



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Tab27 June 2024
EMA/328958/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eurneffy

International non-proprietary name: epinephrine

Procedure No. EMEA/H/C/006139/0000

Note

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



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List of abbreviations

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	Benzalkonium 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	Fourier transform infra-red (spectroscopy)
GC	Gas chromatography
GLP	Good Laboratory Practice
GRAS	Generally recognised as safe
HbSAg	Hepatitis B surface antigen
HPLC	High performance liquid chromatography
HR	Heart rate
ICP	Inductively coupled plasma
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control test
ICH	International Conference on Harmonization
IFU	Instructions for use
IM	Intramuscular
IN	Intranasal
IP	Investigational (medicinal) product
IR	Infrared spectroscopy

IRB/EC	Institutional Review Board/Ethics Committee
IV	Intravenous
kg	Kilogram(s)
lbs	Pounds
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LS	Least squares
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetre of mercury
msec	Milliseconds
Min	Minimum
mIU/mL	Milli-international units per millilitre
mg	Milligram(s)
mL	Millilitre
MS	Mass spectrometry
NAC	Nasal allergen challenge
NMR	Nuclear magnetic resonance
NOEL	No observable effect level
OTC	Over-the-counter
PBMCs	Peripheral mononuclear cells
PD	Pharmacodynamics
PE	Physical exam
PG	Picograms
Ph. Eur.	European Pharmacopeia
PI	Principal investigator
PK	Pharmacokinetics
QOS	Quality Overall Summary
Rprt	Relative retention time
Rt	Retention time
RT	Room temperature
SPC	Summary of Product Characteristics
UDS	Unit dose sprayer
WFI	Water for injection

Adrenaline = epinephrine and ARS-1 = neffy = Eurneffy are used interchangeably within the report.

NOT ALL ABBREVIATIONS ARE USED IN THIS REPORT

1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant ARS Pharmaceuticals IRL Limited submitted on 7 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Eurneffy, through the centralised procedure under Article 3 (2) b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2022.

The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication: 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.

1.2. *Legal basis, dossier content*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. *Information on paediatric requirements*

Pursuant to Article 7 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.

The PDCO issued an opinion on compliance for the PIP P0431/ 2020.

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, the applicant 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.

1.4.2. New active substance status

Not applicable

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP coordinators
26 April 2019	EMA/H/SA/4077/1/2019/SME/III	Caroline Auriche, Birgitte Bloch Daum

The scientific advice pertained to the following non-clinical and clinical aspects:

- Non-clinical data package related to excipients used for the nasal formulation
- Clinical data
 - Clinical pharmacology data, advice on PK assessments and timepoints used to support efficacy and safety outcomes in comparison to existing IM formulations.
 - PK study design of EPI03 study
 - PD assessments supporting efficacy.

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	7 October 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 August 2023
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	19 & 25 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
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 October 2023

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 May 2024
The CHMP agreed on a 2 nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the 2 nd CHMP List of Outstanding Issues on	04 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2 nd List of Outstanding Issues to all CHMP and PRAC members on	11 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the 2 nd List of Outstanding Issues to all CHMP and PRAC members on	20 June 2024
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	27 June 2024

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). Delay in clinical diagnosis and treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters-2015).

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).

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), 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.

A recent retrospective study of anaphylaxis presentations to a paediatric emergency department reported that foods were the causative trigger in 86% of presentations, with medication and insect stings accounting for 5 and 4% of presentations, respectively, and no cause identified in 5%. In this study, a prior history of anaphylaxis was noted in only 14% of cases, whereas concurrent diagnosis of other allergic disorders (asthma, eczema, or allergic rhinitis) was common (60%). This highlights the difficulties associated with identification of those at risk of anaphylaxis and suggests that presence of other allergic conditions may provide some assistance in this regard (Tang, 2009).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

(1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) and at least of the following:

(a) Respiratory compromise [e.g. dyspnoea, wheeze bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia]

(b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]

(2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

(a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (e.g. dyspnoea, wheeze bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced BP or associated symptoms [e.g. hypotonia (collapse), syncope, incontinence]

(d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

(3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

(a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (low systolic blood pressure for children is defined as: less than 70mmHg from 1 month to 1 year; less than [70mmHg*(age_2)] from 1 to 10 years, and less than 90mmHg from 11 to 17 years)

(b) Adults: systolic BP of less than 90mm Hg or greater than 30% decrease from that person's baseline.

2.1.5. Management

Adrenaline has been used 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, Upton-2014). Although no prospective, controlled clinical trials have been performed to substantiate the use of adrenaline for treatment of anaphylaxis (Sheikh-2008), 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, Brown-2006).

To date, there are several routes of adrenaline administration used for the treatment of severe allergic reactions and anaphylaxis including IV infusion, IV bolus, IM, and SC administration.

Although adrenaline injection has an excellent post-approval safety profile and is highly effective in the management of anaphylaxis, the auto-injectors can be considered inconvenient and cumbersome, and the devices are not always available when needed. One particular barrier to effective use of injectable adrenaline in paediatric patients is the requirement that the needle be held in place for more than 3 seconds following initial injection.

Further, apprehension to use an auto-injector due to the pain, fear of needles and, cost and reluctance to use the device in a public setting often leads to critical delays in treatment. Delayed treatment is known to lead to more severe events and more frequent fatalities, (Simons-2010b, Campbell-2014).

2.2. *About the product*

Eurneffy (adrenaline nasal spray) is a novel formulation of adrenaline that includes an absorption enhancing agent called dodecylmaltoside (DDM) to improve the bioavailability of drugs administered by the intranasal (IN) route. Neffy is delivered using a commercial unit dose sprayer (UDS) that is ideally designed to produce a spray pattern and droplet size that maximises the delivery to the turbinates. Once administered, adrenaline is primarily absorbed into the systemic circulation rapidly via the highly vascularised turbinates (Kapoor-2016).

2.3. *Type of application and aspects on development*

The applicant received CHMP SA on the development of Eurneffy on 26 April 2019 (EMA/H/SA/4077/1/2019/SME/III). Generally, all recommendations have been followed by the applicant. On the non-clinical programme, CHMP concluded that extensive and complete non-clinical studies have been conducted with Intranasal A3 including a 26-week study in rats and a 39-weeks study in dogs both using the intranasal route. In rats and dogs, the 20% concentration of Intranasal A3, administered at 10 mg/day, was considered a NOAEL.

The study design of EPI-03 pharmacokinetic study in healthy volunteers was considered adequate to demonstrate comparative bioavailability and pharmacodynamics of intranasal administration (ARS-1) of adrenaline with intramuscular injection of adrenaline. Moreover, it was agreed that demonstrating that pharmacodynamic responses in the EPI-03 trial can provide supportive evidence of similar efficacy between the IM injection and intranasal routes of administration.

Furthermore, CHMP agreed that the proposed pharmacokinetic and pharmacodynamic studies can be considered adequate to support a marketing authorisation application for ARS-1 for the indication of treatment of Type 1 hypersensitivity reactions, including anaphylaxis, in adults.

2.4. Quality aspects

2.4.1. Introduction

Introduction

The finished product is presented as a nasal spray solution in single-dose container containing adrenaline (epinephrine) 2 mg in 100 microlitres.

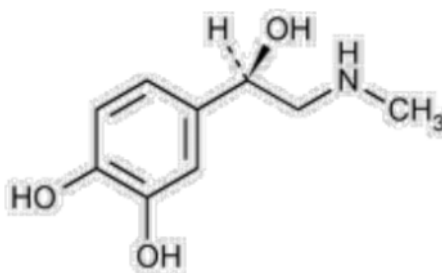
Other ingredients are: sodium chloride, dodecylmaltoside, disodium edetate, benzalkonium chloride, sodium metabisulphite (E 223), concentrated hydrochloric acid (for pH-adjustment), sodium de (for pH-adjustment) and water for injections. The product is available in a unit dose container contained within a single use nasal spray.

2.4.2. Active substance

General information

The chemical name of adrenaline (epinephrine) is 4-[(1*R*)-1-hydroxy-2-(methylamino)ethyl]benzene-1,2-diol corresponding to the molecular formula $C_9H_{13}NO_3$. It has a relative molecular mass of 183.20 and the following structure:

Figure 1 active substance structure



As there is a monograph of adrenaline (epinephrine) in the European Pharmacopoeia (Ph. Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability to the monograph of the European Pharmacopoeia (CEP) for adrenaline (epinephrine) which has been provided within the current Marketing Authorisation Application.

The chemical structure of adrenaline (epinephrine) was elucidated by a combination of 1H -NMR, ^{13}C -NMR, mass spectrometry (MS) and infrared (IR) spectroscopy and elemental analysis data. The solid-state properties of the active substance were measured by Differential Scanning Calorimetry (DSC) and Fourier-transform infrared spectroscopy (FT-IR).

The active substance is a white to practically white, crystalline powder. It is practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. It dissolves in hydrochloric acid. Adrenaline exhibits stereoisomerism due to the presence of 1 chiral centre. Enantiomeric purity is specified in the Ph. Eur. monograph and is controlled at release and monitored on stability with a stability specification for D-adrenaline of NMT 10.0%.

Polymorphism has not been observed for adrenaline (epinephrine), as also confirmed by FTIR and DSC thermograms.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP.

Specification

The active substance specification, as applied by the finished product manufacturer, includes tests for description (visual), identification (FT-IR, specific optical rotation), appearance of solution (Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), assay (titration), enantiomeric purity line (HPLC), impurities (HPLC), residual solvents (GC), palladium Inductively coupled plasma mass spectrometry ((ICP-MS)), microbial limit testing (total aerobic microbial count, total combined yeast/moulds count, Ph. Eur.).

The specification tests and limits are compliant with the Ph. Eur. monograph for adrenaline and include the following additional tests as stated in the CEP: test for residual solvents by gas chromatography (methanol), test for elemental impurity by ICP-MS (Palladium.) The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities testing has been presented.

Batch analysis data on three full scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

According to CEP the retest period of active substance is 60 months when stored in a triple laminated bag (polyethylene terephthalate / aluminium / polyethylene) in a polyethylene bag, placed in a polyethylene drum.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The applied finished product (Eurneffy) is an aqueous solution in a single use container. The solution is a clear and colourless to pink brownish that is filled into unit dose 400 µL Type I glass vials and closed with a grey bromobutyl rubber stopper and then assembled into a Unit Dose Sprayer (UDS) device. The device is a non-pressurised dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL per actuation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of Intravail A (dodecylmaltoside or DDM), for which an adequate specification and related analytical tests have been provided. There are no novel excipients used in the finished product formulation; DDM has been used as a permeation enhancer in products for nasal administration approved in the USA by FDA: Tosymra (sumatriptan) nasal spray for chronic treatment of migraine headaches (January 2019) and Valtoco (diazepam) nasal spray for the emergency treatment of repetitive epileptic seizures (January 2020).

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Eurneffy includes an overage of adrenaline. The use of an overage has been justified. Eurneffy finished product was developed as a nasal spray because the intranasal route of administration is considered less invasive and a lower risk for administration of intramuscular. Risk assessment was used throughout development to identify potentially high-risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding and thus,

define a control strategy. The quality target product profile (QTPP) and critical quality attributes (CQAs) of the finished product are given

The finished product consists of adrenaline in solution. The solubility of adrenaline is a CQA, whilst particle size is not, hence it is not controlled.

The container closure system and spray pump used throughout development and for commercial batches is summarised.

Given the life-threatening condition targeted and the impact that the safety and performance of the device part can have on the benefit/risk of the finished product, the CHMP considered that an EC declaration of conformity alone, which was submitted by both manufacturers of the device in relation to Article 117 of Medical Regulation EU 2017/745, could not be considered sufficient to support the quality, the safety and the efficacy of Eurneffy. To address the major objection (MO), the applicant performed full characterisation of the nasal spray in line with the EU guideline requirements of the "Guideline on quality documentation for medicinal products when used with a medical device" (EMA/CHMP/QWP/BWP/259165/2019) and provided a full demonstration that the proposed unit dose devices from both manufacturers comply with all the relevant General Safety and Performance Requirements of the Medical Device Regulation. It was hence concluded that the safety and performance of the device for use in this medicinal product are demonstrated.

The compatibility of the adrenaline solution with the glass vial and rubber stopper was investigated by extractable and leachable studies. It was concluded that there is no safety concern from any potential leachables from the container closure system in the adrenaline nasal spray.

The CHMP raised an MO as it had not been demonstrated that the device was suitable for the intended paediatric population in line with EMA/CHMP/QWP/805880/2012 Rev. 2. In response, the applicant provided data and justification that demonstrate the acceptability of formulation (choice of excipients, the palatability and sensation of the finished product on administration) and pharmaceutical form (e.g. suitability of the selected device, intended delivered volume, ensuring that the dose will reach the deposition site (nostril/nasal cavity)) for the paediatric population.

Manufacture of the product and process controls

The finished product is manufactured and released by the manufacturers stated in the application.

Major steps of the manufacturing process have been validated on 3 consecutive commercial scale batches for Eurneffy including filling into the unit dose vials. A bulk hold time study was performed only one batch of the finished product, demonstrating sufficient stability. However, the applicant is recommended to perform a hold time study before the first batch is introduced to the market and any deviations/results out of trends should be communicated to authorities (REC1). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

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 impurities (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 (Ph. Eur.).

The finished product specification covers all required parameters.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities testing has been presented.

However, during the assessment it was concluded that the method use for the determination of impurity F could be improved for accuracy; the applicant is therefore recommended to develop a new validated analytical method for the quantification of impurity F to replace the currently approved one and submit a type A post-approval variation (REC2).

Batch analysis results are provided for commercial scale 2 mg Eurneffy batches and supportive 1 mg batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. No out-of-specification results have been reported. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). An MO was raised as the information initially provided was incomplete since it did not fully address risks from all manufacturers involved in the API process and identified the possibility of nitrosation of epinephrine and other amines in the formulation in the slightly acidic solution environment. In response, the applicant provided an updated risk assessment arguing there is no source of nitrosating agents in the formulation. Furthermore, test data demonstrated that none of the tested nitrosamines, including N-nitrosoepinephrine (AI = 100 ng/day based on CPCA), were detected using a suitably sensitive analytical method. Based on the data and risk assessment presented, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 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.

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.

Supportive stability data was also provided for multiple batches of the previous 1 mg formulation under long term conditions for up to 24 months.

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 epimerisation, 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 as summarised in Table 1 below.

Table 1 Forced Degradation Conditions

Sample	Exposure Conditions
Control	No exposure to degradants
Light	1 X ICH Q1B photostability conditions. (Illumination not less than 1.2 million lux hours and integrated near UV energy of not less than 200 watt/square meter.)
Heat	80 °C for 120 hours
Acid	1 N HCl at room temperature for 24 hours.
Base - initial	0.1 N NaOH at room temperature for 4 hours.
Base - repeated	0.05 N NaOH at room temperature for 1 hour.
Oxidation	3% H ₂ O ₂ at ambient conditions for 24 hours

Degradation was observed primarily under 0.1 N NaOH conditions. ICH photostability studies indicate that the product is photostable when stored in the proposed container.

The applicant conducted further studies at higher temperature (50 °C, 3 months) and examining the impact of temperature cycling including freezing. Users would need to keep the medicine with them in case of anaphylaxis and this result in exposure of Eurneffy to extreme temperatures (e.g., in a hot car during summer, outdoors during winter). 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.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

Several major objections were raised during the procedure on the following issues: presence of antioxidant and antimicrobial in the composition, for the device components, the suitability of the finished product for the paediatric population, full characterisation of the nasal spray and potential presence of nitrosamine impurities. These have all been adequately resolved.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to the holding time of the finished product during manufacture and the development of a new validated analytical method for the quantification of impurity F. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

In the context of the obligation of the marketing authorisation holder (MAH) to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to perform a hold time study; EMA should be informed of any deviations/results out of trends (REC1).
2. The applicant is recommended to develop a new validated analytical method for the quantification of impurity F to replace the currently approved one and submit a post-approval quality variation (REC2).

2.5. *Non-clinical aspects*

2.5.1. Introduction

The nonclinical evaluation of Eurneffy (also referred as ARS-1) was conducted in accordance with ICH M3 and the CHMP Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95).

The nonclinical testing strategy to determine the nonclinical profile of Eurneffy includes:

- Bioavailability studies in the rat and dog
- Pharmacokinetic studies in the dog with and without anaphylaxis to show absorption intranasally during an anaphylactic event
- C¹⁴ cytochrome P450 metabolism study in the rat
- Single-dose local toxicology study conducted with ARS-1 in the rat; other data from literature
- Repeat-dose toxicology data from the literature
- Genotoxicity data from the literature
- Carcinogenicity data from the literature
- Reproductive and developmental toxicity data from the literature
- Ocular tolerance study conducted in the rabbit with Eurneffy

Moreover, the toxicology evaluation of dodecylmaltoside (DDM) was conducted in accordance with applicable CHMP guidelines in support of its use as a functional excipient.

This nonclinical testing strategy to determine the toxicological profile of DDM includes:

- Repeat-dose toxicology studies conducted in the rat and dog for up to 12 weeks
- *In vitro* and *in vivo* genotoxicity
- Carcinogenicity in the rat
- *In vivo* impairment of fertility in the rat

- Local tolerance in guinea pigs, rabbits, and dogs.

Toxicology data published by the Environmental Protection Agency and Spack *et. al.* (Federal Register-2005, Spack-1998) were also submitted.

2.5.2. Pharmacology

Two primary pharmacodynamics studies were conducted by the applicant to evaluate the cardiovascular effects and pharmacokinetics of ARS-1 in beagle dogs (study 2021-4052 and study 1021-4072). No other pharmacology studies have been undertaken by the applicant.

Given the clinical history of adrenaline, pharmacology data were derived from literature, supported by prior extensive clinical use, as well as clinical data obtained with ARS-1. Therefore, nonclinical secondary pharmacodynamic studies were not conducted with ARS-1.

The absence of the pharmacology data is justified per the Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications as new studies are unlikely to complement current scientific knowledge of the pharmacologic profile of adrenaline.

2.5.2.1. Primary pharmacodynamic studies

The applicant conducted a non-GLP randomised, cross-over pilot study 2021-4052 in beagle dogs with 7 treatment groups. In total three doses of 0.5, 1.0, and 1.5 mg ARS-1 administered intranasally, two doses of 0.15 and 0.30 mg of adrenaline administered IM without anaphylaxis conditions were compared to 1.0 mg ARS-1 or placebo administered intranasally with anaphylaxis conditions induced by Tween 80 (3 mg/kg IV). This study was conducted in the conscious and unconscious (anesthetised) dog. In conscious animals administered ARS-1 or placebo and Tween 80, histamine concentrations reached average peak values of 862 ng/mL and 271 ng/mL, respectively. In anesthetised males administered ARS-1 or placebo together with Tween 80, histamine concentrations reached average peak values of 918 ng/mL and 295 ng/mL, respectively.

ARS-1 transiently increased dP/dtmax in dogs at a similar extent in all tested doses. dP/dtmax was comparable for intra-nasal (IN) ARS-1 and IM adrenalin. At lower doses (0.5, 1 mg) ARS-1 administration was associated with a decrease in arterial blood pressure and decrease in heart rate (HR) was observed at 1.0 and 1.5 mg ARS-1. ARS-1 administration resulted in higher mean arterial blood pressure values compared to adrenaline IM administration. Effect on HR was comparable between IN and IM adrenaline.

A GLP, randomised, cross-over study 1021-4072 was performed to evaluate the pharmacokinetics and cardiovascular effect of adrenaline nasal spray after administration with and without anaphylaxis conditions in beagle dogs. 0.9% Saline Solution or Tween 80 (0.25%) was administered by IV 7 minutes prior to dose administration of 1.0 mg ARS-1.

No changes in ECG parameters and body temperature were reported following ARS-1 administration. However, an immediate and transient increase in heart rate and in systolic and mean arterial blood pressure was observed. Moreover, increases in contractility parameters were also observed.

Lower increase in heart rate changes were observed after co-administration of Tween 80 with ARS-1 compared to ARS-1 with saline. However, after 30 to 60 minutes after adrenaline administration, SBP achieved pre-induction levels.

Administration of ARS-1 (without Tween-80) increased HR, however according to the raw data provided in the study report, administration of ARS-1 after Tween-80 induction, did not change the HR

and it was comparable to a pre-dose level in male and female dogs.

SBP and MABP values in males after ARS-1 administrations were relatively stable. After the administrations of Tween-80 and ARS-1 a relevant drop in SBP was observed in males while MABP values were stable. DBP decrease was reported in males.

A trend towards an increase in SBP was observed in female dogs after ARS-1 administration. After Tween-ARS-1 administration in female dogs SBP and MABP dropped and started to increase back to pre-dose levels within approximately 1h post-dose. DBP in females was stable after the administration of ARS-1 while a reduction of DBP was observed after Tween-ARS-1 administration.

Altogether the data shows a very high inter-animal variability especially in male dogs. Clinical signs of elevated histamine levels, significant hypotension, facial oedema confirm the induction of anaphylaxis in dogs using Tween-80 as a challenge agent. However, the effect of ARS-1 on cardiovascular parameters was inconsistent.

2.5.2.2. Secondary pharmacodynamic studies

Non-clinical secondary pharmacodynamics studies have not been undertaken. The absence of the additional secondary pharmacodynamic data is justified considering that new studies are unlikely to complement current scientific knowledge.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were not conducted with ARS-1. The absence of the additional safety pharmacology data is justified considering current well known scientific knowledge of the pharmacologic profile of adrenaline. However, cardiovascular telemetry studies in conscious and anaesthetised dogs with and without anaphylaxis conditions were conducted as part of the primary pharmacodynamic assessment above described.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interactions have not been undertaken. Pharmacodynamic drug interaction data was derived from literature, prior clinical use, as well as clinical data obtained with ARS-1.

2.5.3. Pharmacokinetics

A reduced non-clinical programme concerning pharmacokinetics has been conducted by the applicant. Two non-clinical studies (2021-4052 and 1021-4072) aimed to evaluate the pharmacokinetics of ARS-1 after administration with and without anaphylaxis conditions using beagle dogs.

No distribution, excretion and pharmacokinetic drug interactions studies have been performed by the applicant.

The applicant evaluated the pharmacokinetic profile of different formulations of ARS-1 (aqueous and non-aqueous) with and without DDM in four studies. The results of study WIL-28501 showed that ARS-1 with 0.25% DDM administered intranasally in rats exhibited the greatest absorption amongst the three formulations. The results of Study WIL-28503 demonstrated that the optimal ARS-1 formulation containing 0.25% DDM exhibited a relative bioavailability of 80.2% compared to adrenaline injection administered intramuscularly.

A radiolabelled adrenaline pharmacokinetic study, which evaluated 11 formulations containing different

excipients, after nasal administration in rats compared to IV adrenaline showed that ¹⁴C-adrenaline was absorbed relatively rapidly following intranasal installation in all of the formulations. Maximum plasma concentrations between 46.3 and 90.9 ng/ml following a nominal dose of 44 mg of adrenaline were observed between 15- and 180-minutes following dosing. This study also demonstrated that EDTA and benzalkonium chloride (BZK) did not appear to be important components for absorption of adrenaline in the formulation. It was concluded that formulations without DDM showed poorer or slower absorption than with DDT. However, according to the pharmacokinetic results from study 2555-003, Group 2 (without DDM, without other excipients, ARS-1-WOE) had a higher C_{max}, equal t_{max} and higher AUC_{0-240min} comparing to Group 1 with 0.25% DDM (ADR-1) which is not in line with the conclusion on DDM. Summarizing the data from all 0.25% DDM groups, the effect of DDM appeared to be more pronounced.

An *in vitro* metabolism study was conducted to demonstrate that nasal mucosa does not significantly impact the metabolism of adrenaline by exploring the difference between degradation with or without enzyme inhibitors. The study showed that adrenaline was degraded not due to the CYP enzymes but due to the experimental system. No formation of noradrenaline was observed.

Study 2021-4052

The applicant conducted a non-GLP pilot pharmacokinetics study to evaluate the pharmacokinetics of ARS-1 after administration with and without anaphylaxis conditions in beagle dogs. In both anaesthetised and conscious animals, anaphylaxis potentiated the absorption of epinephrine relative to animals that were not in anaphylaxis.

Pharmacokinetic Evaluations

Conscious Animals

In conscious animals, the highest peak epinephrine level was observed following ARS-1 1.0 mg + Tween 80 (3710 pg/mL), followed by Tween 80 + Placebo (1860 pg/mL). In animals who were not administered Tween 80, the highest peak epinephrine exposure was observed following ARS-1 1.5 mg + Saline (942 pg/mL), followed by IM epinephrine 0.3 mg (928 pg/mL), ARS-1 1.0 mg + Saline (728 pg/mL), ARS-1 0.5 mg (626 pg/mL), and IM epinephrine 0.15 mg (618 pg/mL).

