 8 to 17 years. Six subjects (66.7%) were male, and 3 subjects (33.3%) were female. All subjects (100.0%) were Asian and not Hispanic or Latino.

Table 70: Demographic Data

DEMOGRAPHICS	ARS-1 Dose		Total (n = 15) n(%)
	ARS-1 1.0 mg (n = 6) n(%)	ARS-1 2.0 mg (n = 9) n(%)	
Age			
Mean (SD)	7.5 (1.97)	12.3 (2.50)	10.4 (3.31)
Median	7	12	11
Minimum, Maximum	6,11	8,17	6,17
Gender			
Male	1 (16.7)	6 (66.7)	7 (46.7)
Female	5 (83.3)	3 (33.3)	8 (53.3)
Race			
Asian	6 (100.0)	9 (100.0)	15 (100.0)
Ethnicity			
Not Hispanic or Latino	6 (100.0)	9 (100.0)	15 (100.0)

Extent of Exposure

Six subjects received a single dose of ARS-1 1.0 mg, and nine subjects received a single dose of ARS-1 2.0 mg.

- **Numbers analysed**

A total of 15 subjects were enrolled, with all subjects receiving at least one dose of study medication and all 15 subjects completing the study.

- **Outcomes and estimation**

All 15 patients exhibited at least one Grade 2 CR to the OFC, with a total of 18 Grade 2 events reported (**Table *71***). Fifteen of those events were considered to be main symptoms (**Table *72***).

Table 71: Total Grade 2 Events

Organ System	ARS-1 1.0 mg (n = 6) n(%)	ARS-1 2.0 mg (n = 9) n(%)	Total (n = 15) n(%)
Cardiovascular	0 (0)	1 (8.3)	1 (5.6)
Gastrointestinal	3 (50.0)	4 (33.3)	7 (38.9)
Respiratory	3 (50.0)	5 (41.7)	8 (44.4)
Skin and Mucosal	0 (0)	2 (16.7)	2 (11.1)
Total	6	12	18

Table 72: Main Symptoms

Organ System	ARS-1 1.0 mg (n = 6) n(%)	ARS-1 2.0 mg (n = 9) n(%)	Total (n = 15) n(%)
Cardiovascular	0 (0)	1 (11.1)	1 (6.7)
Gastrointestinal	3 (50.0)	4 (44.4)	7 (46.7)
Respiratory	3 (50.0)	4 (44.4)	7 (46.7)
Total	6	9	15

Primary Efficacy Endpoint - Improvement at 15 Minutes

Subjects received a dose of ARS-1 (1.0 mg or 2.0 mg) immediately upon CR and were assessed at 15 minutes post-dose.

• Five of the six patients (83.3%) receiving ARS-1 1.0 mg improved by at least one grade.

• Six of the nine patients (66.7%) receiving ARS-1 2.0 mg improved by at least one grade.

• Across both doses, 11 out of 15 patients (73.3%) improved by at least one grade.

While there were four patients who did not improve by ≥1 Grade by 15 minutes post-dose, all four did demonstrate clinically meaningful improvement by the first assessment, however the improvement was not reflected by a change in symptom grade. None of these four subjects required additional epinephrine treatment.

Secondary Efficacy Endpoints

Proportion of Patients Not Requiring Alternative Treatment

No patients required a second dose of epinephrine within the first 15 minutes following administration of ARS-1. One patient received procaterol hydrochloride (ß2 adrenoreceptor agonist) to treat respiratory symptoms, and this treatment was given within 15 minutes of ARS-1 administration. No additional epinephrine was required for this patient.

Additional alternative treatments were provided to eight patients beyond 15 minutes post ARS-1 administration. These medications included antihistamine (levocetirizine hydrochloride, dexchlorpheniramine), ß2 adrenoreceptor agonist (procaterol hydrochloride) as nebulizer, mast cell stabilizer (cromoglicate sodium), hydrocortisone sodium succinate, oxygen, and cooling. One patient developed a biphasic reaction 2 hours and 45 minutes following administration of ARS-1 and was treated with epinephrine at the time of that reaction.

Table 73: Proportion of Patients Not Requiring Alternative Treatment

	ARS-1 1.0 mg (n = 6) n(%)	ARS-1 2.0 mg (n = 9) n(%)	Total (n = 15) n(%)
Number of subjects who did not require epinephrine within 15 minutes	6 (100.0)	9 (100.0)	15 (100.0)
Number of subjects who did not require epinephrine in entire treatment	6 (100.0)	8 (88.9)	14 (93.3)
Number of subjects who did not require other alternative medicines within 15 minutes	6 (100.0)	8 (88.9)	14 (93.3)
Number of subjects who did not require other alternative medicines in entire treatment	3 (50.0)	4 (44.4)	7 (46.7)

Grade of Each Organ System by Timepoint

Assessment of all organ symptoms began five minutes following ARS-1 administration.

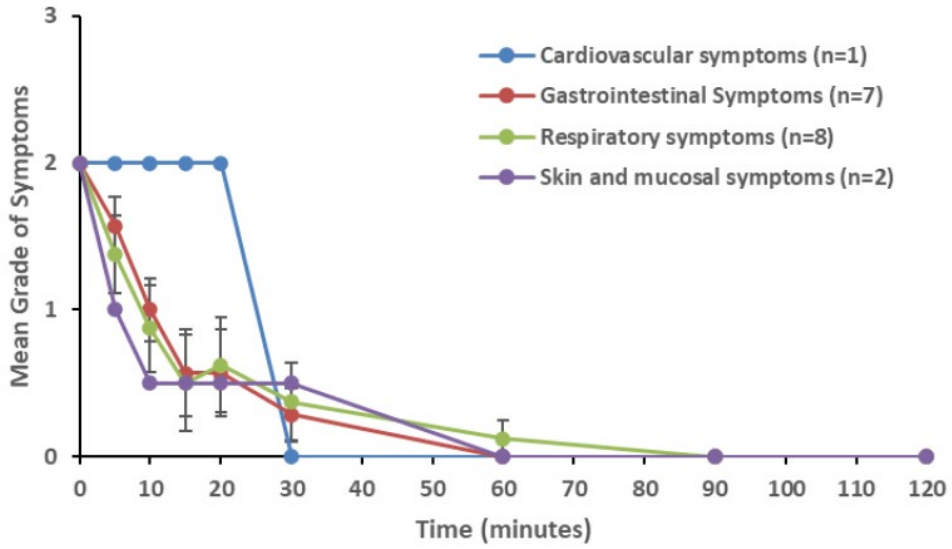

Figure 14: Time Course for the Resolution of Grade 2 Symptoms

Note: The grade for cardiovascular does not have Grade 1, therefore, the next grade from Grade 2 (pale face, mild hypotension, tachycardia) was no symptom (Grade 0).