Table 2 Pharmacokinetic Parameters of Epinephrine, by Treatment – Conscious Animals

Treatment	Pharmacokinetic Parameter										
	T _{max} (min) median (range)	C _{max} (pg/mL) geo. mean (geo. CV%)	AUC (h*pg/mL) geo. mean (geo. CV%)								
			AUC 0-2.5	AUC 0-5	AUC 0-7.5	AUC 0-10	AUC 0-15	AUC 0-20	AUC 0-30	AUC 0-45	AUC last
ARS-1 0.5 mg + Saline	20.0 (2.50 - 45.0)	626 (173)	9.52 (156)	21.1 (127)	33.3 (99.4)	45.5 (84.4)	72.5 (72.0)	99.8 (65.2)	157 (60.3)	244 (70.1)	244 (70.1)
ARS-1 1.0 mg + Saline	7.5 (15.0- 30.0)	728 (109)	7.79 (58.5)	18.8 (67.5)	33.2 (76.3)	49.6 (84.2)	95.0 (78.5)	133 (73.2)	201 (64.1)	300 (64.8)	300 (64.8)
ARS-1 1.5 mg + Saline	10.0 (30.0 - 45.0)	942 (415)	6.96 (33.1)	14.7 (35.3)	23.0 (38.4)	31.7 (39.4)	63.7 (97.1)	131 (167)	250 (270)	384 (226)	384 (226)
IM Epinephrine 0.15 mg + Saline	30.0 (2.50 - 45.0)	618 (72.2)	8.63 (74.6)	19.7 (81.1)	30.8 (80.2)	41.9 (82.1)	65.4 (79.4)	94.4 (75.4)	161 (70.6)	267 (56.8)	267 (56.8)
IM Epinephrine 0.3 mg + Saline	30.0 (7.50 - 45.0)	928 (77.4)	8.41 (46.1)	20.2 (48.3)	34.2 (44.4)	50.3 (46.5)	86.0 (49.7)	123 (49.9)	223 (53.2)	405 (61.0)	405 (61.0)
ARS-1 1.0 mg + Challenge Agent	7.5 (2.50 - 45.0)	3710 (41.1)	43.2 (152)	111 (178)	184 (190)	282 (145)	493 (88.3)	682 (71.0)	987 (57.0)	1380 (38.6)	1380 (38.6)
Challenge Agent + Placebo	10.0 (2.50- 45.0)	1860 (35.4)	24.9 (48.6)	66.3 (37.4)	116 (31.4)	177 (33.2)	296 (38.6)	399 (36.1)	568 (32.5)	756 (35.5)	756 (35.5)

Anaesthetised Animals

In anaesthetised animals, the highest peak epinephrine levels were observed following ARS-1 treatments. The highest peak exposure was observed following ARS-1 1.0 mg + Tween 80 (1840 pg/mL), followed by ARS-1 1.5 mg + Saline (1760 pg/mL), ARS-1 0.5 mg + Saline (900 pg/mL), ARS-1 1.0 mg + Saline (644 pg/mL). Lower peak epinephrine levels were observed following IM epinephrine (517 pg/mL following IM epinephrine 0.3 mg + Saline and 370 pg/mL following IM epinephrine 0.15 mg + Saline). Peak exposure following Tween 80 + Placebo was 473 pg/mL.

Table 3 Pharmacokinetic Parameters of Epinephrine, by Treatment – Anaesthetised Animals

Treatment	Pharmacokinetic Parameter										
	T _{max} (min) median (range)	C _{max} (pg/mL) geo. mean (geo. CV%)	AUC (h*pg/mL) geo. mean (geo. CV%)								
			AUC 0-2.5	AUC 0-5	AUC 0-7.5	AUC 0-10	AUC 0-15	AUC 0-20	AUC 0-30	AUC 0-45	AUC last
ARS-1 0.5 mg + Saline	10.0 (2.50 - 45.0)	900 (52.1)	8.70 (41.1)	24.7 (40.4)	44.8 (34.8)	67.9 (32.4)	117 (27.7)	163 (26.6)	245 (28.4)	371 (35.3)	371 (35.3)
ARS-1 1.0 mg + Saline	5.00 (0.00- 45.0)	644 (171)	8.61 (54.4)	24.4 (106)	43.9 (137)	62.1 (145)	94.7 (134)	123 (126)	185 (125)	286 (123)	286 (123)
ARS-1 1.5 mg + Saline	10.00 (0.00- 45.0)	1760 (343)	10.1 (73.0)	32.6 (129)	71.4 (191)	121 (230)	231 (253)	329 (247)	494 (226)	745 (215)	745 (215)
IM Epinephrine 0.15 mg + Saline	45.0 (20.0 - 45.0)	370 (47.6)	5.40 (22.1)	11.5 (30.9)	17.7 (34.7)	23.8 (35.5)	37.0 (38.9)	53.0 (43.0)	94.1 (44.0)	172 (39.5)	172 (39.5)
IM Epinephrine 0.3 mg + Saline	45.0 (10.0 - 45.0)	517 (56.3)	8.62 (65.1)	18.3 (78.0)	27.8 (78.8)	38.3 (82.5)	59.1 (84.1)	79.6 (80.1)	129 (68.1)	236 (56.7)	236 (56.7)
ARS-1 1.0 mg + Challenge Agent	20.0 (2.50 - 45.0)	1840 (69.1)	19.9 (99.7)	54.2 (106)	93.7 (93.5)	133 (89.0)	213 (90.5)	295 (91.3)	491 (76.8)	840 (65.7)	840 (65.7)
Challenge Agent + Placebo	15.0 (2.50- 45.0)	473 (91.3)	9.87 (48.0)	22.3 (61.3)	34.8 (74.3)	47.7 (79.8)	72.5 (77.3)	96.5 (77.3)	138 (73.8)	200 (67.9)	200 (67.9)

In both anaesthetised and conscious animals, anaphylaxis potentiated the absorption of epinephrine relative to animals that were not in anaphylaxis.

Study 1021-4072

The applicant conducted a GLP pharmacokinetics study to evaluate the pharmacokinetics of ARS-1 after administration with and without anaphylaxis conditions using male (10) and female (4) beagle dogs. The study was a two-way crossover study, the animals were administered ARS-1 1 mg intranasal (IN) with and without anaphylaxis induction. Treatments were separated by a seven-day washout period. More pronounced absorption of intranasal epinephrine was reported in animals with anaphylaxis at earlier timepoints compared to animals without anaphylaxis.

Pharmacokinetic results

Pre-dose epinephrine concentrations are presented in Table 4. Post-dose PK parameters for both observed (total) epinephrine concentrations as well as baseline-adjusted concentrations are presented in Table 5. Epinephrine concentrations by time are presented in Table 6. Baseline epinephrine levels one hour prior to induction of anaphylaxis were similar between the two groups (56.4 pg/mL versus 56.2 pg/mL). Epinephrine levels increased markedly after induction of anaphylaxis, with this increase most likely due to the stress from anaphylaxis. After baseline adjustment, anaphylaxis resulted in higher maximum concentrations relative to the normal state (geometric mean C_{max} of 1930 pg/mL versus 998 pg/mL for baseline-adjusted concentrations) and higher overall exposure (geometric mean AUC₀₋₄₅ values of 51800 min*pg/mL versus 25300 min*pg/mL). The higher epinephrine concentrations during anaphylaxis relative to the normal state were most pronounced during the early timepoints, suggesting that anaphylaxis increases the rate of epinephrine absorption. Similar trends were noted for the observed epinephrine data, without baseline adjustment.

Table 4 Pre-Dose Epinephrine Concentrations

Group	Pre-Dose Epinephrine Concentrations (pg/mL) Geo. mean	
	-60.0 minutes	-3.00 minutes
Normal State	56.2	50.0
Anaphylaxis	56.4	274

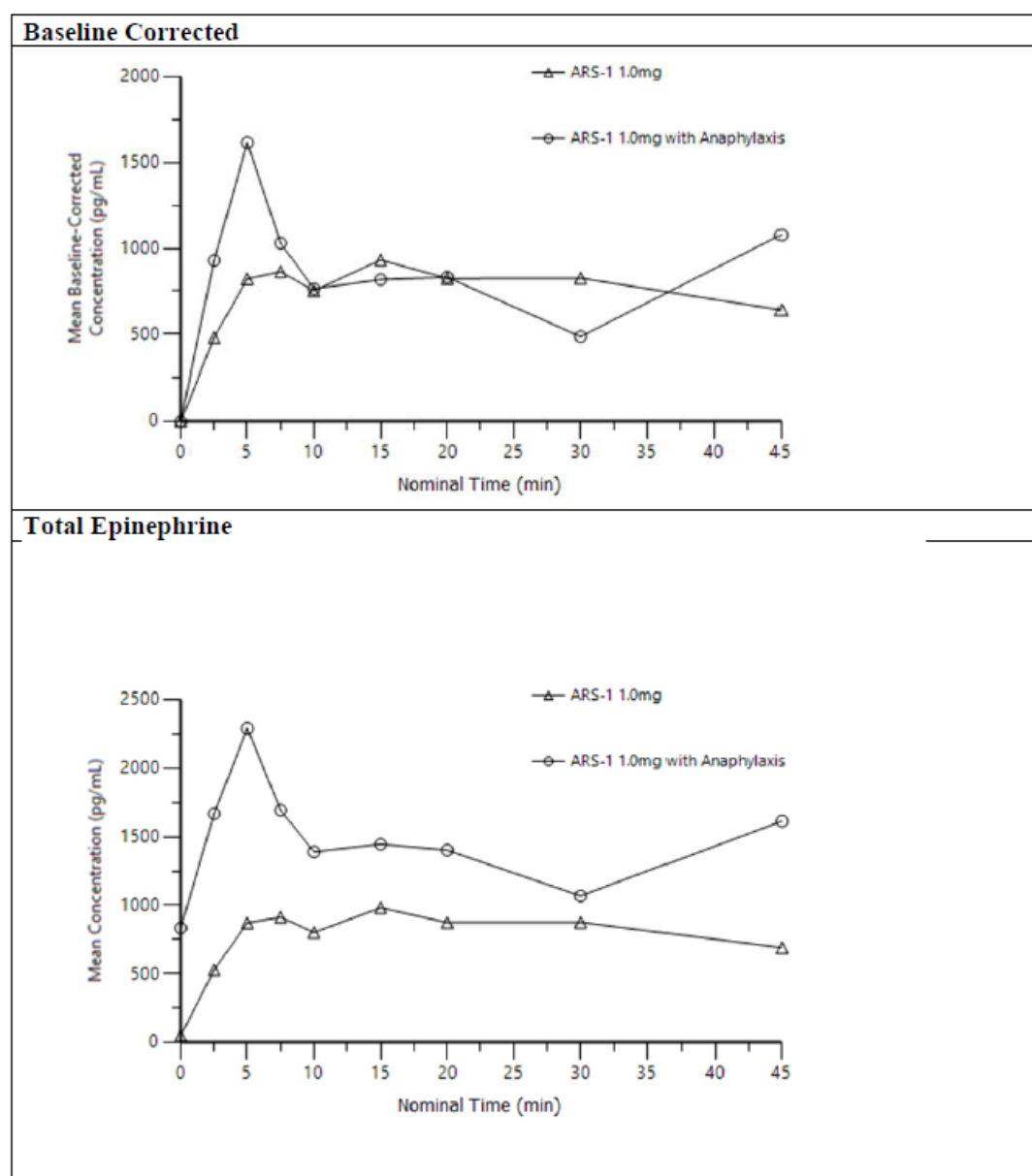
Table 5 Pharmacokinetic Parameters of Epinephrine Following Administration of ARS-1 1 mg

Group	Pharmacokinetic Parameter										
	T _{max} (min) median (range)	C _{max} (pg/mL) geo. mean (geo. CV%)	AUC (h*pg/mL) geo. mean (geo. CV%)								
			AUC 0-1.5	AUC 0-5	AUC 0-7.5	AUC 0-10	AUC 0-15	AUC 0-20	AUC 0-30	AUC 0-45	AUC last
Baseline Adjusted Parameters											
Anaphylaxis	5.00 (2.50 – 45.0)	2420 (169)	NC	NC	4840 (730)	8810 (354)	15500 (179)	25900 (116)	37800 (91.8)	59400 (58.0)	28900 (267)
Anaphylaxis, excluding Subject 1101A	10.0 (2.50 – 45.0)	1930 (107)	NC	NC	3710 (527)	6660 (244)	12200 (117)	20800 (72.1)	31500 (60.2)	51800 (34.5)	24600 (239)
Normal State	7.50 (2.50 – 45.0)	998 (126)	NC	1600 (141)	3190 (124)	4680 (120)	7970 (114)	11400 (114)	17400 (118)	25300 (121)	24300 (144)
Observed (Total) Epinephrine Parameters											
Anaphylaxis	5.00 (0.00 – 45.0)	3420 (109)	2710 (195)	7330 (169)	11600 (153)	15200 (145)	22800 (119)	30600 (98.4)	43300 (84.7)	64800 (65.6)	64800 (65.6)
Anaphylaxis, excluding Subject 1101A	5.00 (0.00 – 45.0)	2850 (63.6)	2170 (127)	5980 (114)	9680 (110)	12700 (104)	19300 (84.5)	26400 (70.2)	38100 (63.4)	58400 (50.6)	58400 (50.6)
Normal State	7.50 (2.50 – 45.0)	1080 (107)	590 (83.8)	2000 (90.8)	3760 (92.3)	5430 (92.9)	9090 (90.7)	12900 (91.6)	19600 (94.9)	28700 (96.9)	27400 (117)

Table 6 Epinephrine Concentration-Time Profiles by Treatment

Group	Epinephrine Concentration (pg/ml) Mean (SD)								
	0.00 minutes	2.50 minutes	5.00 minutes	7.50 minutes	10.0 minutes	15.0 minutes	20.0 minutes	30.0 minutes	45.0 minutes
Baseline Adjusted Parameters									
Anaphylaxis	0.00 (0.00)	3430 (9380)	1960 (2430)	1610 (2520)	1630 (3370)	833 (830)	872 (913)	449 (508)	1010 (1380)
Anaphylaxis, excluding Subject 1101A	0.00 (0.00)	929 (858)	1620 (2160)	1030 (1310)	764 (966)	818 (862)	831 (937)	486 (512)	1080 (1420)
Normal State	0.00 (0.00)	480 (347)	822 (546)	864 (676)	753 (547)	933 (626)	825 (688)	827 (641)	641 (488)
Observed (Total) Epinephrine Parameters									
Anaphylaxis	862 (1210)	4200 (9510)	2670 (2410)	2310 (2620)	2300 (3510)	1500 (847)	1490 (815)	1060 (562)	1600 (1280)
Anaphylaxis, excluding Subject 1101A	835 (1260)	1670 (948)	2290 (2030)	1690 (1250)	1390 (925)	1450 (853)	1400 (778)	1070 (587)	1610 (1330)
Normal State	50.0 (0.00)	530 (347)	872 (546)	914 (676)	803 (547)	983 (626)	875 (688)	877 (641)	691 (488)

Figure 2 Concentration-Time Curves



For both observed (total) and baseline-adjusted concentrations, absorption of intranasal epinephrine from Eurneffy was more pronounced following anaphylaxis induction, resulting in higher epinephrine concentrations, particularly at earlier timepoints. Overall exposure (AUC₀₋₄₅) was also increased during anaphylaxis.

During anaphylaxis induction, animals experienced the range of symptoms typically associated with anaphylaxis, including significant hypotension, increased histamine levels, and facial oedema.

These results confirm that epinephrine can be delivered intranasally by the Eurneffy formulation, even during the severe hypotension that occurs with anaphylaxis. Anaphylaxis also appeared to increase the rate of epinephrine absorption in some animals, which may be due to the facial (i.e., nasal) oedema that is associated with the anaphylactic event.

Induction of anaphylaxis resulted in an unexpected and relevant decrease in adrenaline plasma levels in the anaphylaxis group compared with the normal state in females (C_{max} were 1120 pg/mL vs. 1712.5 pg/mL; mean AUC_{last} values were 17153.3 min*pg/mL vs. 44975 min*pg/mL).

Moreover, at 3 minutes prior to dosing (4 minutes after induction of anaphylaxis), baseline levels of adrenaline were higher in the females than in the males (240 pg/mL for males (n=10) and 2415 pg/mL for females (n=4)).

Significant differences were observed between female and male in absorption of intranasal epinephrine following anaphylaxis induction. However, it was clarified that differences between female and male animals in the dog anaphylaxis model were due to small number of animals and due to differences in the tolerance of the induction agent, Tween-80, between male and female animals as well as in differences in baseline adrenaline levels prior to dosing.

2.5.4. Toxicology

The toxicological profile of ARS-1 has been evaluated after intranasal and ocular exposure. The single-dose toxicity study was conducted in rats, ocular tolerability study was performed in rabbits.

In addition, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity and local tolerance studies have been conducted to evaluate the toxicological profile of DDM.

ARS-1

The applicant conducted a single dose toxicity study (GLP) to evaluate the toxicity and toxicokinetics of ARS-1 following intranasal administration in the rat model. A single intranasal administration of ARS-1 at a dose up to 0.8 mg was not associated with any mortality or relevant clinical observations.

Several microscopic changes in the nose and nasal passages were observed, which were considered related to trauma and independent of the ARS-1 administration. No treatment related changes in olfactory mucosa were observed. Based on the results, a NOAEL of 0.8 mg administered as a single intranasal instillation has been established in the rat, which corresponds to a dose of 4 mg/kg.

In addition, a non-GLP Study 2555-004 was conducted to investigate the ocular tolerability of ARS-1 following instillation in the eyes of rabbits, as requested by the CHMP in the SA. No significant findings on ophthalmological examination were shown. ARS-1 was well tolerated based on indirect ophthalmoscopy, slit-lamp biomicroscopy and Modified Hackett-McDonald Scoring. Repeat-dose toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity data were provided from the literature.

DDM excipient

Dodecylmaltoside (DDM) is a novel excipient in the EU. However, it is an approved excipient in the US FDA database of inactive ingredients. GLP toxicology studies were conducted to determine the safety profiles in mice, rats, Guinea pigs, rabbits, dogs, and monkeys. The toxicology evaluation of DDM was conducted in accordance with applicable CHMP guidelines.

Intranasal administration of n-Dodecyl-13-D-maltoside once every other day for approximately two weeks was associated with inflammation in the nasal cavity of rats at doses of 200 and 400 µg/dose. The inflammation was characterised by an accumulation of fluid and neutrophils in the nasal cavity. In some animals, focal areas of epithelial hyperplasia, degeneration and/or necrosis were present as a change secondary to the inflammation. All evidence of inflammation in the nasal cavity resolved during a two-week recovery period.

Based on the results of this study, a no observed effect level (NOEL) of 80 µg of DDM per dose for seven total intranasal administrations over a two-week period was established.

In order to investigate the potential acute toxicity of dodecylmaltoside and to determine suitable dose levels for a future 28-day repeat dose study in rats, following dosing by 24-hour intravenous infusion on Days 1 and 8 was performed. The study showed that two doses of dodecylmaltoside, administered once weekly in rats by 24-hour intravenous infusion at dose levels of 0.86, 3 and 10 mg/kg/dose were well tolerated. No changes were observed in clinical condition, body weight, clinical or gross pathology parameters examined. Therefore, dose levels of up to 10 mg/kg/dose (0.139 mg/mL) were considered suitable for a future 28-day repeat dose study.

Dodecylmaltoside toxicity was investigated following once weekly 24 hours continuous intravenous infusion over a span of 12 weeks, with a dosing holiday between Weeks 4 to 10 (doses scheduled on Days 1, 8, 15, 22, 71, 78, and 85) in Beagle dogs. The maximum tolerated dose (MTD) via intravenous infusion was identified at 400 mg/kg based on occurrence of increased total bilirubin and red/brown urine at this dose level.

A GLP study conducted to evaluate the local tolerance of DDM following daily intranasal administration by nasal spray to male Beagle dogs for 13 weeks did not reveal any article related histopathologic changes. The NOEL was estimated 330 µg/day (equivalent to 3 µg/cm²/animal) for daily intranasal administration of DDM to dogs for 13 weeks.

Dodecylmaltoside did not show any evidence of genotoxic activity in *in vitro* bacterial mutation test and in *in vitro* chromosome aberration test when tested in accordance with regulatory guidelines.

Moreover, no evidence of genotoxic activity in *in vivo* test for induction of chromosome damage was demonstrated in a GLP rat bone marrow micronucleus test. 24-hour continuous infusion to the pregnant rat during organogenesis (Days 6 to 17 of gestation) at the dose level of 30 mg/kg/day, was well tolerated. DDM was not associated with any maternal changes or embryo-fetal toxicity. The NOAEL was estimated at 30 mg/kg/day.

No evidence of carcinogenicity associated with prolonged intranasal administration of DDM in rat was observed. Minimal to slight in severity squamous metaplasia of the transitional and/or respiratory epithelium in the rostral nasal cavity and nasopharynx, inflammation and exudate in the nasal cavity, and squamous cell hyperplasia in the nose/nares were observed. However, these changes can be considered adaptive changes to local irritation. No local or systemic neoplastic findings were induced by DDM.

Based on the results of a GLP studies conducted in Guinea pigs and Rabbits, DDM was not considered to be a skin sensitiser. DDM was well tolerated with minimal to marked subacute inflammation seen histologically at the injection sites.

In conclusion, the Eurneffy formulation contains 0.275% (0.0275 mg/100 µL) of DDM. The calculated safety margins based on a rat No Observable Effect Level (NOEL) of 80 µg/day and a dog NOEL of 330 µg/day for DDM are provided in the table below.

Table 7 Dodecylmaltoside Safety Margins Based on Current Eurneffy 2 mg formulation

Species	NOEL	Human Equivalent Dose (HED)	DDM Safety Margins
Rat	0.32 mg/kg (80 µg/day)	0.05 mg/kg	6 – 11-fold
Dog	0.036 mg/kg (330 µg/day)	0.02 mg/kg	2 – 4-fold
Human		0.0045 - 0.009 mg/kg (0.275 mg/spray)	

Impurities

The impurities and degradants profile of adrenaline formulated for intranasal administration are in accordance with the ICH guidelines and Ph.Eur./USP/BP monograph. The impurities present in the product do not impend over the safety of the medicinal product.

2.5.5. Ecotoxicity / environmental risk assessment

Adrenaline PEC surface water 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. Therefore, adrenaline is not expected to pose a risk to the environment.

Table 8 provides the main study results of the environmental risk assessment.

Table 8 Summary of main study results

Substance (INN/ Invented Name): Eurneffy			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K _{ow}	OECD107	-0.82 -0.43 -1.37 -1.2 -2.59 -1.37	Potential PBT (No)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K _{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)		0.00001718 µg / L	> 0.01 threshold (Yes)
Other concerns (e.g. chemical class)			(No)
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Adsorption-Desorption	OECD 106 or ...	K _{oc} =	List all values

Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water} = DT _{50, sediment} = DT _{50, whole system} = % shifting to sediment =			Not required if readily biodegradable
<i>Phase IIa Effect studies</i>					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC		µg/L	Species
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/ <i>Species</i>	OECD 210	NOEC		µg/L	Species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
<i>Phase IIb Studies</i>					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO ₂			for all 4 soils
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/ <i>Species</i>	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	Species

2.5.6. Discussion on non-clinical aspects

Pharmacology

The applicant conducted two non-clinical studies to evaluate the cardiovascular effect of adrenaline nasal spray after administration with and without anaphylaxis conditions in beagle dogs. Animals exposed to Tween 80 experienced the range of symptoms typically associated with anaphylaxis, including hypotension, increased histamine levels, and general redness and swelling. Lower increase in heart rate changes were observed after co-administration of Tween 80 with ARS-1 compared to ARS-1 with saline. However, after 30 to 60 minutes after adrenaline administration, SBP achieved pre-induction levels.

No secondary nor safety pharmacology studies have been undertaken by the applicant. The data are based on literature and clinical use. However, cardiovascular telemetry studies in conscious and anaesthetised dogs with and without anaphylaxis conditions were conducted as part of the primary pharmacodynamic assessment.

Altogether the data in beagle dogs show a very high inter-animal variability especially in male dogs. Clinical signs of elevated histamine levels, significant hypotension, facial oedema confirms the induction of anaphylaxis in dogs using Tween-80 as a challenge agent. However, the effect of ARS-1 on cardiovascular parameters was inconsistent. Despite that efficacy of Eurneffy could not be confirmed in anaphylaxis Beagle dog model, the pharmacokinetics has been demonstrated and that was the primary objective of the study.

A reduced non-clinical programme has been conducted by the applicant. No secondary pharmacology, PK distribution, excretion and pharmacokinetic drug interactions studies have been performed by the applicant. Considering clinical history of use of adrenaline and the guideline on the Non-Clinical

Documentation for Mixed Marketing Authorisation Applications the proposed non-clinical development programme is acceptable to the CHMP.

Pharmacokinetics

The applicant evaluated the pharmacokinetic profile of different formulations of ARS-1 (aqueous and non-aqueous) with and without DDM in four studies. ARS-1 with 0.25% DDM administered intranasally in rats exhibited the greatest absorption amongst the three formulations tested. The optimal ARS-1 formulation containing 0.25% DDM exhibited a relative bioavailability of 80.2% compared to adrenaline injection administered intramuscularly.

The applicant conducted two pharmacokinetics studies (one pilot non-GLP study and one GLP study) to evaluate the pharmacokinetics of ARS-1 after administration with and without anaphylaxis conditions in Beagle dogs. More pronounced absorption of intranasal epinephrine was reported in animals with anaphylaxis at earlier timepoints compared to animals without anaphylaxis.

Significant differences were observed between female and male in absorption of intranasal epinephrine following anaphylaxis induction. However, it was clarified that differences between female and male animals in the dog anaphylaxis model were due to small number of animals and due to differences in the tolerance of the induction agent, Tween-80, between male and female animals as well as in differences in baseline adrenaline levels prior to dosing. See also discussion 2.6.3. on clinical pharmacology.

An *in vitro* metabolism study was conducted to demonstrate that nasal mucosa does not significantly impact the metabolism of adrenaline by exploring the difference between degradation with or without enzyme inhibitors. The study showed that adrenaline was degraded not due to the CYP enzymes but due to the experimental system. No formation of noradrenaline was observed.

Single dose study in rats showed that 0.25% DDM ensures a higher bioavailability (165%) comparing to that of IV adrenaline. The bioavailability was twice higher than for the formulation without DDM added. The absorption results in rats indicate that the use of 0.125% DDM decreases AUC, C_{max} and bioavailability comparing to a formulation where DDM is not added. It is agreed with the applicant that intranasal absorption of adrenalin in rats is not fully comparable to the absorption in humans as rats exert a higher absorption even in the absence of DDM, which is not the case for humans. 0.25% DDM is confirmed as a suitable concentration for the improvement of absorption in other already approved intranasal products.

Toxicology

The toxicological profile of ARS-1 has been evaluated after intranasal and ocular exposure. The single-dose toxicity study was conducted in rats, ocular tolerability study was performed in rabbits.

A single intranasal administration of ARS-1 at a dose up to 0.8mg was not associated with any mortality or relevant clinical observations.

Several microscopic changes in the nose and nasal passages were observed, which were considered related to trauma and independent of the ARS-1 administration. No treatment related changes in olfactory mucosa were observed. Based on the results, a NOAEL of 0.8 mg administered as a single intranasal instillation has been established in the rat, which corresponds to a dose of 4 mg/kg.

In addition, a non-GLP Study 2555-004 was conducted to investigate the ocular tolerability of ARS-1 following instillation in the eyes of rabbits, as requested by the CHMP in the Scientific Advice. No significant findings on ophthalmological examination were shown. ARS-1 was well tolerated based on indirect ophthalmoscopy, slit-lamp biomicroscopy and Modified Hackett-McDonald Scoring.

Additional data from literature

Repeat-dose toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity data were provided from the literature. Adrenaline is an endogenous substance and is intended to be used in the acute treatment of severe allergic reactions. This is considered acceptable for the current application, given the clinical use history of adrenaline. The applicant did not provide animal data on the effects of adrenaline in lactation. However, it can be assumed that well-indicated use of adrenaline in nursing mothers should not present any significant risk to the offspring, since pharmacologically active plasma concentrations are not achieved by the oral route.

DDM

The ARS-1 formulation contains 0.275% dodecylmaltoside (DDM) (0.025 mg/100 microliter) a novel excipient in the EU. GLP toxicology studies were conducted to determine the safety profiles in mice, rats, Guinea pigs, rabbits, dogs, and monkeys. The toxicology evaluation of DDM was conducted in accordance with applicable CHMP guidelines.

Intranasal administration of n-Dodecyl-13-D-maltoside once every other day for approximately two weeks was associated with inflammation in the nasal cavity of rats at doses of 200 and 400 µg/dose. A no observed effect level (NOEL) of 80 µg of DDM per dose for seven total intranasal administrations over a two-week period was established.

The study showed that two doses of dodecylmaltoside administered once weekly in rats by 24-hour intravenous infusion at dose levels of 0.86, 3 and 10 mg/kg/dose were well tolerated. No changes were observed in clinical condition, body weight, clinical or gross pathology parameters examined. Therefore, dose levels of up to 10 mg/kg/dose (0.139 mg/mL) were considered suitable for a future 28-day repeat dose study.

Another study aimed to investigate the potential toxicity of dodecylmaltoside following once weekly 24 hours continuous intravenous infusion over a span of 12 weeks, with a dosing holiday between Weeks 4 to 10 (doses scheduled on Days 1, 8, 15, 22, 71, 78, and 85) in Beagle dogs, showed that the MTD via intravenous infusion was identified at 400 mg/kg.

A GLP study conducted to evaluate the local tolerance of DDM following daily intranasal administration by nasal spray to male Beagle dogs for 13 weeks did not reveal any article related histopathologic changes. The NOEL was estimated at 330 µg/day (equivalent to 3 µg/cm²/animal) for daily intranasal administration of DDM to dogs for 13 weeks.

Dodecylmaltoside did not show any evidence of genotoxic potential based on *in vitro* bacterial mutation test, *in vitro* chromosome aberration test and *in vivo* test for induction of chromosome damage in a GLP rat bone marrow micronucleus test. DDM was not associated with any maternal changes or embryo-fetal toxicity. The NOAEL was estimated at 30 mg/kg/day.

No evidence of carcinogenicity associated with prolonged intranasal administration of DDM in rat was observed. Minimal to slight in severity squamous metaplasia of the transitional and/or respiratory epithelium in the rostral nasal cavity and nasopharynx, inflammation and exudate in the nasal cavity, and squamous cell hyperplasia in the nose/nares were observed. However, these changes can be considered adaptive changes to local irritation. No local or systemic neoplastic findings were induced by DDM.

DDM was not considered to be a skin sensitiser and was well tolerated with minimal to marked subacute inflammation seen histologically at the injection sites.

ERA

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.

2.5.7. Conclusion on the non-clinical aspects

Nonclinical data carried out on Eurneffy formulation and on adrenaline based on scientific literature, are acceptable to support an authorisation in adults and children above 30 kgs. The section 5.3 of the SmPC is acceptable.

Eurneffy is considered approvable for a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

2.6.2. Clinical pharmacology

Tabular overview of clinical studies

Study Identifier	Type of study	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	Study Status; Type of Report
EPI 10	PK/PD	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 0.65 mg ARS 1.0 mg ARS 2.0 mg	57 (at the time of interim analysis)	Paediatric subjects with Type I allergies	Ongoing; Interim CSR
EPI 15	PK/PD	To assess the comparative bioavailability of epinephrine after ARS-1 (2.0 mg), EpiPen 0.3 mg, and epinephrine and IM injection 0.3 mg in healthy volunteers. To evaluate the comparative PD response	Phase 1, two-part, six-treatment, six-period, single and repeat dose, crossover study	Part 1 Single dose of ARS-1 2.0 mg Single dose of EpiPen 0.3 mg Single dose of IM epinephrine 0.3 mg Part 2 Two doses of ARS-1 2.0 mg, both in the right naris, spaced 10 minutes apart Two doses of ARS-1 2.0 mg, one in the left and one in the right nares, spaced 10 minutes apart, Two doses of EpiPen 0.3 mg in the left and right anterolateral thigh, 10 minutes apart.	59	Healthy subjects	Completed CSR
EPI 16	PK/PD	To assess the comparative	Phase 1, four-treatment,	ARS-1 2.0 mg IM Epinephrine 0.3	36	Subjects with history of	Completed

		bioavailability of epinephrine after ARS-1 2.0 mg, EpiPen 0.3 mg, and IM epinephrine 0.3 mg epinephrine in healthy volunteers. To evaluate the comparative PD response	partially randomised, crossover study	mg IM Epinephrine 0.5 mg ARS-1 2.0 mg after nasal challenge.		allergic rhinitis	CSR
EPI 17	PK/PD	To assess the comparative bioavailability of epinephrine after self-administration of ARS-1 2.0 mg or study staff-administered IM injection in subjects with Type I allergies To evaluate the comparative PD response	Phase 1, single-dose, two-treatment, two-period, randomised crossover study	ARS-1 2.0 mg, self-administered IM epinephrine injection 0.3 mg, study staff-administered	42	Subjects with Type I allergies	Completed CSR
EPI 18	PK/PD	To evaluate the comparative PK and PD of two doses of Eurneffy 2.0 mg with IM 0.3 mg under allergic rhinitis conditions compared to two dose administration under normal conditions.	Phase 1, five-treatment period, randomised, cross-over study in Type 1 allergy patients.	Normal Nasal Conditions Two doses of Eurneffy 2.0 mg in the right and left naris Two doses of IM 0.3 mg in the right and left anterolateral thigh Rhinitis Conditions Two doses of IM 0.3 mg in the right and left anterolateral thigh Two doses of Eurneffy 2.0 mg in the right and left naris Two doses of Eurneffy 2.0 mg, both in the right naris	43	Type 1 allergy patients	Completed; CSR
Pilot and Supportive studies							
EPI 02	PK	Part 1: PK dose proportionality of three concentrations of ARS-1; Part 2: To assess the comparative bioavailability of ARS-1 and IM epinephrine injection	Phase 1, randomised, open-label 3-treatment dose-escalation followed by 2 randomised, open-label, single-dose, 2-treatment, 2-period crossover studies	Part 1: ARS-1 IN, 0.5 mg, 1 mg and 2 mg Part 2: ARS-1 IN, 1 mg Epinephrine IM, 0.3 mg Part 3 ARS-1 IN, 1 mg Epinephrine IM, 0.3 mg	3 12 12	Healthy subjects	Completed CSR
EPI 03	PK	To assess the PK and PD of ARS-1 dosed once and twice, compared to IM epinephrine injection dosed once and twice with continuous EKG monitoring	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	ARS-1 IN, 1 mg ARS-1 IN, 1 mg, twice Epinephrine IM, 0.3 mg Epinephrine IM, 0.3 mg, twice Epinephrine IM, 0.5 mg	70	Healthy subjects	Completed CSR

EPI 04	PK	To assess the comparative bioavailability of ARS-1 dosed once to evaluate the impact of nasal oedema and congestion; comparative bioavailability with epinephrine IM and SC.	Phase 1, randomised, single-dose, 5-period, partial cross-over study	ARS-1 IN, 1 mg ARS-1 IN, 1 mg, Rhinitis Epinephrine IM, 0.3 mg Epinephrine SC, 0.3 mg Epinephrine IM, 0.5 mg	36	Allergy Patients	Completed CSR
EPI 07	PK	To assess the PK and PD of ARS-1 dosed once and twice compared with EpiPen dosed once and twice.	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	ARS-1 IN, 1 mg (L nostril) ARS-1 IN, 1 mg, twice (L/R) ARS-1 IN, 1 mg, twice (L/L) EpiPen 0.3 mg (L thigh) EpiPen 0.3 mg, twice (L/R)	36	Healthy subjects	Completed CSR
EPI 12	PK/PD	To assess the comparative bioavailability of epinephrine after self-administration of ARS-1 (1 milligrams (mg); 0.25% DDM), ARS-1 (1 mg; 0.35% DDM), EpiPen (0.3 mg epinephrine auto-injector) and Symjepi (0.3 mg epinephrine pre-filled syringe) after self-administration by subjects who have Type I allergy conditions.	Phase1, Randomised crossover, self-administration study	ARS-1 1 mg 0.25% ARS-1 1 mg 0.35% EpiPen 0.3 mg Symjepi 0.3 mg	36	Subjects with Type I allergies	Completed; CSR

2.6.2.1. Pharmacokinetics

2.6.2.1.1. Methods

Two validation methods for epinephrine determination were developed:

1. in bufferised human plasma using LC-MS/MS and
2. in human acidified K2-EDTA plasma by LC-MS-MS.

During the validation process, all parameters recommended for assessment according to guideline for bioanalytical methods (EMA/CHMP/ICH/172948/2019) were assessed during validation and all of them were acceptable.

Pharmacokinetic data analysis

The following PK studies were conducted and considered pivotal by the applicant.

EPI 10 study: A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Paediatric Subjects with Systemic Allergies.

Primary objectives: to assess the PKs of epinephrine after IN administration of 0.65 milligram (mg,) 1.0 mg, or 2.0 mg dose of ARS- 1 in paediatric allergy subjects; to evaluate the PD response based on PR and BP using an automated blood pressure monitoring (ABPM) device after IN administration of

0.65 mg, 1.0 mg, or 2.0 mg dose of ARS-1 in paediatric allergy subjects.

Secondary objectives:

to evaluate the impact of nasal congestion and rhinitis on the PKs of ARS-1 in paediatric subjects and to evaluate the safety and tolerability of ARS-1 in paediatric allergy subjects

Pharmacokinetic (PK) Assessments: Blood samples were collected at pre-dose each treatment period (at -10 and -5 minutes) and at 2.5, 5, 7.5, 10, 12.5, 15, 20, 30, 45, 60, 90, and 120 minutes after dosing. The PK parameters were calculated without the subtraction of the pre-dose epinephrine concentrations. The rationale for using epinephrine plasma levels without subtraction of the baseline values was based on both clinical and PK considerations. First, the endogenous levels of epinephrine change based on both the diurnal cycle and due to stimuli. Second, clinically, the absolute plasma levels (e.g., 100 pg/mL) are considered more important to illicit an efficacious response.

The following PK parameters for epinephrine will be calculated using non-compartmental analysis for each group based on body weight category (15 kg to <30 kg, or ≥ 30 kg body weight) and dose (0.65 mg, 1.0 mg, or 2.0 mg): C_{max}, t_{max}, AUC(0-t), Partial AUC values for each time point for the first 20 minutes after administration of study medication [AUC(0-2.5min), AUC(0-5min), AUC(0-7.5min), AUC(0-10min), AUC(0-12.5min), AUC(0-15min), AUC(0-20min)].

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

Objectives

The primary objectives of this study were:

- to assess the comparative bioavailability of epinephrine after intranasal (IN) administration of ARS-1 (2.0 mg) with EpiPen 0.3 mg epinephrine and intramuscular (IM) injection 0.3 mg epinephrine (needle and syringe) in healthy volunteers under fasted conditions.
- to evaluate the comparative pharmacodynamic (PD) response between products and doses based on Systolic blood pressure (SBP), Diastolic blood pressure (DBP), and pulse rate (PR) using an automated blood pressure monitoring (ABPM) device between treatment groups.

The secondary objectives of this study were:

- to assess the relative bioavailability of two doses of ARS-1 (2.0 mg IN) given as in the right and left nares, as compared to two doses in the right naris.
- to evaluate the safety and tolerability of ARS-1 and EpiPen in healthy volunteers

Pharmacokinetic Assessments

Blood samples were collected at pre-dose each treatment period (at -10 and -5 minutes) for at least 20 minutes, and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240 and 360 minutes after dosing.

The following PK parameters for epinephrine were calculated using noncompartmental analysis: C_{max}, T_{max}, AUC_{0-xmin}: Area under the plasma concentration-time curve from time-zero to x min post dose, where x is every post-dose time point through 60 min (i.e., 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, and 60 min), AUC_{0-120min}, AUC_{60-360min}, AUClast, Clast, Tlast, T₁₀₀: Time (min) after dosing to reach concentration of 100 pg/mL, T_{>100}: Time (min) duration for concentrations >100 pg/mL, T_{>100 60min}: Time (min) duration for concentrations > 100pg/mL within 60 min of dosing, T₅₀: Time (min) after dosing to reach concentration of 50 pg/mL, T_{>50}: Time (min) duration for concentrations

>50 pg/mL, T>50-60min: Time (min) duration for concentrations > 50pg/mL within 60 min of dosing.

EPI 16 study: A Four-Treatment, Partially Randomized, Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis.

The objectives of this study were as follows:

Primary objective:

- to evaluate the comparative bioavailability after intranasal (IN) administration of a 2 mg dose of ARS-1 in subjects with and without induced allergic rhinitis (nasal challenge) and to evaluate the impact of nasal oedema and congestion on the absorption of epinephrine.

Secondary objectives:

- to evaluate the comparative bioavailability of ARS-1 and IM epinephrine injection when administered in subjects under normal conditions.
- to evaluate the safety and tolerability of ARS-1 in subjects after IN administration of epinephrine as compared to the IM epinephrine administration

Pharmacokinetic Assessments

Blood samples were collected at pre-dose each treatment period (at -10 and -5 minutes) for at least 20 minutes, and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240, and 360 minutes after dosing.

The following PK parameters for epinephrine were calculated using non-compartmental analysis: C_{max}, T_{max}, AUC(0-t), AUC(0-60min), AUC_{0-xmin}: Area under the plasma concentration-time curve for the first 20 minutes after administration of study medication [AUC(0-2min), AUC(0-4min), AUC(0-6min), AUC(0-8min), AUC(0-10min), AUC(0-12.5min), AUC(0-15min), AUC(0- 20min)]. Additional blood samples (4 mL each) for the measurement of plasma concentrations of histamine and chymase levels were collected pre-dose (at -10 minutes) and at 10, 20, and 30 minutes after dosing in Treatment Periods 1 and 4 (ARS-1 dosing).

EPI 17 study: A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self- Administration of Epinephrine with Intranasal ARS-1 as compared to IM injection in Subjects with Type I Allergy.

Objectives

The primary objectives of this study were as follows:

- to assess the comparative bioavailability of epinephrine after self-administration of ARS-1 (2.0 mg IN epinephrine) or study staff-administered intramuscular (IM) injection in subjects who have Type I allergy conditions
- to evaluate the comparative PD response based on systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) using an automated blood pressure monitoring (ABPM) device between the two treatment groups

The secondary endpoints of this study were as follows:

- the dosing error rates with ARS-1 after self-administration
- the pharmacokinetics of ARS-1 following significant dosing errors by subjects who self-administer with ARS-1
- the safety and tolerability of ARS-1 and IM injection

Pharmacokinetic Assessments

Blood samples were collected at -10 and -5 minutes prior to instructing or dosing, and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240, and 360 minutes after dosing.

The following PK parameters for epinephrine was calculated using non-compartmental analysis: C_{max}, T_{max}, AUC(0-x), AUC (0-120), AUC (60-360), AUC(0-t), AUC (0-360).

The following PK parameters for epinephrine was calculated using non-compartmental analysis: C_{max}, T_{max}, AUC(0-x): partial AUC values for each time point for the first 60 minutes after administration, AUC (0-120), AUC (60-360), AUC(0-t), AUC (0-360).

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

Study EPI 18

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

Objectives

The primary objectives of the study were:

- To evaluate the comparative PK of two doses of Eurneffy 2.0 mg with IM 0.3 mg under allergic rhinitis conditions compared to two dose administration under normal conditions.
- To evaluate the comparative PD of two doses of Eurneffy 2.0 mg with IM 0.3 mg based on SBP, DBP and PR using an automated blood pressure measuring (ABPM) device under allergic rhinitis conditions compared to two dose administration under normal conditions.

The secondary objectives of the study were:

- To evaluate the comparative PK/PD relationship of Eurneffy 2 mg after two doses under normal and allergic rhinitis conditions.
- To evaluate the comparative PK/PD relationship of IM 0.3 mg after two doses under normal and allergic rhinitis conditions.
- To evaluate the safety and tolerability of Eurneffy in subjects as compared to IM 0.3 mg.

Study population

Eligible subjects, 18 to 64 years of age, with seasonal allergies (positive case history of seasonal allergic rhinitis related to tree or grass allergens with positive skin prick test within 12 months of enrolment and positive nasal allergen challenge [NAC] with Allergen Panel at Subjects were required to have a Total Nasal Symptom Score (TNSS) of ≥ 5 out of 12 and a congestion score of ≥ 2 out of 3 on at least one test allergen during the screening NAC.

Subjects reporting a TNSS response greater than 2 from the diluent dose were excluded.

Subjects were challenged in both nostrils with escalating (fourfold) increments in allergen at 15-minute (± 5 min) intervals until a positive reaction (i.e., TNSS ≥ 5 out of 12 and a congestion score of ≥ 2 out of 3) was reached. If the subject reached the highest concentration of 1:2 without qualifying, the subject was excluded. Once a positive reaction was confirmed, any further dosing was stopped, and rescue medicine was permitted to be given.

Study design

Treatment Periods 1-2: Normal Nasal Conditions

The PKs of two doses of Eurneffy 2.0 mg were assessed and compared to two doses of IM 0.3 mg, all during normal nasal conditions. Each subject was randomised to receive each of the following

treatments and then crossed over to the other product treatment. The following treatments were administered, separated by a 24-hour washout period.

- Two doses of Eurneffy 2.0 mg in the right and left naris administered 10 minutes apart,
- Two doses of IM 0.3 mg in the right and left anterolateral thigh administered 10 minutes apart.

Treatment Periods 3-5: Rhinitis

The PKs of two doses of Eurneffy 2.0 mg were assessed and compared to two doses of IM 0.3 mg, all following the induction of rhinitis via NAC. The following treatments were administered, separated by a three-week washout period:

- Two doses of IM 0.3 mg in the left and right anterolateral thigh administered 10 minutes apart,
- Two doses of Eurneffy 2.0 mg in the left and right naris administered 10 minutes apart,
- Two doses of Eurneffy 2.0 mg, both in the right naris administered 10 minutes apart.

2.6.2.1.2. Evaluation and qualification of models

A population pharmacokinetic (PPK) and population pharmacokinetic/pharmacodynamics (PPK/PD) was performed. The model was developed based on all results from EPI 03, 04, and 07 with ARS-1 1.0 mg. In addition, the applicant provided an updated popPK model, including data from the Eurneffy 2 mg clinical trials.

Population PK Modelling (POP PK)

The following objectives were addressed:

Objective 1: Pharmacokinetic Modelling for ARS-1 in Adults

- To develop a population PK model to characterise the absorption and disposition of epinephrine in adults after intranasal administration via ARS-1 and intramuscular administration via injection including needle/syringe and EpiPen.
- To identify potential covariates which account for the inter-individual variability (IIV) in ARS-1 PK parameters.

Objective 2: Pharmacokinetics/Pharmacodynamic Modelling of Systolic Blood Pressure (SBP) and Heart Rate (HR)

- To develop a population PK/PD model to characterise relationship of PK of ARS-1, IM with needle/syringe and EpiPen with SBP and HR.
- Various PK metrics including AUC, C_{max}, AUC/C_{max}, t_{max} and others may also be explored to develop this relationship. A time shift between the observed effect and ARS-1 concentrations may be explored using indirect response or indirect link models or involving resolution of any hysteresis.

Objective 3: Simulation of Pharmacokinetics (and PD) of ARS-1 to Determine Dosing in Paediatric Subjects

- Leveraging the pharmacokinetic models of components of ARS-1 using internal (and external data if available), the doses of ARS-1 and optimal PK sampling time in proposed trials in paediatric subjects can be simulated.

The applicant adjusted the iPSP and future planned EPI 10 protocol to include the population of subjects from age 4 to 11 in the younger age group. Hence, simulations will include age groups: 4- <6 y, 6-<12 and 12-18 years.

- Simulate the PK of ARS-1 for the EPI 10 Study.
- Using the PK/PD relationship established in adults, simulate the effect of ARS-1 on SBP and HR in

paediatrics.

Objective 4: Bridging Analysis

- To examine ethnic differences in PK relationships between various epinephrine treatments (formulations / route of administrations) under evaluation via exploratory population PK-based, post hoc analysis.

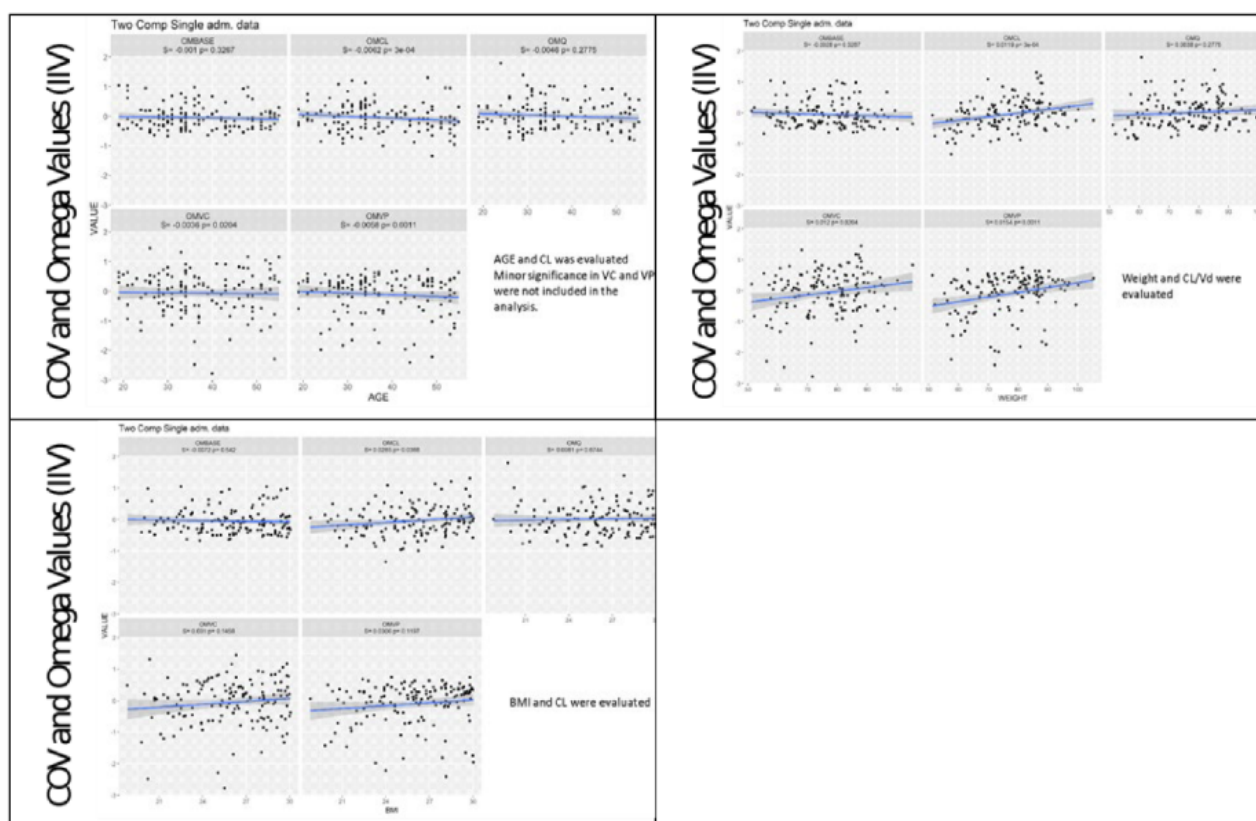
Pharmacokinetic Modelling for ARS-1 in Adults- Base Model

Two-compartment models with absorption compartments for IM, SC, EpiPen, nasal, and nasal administration in rhinitis subjects were developed. Absorption rate constants and relative bioavailability in reference to epinephrine IM/EpiPen injection were evaluated and suggest that ARS-1 nasal and nasal administration in rhinitis patients have a faster absorption as compared to IM/EpiPen or SC administration.