Total Grade of Each Organ Symptom

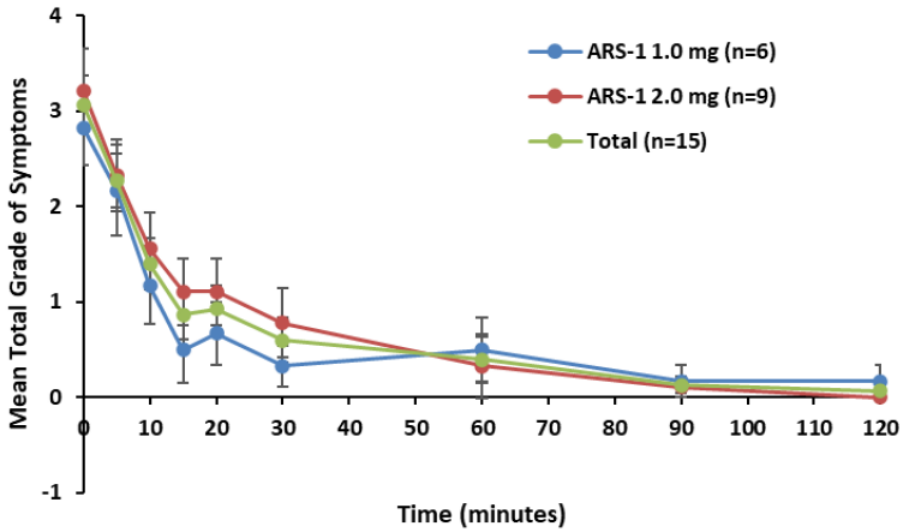

Figure 15: Time Course for Total Grade of Each Organ Symptom

Time to Resolution by Organ Symptom

Table 74: Time to Symptom Resolution (Grade 2 to Grade 0), Total Symptoms

Statistic by Timepoint	Time to Resolution to Grade 0 (minutes)		
	ARS-1 1.0 mg n = 6	ARS-1 2.0 mg n = 9	Total n = 15
n	6	12	18
Median	22.5	15.0	16.0
Minimum, Maximum	10.0,60.0	1.0,90.0	1.0,90.0
95% Confidence interval	7.44,45.23	13.35,49.15	17.29,41.94

Table 75: Time to Resolution (Grade 2 to 0) by Organ System and Dose, Total Symptoms

Organ System	Statistic by Timepoint	Time to Resolution to Grade 0 (minutes)		
		ARS-1 1.0 mg n = 6	ARS-1 2.0 mg n = 9	Total n = 15
Cardiovascular	n	0	1	1
	Median	N/A	32.0	32.0
	Minimum, Maximum	N/A	N/A	N/A
	95% Confidence interval	N/A	N/A	N/A
Gastrointestinal	n	3	4	7
	Median	28.0	15.0	15.0

Organ System	Statistic by Timepoint	Time to Resolution to Grade 0 (minutes)		
		ARS-1 1.0 mg n = 6	ARS-1 2.0 mg n = 9	Total n = 15
	Minimum, Maximum	15.0,60.0	10.0,59.0	10.0,60.0
	95% Confidence interval	-23.20,91.86	-11.78,61.28	8.84,48.87
Respiratory	n	3	5	8
	Median	17.0	14.0	15.5
	Minimum, Maximum	10.0,28.0	1.0,90.0	1.0,90.0
	95% Confidence interval	-4.21,40.87	-11.80,81.40	3.53,53.72
Skin/mucosal	n	0	2	2
	Median	N/A	35.0	35.0
	Minimum, Maximum	N/A	10.0,60.0	10.0,60.0
	95% Confidence interval	N/A	-282.66,352.66	-282.66,352.66

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The data supporting this extension of marketing authorisation for EURneffy with respect to efficacy (and safety) are primarily based on surrogate pharmacodynamic endpoints considering difficulties and ethical issues in conducting randomised clinical trials in the indication population as also discussed in the initial MAA. The mechanism of action of adrenaline that leads to its therapeutic efficacy is well understood and results from its direct agonism of α- and β-adrenergic receptors, leading to a reversal of the pathological response to the histamine cascade caused by an antigen.

Considering the well-studied pharmacodynamics of adrenaline, changes in blood pressure (α_1 effect) and heart rate (β_1 effect) are considered appropriate surrogate endpoints for assessing adrenaline's efficacy in treating Type I allergic reactions. As discussed in the clinical pharmacology section, the submitted pharmacodynamic data indicate that EURneffy reaches systemic adrenaline levels as quickly as, or even faster than, injections, leading to rapid activation of α- and β-adrenergic receptors. This activation increases systolic blood pressure and heart rate, which are key markers of efficacy. Although the average response over time with EURneffy is greater, the maximum changes in these parameters are similar between EURneffy and injection. Notably, Study EPI 10 showed slightly higher maximum values in the 15–30 kg group; however, this does not suggest any important safety concerns in patients with severe systemic allergic reactions.

The MAH conducted a phase 3, single-period, single-dose study EPI JP03 that consisted of a screening period and an open-label treatment period to assess efficacy and safety of a single dose of ARS-1 (1.0 mg or 2.0 mg adrenaline) in 15 Asian subjects aged 6-17 with symptoms (grade 2 or greater based on anaphylaxis guideline) induced by an oral food challenge (OFC). Patients had a confirmed diagnosis of a food allergy that elicited symptoms of either Grade 2 or higher gastrointestinal, respiratory, or circulatory symptoms according to the Severity Classification of Organ Symptoms Induced by Anaphylaxis in the Anaphylaxis Guidelines of the Japanese Society of Allergology of 2022 [10].

Subjects 15 to <30-kilogram (kg) body weight received a single 1.0 mg/100 µL dose of ARS-1 in the nare and subjects 30 kg or greater body weight received a single 2.0 mg/100 µL dose of ARS-1 in the nare. 100.0% of the study subjects completed the study.

The primary endpoint was the change from baseline in main symptom (improvement rate) at 15 minutes or final assessment before alternative treatment until 15 minutes after dosing. Secondary endpoints included the following: 1) Proportion of patients who did not require alternative treatment; 2) Grade of each organ symptom at each timepoint; 3) Total grade of each organ symptom at each timepoint; 4) Time to resolution by organ symptoms.

Efficacy data and additional analyses

Six subjects received a single dose of ARS-1 1.0 mg, and nine subjects received a single dose of ARS-1 2.0 mg. Five of the six patients (83.3%) receiving ARS-1 1.0 mg improved by at least one grade and six of the nine patients (66.7%) receiving ARS-1 2.0 mg improved by at least one grade. Across both doses, 11 out of 15 patients (73.3%) improved by at least one grade.

All 15 patients (100.0%) responded to ARS-1 administration with a clinically meaningful reduction of symptoms, with no patient requiring additional epinephrine treatment within 15 minutes of ARS-1 administration.

In four patients who did not improve by ≥1 Grade by 15 minutes post-dose, clinically meaningful improvement by the first assessment was observed. None of these four subjects required additional epinephrine treatment.