Pharmacokinetic Modelling for ARS-1 in Adults –Covariate Analysis

These analyses suggest that weight may be a more important covariate as compared to either BMI or age based on the graphical analysis and the associated p-values. The data suggests the maximum decline in the objective function was with weight on clearance and hence weight is the covariate that explains most of the variability and is consistent with the graphical analysis.

Figure 3 Relationship between Covariates (continuous) and Inter-individual Variations (omega)

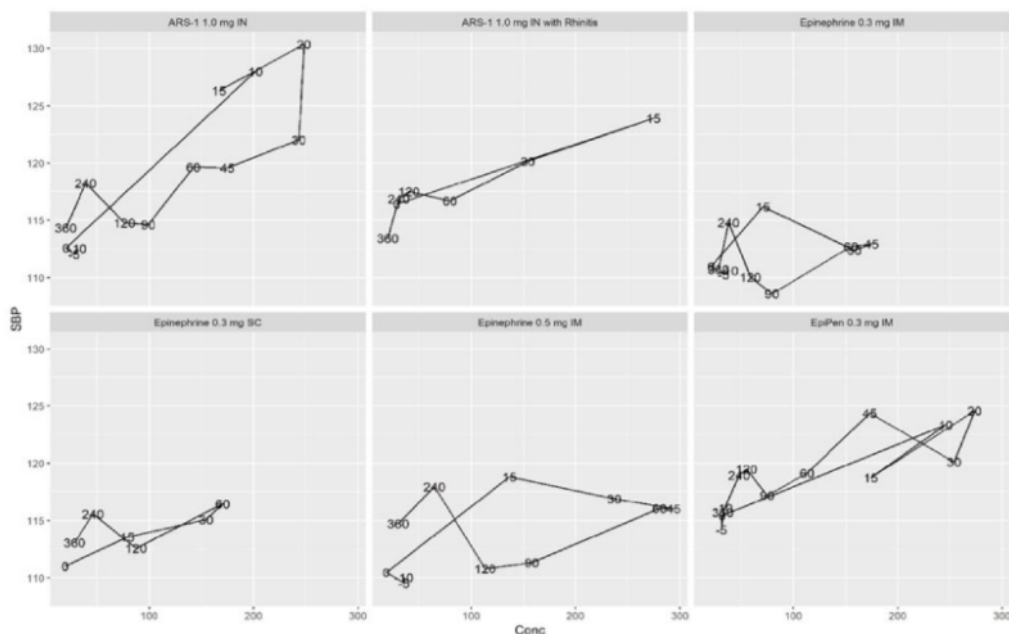


Pharmacokinetics/Pharmacodynamic Modelling of Systolic Blood Pressure

The result of this analysis suggests a potential clockwise hysteresis plot for the relationship between adrenaline concentrations and SBP. This is similar to reports in literature where intragastric administration of morphine in rats can lead to clockwise hysteresis plots between morphine

concentrations and short-lasting pain; this hysteresis is decreased with faster administration of the drug, such as intravenous bolus.

Figure 4 PK/PD data: Epinephrine Concentration and Systolic Blood Pressure (SBP) Plots



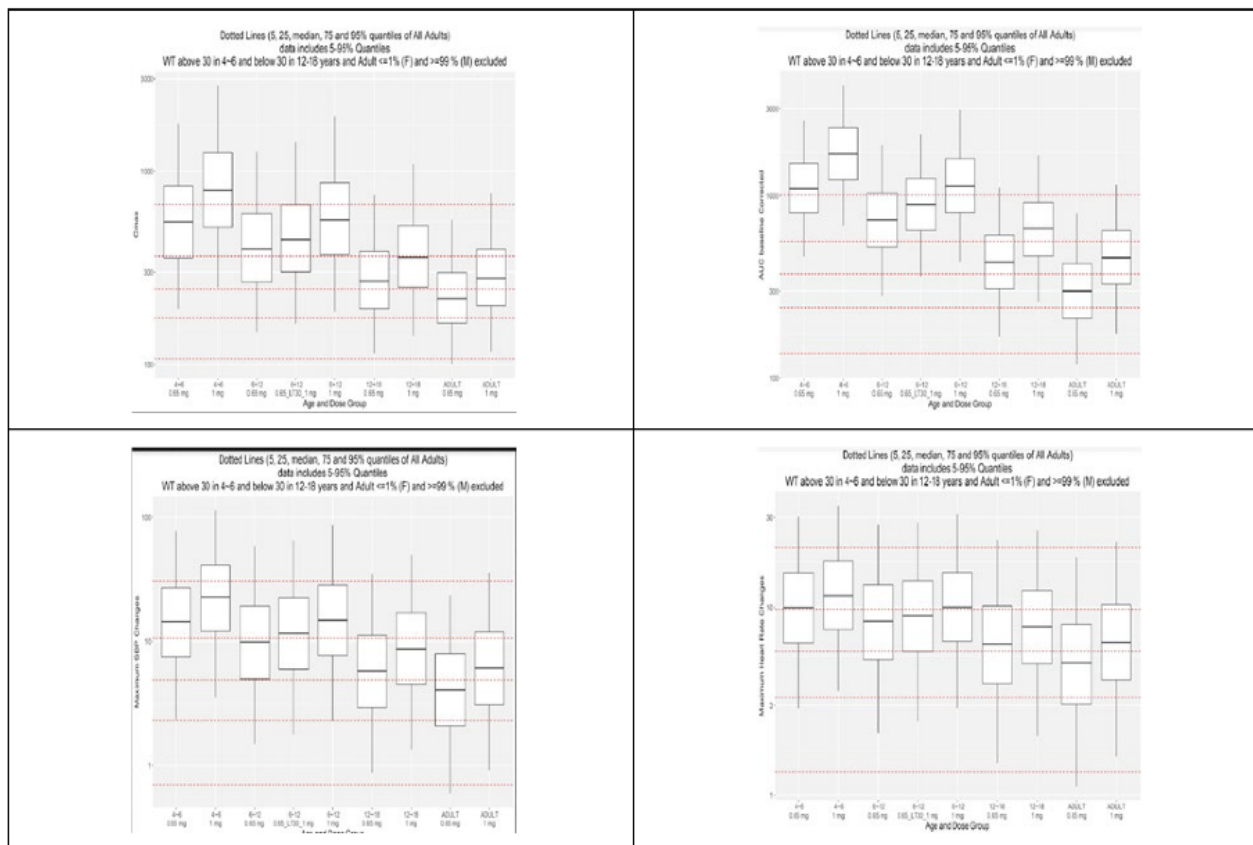
Pharmacokinetics/Pharmacodynamic Modelling of Heart Rate

This analysis suggested a potential clockwise hysteresis plot for the relationship between adrenaline concentrations and HR, but to a much lesser extent than what was observed for SBP.

Simulation of Pharmacokinetics (and PD) of ARS-1 to Determine Dosing in Paediatric Subjects

Paediatric simulations suggest that AUC and C_{max} values overlap with adult AUC and C_{max} values except for the 1 mg dose for the 4 to 6 years age group for both C_{max} and AUC and the 1 mg dose for the 6-12 years age group for AUC, where the overlap is to a lesser extent. Changes in SBP and HR values in the paediatric groups overlap with adult values and thus support that the anticipated response based on these surrogate endpoints should be no different in children than adults.

Figure 5 Simulation of Cmax, AUC, SBP and HR for Paediatric Population



Ethnic Bridging Analysis

Relative bioavailability for Japanese patients is 2.3, 2.17, and 1.0, for IM, EpiPen and Eurneffy respectively, suggesting that IM/EpiPen absorption is different in Japanese patients as compared to US populations but the same for Eurneffy in Japanese and US populations. Further when covariate was used on F (bioavailability) only without the Japanese data (using US data only), weight became a more important covariate. Two-fold greater exposure after IM/EpiPen administration in Japanese patients is explained by the fact of smaller muscle weight and greater volume of distribution relative to the total muscle mass.

Adjustment of F, weight (and not BMI) can explain the further difference in the MOFV (the model objective function) on the Vd/Vc and Clearance. Taking relative bioavailability into account it can explain most of the variability that is seen between Japanese and US populations.

Data from literature (Al-Gindan-2014, Hill-2016, Hasunuma-2016) suggests that people with lower weight have smaller and likely, leaner muscle and therefore it is reasonable to assume that the relative volume of distribution in the muscle may impact absorption of drugs from IM/EpiPen injections. If that is the case, the volume of distribution relative to muscle mass is higher in lower weight people and may result in a greater absorption. This factor would likely be a significant contributor to the observation of two-fold increase in exposure following IM/EpiPen administration to the lower weight Japanese subjects.

A two-compartment model was used to describe PK after IM, SC, EpiPen, nasal and nasal administration in rhinitis subjects. Faster absorption was observed after ARS-1 nasal and ARS-1 nasal in patients with rhinitis administration compared to IM/EpiPen or SC administration. Based on graphical

analysis and covariate analysis, weight has been revealed to be the most important covariate compared to BMI or age.

Paediatrics stimulations showed that AUC and C_{max} are similar with adult values except for 1 mg in the 4-6 years old group for both C_{max} and AUC and in the group 6-12 years of age for AUCs. However, changes in the SBP and HR are similar for adults and paediatric population (even for 1 mg dose for 4-6 years of age group).

The updated popPK model

The initial POP PK model 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. A covariate analysis was conducted based on Visual Checks of relationships between covariates and inter-individual variances of CL, Q, VC, and VP. Available covariates were age, sex, race, race/ethnicity, weight, and BMI. Omega variability values were plotted versus the covariates of interest such as weight, BMI, gender and other discrete and continuous variables. These results suggest that weight may be a more important covariate as compared to either BMI or age based on the graphical analysis and the associated p-values.

Of note only simulations for the ≥ 30 kg population are presented in this report, as the indication pursued is for a population above 30 kgs.

In the EPI 10 study the mean C_{max} for paediatric patients ≥ 30 kg was 540 pg/mL, similar to results predicted in the POP PK analysis. These results demonstrated that the observed PK exposures in EPI 10 are well within the range of that predicted by the POP PK model for both adults and paediatric subjects, which validates the model. Simulations comparing 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.

Simulated C_{max} and AUC results for dosing Eurneffy 2 mg relative to IM adrenaline 0.3 mg and EpiPen 0.3 mg injections are provided in Figure 6 (dosed once) and Figure 7 (dosed twice). These results demonstrated that the mean expected peak exposures (C_{max}) for Eurneffy 2 mg in the ≥ 30 kg paediatric population are bracketed by the approved injection products, with greater and more rapid exposures relative to IM adrenaline 0.3 mg and slightly lower exposures compared to EpiPen.

In all four scenarios, even after the correction for body weight, Eurneffy administration in children demonstrated similar or higher C_{max} or AUC values as compared to adults.

Figure 6 The Effect of Body Weight on Cmax and AUC for Paediatric Population 30 kg to 50 kg: Eurneffy 2 mg Dosed Once

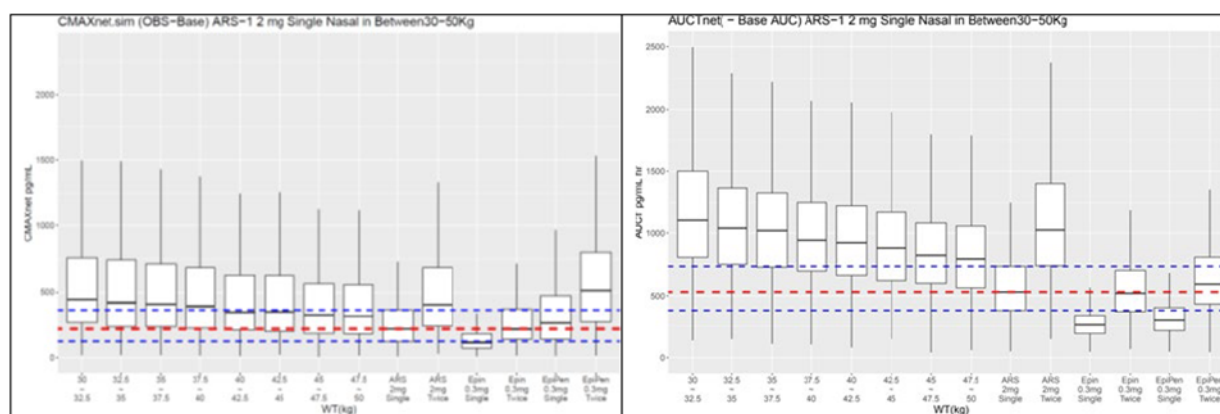


Figure 7 The Effect of Body Weight on Cmax and AUC for Paediatric Population 30kg to 50 kg: Eurneffy 2 mg Dosed Twice (4 mg)

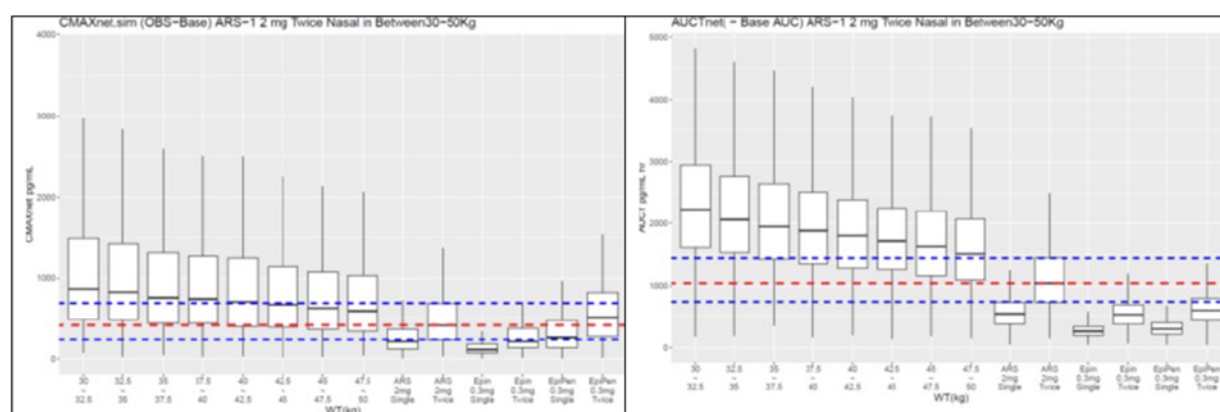


Figure 8 (once dosed) and Figure 9 (twice dosed) provides the predicted exposures from Eurneffy 2 mg by age, assuming a body weight of 30 kg to 50 kg, as compared to approved injection products dosed once and twice. These results demonstrated that Eurneffy's predicted Cmax is expected to be greater than IM adrenaline 0.3 mg and similar to EpiPen, with peak exposures increasing with decreasing age. Similar trends were noted for predicted AUC, with Eurneffy showing a higher overall AUC compared to IM adrenaline 0.3 mg in adults. Given the relationship between weight and age in younger children, these age-related trends may be more related to the weight of the child, suggesting that weight may be a more accurate predictor of exposure.

Figure 8 Simulation of Cmax and AUC for Paediatric Population 30kg to 50kg by Age (4 or greater years of age): Eurneffy 2 mg Dosed Once

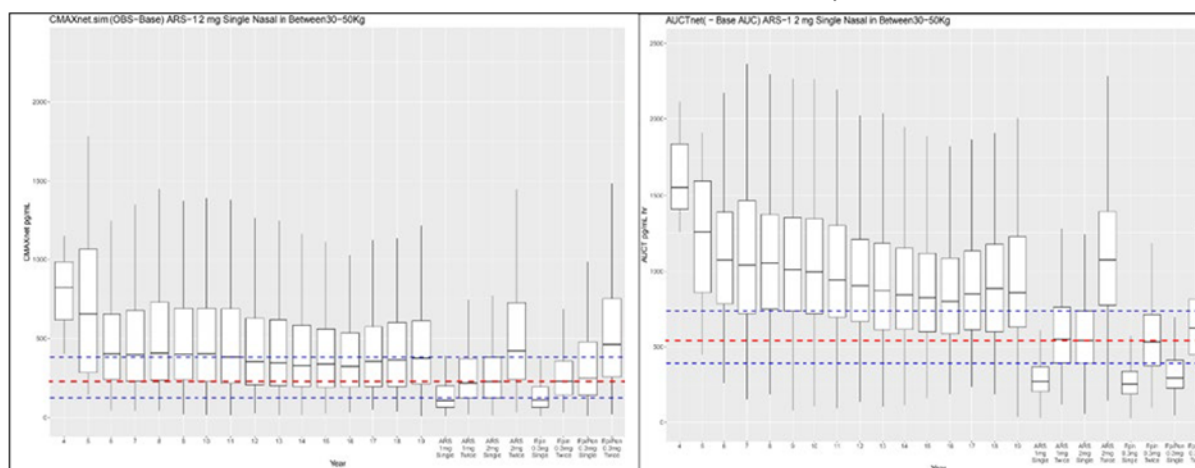
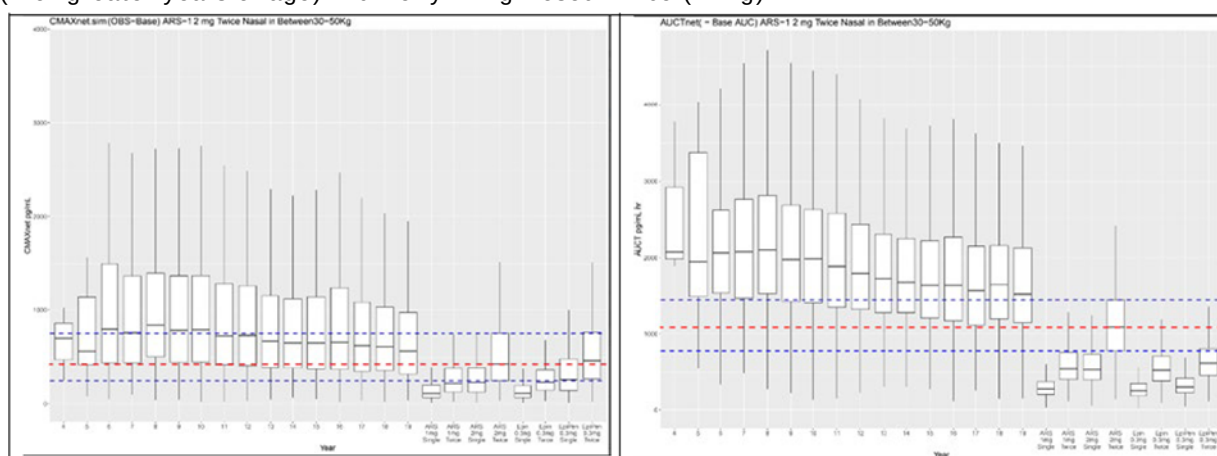


Figure 9 Simulation of Cmax and AUC for Paediatric Population 30kg to 50kg by Age (4 or greater years of age): Eurneffy 2 mg Dosed Twice (4 mg)



Overall, the results of the POP PK model were consistent with the physiologically based pharmacokinetic model (PBAM) model. In paediatric allergy patients ≥ 30 kg Eurneffy 2 mg has a predicted Cmax that is bracketed by IM adrenaline 0.3 mg injection on the lower end and by EpiPen on peak exposure. The overall AUC for Eurneffy 2 mg is predicted to be similar to IM adrenaline 0.3 mg in paediatric allergy patients ≥ 30 kg. Both peak and overall exposures increase as body weight decreases.

Physiologically Based Absorption Model (PBAM) Analysis

The first goal of the study was to develop a physiologically based pharmacokinetic model for adrenaline after the IN administration of ARS-1 using data from clinical studies in healthy subjects (EPI-03, EPI-04, EPI-07 (1 mg) and EPI-16 (2mg)). The second goal was to extrapolate this model to paediatric subjects receiving different ARS-1 doses as part of the clinical trial EPI-10 to understand possible differences in the nasal absorption between adults and paediatrics that could lead to possible dose adjustments in the paediatric population. The predictive capacity of the model was evaluated with mean paediatric clinical data from study EPI-10. The model was then used for dose evaluation purposes in the paediatric population based on PK exposure matching criteria (reference exposure:

adults 2 mg). In the case of EPI-03 and EPI-07 only data after the first dose administration of ARS-1 were included in the analysis to avoid the carry-over effect of the absorption enhancer.

Different scaling factors were used to account for the possible differences in the ontogeny/physiology of this population in comparison to adult subjects, mainly related with the differences in the body size. Model predictions support the conclusion that the turbinates are the main physiological structure involved in the nasal absorption which is already mature in children ≥ 6 of age weighting more than 30 kg, and therefore no significant differences are expected between this paediatric age group and adults. A 2 mg dose in children weighting more than 30 kg led to a similar exposure to 2 mg dose in adults (C_{max} and AUC 0 to 2 hours). More uncertainty exists in younger children weighting less than 30 kg where in addition to account for the body size differences, a model refinement (increase of the absorption rate from the epithelial cell to the blood (K_A) and of mucociliary clearance (t_{2gi})) was needed in the 15-30 kg children to capture the observed plasma concentrations after 0.65 mg.

Comparisons of the simulated plasma concentration – time profiles after the 1 mg dose in children with the refined model (for children weighting 15-30 kg) lead to overall plasma exposures (C_{max} and AUC 0 to 2 hours) within the expected values based on the adult simulated exposures after 2 mg (C_{max} and AUC 0 to 2 hours), and slightly higher 97th percentile.

Simulations in Adults

All model development and verification simulations were done using virtual subjects matching as close as possible to those in clinical trials EPI-03, EPI-04, EPI-07 and EPI-16 following the clinical study designs. Verification simulations were performed using a population of $N=1500$ subjects to assess the PK variability and simulated C_{max} , T_{max} and AUC were calculated and compared to those from observed data.

The simulated trial design was based on the study described in the clinical study reports where patients received a single 1 mg/100 μ L IN dose or 2 mg/ of 100 μ L IN dose of ARS-1. Blood samples for PK analysis were collected over 8 hours. To account for the endogenous adrenaline an infusion of adrenaline was used starting two hours before the administration of ARS-1 to ensure adrenaline baseline concentration values at steady state (in line with the i.v. model).

Figure 10 Comparison of Adrenaline Plasma Profiles in Healthy Adults from EPI 03

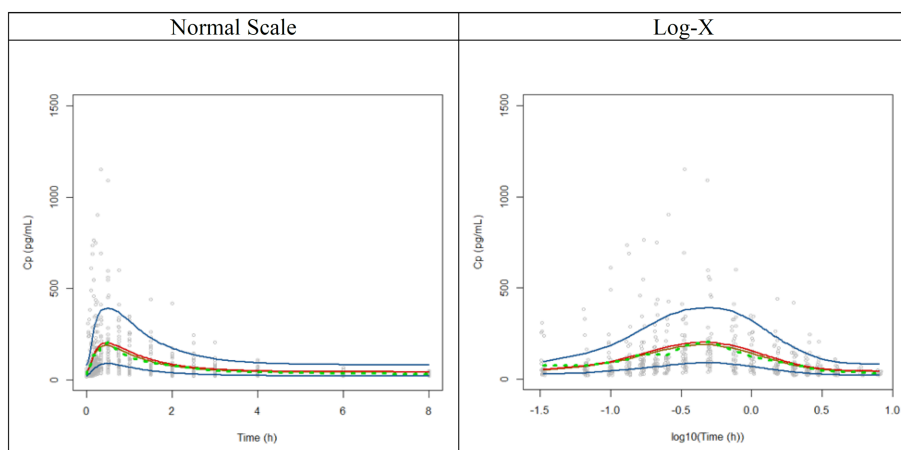


Figure 11 Comparison of Adrenaline Plasma Profiles in Healthy Adults from EPI 04

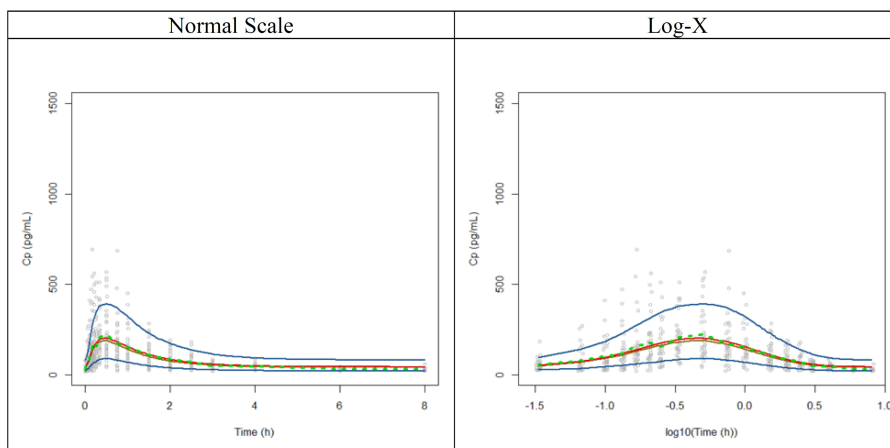


Figure 12 Comparison of Adrenaline Plasma Profiles in Healthy Adults from EPI 07

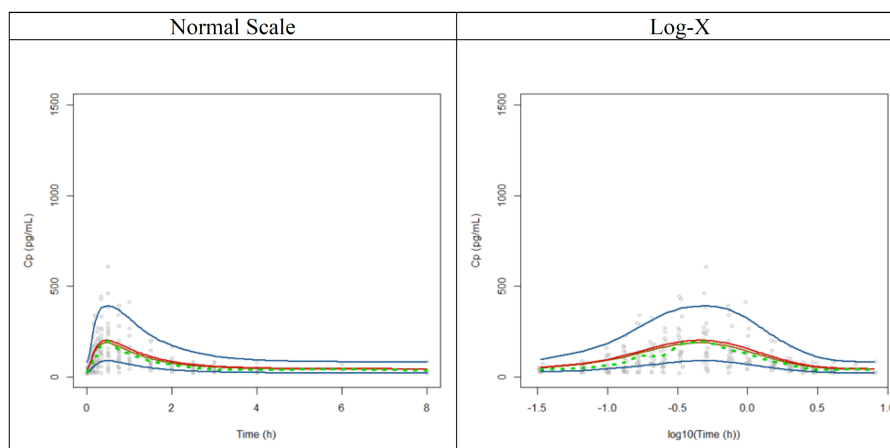
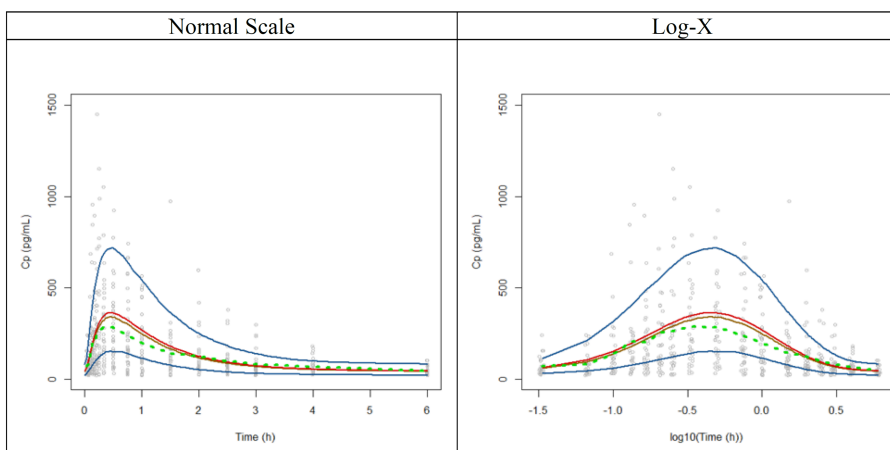


Figure 13 Comparison of Adrenaline Plasma Profiles in Healthy Adults from EPI 16



Comparison of adrenaline plasma profiles in healthy adults from study EPI-16 with the PBAM model predictions (grey dots are observations and the dashed green line is the mean profile from the observation; solid yellow, red and blue lines are the predicted median, mean and 95% PI using the PBAM model). Left panel: normal scale. Right panel: log-X

The model appropriately predicted the mean PK behaviour in all the four studies as well as the variability. Moreover, as shown in the right panel of above figures with the log-X scale, the model adequately predicts the absorption behaviour. Predicted and observed plasma AUClast and Cmax mean

values and Tmax median values as well as the predicted over observed ratios for AUClast and Cmax are shown in Table 9.

Table 9 Simulated and Observed Cmax and AUC(0-t) and Ratios, and Median Tmax Values for ARS-1 Following a Single 1 & 2mg IN Dose to Healthy Adult Volunteers

	Median T_{max} (min)	Mean C_{max} (pg/ml)	ratio	Mean AUC_{last} (pg.min/ml)	ratio
PBAM_1mg	26	201	-	34542	-
EPI-03_1mg*	30	203	0.99	29817	1.16
EPI-04_1mg*	30	222	0.91	31920	1.08
EPI-07_1mg*	30	197	1.02	28367	1.22
PBAM_2mg	28	363	-	43642	-
EPI-15/16_2mg**	20	485	1.27	39921	1.09

*Mean C_{max} and AUC_{last} calculate from the mean observed plasma profile

**Integrated analysis of EPI 15 and EPI 16 results

The simulated profiles were comparable to the clinical data and the predicted AUClast and Cmax values were within 1.5-fold of the observed value for all the three trials. Considering all above, the model was considered appropriate to predict adrenaline mean and population plasma concentrations after the IN administration of ARS-1 in healthy adults.

Simulations in Paediatrics

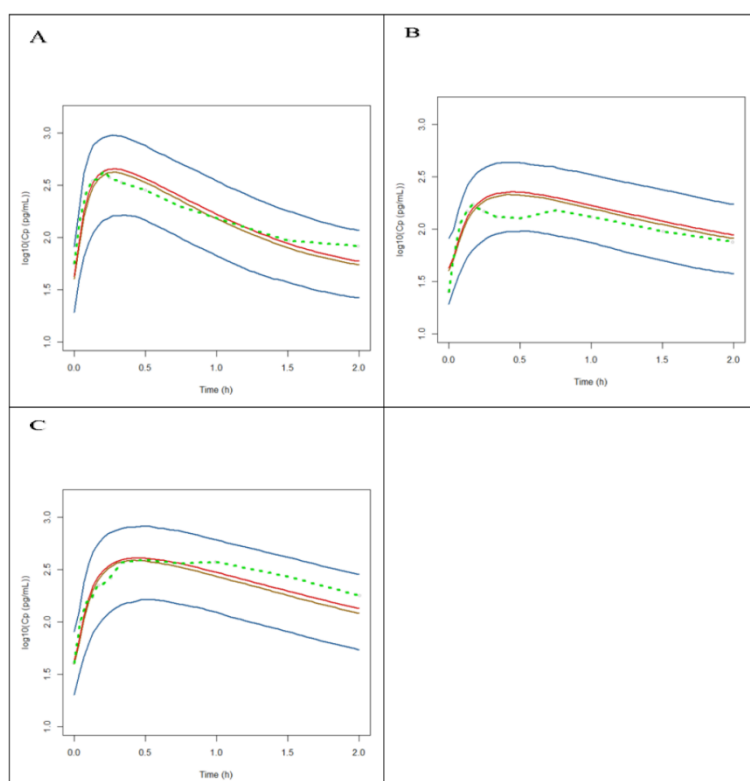
The parameters of the population PBAM model for ARS-1 were scaled to paediatrics to bridge the information to this population. Modelling was based on the adult population PK data in healthy subjects and then the inclusion of different scaling factors to extend adrenaline PK into paediatrics from 4 to 17 years of age.

All model development and verification simulations were done using virtual subjects matching as close as possible to those in clinical trials EPI-10 following the clinical study designs. Verification simulations were performed using a population of N=1500 subjects to assess the PK variability and simulated Cmax, Tmax and AUC were calculated and compared to the mean observed data.

The simulated trial design was based on the study described in the clinical study where subjects weighting 15-30kg received a single 0.65 mg/100 µL IN dose of ARS-1, subjects weighting >30kg received either a single 1 mg/100 µL or 2 mg/100 µL IN dose of ARS-1. Blood samples for PK analysis were collected over 2 hours. To account for the endogenous adrenaline an infusion of adrenaline was used starting two hours before the administration of ARS-1 to ensure adrenaline baseline concentration values at steady state (in line with the i.v. model).

A comparison of the simulated and observed plasma concentrations of adrenaline after the single IN dosing of ARS-1 in study EPI-10 is shown in Figure 14 . Mean of observed concentrations of patients in EPI-10 and the predictions using the PBAM model in a virtual population (n =1500) are displayed in Figure 15.

Figure 14 Comparison of Adrenaline Plasma Profiles in Paediatrics from EPI 10



The model appropriately predicted the mean PK behaviour in paediatric subjects. Predicted and observed plasma AUClast and Cmax mean values and Tmax median values as well as the predicted over observed ratios for AUClast and Cmax are shown in Table 10.

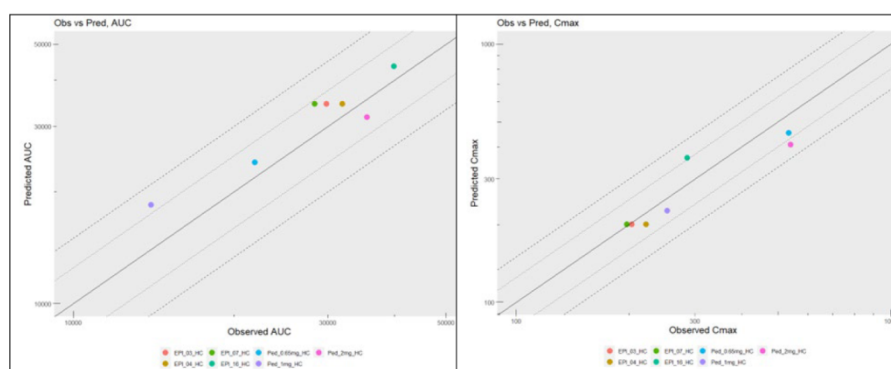
Table 10 Simulated and Observed Tmax, Cmax and AUC(0-t) values and Ratios for ARS-1 Following a Single Dose in Children from EPI 10

	Median Tmax (min)	Mean Cmax (pg/ml)	ratio	Mean AUClast (pg.min/ml)	ratio
PBAM_0.65_15_30kg	16	453	-	24007	-
EPI_10_0.65_15_30kg *	12.5	534	0.85	21900	1.10
PBAM_1_>30kg	26	226	-	18443	-
EPI_10_1_>30kg*	20	253	0.89	14000	1.32
PBAM_2_>30kg	26	408	-	31809	-
EPI_10_2_>30kg*	25	540	0.76	35500	0.90

*Mean Cmax and AUClast calculate from non-compartment analysis of individual plasma profiles

Goodness-of-fit plots of predicted versus observed AUClast values and of predicted versus observed Cmax are shown in Figure 14, both for adults (study EPI-03, EPI-04, EPI-7 and EPI-16) and paediatrics (EPI-10). Six out of seven predicted AUClast values fell within the 1.25- fold acceptance criterion with only one AUClast value (corresponding to children >30 kg receiving 1 mg of ARS-1) fell within the 1.5-fold acceptance criterion. Five out of seven predicted Cmax values fell within the 1.25-fold acceptance criterion with only two Cmax values (corresponding to adults and children >30 kg receiving 2 mg of ARS-1) fell within the 1.5-fold acceptance criterion. In any case, all the values are within the 1.5-fold range demonstrating the descriptive and predictive performance of ARS-1 PBAM model both in adults and paediatrics.

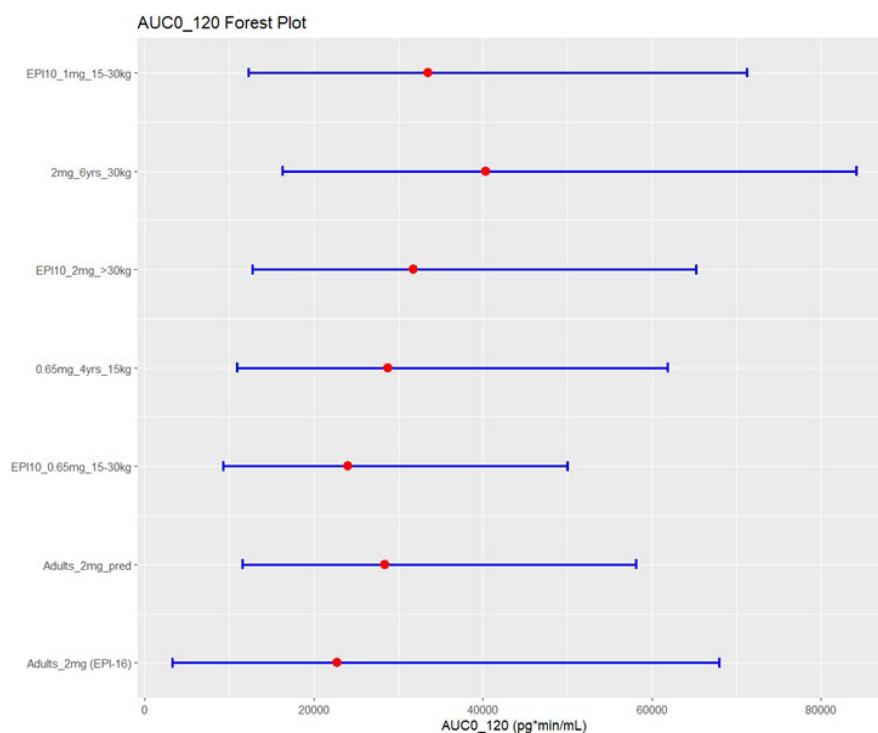
Figure 15 Predicted vs Observed AUC (left panel) and Cmax (right panel) From Adult and Paediatric Subjects



Predicted vs Observed AUC (left panel) and Cmax (right panel) from all adult and pediatric subjects. The dotted lines represent 1.25-fold, and the dashed lines represent the 1.5-fold

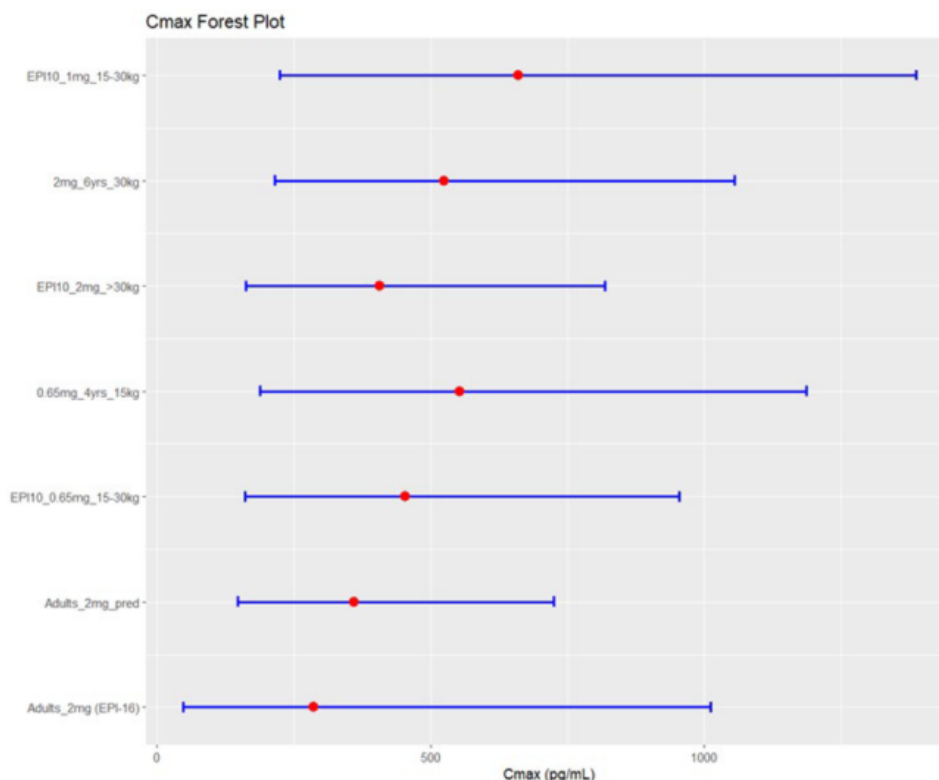
Considering all above, the model was considered appropriate to predict adrenaline plasma concentrations after the IN administration of ARS-1 in adult and paediatric subjects. For children weighting 15-30 kg a model refinement was needed to capture the mean observations from study EPI-10. The final PBAM model was used to simulate the PK in the following proposed regimes for the ages using also variability permitting inference regarding the PK outcomes. For children 15 to <30 kg body weight, a 1.0 mg dose administered in the nose. For children 30 kg body weight or greater, a 2.0 mg dose administered in the nose. In order to ensure the safety and efficacy of the selected dose for the paediatric clinical trial the simulated plasma profiles were compared to that in adult healthy subjects after the 2 mg dose. The results of the simulations are shown in as AUC0_120 and Cmax. The plot also includes the 2mg administration of ARS-1 in healthy adults as a reference.

Figure 16 Comparison of Predicted AUC0-120



Comparison of predicted AUC0-120 min in adults with 2mg dose and various other pediatric clinical scenarios as mentioned above using the PBAM model. The red dots and bars represent the mean and the 95% CI, respectively.

Figure 17 Comparison of Predicted C_{max}



Comparison of predicted C_{max} in adults with 2mg dose and various other pediatric clinical scenarios as mentioned above using the PBAM model. The red dots and bars represent the mean and the 95% CI, respectively.

The predicted exposures, including the 95% confidence intervals are within the expected values from the 2 mg in >30 kg children and 1 mg in 15-30 kg administration of ARS-1 in adults. The 2 mg IN dose produces plasma exposures in paediatrics (>30 kg) comparable to that in adults and slightly higher 97.5 percentile in 6-year-old children weighting 30 kg. Similarly, the 1 mg IN dose produces plasma exposures in paediatrics (15-30 kg) comparable to that in adults and slightly higher 97.5 percentile. However, the predicted exposure values in these paediatric scenarios (2mg_6yrs_30 kg; EPI10_1mg_15-30kg) were still within the observed exposures reported in the literature for adrenaline administered in different formulations. Based on this, the predicted exposures are considered appropriate

Results in Subjects With Allergic Rhinitis

The simulated profiles were comparable to the clinical data and the predicted AUC, C_{max} and T_{max} values were within 1.5-fold of the observed value. The model was considered appropriate to predict epinephrine mean and population plasma concentrations after the IN administration of ARS-1 in adult patients with allergic rhinitis. A comparison of the simulated and observed plasma concentrations of epinephrine after the single IN dosing of ARS-1 in patients with allergic rhinitis in study EPI-04 is shown in Figure 18. Mean of observed concentrations of patients in EPI-04 and the predictions using the PBAM model in a virtual population (n =1500) are displayed on each figure.

Predicted and observed plasma AUC and C_{max} mean values and T_{max} median values as well as the predicted over observed ratios for AUC and C_{max} are shown in Table 11.

Figure 18 Comparison of epinephrine plasma profiles in adult rhinitis patients from study EPI-04 with the PBAM model predications

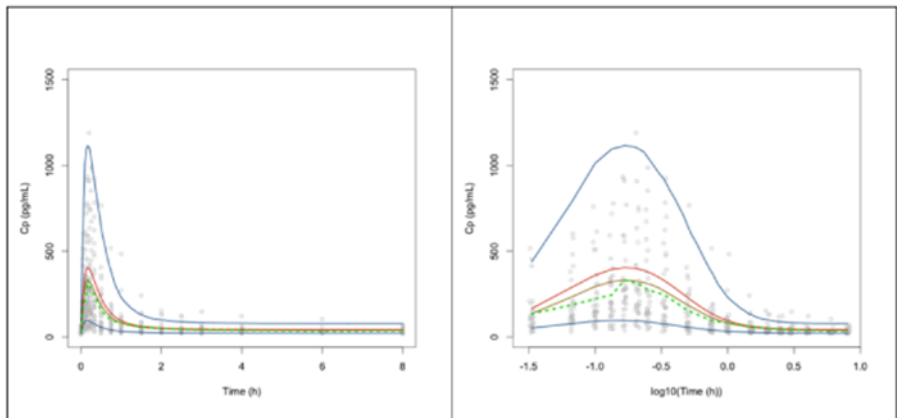


Table 11 Mean simulated and observed Tmax, Cmax and AUC(0-t) values and ratios for ARS-1 following a single 1 mg IN dose to patients with allergic rhinitis.

	Median Tmax (min)	Mean Cmax (pg/ml)	ratio	Mean AUC (pg.h/ml)	ratio
PBAM	10	415.0	-	556.2	-
EPI-04	10	401.0	1.03	374.7	1.48

Model Application to Evaluate the Clinical Doses in Paediatrics

The paediatric PBAM model for ARS-1 was used to simulate epinephrine plasma profiles in paediatric patients of different ages (4 to < 17 years) receiving two different doses of ARS-1 depending on the body weight. A single 0.65 mg dose was used for children of 4- to 6-years old children based on the median body weight, and 1 mg was used for 12- and 16-years old subjects.

The predicted exposures, including the 95% confidence intervals are within the expected values from the clinical trials in adults. The model predicts that the 1 mg IN dose produces plasma exposures in adolescents comparable to that in adults and slightly higher in children of 12 years old after the 1 mg IN dose and in children of 6 and 4 years old after the 0.65 mg IN dose.

Figure 19 Simulated plasma concentration-time profiles of for 8 hours following a single 0.65 mg IN dose of ARS-1 to normal weight 4-year-old children

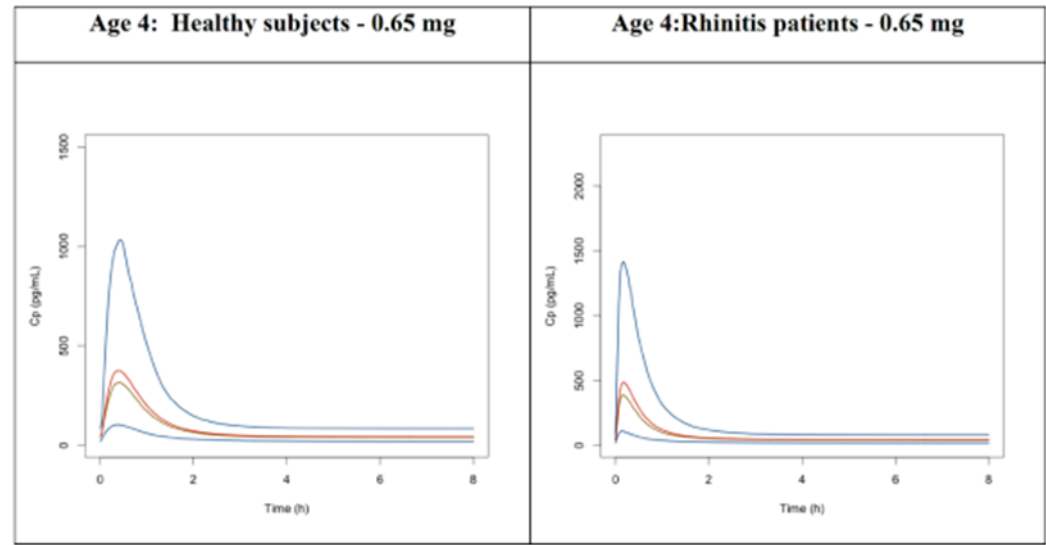


Figure 20 Simulated plasma concentration-time profiles of for 8 hours following a single 0.65 mg IN dose of ARS-1 to normal weight 6-year-old children

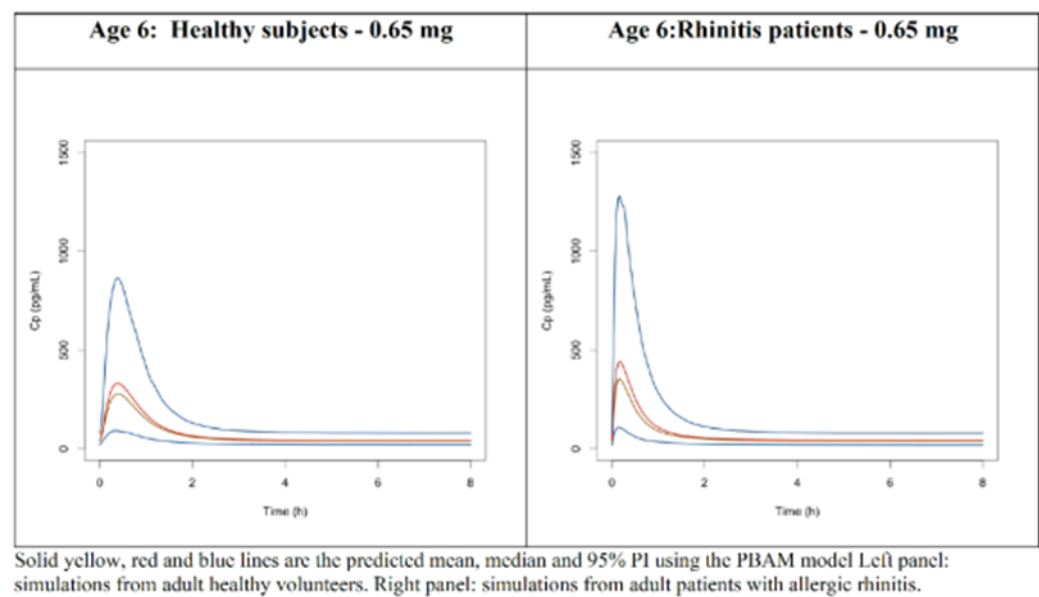


Figure 21 Simulated plasma concentration-time profiles of for 8 hours following a single 1 mg IN dose of ARS-1 to normal weight 12-year-old children