One patient required additional treatment (procaterol hydrochloride - ß2 adrenoreceptor agonist) to treat respiratory symptoms within 15 minutes of ARS-1 administration.

Additional alternative treatments which were provided to eight patients beyond 15 minutes post ARS-1 administration included antihistamine (levocetirizine hydrochloride, dexchlorpheniramine), ß2 adrenoreceptor agonist (procaterol hydrochloride) as nebulizer, mast cell stabilizer (cromoglicate sodium), hydrocortisone sodium succinate, oxygen, and cooling. One patient developed a biphasic reaction 2 hours and 45 minutes following administration of ARS-1 and was treated with epinephrine at the time of that reaction.

The rapid improvement of symptoms following ARS-1 administration is consistent with the observed and expected clinical response to currently approved epinephrine injection therapies, with most patients exhibiting marked symptom relief within five minutes of dosing.

With respect to pharmacodynamic results, mean baseline SBP was higher in ARS-1 2.0 mg group relative to the ARS-1 1.0 mg group, while mean baseline PR was higher in ARS-1 1.0 mg group relative to the ARS-1 2.0 mg group. These findings are most likely attributable to age-related physiological differences.

[10] Japanese Society of Allergology. *Anaphylaxis Guideline 2022*. Japanese Society of Allergology; 2022

There was an initial decrease in DBP in both dose groups resulting from the ß2 mediated vasodilation. As expected, the initial decrease in DBP modulated the initial increase of SBP. However, once the DBP started to increase, the SBP also started to increase, a finding that is consistent with the epinephrine physiology where increasing concentrations of epinephrine results in further cardiac stimulation along with α-adrenoceptor–mediated activation of vascular smooth muscle leading to vasoconstriction that offsets to the β2-mediated vasodilatation[11]. Limited effect of epinephrine on the cardiovascular system is reported in adult peanut-induced anaphylaxis[12].

Since the study was open-label, no conclusions regarding EURneffy efficacy can be drawn. Administration of additional treatments is a clinical standard in the treatment of anaphylactic reaction. However, the results of this study are considered supportive.

The sections 5.1 and 5.2 of the SmPC have been updated to reflect the final PK/PD results of study EPI 10 as discussed in the PK/PK section.

2.6.7. Conclusions on the clinical efficacy

Although conducting randomised controlled clinical trials in patients with severe allergic reactions or anaphylaxis is inherently challenging, the interpretation of the results of study EPI JP03 remains limited. Nonetheless, it is noted that all participants (100.0%) demonstrated a clinically meaningful reduction in symptoms following administration of ARS-1, and none required additional epinephrine within 15 minutes of treatment. Moreover, the pharmacodynamic data consistently support that EURneffy 1 mg provides adequate therapeutic activity, supporting its efficacy in patients weighing between 15 kg and less than 30 kg. However, in absence of an age-appropriate device for patients under 4 years of age, the indication has been updated to reflect this age cut-off as mentioned in the clinical pharmacology discussion.

2.6.8. Clinical safety

The applicant provided an integrated safety analysis (ISS), including pooled safety data from 10 completed phase 1 clinical studies involving 165 healthy subjects aged 19-54 years (EPI 03, EPI 07 and EPI 15), 78 patients aged 21-54 years with type I allergies (EPI 12 and EPI 17), 115 patients aged 19-63 years with allergic rhinitis (EPI 04, EPI 16, and EPI 18), 21 patients aged 19-55 years with upper respiratory tract infection (EPI 14) and 80 paediatric patients aged 4-17 years with type 1 allergies (EPI 10).

2.6.8.1. Patient exposure

In total 595 subjects or patients were exposed to EURneffy across the ten completed studies. 33 subjects were between 4 and 11 years of age weighed 15 to <30 kg, and 562 subjects were between 8 and 63 years of age weighed ⩾30 kg. In general, the patients in these studies were well balanced in terms of gender and race.

In total, 221 out of 595 patients were exposed to the 1 mg dose of EURneffy in the studies included in the pooled safety studies. 277 out of 595 patients received a 2 mg dose of EURneffy, including subjects who received a single 2 mg dose and subjects who received two 1 mg doses spaced 10 minutes apart. 85 out of 595 subjects received a 4 mg dose EURneffy, which included subjects who

[11] Klabundel, R PhD. Cardiovascular Physiology Concepts (Lippincott Connect) (Third ed.). 2021. LWW.
[12] Turner PJ, Ruiz-Garcia M, Durham SR, Boyle RJ. Limited effect of intramuscular epinephrine on cardiovascular parameters during peanut-induced anaphylaxis: an observational cohort study. The Journal of Allergy and Clinical Immunology: In Practice. 2021 Jan 1;9(1):527-30.

received two 2 mg doses spaced 10 minutes apart. Due to the crossover design of some studies, subjects received more than one exposure to EURneffy per study.

64 subjects included in the supportive safety studies EPI JP01, EPI JP02, and EPI JP03 were between 6 and 55 years of age. Between them, 6 patients with a body weight of 15 to <30 kg and 36 patients with a body weight of ⩾30 kg were exposed to EURneffy 1 mg.

In EPI 10 study, in total 21 subjects from 15 to < 30 kg received EURneffy 1 mg intranasal (IN).

The average age of subjects 15 to < 30 kg was the following:

• EURneffy 0.65 mg IN: 7.8 years (from 4 to 11 years)

• EURneffy 1.0 mg IN: 7.8 years (from 4 to 11 years)

The gender distribution of subjects 15 to < 30 kg was the following:

• EURneffy 0.65 mg IN: 6 male (50.0%) and 6 female (50.0%)

• EURneffy 1.0 mg IN: 13 male (61.9%) and 8 female (38.1%)

2.6.8.2. Adverse events

A display of treatment-emergent adverse events and occurrences rates regardless of relatedness for the pooled population is presented in Table 76.

Table 76: Incidence of Treatment-Emergent Adverse Events Regardless of Relatedness - Pooled Population