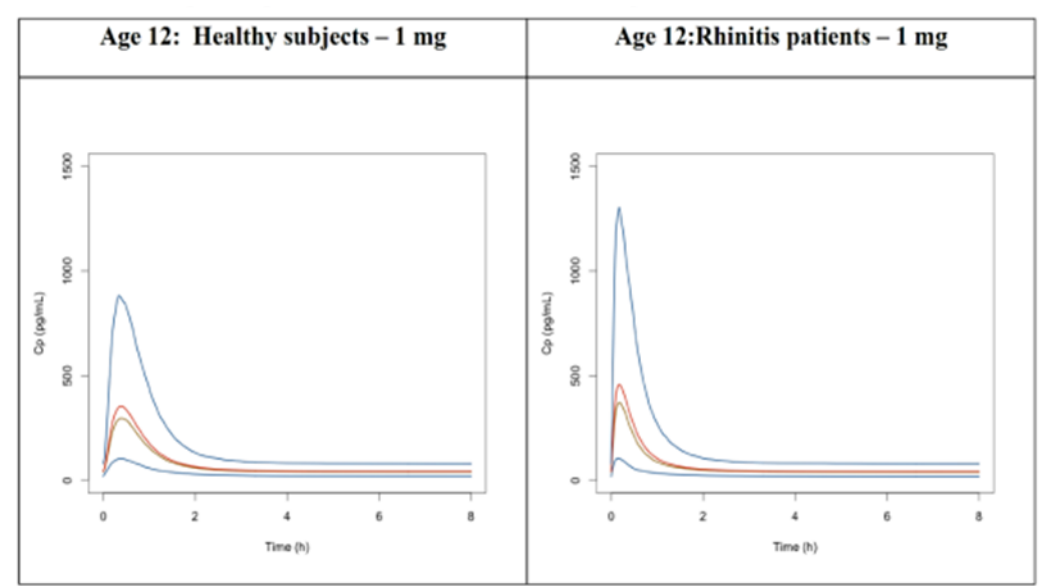


Figure 22 Simulated plasma concentration-time profiles of for 8 hours following a single 1 mg IN dose of ARS-1 to normal weight 12-year-old children

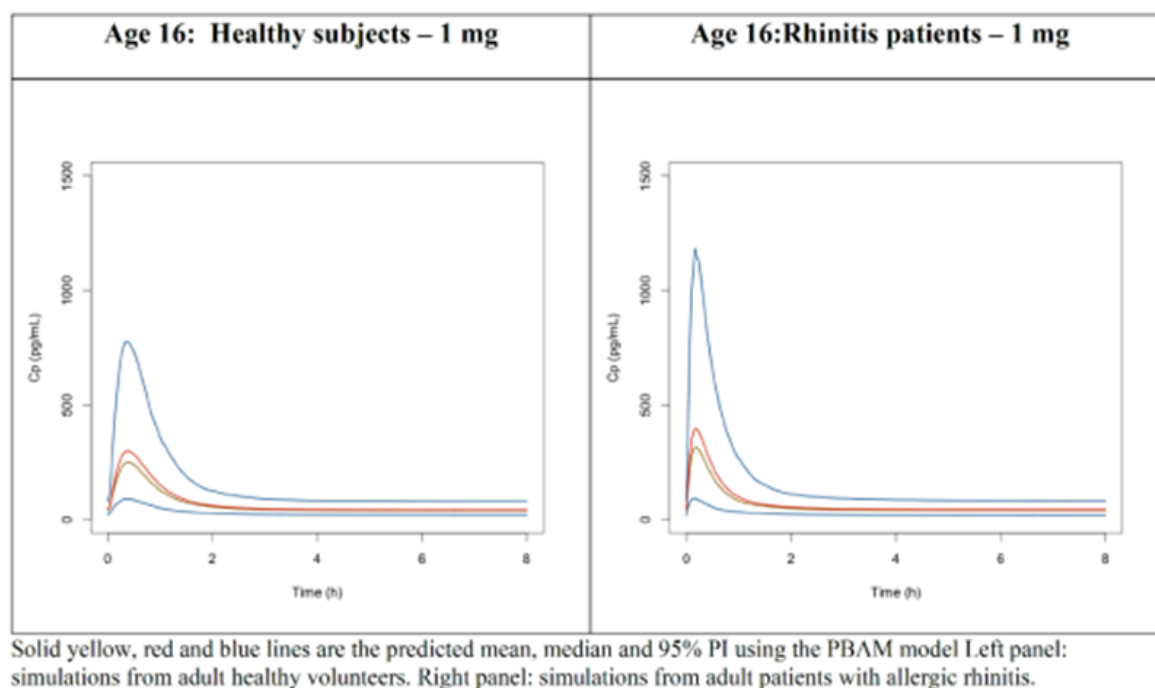


Table 12 Predicted Tmax, Cmax, and AUC for the paediatric model

		Healthy Subjects				Rhinitis Patients			
		Mean	Median	Lower 95%CI	Upper 95%CI	Mean	Median	Lower 95%CI	Upper 95%CI
4 years 0.65 mg	T _{max} (min)	24.2	24.0	18.0	32.0	10.3	10.0	6.0	16.0
	C _{max} (pg/ml)	381.5	320.0	104.7	1063.0	496.0	397.8	111.4	1442.6
	AUC (pg.h/ml)	677.7	614.7	281.2	1428.4	627.5	561.7	242.3	1375.0
6 years 0.65 mg	T _{max} (min)	23.6	24.0	18.0	32.0	10.3	10.0	6.0	16.0
	C _{max} (pg/ml)	335.5	280.4	90.7	875.7	451.2	360.6	110.9	1315.9
	AUC (pg.h/ml)	616.7	571.1	268.2	1231.8	592.6	537.5	248.4	1279.0
12 years 1 mg	T _{max} (min)	23.6	24.0	18.0	32.0	10.7	10.0	6.0	16.0
	C _{max} (pg/ml)	359.7	300.1	103.9	884.4	471.2	386.0	106.8	1369.0
	AUC (pg.h/ml)	635.9	591.4	279.7	1302.3	588.4	542.2	247.0	1263.3
16 years 1 mg	T _{max} (min)	23.6	24.0	18.0	32.0	11.1	10.0	6.0	18.0
	C _{max} (pg/ml)	304.0	254.2	91.2	790.7	408.6	324.5	94.4	1210.5
	AUC (pg.h/ml)	579.8	532.1	255.7	1164.0	567.6	517.7	227.0	1175.6

Paediatric Model – Extreme Scenarios

Figure 23 depicts additional simulations that were also performed to evaluate some extreme scenarios and ensure that the selected doses lead to exposures in paediatric subjects (4 to <18 years) within the expected values based on the clinical trials in adults and the administration of epinephrine subcutaneously or intramuscularly to paediatrics from the literature. All these scenarios were simulated using the model extrapolated from patients and include the following:

- 4 years old with mean body weight and receiving the 0.65 mg dose (4_0.65mg_meanBW_PT)
- 4 years old with mean body weight and receiving the 0.65 mg dose but increasing the variability on

the permeability up to 100% (4_0.65mg_meanBW_Pcv100_PT)

- 4 years old weighting 15 kg and receiving the 0.65 mg dose (4_0.65mg_15kg_PT)

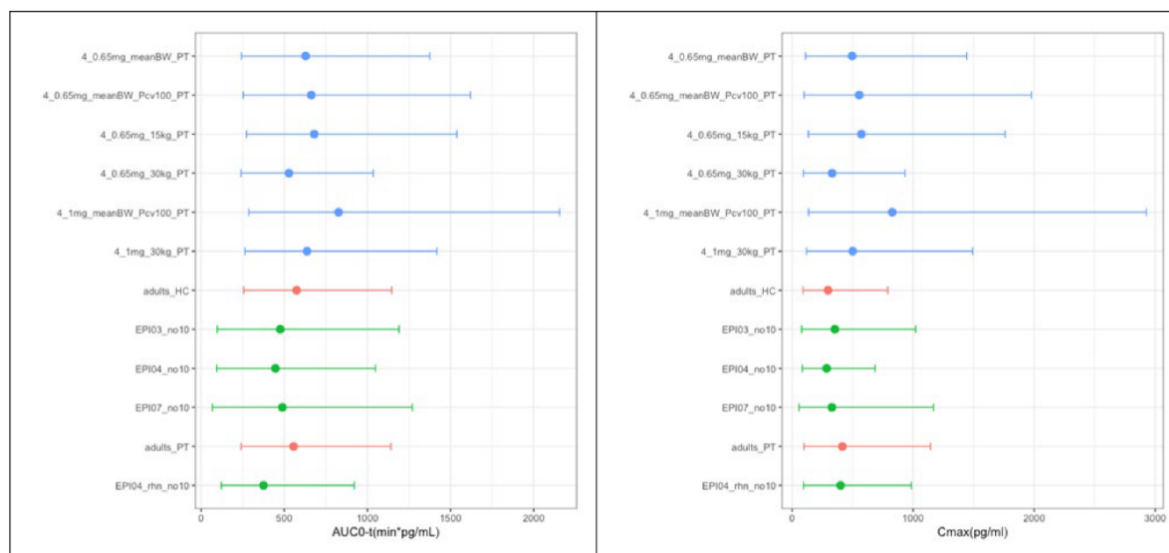
- 4 years old weighting 30kg and receiving the 0.65 mg dose (4_0.65mg_30kg_PT)

- 4 years old with mean body weight and receiving the 1 mg dose but increasing the variability on the permeability up to 100% (4_1 mg_meanBW_Pcv100_PT)

- 4 years old weighting 30kg and receiving the 1 mg dose (4_1 mg_30kg_PT) where mean body weight of 4 years old is 18.1kg (CDC, 2012).

Although the predicted C_{max} values are higher than the observed in adults mainly for scenario 5, i.e., when the variability in the permeability is increased up to 100% and 1 mg dose, the predicted values are within the observed values after the IN administration of 2 mg of ARS-1 in the dose rasing study (EPI-02 Part I, 2,767 pg.h/mL and 2,470 pg/mL for mean AUC and C_{max}, respectively). In study EPI-02 Part I ARS-1 exhibited a favourable safety profile in healthy volunteers administered a single dose of 0.5 mg, 1 mg, or 2 mg, and no severe or serious adverse events were observed.

Figure 23 Comparison of predicted AUC (left panel) and C_{max} (right panel) in paediatric subjects in some extreme scenarios with the observed values in adults from the clinical trials



Dots and bars represent the median and 95%CI, respectively.

The final PBAM model was composed by two deposition compartments in the nose, one representing the anterior cavity (deposition) and one representing the middle cavity (deposition and absorption). In line with the characteristics of the drug in the formulation, most of the drug is initially deposited in the middle cavity (deposition ratio 20:80) and from this compartment the drug can be either swallowed, in which case is eliminated through metabolism by the COMT and MAO in the gastrointestinal track and the liver or can be absorbed. The same structural model was used to account for the nasal PK in patients with allergic rhinitis but absorption rate constant from the middle cavity to plasma (mainly), and permeability were optimised to account for the higher and faster C_{max} and lower AUC observed in patients with allergic rhinitis in study EPI-04. Moreover, the interindividual variability of the model parameters was increased to 10% to account for the higher variability expected in patients due to the allergic reaction in the absorption site.

The robustness of the PBAM model developed to predict epinephrine plasma concentrations after the administration of ARS-1 was tested using the clinical data from studies EPI- 04 and EPI-07, both in

healthy subjects, and further refine to account for the differences in the absorption in patients with allergic rhinitis (EPI-04) before the extrapolation to paediatrics.

The aim of the study was to develop PBA model for epinephrine after IN administration according to the data obtained from EPI 03 study in healthy subjects to justify the selected doses of ARS-1 for the paediatric trial EPI-10. According to the analysis, predicted exposures in paediatrics are in line with expected values in adults supporting the use of 0.65 mg in children between 15 to 30 kg and the 1 mg dose for children above 30 kg (as in general adolescents and adult population).

The pharmacodynamic response in paediatrics including effects on BP and HR, is expected to be similar in both children and adults under the same epinephrine exposure. Similarly, the underlying disease process is considered the same in both populations regardless of age. Based on above considerations and the similar response predicted in children of different ages, including C_{max}, T_{max} and AUC, similar PD response is expected in children >4 years old to that in adults, and any possible difference could be derived from differences in the disease condition of paediatric subjects in study EPI-10.

The updated PBAM model

The applicant provided an updated pharmacologically based absorption model (PBAM) that includes extrapolation of PK and PD data from adults to paediatric allergy patients based on age and weight (PBAM Model Development Report).

The PBAM model was validated by modelling the PK in a virtual population of children (n=1500) based on data from adult 1 mg and 2 mg studies with Eurneffy and comparing these results to the actual exposure data from the EPI 10 clinical study in paediatric allergy patients.

The PBAM model above described was updated to include predicted outcomes from dosing with injection products including IM adrenaline and EpiPen and now provides a comparison with exposures from Eurneffy 2 mg (and 1 mg) by age (8 to 16 years) and weight (30 kg to 70 kg). These comparisons also include partial pAUC results for pAUC_{0-20min}, pAUC_{0-30min}, pAUC_{0-45min}, and pAUC_{0-120min}. These results demonstrate that the PK of Eurneffy 2 mg is well bracketed by both IM adrenaline 0.3 mg and EpiPen 0.3 mg injections in all age and weight groups expected to receive these doses. As an example, the results for pAUC_{0-30min} are shown in Figure 23 and demonstrate that Eurneffy 2 mg exposures are greater than IM adrenaline injection and slightly lower than EpiPen in all groups regardless of age or weight.

Figure 24 Comparison of pAUC0-30min Following Eurneffy, IM Injection, and EpiPen by Age and Weight

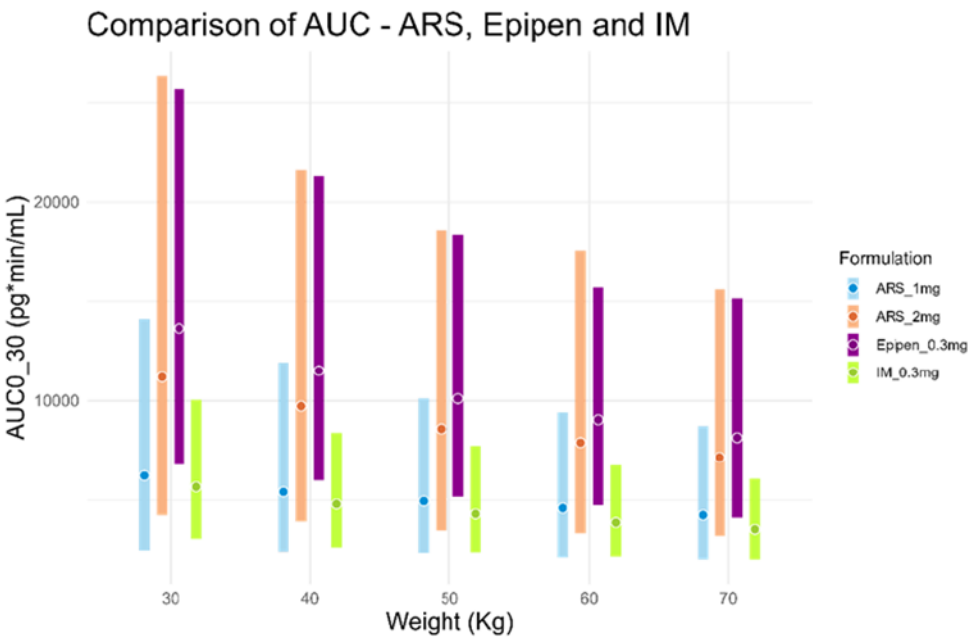
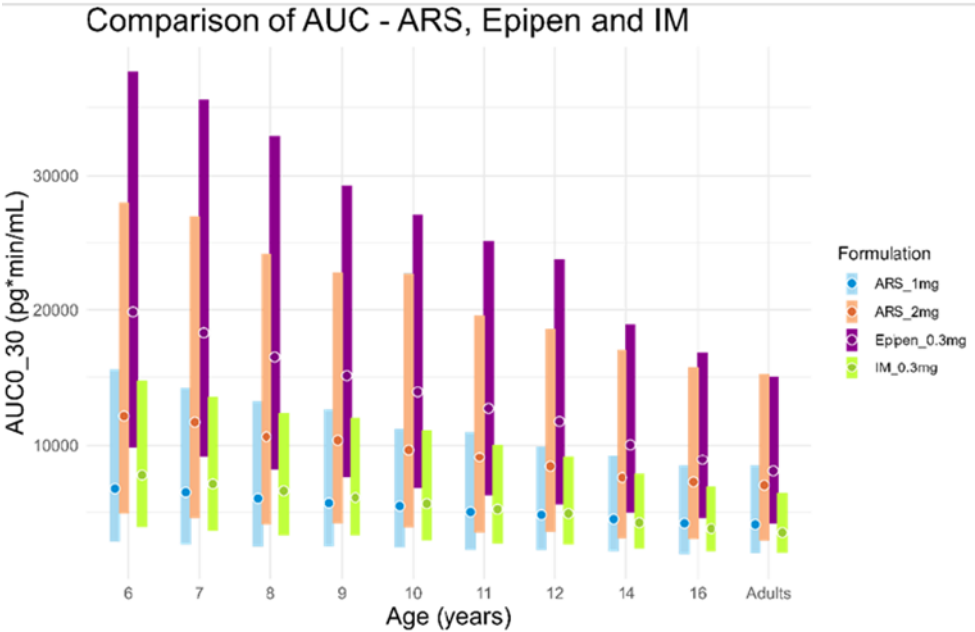
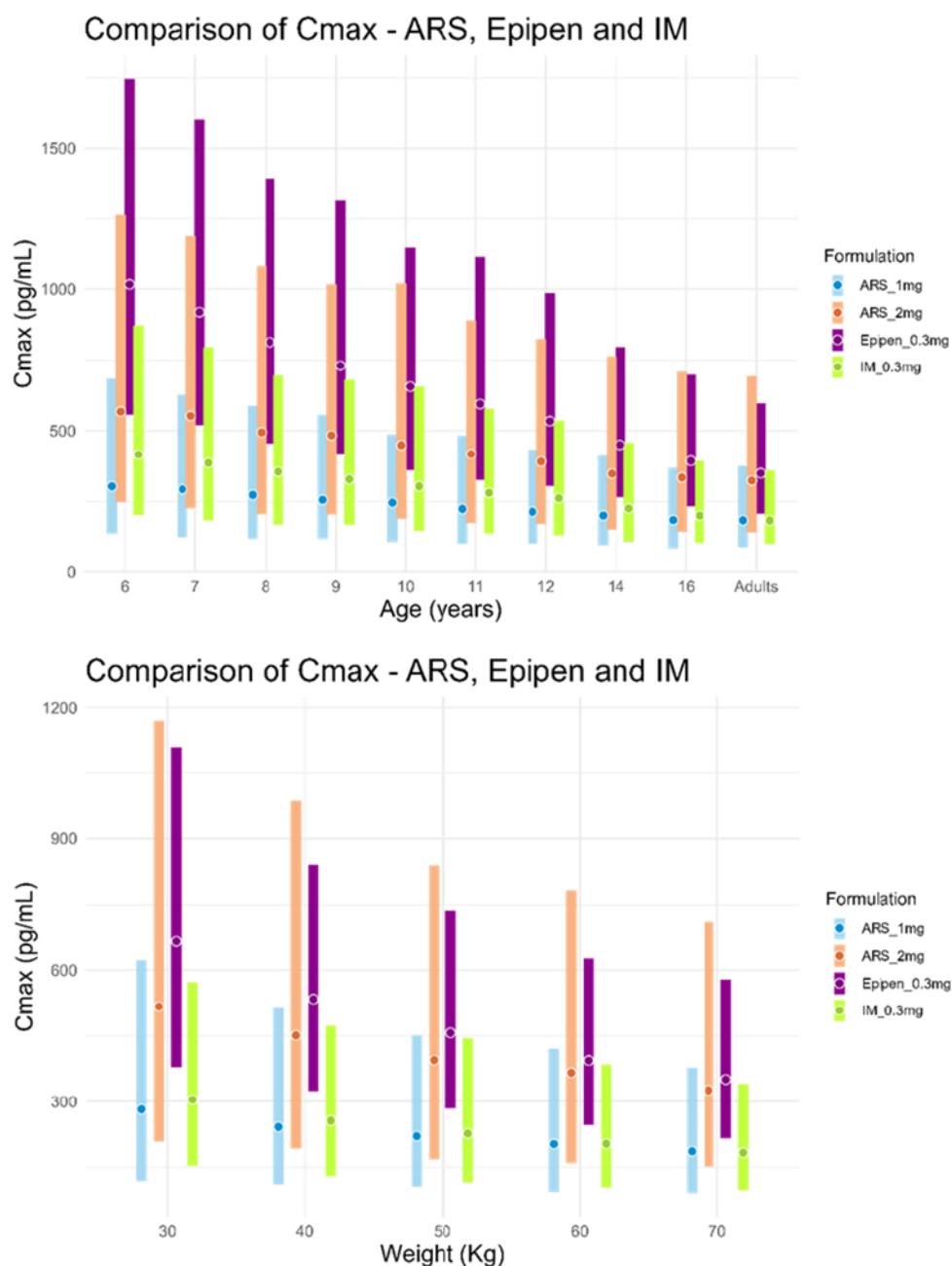


Figure 25 Comparison of Cmax Following Eurneffy, IM Injection, and EpiPen by Age and Weight



2.6.2.1.3. Absorption

This section summarises the results of the pivotal studies EPI015, 016,017 and EPI 18 in adults and of the supportive studies EPI 04, 07, 012. while results of pivotal EPI 010 study are presented under the section “special population”).

Pivotal studies

EPI 15 study results

Pharmacokinetic Parameters – Part 1 (Primary Population)

Cmax: Mean Cmax values were highest after EpiPen (612 pg/mL), followed by ARS-1 (481 pg/mL),

and Epinephrine IM injection (309 pg/mL).

tmax: Median tmax values were fastest following EpiPen (8.00 minutes), followed by ARS-1 (30.0 minutes), and Epinephrine IM injection (45.0 minutes).

AUClast: The greatest total exposure was observed after ARS-1 (43500 min*pg/mL), followed by EpiPen (30900 min*pg/mL), and Epinephrine injection IM (29000 min*pg/mL).

Partial AUC: The exposure to epinephrine from 20 min to 60 min (based on AUC0-20min - AUC0-60min) after ARS-1 was lower compared to EpiPen but greater than Epinephrine injection IM.

Pharmacokinetic Parameters – Part 2 (Primary Population)

Cmax: Mean Cmax values were similar for all treatments with ARS-1 (R/R) (946 pg/mL), followed by ARS 1 (L/R) (805 pg/mL) and EpiPen (719 pg/mL). These differences were not statistically significant. The differences between ARS-1 (R/R) and (L/R) were not significant and not considered clinically meaningful. Tmax: Median tmax values were fastest following EpiPen (15.0 minutes). The median tmax value following both ARS-1 (R/R) and ARS-1 (L/R) was 30.0 minutes.

AUClast: The mean total exposure was lower following EpiPen (49,900 min*pg/mL) relative to both ARS-1 (R/R) (85,000 min*pg/mL) and (ARS- (L/R) (72,500 min*pg/mL). ARS-1 appeared to be relatively dose proportional between single dose and twice dosing, while EpiPen was less than dose proportional.

Partial AUC: Epinephrine exposure from 2 min to 60 min (based on AUC0-2min - AUC0-60min) was lower after ARS-1 compared to EpiPen. Epinephrine exposure after 60 min (based on AUC60-360min, AUC0-120min and AUC0- 360), was higher after ARS-1 compared to EpiPen. The partial AUC60-360min values were 55800 min*pg/mL after ARS-1 (R/R), 48900 min*pg/mL after ARS-1 (L/R), and 25900 min*pg/mL after EpiPen.

Noncompartmental Analysis

Table 13 Summary Statistics of Epinephrine Pharmacokinetic Parameters – Part 1 (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 2.0 mg	42	30.0 (6.00 – 150)	481 (76.0)	340	43500 (69.4)	34400
EpiPen 0.3 mg	35	8.00 (2.00 – 45.0)	612 (58.4)	511	30900 (37.1)	28500
Epinephrine IM 0.3 mg	41	45.0 (4.00 – 90.0)	309 (53.2)	272	29000 (42.1)	26700

Table 14 Summary Statistics of Epinephrine Pharmacokinetic Parameters – Part 2 (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 2.0 mg (L/R)	36	30.0 (6.00 – 150)	805 (69.2)	623	72500 (61.4)	60000
ARS-1 2.0 mg (R/R)	38	30.0 (12.0 – 150)	946 (74.0)	705	85000 (61.6)	68300
EpiPen 0.3 mg (L/R)	37	15.0 (0.00 – 360)	719 (43.3)	648	49900 (38.7)	46300

Table 15 Epinephrine Partial AUCs, by Treatment – Part 1 (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 2.0 mg	42	71.9 (98.5)	56.4	186 (116)	139	351 (113)	262	615 (110)	448	976 (106)	704	1550 (95.4)	1110	2200 (91.9)	1570
EpiPen 0.3 mg	35	118 (109)	81.3	563 (79.2)	398	1360 (73.9)	963	2250 (70.5)	1630	3040 (68.1)	2260	3890 (64.7)	3000	4690 (62.2)	3720
Epinephrine IM 0.3 mg	41	94.9 (95.6)	69.4	294 (105)	196	587 (100)	389	909 (95.6)	613	1210 (91.5)	837	1550 (86.8)	1120	1870 (83.6)	1390
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)	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 2.0 mg	42	3600 (89.3)	2590	6840 (84.5)	4880	11700 (83.2)	8160	15700 (82.7)	10900	26300 (80.3)	18900	43700 (68.9)	34700	27900 (69.7)	22400
EpiPen 0.3 mg	35	6190 (59.9)	5030	9040 (55.4)	7620	13000 (48.0)	11300	15800 (45.2)	13900	21200 (42.6)	19100	31400 (36.4)	29200	15600 (37.9)	14400
Epinephrine IM 0.3 mg	41	2550 (78.3)	1970	4140 (69.6)	3340	7210 (61.4)	6070	10500 (56.1)	9090	18200 (46.7)	16500	29400 (41.0)	27200	18900 (44.3)	17100

Table 16 Epinephrine Partial AUCs, by Treatment – Part 2 (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 2.0 mg (L/R)	36	83.8 (88.8)	64.5	213 (91.1)	160	403 (92.0)	298	674 (92.2)	487	1030 (86.4)	746	1700 (89.3)	1200	2460 (83.4)	1750
ARS-1 2.0 mg (R/R)	38	64.4 (55.8)	54.7	167 (65.6)	135	305 (79.1)	236	504 (82.5)	382	788 (83.7)	583	1470 (83.6)	1050	2530 (91.2)	1720
EpiPen 0.3 mg (L/R)	37	156 (179)	85.3	596 (106)	381	1290 (84.4)	849	2010 (77.5)	1380	2710 (72.3)	1990	3650 (67.3)	2810	4830 (62.4)	3850
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)	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 2.0 mg (L/R)	36	4260 (71.6)	3170	9110 (70.7)	6920	17000 (69.5)	13100	23900 (70.2)	18300	41300 (72.6)	31900	72900 (61.1)	60400	48900 (66.7)	40100
ARS-1 2.0 mg (R/R)	38	5430 (95.9)	3540	12000 (90.1)	8070	21500 (81.6)	15200	29800 (79.0)	21300	51200 (71.7)	38800	85700 (61.7)	69000	55800 (63.7)	44600
EpiPen 0.3 mg (L/R)	37	7350 (56.7)	6090	12000 (52.7)	10300	18800 (47.0)	16600	24200 (42.9)	21800	33600 (41.7)	30700	50000 (38.5)	46400	25900 (50.8)	22800

Comparative Bioavailability – Part 1 (Primary Population)

Epinephrine Exposure: ARS-1 resulted in C_{max} values that were 38% lower compared to EpiPen and 26% higher compared to Epinephrine IM injection. Total exposure after ARS-1 (based on AUC_{last}) was 17% higher compared to EpiPen and 30% higher compared to Epinephrine IM injection.