	EURneffy Dose				
System Organ Class Preferred Term	**0.65 mg (N=12) n(%)**	**1.0 mg (N=21) n(%)**	**1.0 mg (N=200) n(%)**	**2.0 mg[1] (N=277) n(%)**	**4.0 mg[2] (N=85) n(%)**
	15 to < 30 kg		**≥ 30 kg**		
Subjects with at least One Adverse Event	6 (50.0)	11 (52.4)	102 (51.0)	124 (44.8)	42 (49.4)
Respiratory, Thoracic and Mediastinal Disorders	**5 (41.7)**	**9 (42.9)**	**70 (35.0)**	**66 (23.8)**	**34 (40.0)**
Nasal Discomfort	1 (8.3)	1 (4.8)	44 (22.0)	48 (17.3)	11 (12.9)
Rhinorrhea	1 (8.3)	1 (4.8)	9 (4.5)	11 (4.0)	6 (7.1)
Throat Irritation	2 (16.7)	1 (4.8)	7 (3.5)	11 (4.0)	16 (18.8)
Intranasal Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)
Epistaxis	1 (8.3)	0 (0.0))	0 (0.0)	3 (1.1)	0 (0.0)
Rhinalgia	0 (0.0)	1 (4.8)	6 (3.0)	3 (1.1)	1 (1.2)
Sneezing	0 (0.0)	0 (0.0)	3 (1.5)	3 (1.1)	3 (3.5)
Nasal Congestion	0 (0.0)	**4 (19.0)**	10 (5.0)	1 (0.4)	2 (2.4)
Nasal Edema	0 (0.0)	0 (0.0)	12 (6.0)	1 (0.4)	0 (0.0)
Nasal Pruritus	0 (0.0)	1 (4.8)	5 (2.5)	1 (0.4)	3 (3.5)
Oropharyngeal Pain	0 (0.0)	1 (4.8)	5 (2.5)	1 (0.4)	1 (1.2)
Pharyngeal Paraesthesia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	1 (1.2)
Dry Throat	0 (0.0)	**2 (9.5)**	0 (0.0)	0 (0.0)	1 (1.2)
Increased Upper Airway Secretion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Nasal Dryness	0 (0.0)	**2 (9.5)**	1 (0.5)	0 (0.0)	0 (0.0)
Nasal Mucosal Disorder	0 (0.0)	0 (0.0)	6 (3.0)	0 (0.0)	0 (0.0)
Paranasal Sinus Discomfort	0 (0.0)	0 (0.0)	5 (2.5)	0 (0.0)	0 (0.0)
Pharyngeal Hypoesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

	EURneffy Dose				
System Organ Class Preferred Term	**0.65 mg (N=12) n(%)**	**1.0 mg (N=21) n(%)**	**1.0 mg (N=200) n(%)**	**2.0 mg[1] (N=277) n(%)**	**4.0 mg[2] (N=85) n(%)**
	15 to < 30 kg		**≥ 30 kg**		
Upper Respiratory Tract Congestion	0 (0.0)	**3 (14.3)**	0 (0.0)	0 (0.0)	0 (0.0)
Upper-airway Cough Syndrome	0 (0.0)	1 (4.8)	1 (0.5)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**1 (4.8)**	**20 (10.0)**	**37 (13.4)**	**1 (1.2)**
Blood Pressure Increased	0 (0.0)	0 (0.0)	16 (8.0)	31 (11.2)	0 (0.0)
Heart Rate Increased	0 (0.0)	0 (0.0)	1 (0.5)	10 (3.6)	0 (0.0)
Body Temperature Increased	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.7)	1 (1.2)
Body Temperature Decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Heart Rate Decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Blood Pressure Decreased	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Heart Rate Irregular	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	**0 (0.0)**	**2 (9.5)**	**25 (12.5)**	**32 (11.6)**	**20 (23.5)**
Headache	0 (0.0)	0 (0.0)	9 (4.5)	22 (7.9)	15 (17.6)
Dizziness	0 (0.0)	0 (0.0)	5 (2.5)	7 (2.5)	2 (2.4)
Paraesthesia	0 (0.0)	**2 (9.5)**	3 (1.5)	3 (1.1)	0 (0.0)
Head Discomfort	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.7)	0 (0.0)
Hypoaesthesia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Dysgeusia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	7 (3.5)	1 (0.4)	7 (8.2)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Somnolence	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.2)
Taste Disorder	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions	**0 (0.0)**	**0 (0.0)**	**8 (4.0)**	**25 (9.0)**	**13 (15.3)**
Feeling Jittery	0 (0.0)	0 (0.0)	4 (2.0)	21 (7.6)	9 (10.6)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.2)
Feeling Hot	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	1 (1.2)
Asthenia	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Catheter site pruritus	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Feeling Cold	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.2)
Mucosal Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Secretion Discharge	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Vessel Puncture Site Pain	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**1 (8.3)**	**0 (0.0)**	**9 (4.5)**	**22 (7.9)**	**9 (10.6)**
Nausea	0 (0.0)	0 (0.0)	2 (1.0)	9 (3.2)	2 (2.4)
Hypoaesthesia Oral	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.1)	3 (3.5)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	2 (2.4)
Abdominal Pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	3 (3.5)
Hyperaesthesia Teeth	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.7)	0 (0.0)
Salivary Hypersecretion	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.7)	1 (1.2)
Abdominal Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cheilitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gingival Discomfort	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	1 (1.2)
Gingival Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	3 (3.5)
Paraesthesia Oral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Odynophagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

	EURneffy Dose				
System Organ Class Preferred Term	**0.65 mg (N=12) n(%)**	**1.0 mg (N=21) n(%)**	**1.0 mg (N=200) n(%)**	**2.0 mg[1] (N=277) n(%)**	**4.0 mg[2] (N=85) n(%)**
	15 to < 30 kg		**≥ 30 kg**		
Oral Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Oral Pain	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	1 (1.2)
Cardiac Disorders	**0 (0.0)**	**0 (0.0)**	**9 (4.5)**	**21 (7.6)**	**1 (1.2)**
Palpitations	0 (0.0)	0 (0.0)	8 (4.0)	20 (7.2)	1 (1.2)
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Extrasystoles	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Eye Disorders	**0 (0.0)**	**0 (0.0)**	**6 (3.0)**	**10 (3.6)**	**2 (2.4)**
Lacrimation Increased	0 (0.0)	0 (0.0)	5 (2.5)	6 (2.2)	1 (1.2)
Blepharospasm	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Ocular Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Photophobia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Conjunctival Hyperaemia	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Eye Irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Ocular Hyperaemia	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**4 (1.4)**	**1 (1.2)**
Limb Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Neck Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Pain in Extremity	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)
Temporomandibular Joint Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Muscle Spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Pain in Jaw	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Psychiatric Disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**3 (1.1)**	**1 (1.2)**
Anxiety	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	1 (1.2)
Euphoric Mood	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.0)**	**3 (1.1)**	**1 (1.2)**
Hyperhidrosis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)
Pruritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Skin Lesion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Skin Discolouration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Skin Irritation	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.7)	1 (1.2)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Vein Rupture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Hot Flush	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Peripheral Coldness	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**1 (0.4)**	**2 (2.4)**
Ear Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cerumen Impaction	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Ear Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Ear Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Infections and Infestations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**
Corona Virus Infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Metabolism and Nutrition Disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.4)**	**0 (0.0)**
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Injury, Poisoning and Procedural Complications	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**
Skin Laceration	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

	EURneffy Dose				
System Organ Class Preferred Term	**0.65 mg (N=12) n(%)**	**1.0 mg (N=21) n(%)**	**1.0 mg (N=200) n(%)**	**2.0 mg[1] (N=277) n(%)**	**4.0 mg[2] (N=85) n(%)**
	15 to < 30 kg		**≥ 30 kg**		
Reproductive System and Breast Disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**0 (0.0)**
Nipple Disorder	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

N = Unique subjects per treatment received.
Note: MedDRA version 22 used for coding. Subjects with two or more adverse events in the same system organ class (or with the same preferred term) are counted only once for that system organ class (or preferred term).
[1] EURneffy 2 mg dose includes subjects that received a single 2 mg dose and subjects that received two 1 mg doses spaced 10 minutes apart.
[2] EURneffy 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.