T_{max}: Median t_{max} following ARS-1 was significantly longer than following EpiPen. There was no significant difference between ARS-1 and Epinephrine IM injection.

Table 17 Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters after Administration of ARS-1 2.0 mg IN, EpiPen 0.3 mg, and Epinephrine Injection 0.3 mg IM – Part 1 (Primary Population)

Test vs Reference	Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		p-value ^d	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 vs EpiPen	C _{max}	340	548	62.12	48.69	79.26	0.0017	68.98
	AUC ₀₋₂	56.4	83.4	67.63	53.87	84.91	0.0055	63.59
	AUC ₀₋₆	262	1020	25.71	19.39	34.09	<0.0001	82.83
	AUC ₀₋₁₀	704	2450	28.77	21.69	38.15	<0.0001	82.87
	AUC ₀₋₃₀	4880	8190	59.63	46.71	76.12	0.0007	69.18
	AUC ₀₋₆₀	10900	14700	74.38	59.29	93.3	0.0328	63.32
	AUC ₀₋₁₂₀	18900	19500	96.82	78.33	119.67	0.8001	58.52
	AUC _{last}	34400	29300	117.27	97.34	141.28	0.1586	50.57
ARS-1 vs IM Epinephrine Injection	C _{max}	340	270	126.21	100.38	158.69	0.0945	68.98
	AUC ₀₋₂	56.4	68.8	81.93	66.16	101.47	0.1249	63.59
	AUC ₀₋₆	262	391	66.99	51.38	87.34	0.0141	82.83
	AUC ₀₋₁₀	704	837	84.12	64.51	109.69	0.2812	82.87
	AUC ₀₋₃₀	4880	3310	147.62	117.34	185.71	0.0061	69.18
	AUC ₀₋₆₀	10900	8980	121.65	98.31	150.55	0.1297	63.32
	AUC ₀₋₁₂₀	18900	16300	115.93	94.99	141.48	0.2203	58.52
	AUC _{last}	34400	26400	130.42	109.47	155.38	0.0137	50.57

Comparative Bioavailability – Part 2 (Primary Population)

Epinephrine Exposure: ARS-1 (R/R) resulted in C_{max} values that were 7% higher compared to EpiPen and 13% higher compared to ARS-1 (L/R). The total exposure after ARS-1 (R/R) (based on AUC_{last}) was 45% higher compared to EpiPen and 14% higher compared to ARS-1 (L/R). Epinephrine C_{max} and AUC_{last} after ARS-1 (L/R) was 6% lower and 27% higher compared to EpiPen.

T_{max}: Median t_{max} following both ARS-1 (R/R) and ARS-1 (L/R) was significantly longer than following EpiPen. There was no significant difference between ARS-1 (R/R) and ARS-1 (L/R).

Table 18 Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters after Administration of ARS-1 2 x 2.0 mg IN (R/R), EpiPen 2 x 0.3 mg (L/R), and ARS-1 2 x 2.0 mg IN (L/R) – Part 2 (Primary Population)

Test vs Reference	Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		p-value ^d	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 (L/R) vs EpiPen (L/R)	C _{max}	621	655	94.82	74.89	120.05	0.7082	65.3
	AUC ₀₋₂	64.2	85.0	75.48	59.14	96.34	0.0587	67.74
	AUC ₀₋₆	298	848	35.15	26.14	47.27	<0.0001	86.79
	AUC ₀₋₁₀	750	2020	37.11	28.21	48.81	<0.0001	78.3
	AUC ₀₋₃₀	6950	10500	66.33	51.02	86.24	0.0112	74.17
	AUC ₀₋₆₀	18300	21900	83.44	65.06	107.01	0.2291	69.63
	AUC ₀₋₁₂₀	31700	30800	102.77	81.58	129.48	0.844	63.71
ARS-1 (R/R) vs EpiPen (L/R)	AUC _{last}	59500	46700	127.42	104.31	155.64	0.0474	53.9
	C _{max}	701	655	106.88	84.75	134.79	0.6338	65.3
	AUC ₀₋₂	54.9	85.0	64.58	50.81	82.08	0.0034	67.74
	AUC ₀₋₆	238	848	28.01	20.93	37.48	<0.0001	86.79
	AUC ₀₋₁₀	587	2020	29.03	22.17	38.01	<0.0001	78.3
	AUC ₀₋₃₀	8080	10500	77.14	59.6	99.84	0.098	74.17
	AUC ₀₋₆₀	21100	21900	96.09	75.24	122.73	0.7868	69.63
	AUC ₀₋₁₂₀	38200	30800	124.02	98.82	155.65	0.1186	63.71
ARS-1 (R/R) vs ARS-1 (L/R)	AUC _{last}	67800	46700	145.29	119.35	176.88	0.0023	53.9
	C _{max}	701	621	112.72	89.13	142.55	0.398	65.3
	AUC ₀₋₂	54.9	64.2	85.56	67.11	109.09	0.2881	67.74
	AUC ₀₋₆	238	298	79.67	59.34	106.97	0.2026	86.79
	AUC ₀₋₁₀	587	750	78.23	59.55	102.76	0.138	78.3
	AUC ₀₋₃₀	8080	6950	116.29	89.55	151.01	0.3388	74.17
	AUC ₀₋₆₀	21100	18300	115.17	89.91	147.53	0.3449	69.63
	AUC ₀₋₁₂₀	38200	31700	120.68	95.89	151.86	0.1772	63.71
ARS-1 (R/R) vs ARS-1 (L/R)	AUC _{last}	67800	59500	114.03	93.44	139.16	0.2754	53.9

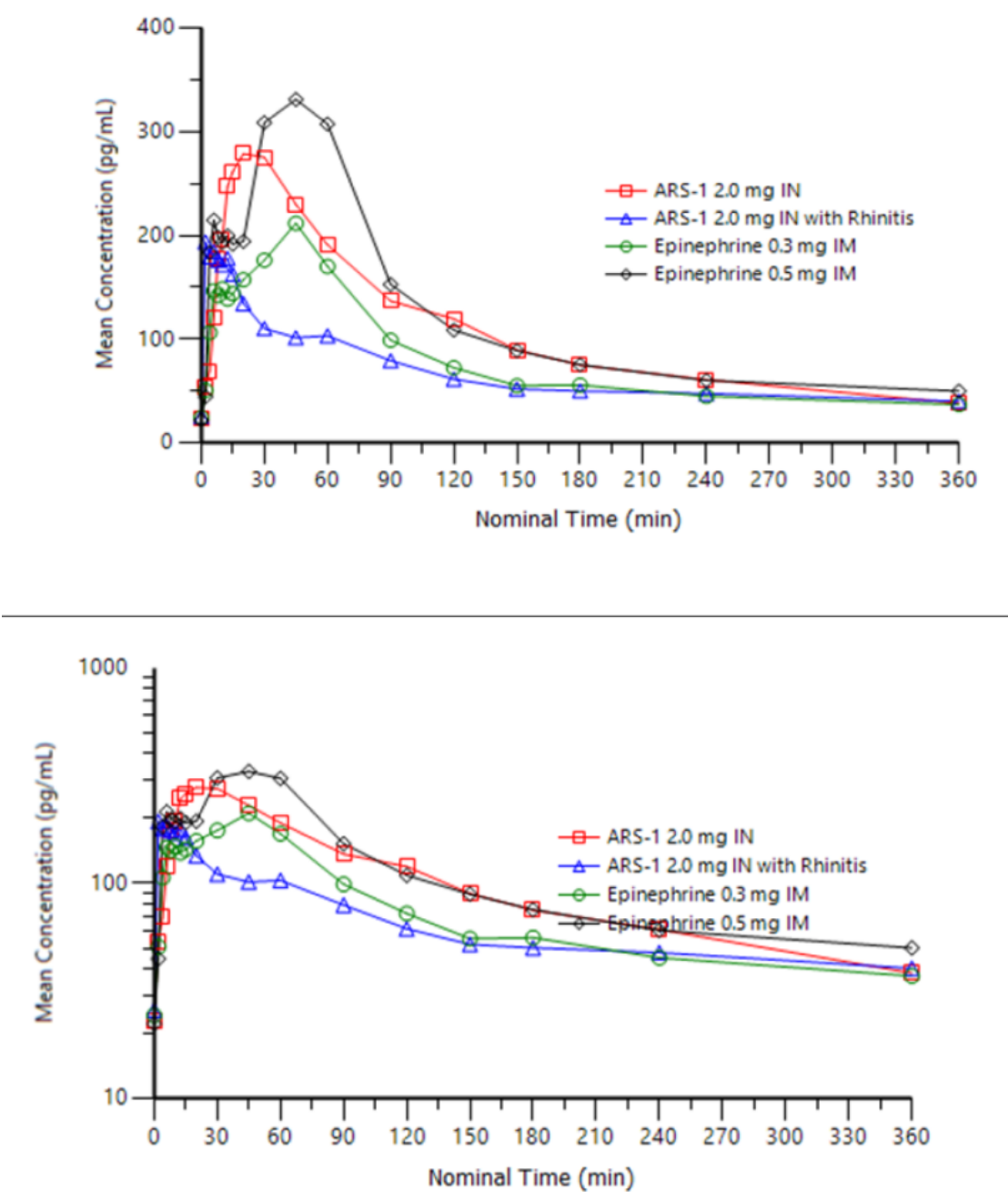
A two-part, crossover PK study of epinephrine after single and repeat administration of intranasal ARS-1 or epinephrine injection to healthy subjects was performed to assess comparative bioavailability of epinephrine after ARS-1 (2.0 mg), with EpiPen 0.3 mg epinephrine and IM injection 0.3 mg epinephrine (needle and syringe) in healthy volunteers under fasted conditions. ARS-1 2.0 mg C_{max} values (481 pg/mL) was 38% lower compared EpiPen (612 pg/mL) and 26% higher compared Epinephrine IM (309 pg/mL). Epinephrine exposure after ARS-1 2.0 mg administration was the highest (43500 min*pg/mL) compared to other formulation tested (EpiPen (30900 min*pg/mL), and Epinephrine injection IM (29000 min*pg/mL)). Total exposure measured by AUC_{last}, was 17% higher with ARS-1 compared to EpiPen and 30% higher compared to Epinephrine IM injection.

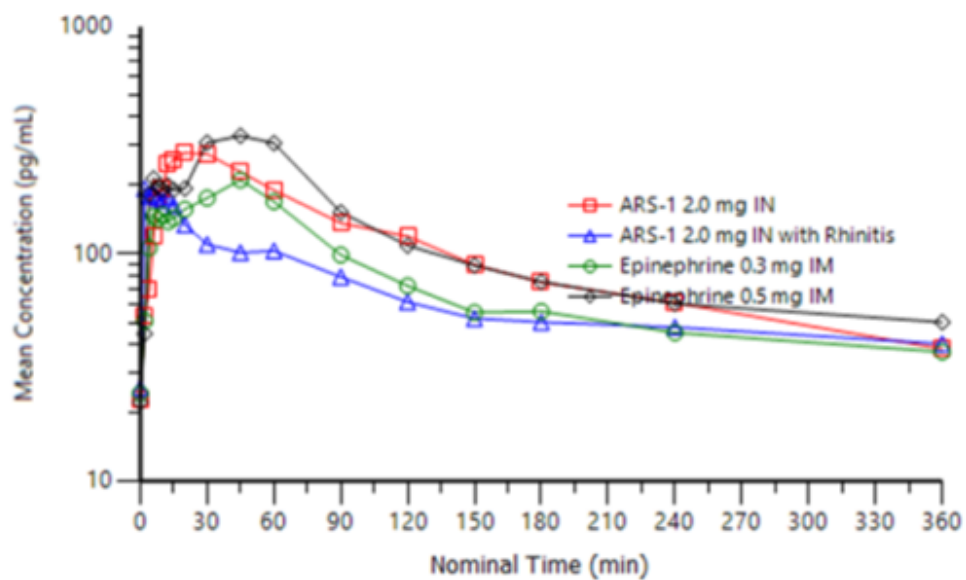
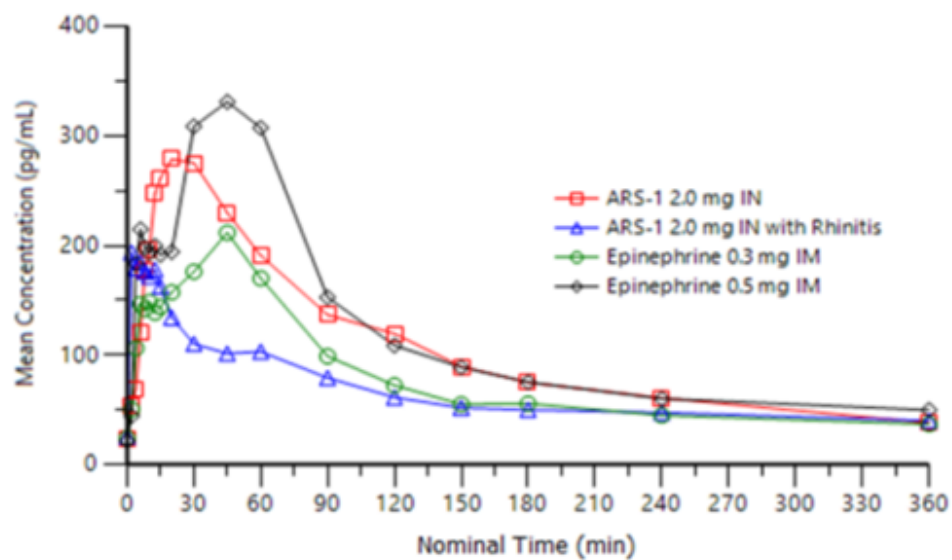
A second dose administration in the same and opposite nostril showed an increase of C_{max} (ARS 1 (L/R) - 805 pg/mL and ARS-1 (R/R) - 946 pg/mL. The mean C_{max} after second dose of EpiPen was 719 pg/mL. C_{max} values were not significant different between treatment groups of twice dosing. Total exposure (AUC_{last}) after ARS-1 (R-R) was 45% higher compared to EpiPen and 14% higher compared to ARS-1 (L/R).

EPI 16. A Four-Treatment, Partially Randomized, Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis (EPI 16).

Pharmacokinetic Results

Figure 26 Mean Epinephrine Concentration-Time Profiles (Primary Population)





Noncompartmental Analysis

Table 19 Summary Statistics of Epinephrine Pharmacokinetic Parameters – 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 2.0 mg	36	20.0 (2.00-120)	491 (65.2)	386	37100 (66.1)	29400
ARS-1 2.0 mg with rhinitis	33	6.00 (2.00-90.0)	309 (66.2)	260	23500 (69.1)	19700
Epinephrine IM 0.3 mg	31	45.0 (4.00 – 60.0)	283 (54.9)	245	27700 (37.5)	25900
Epinephrine IM 0.5 mg	31	45.0 (4.00 – 360)	452 (81.1)	346	42400 (40.2)	39400

Table 20 Epinephrine 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 2.0 mg	36	77.1 (83.4)	56.4	201 (81.0)	149	391 (81.9)	284	688 (90.5)	476	1060 (92.8)	738	1630 (85.6)	1170	2270 (83.5)	1640
ARS-1 2.0 mg with rhinitis	33	218 (76.6)	176	584 (66.6)	490	946 (57.5)	816	1300 (55.5)	1130	1660 (55.4)	1440	2100 (54.1)	1840	2520 (56.6)	2200
Epinephrine IM 0.3 mg	31	73.9 (64.9)	59.6	229 (63.3)	183	480 (71.8)	354	767 (75.7)	548	1060 (72.6)	763	1410 (70.2)	1030	1760 (70.5)	1280
Epinephrine IM 0.5 mg	31	69.5 (72.2)	54.2	293 (118)	202	679 (142)	436	1090 (139)	694	1480 (134)	957	1970 (126)	1310	2460 (119)	1680
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 _{0-360min}	
		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 2.0 mg	36	3630 (78.7)	2700	6400 (67.1)	5120	10200 (62.4)	8240	13400 (62.1)	10700	22200 (65.7)	17600	38700 (62.2)	32100	25000 (76.8)	19800
ARS-1 2.0 mg with rhinitis	33	3270 (64.3)	2800	4490 (69.6)	3800	6080 (72.1)	5140	7620 (75.8)	6380	12500 (77.6)	10300	24300 (66.1)	20700	16600 (65.1)	13900
Epinephrine IM 0.3 mg	31	2490 (72.4)	1820	4150 (69.0)	3250	7060 (61.7)	5900	9920 (57.9)	8530	16500 (46.5)	14900	28300 (36.0)	26600	18400 (36.4)	17200
Epinephrine IM 0.5 mg	31	3420 (107)	2450	5870 (84.6)	4480	10600 (70.4)	8310	15300 (64.8)	12300	26100 (54.8)	22400	42400 (40.1)	39500	27100 (39.3)	25500

Comparative Bioavailability

Statistical analyses of the PK parameters between treatments for the primary population are presented in Table 21. (normal nasal conditions) and Table 22 (rhinitis). Statistical analyses of the PK parameters of ARS-1 2.0 mg under normal nasal conditions versus rhinitis are presented in Table 23.

Table 21 Statistical Analysis of the Pharmacokinetic Parameters after Administration of ARS-1 2.0 mg IN (Normal Nasal Conditions) and Epinephrine IM (0.3 mg and 0.5 mg) – Primary Population

Test vs Ref	Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		p-value ^d	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 2.0 mg IN vs Epinephrine 0.3 mg IM	C _{max}	386	248	155.64	124.36	194.80	0.0015	58.95
	AUC ₀₋₂	56.4	59.1	95.39	74.85	121.55	0.7468	64.55
	AUC ₀₋₄	149	181	82.00	62.72	107.21	0.2218	73.07
	AUC ₀₋₆	284	353	80.46	59.68	108.49	0.2300	83.96
	AUC ₀₋₈	476	546	87.09	63.28	119.86	0.4739	91.70
	AUC ₀₋₁₀	738	763	96.63	70.19	133.03	0.8589	91.90
	AUC _{0-12.5}	1170	1040	112.97	82.81	154.13	0.5157	88.39
	AUC ₀₋₁₅	1640	1290	126.60	93.58	171.28	0.1979	85.16
	AUC ₀₋₂₀	2700	1840	146.49	110.61	194.00	0.0263	77.44
	AUC ₀₋₃₀	5120	3290	155.68	123.63	196.03	0.0019	60.79
	AUC ₀₋₄₅	8240	5940	138.58	113.07	169.86	0.0091	52.61
	AUC ₀₋₆₀	10700	8560	125.28	103.31	151.93	0.0552	49.50
ARS-1 2.0 mg IN vs Epinephrine 0.5 mg IM	AUC ₀₋₁₂₀	17600	14800	118.97	99.03	142.93	0.1191	46.86
	AUC _{last}	29400	25600	115.03	95.82	138.10	0.2060	46.73
	C _{max}	386	344	112.36	89.78	140.63	0.3903	58.95
	AUC ₀₋₂	56.4	54.2	103.99	81.60	132.51	0.7893	64.55
	AUC ₀₋₄	149	201	73.91	56.53	96.63	0.0641	73.07
	AUC ₀₋₆	284	433	65.50	48.58	88.32	0.0208	83.96
	AUC ₀₋₈	476	689	69.09	50.20	95.08	0.0574	91.70
	AUC ₀₋₁₀	738	951	77.54	56.32	106.75	0.1894	91.90
	AUC _{0-12.5}	1170	1300	89.67	65.73	122.33	0.5611	88.39
	AUC ₀₋₁₅	1640	1670	97.88	72.35	132.41	0.9063	85.16
	AUC ₀₋₂₀	2700	2430	110.79	83.66	146.73	0.5459	77.44
	AUC ₀₋₃₀	5120	4430	115.41	91.65	145.32	0.3043	60.79
	AUC ₀₋₄₅	8240	8160	100.97	82.38	123.76	0.9372	52.61
	AUC ₀₋₆₀	10700	12000	89.39	73.71	108.40	0.3364	49.50
	AUC ₀₋₁₂₀	17600	21800	80.91	67.35	97.21	0.0582	46.86
	AUC _{last}	29400	38500	76.37	63.62	91.69	0.0161	46.73

Table 22 Statistical Analysis of the Pharmacokinetic Parameters after Administration of ARS-1 2.0 mg IN (Rhinitis) and Epinephrine IM (0.3 mg and 0.5 mg) – Primary Population

Test vs Ref	Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		p-value ^d	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 2.0 mg IN vs Epinephrine 0.3 mg IM	C _{max}	263	248	106.06	84.32	133.40	0.6711	58.95
	AUC ₀₋₂	174	59.1	294.68	230.02	377.52	<0.0001	64.55
	AUC ₀₋₄	487	181	268.60	204.24	353.24	<0.0001	73.07
	AUC ₀₋₆	813	353	230.71	170.00	313.11	<0.0001	83.96
	AUC ₀₋₈	1130	546	207.16	149.49	287.08	0.0004	91.70
	AUC ₀₋₁₀	1440	763	188.79	136.19	261.71	0.0017	91.90
	AUC _{0-12.5}	1840	1040	177.35	129.12	243.58	0.0035	88.39
	AUC ₀₋₁₅	2200	1290	170.05	124.87	231.57	0.0053	85.16
	AUC ₀₋₂₀	2800	1840	152.23	114.24	202.86	0.0169	77.44
	AUC ₀₋₃₀	3830	3290	116.55	92.09	147.50	0.2829	60.79
	AUC ₀₋₄₅	5190	5940	87.24	70.86	107.40	0.2781	52.61
	AUC ₀₋₆₀	6450	8560	75.31	61.84	91.71	0.0189	49.50
	AUC ₀₋₁₂₀	10400	14800	70.35	58.32	84.86	0.0024	46.86
	AUC _{last}	19800	25600	77.65	64.42	93.59	0.0268	46.73
ARS-1 2.0 mg IN vs Epinephrine 0.5 mg IM	C _{max}	263	344	76.57	60.87	96.30	0.0561	58.95
	AUC ₀₋₂	174	54.2	321.25	250.76	411.56	<0.0001	64.55
	AUC ₀₋₄	487	201	242.09	184.08	318.38	<0.0001	73.07
	AUC ₀₋₆	813	433	187.81	138.39	254.89	0.0009	83.96
	AUC ₀₋₈	1130	689	164.34	118.59	227.74	0.0131	91.70
	AUC ₀₋₁₀	1440	951	151.50	109.29	210.01	0.0373	91.90
	AUC _{0-12.5}	1840	1300	140.76	102.49	193.34	0.0767	88.39
	AUC ₀₋₁₅	2200	1670	131.46	96.54	179.03	0.1444	85.16
	AUC ₀₋₂₀	2800	2430	115.14	86.41	153.43	0.4166	77.44
	AUC ₀₋₃₀	3830	4430	86.40	68.27	109.34	0.3050	60.79
	AUC ₀₋₄₅	5190	8160	63.56	51.63	78.25	0.0005	52.61
	AUC ₀₋₆₀	6450	12000	53.73	44.12	65.44	<0.0001	49.50
	AUC ₀₋₁₂₀	10400	21800	47.84	39.66	57.71	<0.0001	46.86
	AUC _{last}	19800	38500	51.55	42.77	62.14	<0.0001	46.73

Table 23 Statistical Analysis of the Pharmacokinetic Parameters after Administration of ARS-1 2.0 mg IN Under Rhinitis and Normal Nasal Conditions

Test vs Ref	Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		p-value ^d	ANOVA CV%
		Test	Ref		Lower	Upper		
ARS-1 2.0 mg IN (Rhinitis) vs ARS-1 2.0 mg IN	C _{max}	263	386	68.14	54.69	84.90	0.0047	58.95
	AUC ₀₋₂	174	56.4	308.93	243.62	391.77	<0.0001	64.55
	AUC ₀₋₄	487	149	327.56	251.83	426.06	<0.0001	73.07
	AUC ₀₋₆	813	284	286.73	213.83	384.47	<0.0001	83.96
	AUC ₀₋₈	1130	476	237.87	173.84	325.47	<0.0001	91.70
	AUC ₀₋₁₀	1440	738	195.38	142.73	267.45	0.0006	91.90
	AUC _{0-12.5}	1840	1170	156.98	115.72	212.96	0.0159	88.39
	AUC ₀₋₁₅	2200	1640	134.32	99.84	180.69	0.1018	85.16
	AUC ₀₋₂₀	2800	2700	103.92	78.90	136.89	0.8170	77.44
	AUC ₀₋₃₀	3830	5120	74.86	59.73	93.83	0.0358	60.79
	AUC ₀₋₄₅	5190	8240	62.95	51.58	76.83	0.0002	52.61
	AUC ₀₋₆₀	6450	10700	60.11	49.77	72.60	<0.0001	49.50
	AUC ₀₋₁₂₀	10400	17600	59.13	49.41	70.76	<0.0001	46.86
	AUC ₀₋₃₆₀	20800	31700	65.66	55.89	77.15	<0.0001	41.30
	AUC ₆₀₋₃₆₀	14000	19600	71.11	58.90	85.86	0.0034	49.10
	AUC _{last}	19800	29400	67.50	56.44	80.73	0.0004	46.73

A four treatment, crossover study of the bioavailability and PK of epinephrine administrated by ARS -1 or epinephrine injection in subjects with allergic rhinitis was performed.