A display of the summary of Treatment-Emergent Adverse Events by Treatment for the pooled population is presented in Table 77.

Table 77: Summary of Treatment-Emergent Adverse Events by Treatment - Pooled Population for EURneffy

	EURneffy				
	Nasal				
	0.65 mg (N=12) n(%)	**1 mg (N = 21) n(%)**	**1 mg (N=200) n(%)**	**2 mg[1] (N=277) n(%)**	**4 mg[2] (N=85) n(%)**
	15 to < 30 kg		**≥ 30 kg**		
No. (%) of Subjects with at Least 1 TEAE	6 (50.0)	11 (52.4)	102 (51.0)	124 (44.8)	42 (49.4)
No. (%) of Subjects with at Least 1 SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) of Subjects with TEAE Leading to Discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
No. (%) of Subjects with Treatment Related TEAE	2 (16.7)	10 (47.6)	95 (47.5)	118 (42.6)	40 (47.1)
No. (%) of Subjects Who Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Definitions: N = unique subjects per treatment received, No = number, TEAE = treatment emergent adverse event, SAE = serious adverse event, % = percent
[1] ***EURneffy*** 2 mg dose includes subjects that received a single 2 mg dose and subjects that received two 1 mg doses spaced 10 minutes apart.
[2] ***EURneffy*** 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.

Table 78: Incidence of Treatment-Emergent Adverse Occuring in ≥ 2 Subjects (EPI-10)

System Organ Class Preferred Term	Subjects Between 15-30 kg		Subjects ≥ 30 kg		Total (N=80) n(%)
	ARS-1 0.65 mg (N=12) n(%)	ARS-1 1.0 mg (N=21) n(%)	ARS-1 1.0 mg (N=26) n(%)	ARS-1 2.0 mg (N=21) n(%)	
Subjects with at least one AE	6 (50.0)	11 (52.4)	12 (46.2)	14 (66.7)	43 (53.8)
Respiratory, Thoracic and Mediastinal Disorders	5 (41.7)	9 (42.9)	11 (42.3)	12 (57.1)	37 (46.3)
Nasal discomfort	1 (8.3)	1 (4.8)	5 (19.2)	4 (19.0)	11 (13.8)
Rhinorrhea	1 (8.3)	1 (4.8)	3 (11.5)	4 (19.0)	9 (11.3)
Nasal congestion	0 (0.0)	4 (19.0)	0 (0.0)	1 (4.8)	5 (6.3)
Nasal mucosal disorder	0 (0.0)	0 (0.0)	5 (19.2)	0 (0.0)	5 (6.3)
Rhinalgia	0 (0.0)	1 (4.8)	2 (7.7)	2 (9.5)	5 (6.3)
Sneezing	0 (0.0)	0 (0.0)	2 (7.7)	3 (14.3)	5 (6.3)
Intranasal paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	4 (19.0)	4 (5.0)
Oropharyngeal pain	0 (0.0)	1 (4.8)	2 (7.7)	1 (4.8)	4 (5.0)
Throat irritation	2 (16.7)	1 (4.8)	0 (0.0)	1 (4.8)	4 (5.0)
Epistaxis	1 (8.3)	0 (0.0)	0 (0.0)	2 (9.5)	3 (3.8)
Upper respiratory tract congestion	0 (0.0)	3 (14.3)	0 (0.0)	0 (0.0)	3 (3.8)
Dry throat	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (2.5)
Nasal dryness	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (2.5)
Pharyngeal paraesthesia	0 (0.0)	0 (0.0)	1 (3.8)	1 (4.8)	2 (2.5)

System Organ Class Preferred Term	Subjects Between 15-30 kg		Subjects ≥ 30 kg		Total (N=80) n(%)
	ARS-1 0.65 mg (N=12) n(%)	ARS-1 1.0 mg (N=21) n(%)	ARS-1 1.0 mg (N=26) n(%)	ARS-1 2.0 mg (N=21) n(%)	
Upper airway cough syndrome	0 (0.0)	1 (4.8)	1 (3.8)	0 (0.0)	2 (2.5)
Nervous System Disorders	0 (0.0)	2 (9.5)	4 (15.4)	3 (14.3)	9 (11.3)
Paraesthesia	0 (0.0)	2 (9.5)	1 (3.8)	2 (9.5)	5 (6.3)
Taste disorder	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (2.5)
General Disorders and Administrative Site Conditions	0 (0.0)	0 (0.0)	1 (3.8)	5 (23.8)	6 (7.5)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	2 (2.5)
Feeling jittery	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	2 (2.5)
Eye Disorders	0 (0.0)	0 (0.0)	2 (7.7)	1 (4.8)	3 (3.8)
Lacrimation Increased	0 (0.0)	0 (0.0)	2 (7.7)	1 (4.8)	3 (3.8)
Ocular hyperaemia	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	2 (2.5)

Note: MedDRA version 22.0 used for coding. Subjects with two or more AEs in the same SOC (or with the same preferred term) are counted only once for that SOC (or preferred term).

2.6.8.3. Serious adverse event/deaths/other significant events

During the course of the clinical studies, there were no serious adverse event (SAE), death or other significant events reported.

2.6.8.4. Laboratory findings

Clinical laboratory parameters were not systematically monitored in children during the studies. Similarly, ECG was only performed at screening and baseline. EURneffy 1 mg resulted in a significant increase in SBP and did not appear to affect DBP when EURneffy 1 mg administered to paediatric allergy patients weighing 15 -30 kg. EURneffy 1 mg also increased pulse rate in this population. There were no clinically significant changes from baseline in the PR, QRD duration or QTcF values associated with EURneffy 1 mg administered once or twice daily.

2.6.8.5. Safety in special populations

Special population studies were not conducted with EURneffy.

2.6.8.6. Discontinuation due to adverse events

There were no discontinuations due to adverse event in children regardless of weight (15 to < 30 kg or ≥ 30 kg) or by dose (1 mg or 2 mg EURneffy).

2.6.8.7. Post marketing experience

During the procedure, the applicant clarified that there have been no post-marketing AEs reported with the 1 mg dose since it was made available to patients on 07 May 2025 in the US.

2.6.9. Discussion on clinical safety

The safety of epinephrine 1 mg nasal spray was evaluated in 10 completed phase 1 clinical studies involving 165 healthy subjects aged 19-54 years (EPI 03, EPI 07 and EPI 15), 78 patients aged 21-54 years with Type I allergies (EPI 12 and EPI 17), 115 patients aged 19-63 years with allergic rhinitis (EPI 04, EPI 16, and EPI 18), 21 patients aged 19-55 years with upper respiratory tract infection (EPI 14) and 80 paediatric patients aged 4-17 years with Type 1 allergies (EPI 10).

In the phase 1 single-dose study EPI 10, 33 paediatric patients weighing 15 to <30 kg received 0.65 mg EURneffy or 1 mg EURneffy and 47 patients weighing ⩾30 kg received EURneffy 1.0 mg or EURneffy 2.0 mg. Therefore, the number of exposed target population (patients 15 to <30 kg weight) is low. To support the safety data of the need for additional dosing the MAH included EURneffy 2 mg and 4 mg studies in an Integrated Safety Analysis. Additional supportive studies were completed and are summarised as individual studies (EPI JP01, EPI JP02, and EPI JP03). The MAH was asked to justify that safety data from subjects above 30kg can be extrapolated to those < 30 kg body weight. However, when considered together with the updated PopPK model (clinical pharmacology section), the available evidence indicated that adrenaline exposures in 15–30 kg children are generally within the adult reference range and comparable to those in heavier paediatric subjects.

In total 595 subjects or patients were exposed to EURneffy across the ten completed studies. 33 subjects were between 4 and 11 years of age weighed 15 to <30 kg, and 562 subjects were between 8 and 63 years of age weighed ⩾30 kg. In general, the patients in these studies were well balanced in terms of gender and race.

In total, 221 out of 595 patients were exposed to the 1 mg dose of EURneffy in the studies included in the pooled safety studies. 277 out of 595 patients received a 2 mg dose of EURneffy, including subjects who received a single 2 mg dose and subjects who received two 1 mg doses spaced 10 minutes apart. 85 out of 595 subjects received a 4 mg dose EURneffy, which included subjects who received two 2 mg doses spaced 10 minutes apart. Due to the crossover design of some studies, subjects received more than one exposure to EURneffy per study.

64 subjects included in the supportive safety studies EPI JP01, EPI JP02, and EPI JP03 were between 6 and 55 years of age. Between them, 6 patients with a body weight of 15 to <30 kg and 36 patients with a body weight of ⩾30 kg were exposed to EURneffy 1 mg.

Treatment Emergent Adverse Events (TEAE) were reported at a slightly higher frequency in the EURneffy 1 mg treatment group compared to the EURneffy 2 mg treatment group (52.4% (15 to <30 kg) and 51.0 % (⩾30 kg) for EURneffy 1 mg vs. 44.8% for EURneffy 2 mg). Similarly, the treatment related TEAE was also reported at a slightly higher frequency in the EURneffy 1 mg group compared to the EURneffy 2 mg group (47.6% and 47.5% vs. 42.6%, respectively). According to the System Organ Classification, most TEAEs were observed in three groups: 1) Respiratory, Thoracic and Mediastinal Disorders, 2) Investigations and 3) Nervous System Disorders.

The most common observed adverse events in subjects weighing 15 to <30 kg following EURneffy 1 mg were nasal congestion (19%), nasal dryness (9.5%), dry throat (9.5%), upper respiratory tract congestion (14.3%) and paraesthesia (9.5%). The most common adverse events in subjects weighing ⩾30 kg following EURneffy 1 mg were nasal discomfort (22%), increased blood pressure (8%), tremor (3.5%) and palpitations (4.0%).

According to the data presented by the MAH, subjects in the epinephrine 1 mg ⩾30 kg group experienced more commonly nasal discomfort (22.0% of patients), increased blood pressure (8.0% of patients), tremor (3.5% of patients), cardiac disorders (4.5% of patients) and eye disorders (3.0% of patients) than subjects in the epinephrine 1 mg 15 to <30 kg group (nasal discomfort in 4.8% of

patients and increased blood pressure, tremor, cardiac disorders and eye disorders in 0.0% of patients).

The MAH provided a discussion of possible reasons for the differences in the safety profile of EURneffy 1 mg in subjects weighing ⩾30 kg compared to those weighing 15 to <30 kg and submitted a comparison of safety data from the primary EURneffy studies involving both the 1 mg and 2 mg doses. According to the MAH, differences in reported adverse events are considered to reflect age-related variation in how symptoms are perceived, described and classified. As the safety profile appears consistent across subjects weighing ⩾30 kg and subjects weighing 15 to <30 kg, this explanation is agreed.

Other adverse reactions (<1%) following EURneffy 1 mg in subjects weighing 15 to <30 kg were nasal discomfort, throat irritation, nasal pruritus, oropharyngeal pain, rhinalgia, rhinorrhoea, nasal pruritus, irregular heart rate, and upper-airway cough syndrome. The majority of reported TEAEs were mild in severity and all adverse events were transient and resolved without treatment.

Based on the pooled safety data, the MAH proposed the addition of two new ADRs to the product information and the revision of the frequency of two already known ADRs:

- Dry throat was reported in two subjects receiving the 1 mg dose and weighing 15 kg to <30 kg, and in one subject receiving the 4 mg dose and weighing >30 kg. The proposed frequency is *uncommon*. This is acceptable.
- Upper respiratory tract congestion was reported in three subjects receiving the 1 mg dose and weighing 15 kg to <30 kg. The proposed frequency is *uncommon*. This is acceptable.
- Nasal pruritus was reported in one subject receiving the 1 mg dose and weighing 15 kg to <30 kg, in five subjects receiving the 1 mg dose and weighing >30 kg, in one subject receiving the 2 mg dose and weighing >30 kg, and in three subjects receiving the 4 mg dose and weighing >30 kg. Therefore, the frequency has been revised from *uncommon* to *common*. This is acceptable.
- Paraesthesia was reported in two subjects receiving the 1 mg dose and weighing 15 kg to <30 kg, in three subjects receiving the 1 mg dose and weighing >30 kg, and in three subjects receiving the 2 mg dose and weighing >30 kg. Therefore, the frequency has been revised from *uncommon* to *common*. This is acceptable.

Therefore, Table 1 in section 4.8 of the SmPC and the package leaflet have been updated.

Additionally, section 4.4 of the SmPC has been updated to emphasise the need for caregivers to be instructed on recognising symptoms of systemic allergic reactions and anaphylaxis in young children, noting that these symptoms can be difficult to identify because they often resemble normal childhood behaviours.

No specific new safety signals were observed. No cases of serious adverse events or deaths were reported in clinical trials of EURneffy.

No cases of discontinuations due to AEs in children were reported during the clinical development programme.

No clinically meaningful differences were observed by gender, race, and ethnicity.

In clinical studies with EURneffy, there has been no significant clinical laboratory evaluation findings related to the safety of the test product.

No new safety updates have been proposed in the RMP. This is acceptable. However, the RMP version 2.3 was updated to reflect the new strength and indication.

In addition, given the common adverse reactions (nausea, dizziness, somnolence), the section 4.7 of the SmPC on effects on ability to drive and uses machines has been updated to mention that EURneffy may have minor influence on the ability to drive and use machines due to adverse reactions that may occur after administration. It is not recommended that patients who are experiencing an anaphylactic reaction drive or use machines since they may be impacted by symptoms cased by the anaphylactic reaction. The package leaflet was updated accordingly.

2.6.10. Conclusions on the clinical safety

During the initial approval procedure, nasal epinephrine has shown an acceptable safety profile and treatment is generally well tolerated. Submitted safety data in paediatric patients does not indicate any serious safety concerns or new safety risks and overall EURneffy 1 mg safety profile in paediatric patients seems favourable. The size of the safety database is considered limited but acceptable. Sections 4.4, 4.7 and 4.8 of the SmPC have been updated to include a warning for caregiver, to update the information on effects on ability to drive and uses machines, to add the two newly identified ADRs, to revise the frequency of two known ADRs, and to update the paediatric population section. The RMP version 2.3 has been updated to reflect the new strength and indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 79: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication error
Missing information	None

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse event reporting and signal detection include specific follow-up questionnaires for medication errors. No additional pharmacovigilance activities are planned.

2.7.3. Risk minimisation measures

Table 80: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Medication error	*Routine risk minimisation measures:* SmPC section 4.2: Posology and method of administration. PL section 2: What you need to know before you use EURneffy. PL section 3: How to use EURneffy (Instructions for Use: to be included in the blister pack that contains the EURneffy device). *Additional risk minimisation measures:* • training device • training videos • digital educational material • IFU within EURneffy device blister	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal:* Targeted questionnaire in case of medication errors. *Additional pharmacovigilance activities:* None

2.7.4. Conclusion

The CHMP considered that the risk management plan version 2.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by ALK-Abellò A/S fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

The MAH submitted a request for a combined SmPC and package leaflet. The request was considered acceptable and in line with the Policy on combined Summaries of Product Characteristics[13].

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by Alk-Abello A/S and has been found acceptable for the following reasons:

- The active substance and the delivery system in the parent and daughter medicines are the same.
- The design and layout of the leaflet, including the pictograms used, is similar for both the parent and daughter leaflets.

2.9.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory information has been submitted by Alk-Abello A/S and has been found acceptable.

The following elements have been agreed to be provided through a QR code: Package leaflet (PL), Summary of Product Characteristics (SmPC) and educational material as outlined in the Risk Management Plan.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

EURneffy 2 mg is a nasal adrenaline spray indicated for emergency treatment of anaphylaxis caused by foods, insect stings, medications, exercise, or idiopathic triggers, currently approved for adults and children ≥30 kg. Anaphylaxis is a rapid-onset, systemic, mast cell–mediated reaction that can be fatal without immediate recognition and administration of epinephrine. Early treatment is essential to prevent life-threatening respiratory or cardiovascular complications such as airway obstruction, shock, or collapse. In Europe, the incidence of anaphylaxis ranges from 1.5 to 7.9 per 100,000 person-years, corresponding to an estimated lifetime risk of around 0.3%[3].

This application proposes extending EURneffy use with a new 1 mg strength for children weighing 15–30 kg, representing half the standard 2 mg dose used in patients ≥30 kg.

3.1.2. Available therapies and unmet medical need

Adrenaline is the first line treatment for anaphylaxis in adults and children due to its rapid reversal of histamine-mediated symptoms via α and βadrenergic receptor activation. It effectively counteracts rhinitis, urticaria, bronchospasm, and hypotension. Current standard care relies on adrenaline autoinjectors for out-of-hospital use, enabling early intervention to prevent progression to severe or refractory anaphylaxis. Intravenous administration carries risks of overdose and cardiovascular complications and is reserved for life-threatening cases under strict monitoring. Clinical guidelines

[13] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/policy-combined-summaries-product-characteristics-smpcs_en.pdf

recommend intramuscular delivery in the thigh (0.01 mg/kg; 0.15 mg for 15–30 kg children), which provides faster systemic absorption than subcutaneous or deltoid injection. Despite effectiveness, challenges remain with needle-based devices, including misuse, needle phobia, and administration errors.

Since 2024, EURneffy 2 mg nasal spray offers a needle free option but is only approved for ≥30 kg patients. Therefore, a therapeutic gap persists for children 15–30 kg who may benefit from a needle-free, rapidly administered alternative for treating anaphylaxis.

3.1.3. Main clinical studies

The clinical documentation supporting the proposed new strength and indication comprises both studies previously submitted in the initial marketing authorisation application and additional newly generated data. Among these, the primary source of new clinical evidence relevant to this extension of marketing authorisation is the EPI 10 study.

Study EPI 10 was a single-arm study conducted in paediatric patients who weighed either 15 kg to < 30 kg or 30 kg or more (age range: 4 to 17 years) with Type I allergy without anaphylaxis (N=80) that assessed the PK and PD of adrenaline following one nasal dose of EURneffy 0.65 mg, 1 mg or 2 mg. Paediatric patients weighing 15 kg to < 30 kg were given either EURneffy 0.65 mg (N=12) or 1 mg (N=21) and those 30 kg or more received either EURneffy 1 mg (N=26) or 2 mg (N=21).

3.2. Favourable effects

In the EPI 10 study, EURneffy 2 mg in subjects ≥30 kg achieved systemic exposure (C_{max} 690 pg/mL; AUC_{0-t} 40200 min·pg/mL) comparable with EURneffy 1 mg in the 15–30 kg group, (C_{max} 651 pg/mL and AUC_{0-t} of 35100), with slower absorption (median T_{max} 29.5 vs. 20.0 min). Comparative analyses showed that EURneffy 1 mg in lighter children provided systemic exposure comparable to EURneffy 2 mg in heavier children (30 kg). These findings support the use of 1 mg in children 15–30 kg from a pharmacokinetic standpoint, as the exposure is comparable to the adult dosing regimen of 2 mg for patients ≥30 kg.

The observed pharmacodynamic effects of EURneffy were also consistent and showed comparable efficacy between the 1 mg dose in subjects weighing 15–30 kg and the 2 mg dose in subjects ≥30 kg. EURneffy induced increase in systolic blood pressure and heart rate, with no significant or clinically relevant differences between doses in both weight groups.

Furthermore, the results from allometric modelling (updated popPK model) supported the proposed weight-based dosing regimen with the lower bound of the modelled population of ≥ 15 kg.

3.3. Uncertainties and limitations about favourable effects

In EPI 10 study, only two children were 4 years old, three were 6 years old and the remaining participants were older. Furthermore, only two children had a body weight below 20 kg (18.5 and 19.8 kg), and the mean and median body weight was approximately 25 kg.

Although the lower weight limit of 15 kg is adequately supported by the PK bridging data for extrapolating efficacy and pharmacodynamic effects, the suitability of the current device for patients younger than 4 years has not been demonstrated. The PIP also includes a requirement to develop an age-appropriate intranasal device for children from 6 months to less than 4 years of age. Consequently, in absence of an age-appropriate device, the initially proposed indication has been restricted to patients aged 4 years and older, in addition to meeting the weight based criterion of

15 kg: *EURneffy is indicated in the emergency treatment of allergic reactions (anaphylaxis) due to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis. Treatment is indicated for adults and children aged 4 years and over with a body weight of 15 kg or more.*

There are no remaining efficacy uncertainties in the finally agreed indication.

3.4. Unfavourable effects

In subjects 15 kg to < 30 kg exposed to EURneffy 1 mg, 52.4% reported at least one TEAE and 47.6% of subjects experienced Treatment Related TEAE.

The most common adverse reactions in subjects weighing 15 kg to less than 30 kg treated with EURneffy 1 mg included: nasal congestion (19.0 %), upper respiratory tract congestion (14.3 %), dry throat, nasal dryness, and paraesthesia (each 9.5 %). The most common adverse reactions in subjects weighing 30 kg or more treated with EURneffy 1 mg included: nasal discomfort and nasal mucosal disorder (each 19.2 %), and rhinalgia (7.7 %).

Dry throat and upper respiratory tract congestion have been added as new ADRs in section 4.8 of the SmPC, and corresponding section of the package leaflet. In addition, the frequency of nasal pruritus and paraesthesia has been revised from *uncommon* to *common*.

There were no SAEs or deaths reported in subjects exposed to EURneffy,

Overall, no major safety concerns have been identified in the EPI 10 study or pooled safety analysis. There were no clinically relevant differences in the safety between the paediatric and adult populations treated with EURneffy.

3.5. Uncertainties and limitations about unfavourable effects

In total only 21 subjects 15 kg to < 30 kg were exposed to EURneffy 1 mg. Therefore, the size of the safety database is considered very limited. However, epinephrine has a well-established safety profile and observed underprediction in older children did not translate into adverse clinical outcomes. No meaningful differences in the safety profile between the paediatric and adult populations are expected.

3.6. Effects Table

Table 81: Effects Table for EURneffy

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PD response subj. 15-30 kg	SBP (Emax)	mmHg	0.65 mg – 12.3 1.0 mg – 13.4	-	Limited number of subjects below 20 kg and 6 years of age	EPI10
PD response subj. 15-30 kg	PR(Emax)	bpm	0.65 mg – 15.7 1.0 mg – 18.5	-		EPI10
PD response subj. 15-30 kg	DBP (Emax)	mmHg	0.65 mg – 9.5 1.0 mg – 7.0	-		EPI10
Time to symptoms resolution to grade 0	Time	Min (median)	1.0 mg – 22.5 2.0 mg – 15.0		Limited number of subjects below 20 kg and 6 years of age	JP03
Unfavourable Effects						
upper respiratory tract congestion		Number of cases	ARS-1 1.0 mg 3 cases	-	Limited number of subjects exposed	EPI-10
paraesthesia		Number of cases	ARS-1 1.0 mg 2 cases	-	Limited number of subjects exposed	EPI-10
nasal congestion		Number of cases	ARS-1 1.0 mg 4 cases	-	Limited number of subjects exposed	EPI-10

Abbreviations: SBP – systolic blood pressure, DBP – diastolic blood pressure, PR – pulse rate

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects include pharmacokinetic comparability of EURneffy 1 mg in children 15–30 kg with the 2 mg dose in subjects ≥30 kg, supporting appropriate systemic exposure across weight groups. Pharmacodynamic responses—such as increases in systolic blood pressure and heart rate—were consistent between doses, with no clinically relevant differences. Allometric modelling further supports the weight-based dosing strategy with a lower bound of 15 kg. No SAEs or deaths occurred, and overall safety was comparable between paediatric and adult populations, aligning with the known safety profile of epinephrine.

Unfavourable effects primarily relate to limitations in the clinical dataset: only 21 children in the 15–30 kg group, with very few weighing <20 kg and none under 4 years of age. As a result, evidence in younger children (< 4 years) remains insufficient, and device suitability for <4 years is unproven. Common adverse events were mostly mild and local (e.g. nasal congestion, discomfort, mucosal disorders). Despite the small safety database, no major safety concerns emerged, though the limited sample size constrains confidence in rare-event detection.

3.7.2. Balance of benefits and risks

The benefits of EURneffy 1 mg include achieving systemic exposure and pharmacodynamic effects in children 15–30 kg that are comparable to the approved 2 mg dose in ≥30 kg subjects, supporting

effective weight-based dosing. Consistent haemodynamic responses and absence of SAEs further strengthen the favourable profile. Reported adverse events were mostly mild, local, and aligned with intranasal administration. However, the suitability of the current device for patients younger than 4 years has not been demonstrated. Therefore, EURneffy 1 mg is indicated in children aged 4 years and over with a body weight of 15 kg to 30 kg.

3.8. Conclusions

The overall benefit/risk balance of EURneffy is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, EURneffy 1 mg nasal spray is favourable in the following indication:

EURneffy is indicated in the emergency treatment of allergic reactions (anaphylaxis) due to insect stings or bites, foods, medicinal products and other allergens as well as idiopathic or exercise induced anaphylaxis. Treatment is indicated for adults and children aged 4 years and over with a body weight of 15 kg or more.

The CHMP therefore recommends the extension of the marketing authorisation for EURneffy subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

Prior to the launch of EURneffy in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at preventing misuse of the medicinal product in the context of an emergency situation.

The MAH shall ensure that in each Member State where EURneffy is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense, use EURneffy have access to/are provided with the following educational information:

- Physician educational material
- Patient/caregivers information pack

Physician educational material:

- The Summary of Product Characteristics
- Training device
- Healthcare professionals training material (training videos)
    - Training device to familiarise with use of EURneffy device
    - Indications in which EURneffy should be used
    - Detailed description of the administration procedures of EURneffy
    - Importance of seeking medical assistance when using EURneffy
    - Relevant information on the EURneffy single dose device and how to use it
    - Instructions on correct handling of EURneffy device
    - Need to always carry a second device in case of second dose would be required
    - Need to seek emergency medical assistance
    - Patient's preparation for the procedure and subsequent monitoring
    - Management of early signs and symptoms of selected safety concerns, namely severe allergic reaction/anaphylaxis

Patient/caregivers information pack:

- Patient information leaflet
- Training device provided by physician as needed
- The patient/caregivers /digital information brochure/videos:
    - Indication in which EURneffy should be used including anaphylaxis/severe allergic reaction action plan
    - Information on how to identify a serious allergic reaction
    - A description of the correct use of EURneffy and the need to seek emergency medical assistance when using EURneffy
    - Detailed description of the modalities used for the self-administration of EURneffy
    - A description of the best course of action if second dose is needed

- Need to always carry a second device in case of second dose would be required
- Monitoring and guidance for actions following use of EURneffy

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P0431/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.