Mean C_{max} after Ars-1 2.0 mg in normal conditions was 491 pg/mL and after ARS-1 2.0 mg in rhinitis was 309 pg/mL. Mean C_{max} after IM epinephrine 0.5 mg was 452 pg/mL and after IM epinephrine 0.3 mg was 283 pg/mL. Median t_{max} was for ARS-1 2.0 administrated with rhinitis condition 6.0 min and for Ars-1 2.0 administrated under normal conditions was 20.0. min. Median t_{max} values were 45.0 minutes for both the 0.3 mg and 0.5 mg IM Epinephrine doses. AUC_{last} was 37100 min*pg/mL for ARS-1 2.0 mg with normal nasal conditions and 23500 min*pg/mL for ARS-1 2.0 mg with rhinitis.

After ARS-1 2.0 mg administration mean C_{max} values caused 56% higher peak exposure compared to IM Epinephrine 0.3 mg. Under normal nasal conditions, no significant changes in total exposure between ARS-1 2.0 mg and IM Epinephrine 0.3 mg was observed. ARS-1 2.0 mg during rhinitis administration caused comparable to Epinephrine 0.3 mg and 0.5 mg C_{max}. AUC_{last} after ARS-1 2.0 mg administration during rhinitis resulted in lower exposure compared to IM Epinephrine 0.3 mg. C_{max} was higher following ARS-1 2.0 mg under normal nasal compared rhinitis (C_{max} of 386 pg/mL versus 263 pg/mL). Total exposure to epinephrine (AUC_{last}) was reduced under rhinitis conditions compared to normal.

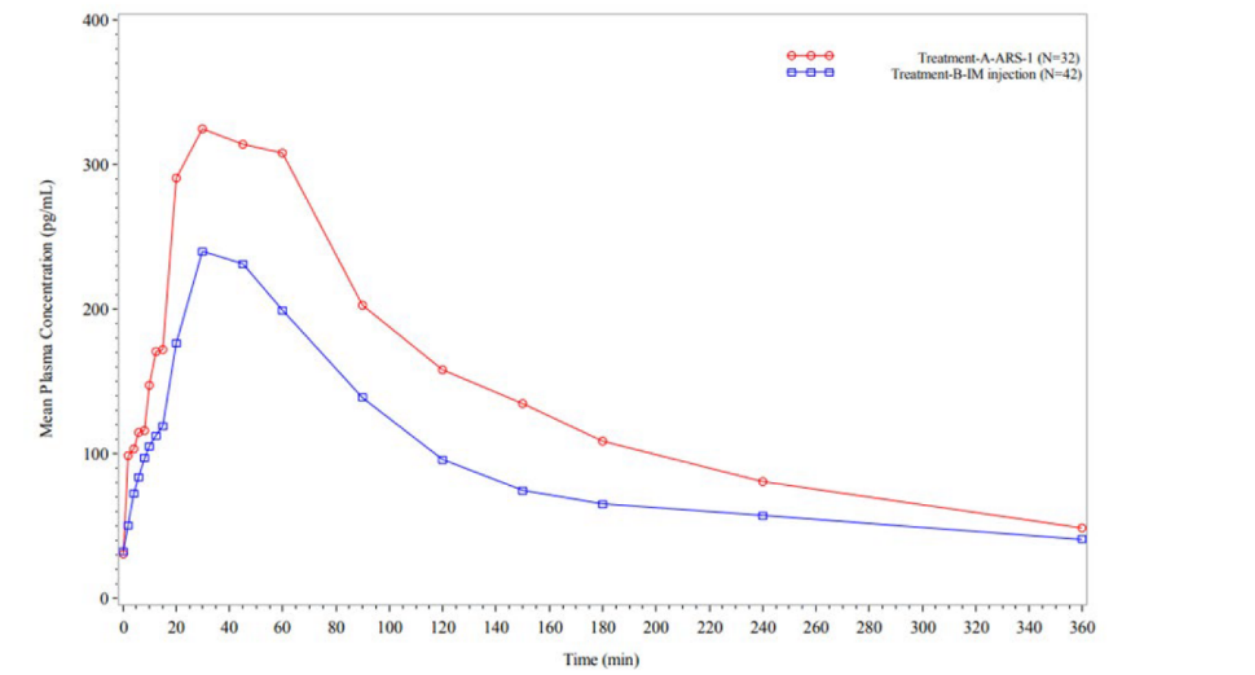
EPI 17 study results

Pharmacokinetic Results

Plasma Concentrations

Mean plasma epinephrine concentrations in the primary population sorted by treatment are presented in Figure 27 (linear scale).

Figure 27 Mean Epinephrine Concentration-Time Profiles after Administration of ARS-1 2.0 mg IN and Epinephrine 0.3 mg IM – Linear Scale (Primary Population)



Pharmacokinetic Parameters

Noncompartmental Analysis

Summary statistics of PK parameters sorted by treatment are presented in Table 24 and Table 25
Summary statistics of epinephrine partial AUCs, sorted by treatment, are presented in Table 26.

Table 24 Summary Statistics of Epinephrine Pharmacokinetic Parameters – 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 2.0 mg	32	30.0 (10.0 – 240)	448 (67.1)	342	50365 (55.5)	41077
Epinephrine 0.3 mg IM	42	45.0 (4.0 – 120)	322 (65.0)	274	33494 (41.0)	31085

Table 25 Summary Statistics of Epinephrine Pharmacokinetic Parameters – Subjects with Nasal Drip (Subjects Excluded from 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 2.0 mg	10	30.0 (6.0 – 60.0)	334 (55.2)	301	35292 (42.7)	32623
Epinephrine 0.3 mg IM	N/A					

Table 26 Epinephrine 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 2.0 mg	32	129 (105.8)	93.7	333 (113.7)	233	550 (106)	392	792 (96.3)	575	1069 (91.5)	779	1478 (88.1)	1074	1936 (83.1)	1415
Epinephrine 0.3 mg IM	42	83.4 (65.2)	68.8	207 (89.1)	157	364 (104)	265	545 (103)	396	748 (98.0)	550	1021 (91.4)	760	1317 (86.7)	985

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 _{0-360min}	
		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 2.0 mg	32	3128 (75.3)	2340	6213 (69.2)	4799	11006 (64.8)	8558	15678 (61.9)	12215	28767 (59.4)	22663	50412 (55.2)	41457	34734 (59.0)	28218
Epinephrine 0.3 mg IM	42	2057 (79.0)	1549	4136 (75.6)	3095	7677 (75.2)	5803	10907 (69.7)	8585	19525 (51.0)	17397	33642 (40.1)	31446	22735 (37.3)	21212

Comparative Bioavailability

Statistical analyses of the PK parameters between ARS-1 2.0 mg and Epinephrine 0.3 mg IM are presented in Table 27.

Table 27 Statistical Analysis of the Pharmacokinetic Parameters after Administration of ARS-1 2.0 mg IN and IM Epinephrine 0.3 mg IM – Primary Population

Test vs Ref	Dependent Variable	In-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 _{max}	335.981	262.635	127.9	97.12	168.50	0.1400	73.6
	AUC ₀₋₂	91.498	66.513	137.6	111.88	169.15	0.0137	50.0
	AUC ₀₋₄	226.931	151.928	149.4	117.53	189.83	0.0079	59.4
	AUC ₀₋₆	379.653	256.521	148.0	114.15	191.89	0.0155	65.8
	AUC ₀₋₈	550.846	381.548	144.4	109.8	189.82	0.0297	70.7
	AUC ₀₋₁₀	739.628	527.183	140.3	107.06	183.86	0.0416	69.6
	AUC _{0-12.5}	1011.254	729.055	138.7	105.31	182.69	0.0525	71.5
	AUC ₀₋₁₅	1329.572	949.055	140.1	105.48	186.07	0.0525	74.4
	AUC ₀₋₂₀	2234.207	1500.239	148.9	110.93	199.93	0.0285	78.5
	AUC ₀₋₃₀	4748.657	2977.097	159.5	118.05	215.51	0.0128	81.1
	AUC ₀₋₄₅	8512.675	5524.213	154.1	113.77	208.73	0.0213	82.4
	AUC ₀₋₆₀	12052.955	8129.951	148.3	110.13	199.57	0.0315	80.5
	AUC ₀₋₁₂₀	22243.095	16575.853	134.2	103.88	173.34	0.0602	67.5
	AUC ₀₋₃₆₀	39382.474	29498.498	133.5	108.50	164.27	0.0242	52.1

Two period- crossover study in subjects with type I allergies was performed to assess PK, PD and Dosing Errors After Self- Administration of Epinephrine with Intranasal ARS-1 as compared to IM injection.

In both primary and secondary population no changes between C_{max} were observed after ARS-1 2.0 mg and Epinephrine 0.3 mg IM administration. In both populations ARS-1 2.0 mg caused greater exposure compared to epinephrine 0.3 mg IM in timepoints of 10-, 20-, and 45-minutes post-dose. AUC_{0-t} was greater after ARS-1 2.0 mg administration compared to Epinephrine 0.3 mg IM.

Exclusion of nasal drip subjects did not influence final analysis results. Nasal drip subjects C_{max} were lower compared to subjects without nasal drip, however it was still greater than in subjected administrated with Epinephrine 0.3 mg IM. Self-administration of ARS-1 2.0 mg resulted in greater C_{max}, more rapid t_{max} and greater overall exposure (AUC_{0-t}) relative to epinephrine 0.3 mg IM.

Study EPI 18 results

- To evaluate the safety and tolerability of Eurneffy in subjects as compared to IM 0.3 mg.

Results

A total of 43 subjects were enrolled, with 41 (95.3%) subjects completing the study. Subjects ranged in age from 24 to 63 years. Nineteen subjects (44.2%) were male, and 24 subjects (55.8%) were female.

Sixteen subjects (37.2%) were White; 18 subjects (41.9%) were Black or African American; six subjects (14.0%) were Asian; and three subjects (7.0%) were American Indian or Alaska Native. Six subjects (14.0%) were Hispanic or Latino and 37 subjects (86.0%) were not Hispanic or Latino.

Pharmacokinetic Parameters – Primary Analysis

Under normal nasal conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean C_{max} of 1064 pg/mL and a mean AUC_{last} of 68230 min*pg/mL and IM 0.3 mg twice resulted in mean C_{max} of 420 pg/mL and a mean AUC_{last} of 37311 min*pg/mL. Median t_{max} values were 20 minutes for Eurneffy 2.0 mg twice (R/L) and 55 minutes for IM 0.3 mg twice.

Under rhinitis conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean C_{max} of 581 pg/mL and mean AUC_{last} of 35723 min*pg/mL and Eurneffy 2.0 mg twice (R/R) resulted in a mean C_{max} of 852 pg/mL and mean AUC_{last} of 66424 min*pg/mL. Under rhinitis conditions, IM 0.3 mg twice resulted in mean C_{max} of 495 pg/mL and a mean AUC_{last} of 42821 min*pg/mL. Median t_{max} values were 15 minutes for Eurneffy 2.0 mg twice (R/L), 20 minutes for Eurneffy 2.0 mg twice (R/R), and 45 minutes for IM 0.3 mg twice.

Comparative Bioavailability – Primary Analysis

Under normal nasal conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater exposure at all timepoints through 60 minutes post-dose. Under rhinitis conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater exposure through 30 minutes post-dose; and Eurneffy 2.0 mg twice (R/R) resulted in significantly greater exposure through 45 minutes post-dose.

Exploratory PK Analyses

- Baseline adjusted analysis: All key PK parameters were consistent between total epinephrine values and baseline adjusted values.
- Comparison Using “Responder” Subjects: The PK results based on Responders (TNSS 5+ and Congestion score 2+) and various nasal conditions were similar to what was observed in the Primary analysis, which was based on all subjects.
- Median and Geometric Mean analysis: Key PK-time profiles and parameters were consistent among mean, median, and geometric mean.

Supportive studies

EPI 04. A Five-Treatment, Partially Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis.

Primary objective was to assess the comparative bioavailability after intranasal (IN) administration of ARS-1 1.0 mg IN in subjects with induced allergic rhinitis and to evaluate the impact of nasal oedema and congestion on the absorption of epinephrine. Secondary objectives were to assess the comparative bioavailability of ARS-1 when administered in subjects under normal conditions to epinephrine injection administered both by the IM and SC routes and to evaluate the safety and tolerability of ARS-1 1.0 mg in subjects after IN administration of epinephrine as compared to alternate routes of administration by IM and SC administration.

Pharmacokinetic Assessments

Pharmacokinetic parameters were calculated without the subtraction of the pre-dose epinephrine concentrations. The following PK parameters for epinephrine were calculated using non-compartmental

analysis: C_{max}, t_{max}, AUC(0-t), for the first 60 minutes [AUC(0-60min)], and partial AUC values for the first 20 minutes after administration of study drug [AUC(0- 10min), AUC(0-15min), AUC(0-20min)).

Pharmacokinetic Results

C_{max}: Under normal conditions, the pharmacokinetic profile of ARS-1 is comparable to Epinephrine 0.3 mg IM and 0.3 mg SC. The mean C_{max} values were similar amongst the three products (ARS-1 1.0 mg IN, Epinephrine 0.3 mg IM and Epinephrine 0.3 mg SC), with geometric mean values of 243, 232, and 214 pg/mL, respectively. The highest value occurred with Epinephrine 0.5 mg IM, with a geometric mean of and 347 pg/mL.

t_{max}: ARS-1 1.0 mg IN reached C_{max} values sooner compared to the Epinephrine 0.3 mg IM, Epinephrine 0.3 mg SC, and Epinephrine 0.5 mg IM with median t_{max} values of 20 minutes following ARS-1 1.0 mg IN administration and 45 minutes following IM and SC administrations.

AUC_{0-t}: The AUC_{0-t} values followed a similar pattern as seen for C_{max} in that the ARS-1 1.0 mg IN resulted in a similar exposure to the Epinephrine 0.3 mg IM and Epinephrine 0.3 mg SC (25200, 25500, and 28400 min•pg/mL, respectively), but the Epinephrine 0.5 mg IM resulted in a notably higher geometric mean AUC_{0-t} value (42500 min•pg/mL).

Partial AUC: A descriptive summarization of the partial AUCs over the initial dosing period for total epinephrine values is presented in Table 28. During the first 4 minutes post dose, under normal conditions, ARS-1 1.0 mg IN resulted in a similar exposure to that of the Epinephrine 0.3 mg IM in terms of the ratios of the C_{max} and partial AUC values. Beyond 10 minutes post dose, ARS-1 1.0 mg IN resulted in noticeably higher partial AUCs, yet the total AUC_{0-t} values were comparable (ratio close to 100%) between the two products.

Table 28 Epinephrine partial AUCs, sorted by treatment and allergic status – total epinephrine values

Treatment	N	AUC 0-2min	AUC 0-4min	AUC 0-6min	AUC 0-8min	AUC 0-10min	AUC 0-12.5min	AUC 0-15min	AUC 0-20min	AUC 0-30min	AUC 0-45min	AUC 0-60min
		Geometric Mean (% CV)										
ARS-1 1.0 mg IN	35	53.8 (70.4)	146 (78.0)	271 (83.4)	422 (89.4)	644 (80.3)	988 (74.4)	1330 (73.6)	2110 (68.3)	3960 (63.2)	6490 (62.9)	8570 (63.5)
ARS-1 1.0 mg IN with Rhinitis	33	130 (72.4)	384 (70.8)	715 (69.2)	1100 (69.7)	1580 (67.4)	2250 (68.8)	2810 (71.6)	3790 (76.4)	5270 (81.2)	6730 (80.8)	7820 (78.7)
Epinephrine 0.3 mg IM	36	59.3 (94.3)	152 (121)	258 (139)	366 (142)	481 (135)	364 (125)	785 (117)	1140 (105)	2160 (87.2)	4420 (69.1)	7030 (57.6)
Epinephrine 0.3 mg SC	35	40.2 (81.4)	96.0 (88.6)	170 (94.0)	254 (101)	370 (97.6)	534 (97.3)	686 (97.2)	1020 (92.6)	2020 (76.7)	4180 (65.6)	6640 (57.7)
Epinephrine 0.5 mg IM	23	52.1 (97.4)	145 (115)	284 (112)	449 (111)	650 (108)	924 (107)	1180 (107)	1790 (105)	3630 (86.7)	7330 (69.1)	11300 (59.5)

Comparative Bioavailability

Compared to administration of ARS-1 1.0 mg IN in the normal state, administration of ARS-1 1.0 mg IN in the rhinitis stated resulted in C_{max} and AUC_{0-t} values that were 133% and 77% of the normal, respectively.

Compared to the Epinephrine 0.3 mg IM, ARS-1 1.0 mg IN resulted in C_{max} and AUC_{0-t} values that were 104% and 98% of the IM, respectively.

Compared to the Epinephrine 0.5 mg IM product, ARS-1 1.0 mg IN resulted in C_{max} and AUC_{0-t} values that were 68% and 58% of the IM, respectively. Compared to the Epinephrine 0.3 mg SC product, ARS-1 1.0 mg IN resulted in C_{max} and AUC_{0-t} values that were 113% and 88% of the SC, respectively. Comparative bioavailability of ARS-1 1.0 mg IN versus Epinephrine 0.3 mg IM resulted in

a ratio % reference for $\ln(\text{AUC}_{0-t}/\text{Dose})$ of 30. Comparative bioavailability of ARS-1 1.0 mg IN versus Epinephrine 0.3 mg SC resulted in a ratio % reference for $\ln(\text{AUC}_{0-t}/\text{Dose})$ of 27.

Effect of rhinitis:

Rhinitis conditions increased the rate of epinephrine absorption when administered via ARS-1. Comparison of the allergic state to that of the normal state for the ARS- 1 1.0 mg IN showed that those subjects with allergic rhinitis reached C_{max} earlier, with a median t_{max} of 10 minutes compared to the normal state, with a median t_{max} value of 20 minutes. The geometric mean C_{max} value was greater for subjects with allergic rhinitis (320 pg/mL) as compared to the normal state (243 pg/mL). The geometric mean AUC_{0-t} values were lower for subjects with allergic rhinitis (19200 min•pg/mL) compared to the normal state (25200 min•pg/mL). All parameters were similar between corrected and uncorrected values.

Table 29 Comparative bioavailability of ARS-1 1.0 mg IN vs epinephrine 0.3 mg IM – total epinephrine values

PK Parameter	Test	FormRef	Ratio % Reference	Upper 90% CI	Lower 90% CI
Calculated Using Total Epinephrine Concentrations					
$\ln(\text{AUC}_{0-t}/\text{Dose})$	Normal: IN 1.0 mg	Normal: IM 0.3 mg	30	26	34

Table 30 Comparative bioavailability of ARS-1 1.0 mg IN vs epinephrine 0.3 mg SC – total epinephrine values

PK Parameter	Test	FormRef	Ratio % Reference	Upper 90% CI	Lower 90% CI
Calculated Using Total Epinephrine Concentrations					
$\ln(\text{AUC}_{0-t}/\text{Dose})$	Normal: IN 1.0 mg	Normal: SC 0.3 mg	27	23	31

Exploratory Pharmacokinetic Analyses

The following exploratory pharmacokinetic analyses were conducted: time to reach and time above 100 pg/mL, baseline corrected pharmacokinetic calculations, dose adjusted analysis, weight adjusted analysis, bioequivalence.

Time to Reach 100 pg / mL and Time Above 100 pg / m

While the overall exposure for ARS-1 1.0 mg IN was proportionally lower relative to Epinephrine 0.5 mg IM, the time to 100 pg/mL and partial AUC exposures in the first 30 minutes were essentially the same. Intranasal administration during the allergic rhinitis state appears to shorten the time it takes to reach 100 pg/mL.

94% of normal subjects and 100% of rhinitis subjects receiving ARS-1 1.0 mg IN reached the critical plasma concentration of 100 pg/mL within 10 minutes of dosing. In contrast 61% of subjects receiving Epinephrine 0.3 mg IM, 66% of subjects receiving Epinephrine 0.3 mg SC, and 78% of subjects receiving Epinephrine 0.5 mg IM reached 100 pg/mL within 10 minutes.

The arithmetic mean time for epinephrine plasma concentrations to reach the 100 pg/mL was found to be dependent both on allergic state and the product used (3.3.1.1.42). Of the four products administered in the normal condition, the mean time it took for epinephrine plasma concentrations to reach the 100 pg/mL level was as follows (from shortest to the longest): 9.68 minutes for ARS-1 1.0 mg IN; 12.6 minutes for Epinephrine 0.5 mg IM; 21.6 minutes for

Epinephrine 0.3 mg IM; and 23.6 minutes for Epinephrine 0.3 mg SC. Intranasal administration of ARS-1 1.0 mg IN in the allergic rhinitis condition appeared to accelerate the absorption of epinephrine, with the mean time to reach the 100 pg/ mL decreasing from 9.68 minutes in the normal condition to 2.42 minutes in the allergic rhinitis condition.

Table 31 Summary statistics time to reach 100 pg / mL, sorted by treatment and allergic status

Treatment	N	Time to Reach 100 mg/mL (min)		
		Mean (SD)	Minimum	Maximum
ARS-1 1.0 mg IN	32	9.68 (7.77)	0.759	32.1
ARS-1 1.0 mg IN with Rhinitis	31	2.42 (1.90)	0.207	8.29
Epinephrine 0.3 mg IM	35	21.6 (17.8)	0.267	59.2
Epinephrine 0.3 mg SC	33	23.6 (17.9)	0.966	81.6
Epinephrine 0.5 mg IM	23	12.6 (11.6)	0.338	47.4

The arithmetic mean for the cumulative time epinephrine plasma concentrations were above the 100 pg/mL level varied both by allergic state and product. Listing the products from longest to shortest, mean time above 100 pg/mL level was as follows: Epinephrine 0.5 mg IM (148 minutes); Epinephrine 0.3 mg SC (85.1 minutes); ARS-1 1.0 mg IN (78.0 minutes); and Epinephrine 0.3 mg IM (63.3 minutes). All drug products were administered in the normal condition. Intranasal administration of ARS-1 1.0 mg IN in the allergic rhinitis condition appeared to shorten the meantime plasma concentrations were above 100 pg/mL from 78.0 minutes in the normal condition to 43.8 minutes in the allergic rhinitis condition.

Table 32 Summary statistics to time above 100 pg / mL, sorted by treatment and allergic status

Treatment	N	Time Above 100 mg/mL (min)		
		Mean (SD)	Minimum	Maximum
ARS-1 1.0 mg IN Normal	35	78.0 (50.7)	0.00	164
ARS-1 1.0 mg IN with Rhinitis	33	43.8 (55.5)	0.00	281
Epinephrine 0.3 mg IM	36	63.3 (43.8)	0.00	247
Epinephrine 0.3 mg SC	33	85.1 (60.3)	0.00	249
Epinephrine 0.5 mg IM	23	148 (69.5)	48.1	313

Compared to IM or SC injections, a higher percentage of subjects reached 50 pg/mL, 100 pg/mL and 200 pg/mL plasma levels within 10 minutes following administration of ARS-1. Following administration of ARS-1 1.0 IN, 94% of normal subjects and 100% of rhinitis subjects reached the critical plasma concentration of 100 pg/mL within 10 minutes of dosing. In contrast only 61% of subjects receiving Epinephrine 0.3 mg IM, 66% of subjects receiving Epinephrine 0.3 mg SC, and 78% of subjects receiving Epinephrine 0.5 mg IM reached 100 pg/mL within 10 minutes. This finding is consistent with the more rapid absorption of ARS-1.

Comparative Bioavailability

All key pharmacokinetic parameters and analyses were consistent between total epinephrine values and baseline corrected values.

While the baseline corrected values give the same overall results, some statistical power is lost with the baseline correction. The primary analysis of the study was based on uncorrected plasma levels, which takes into account the normal variability and fluctuations of endogenous epinephrine.

Table 33 Comparative bioavailability of ARS-1 1.0 mg vs epinephrine 0.3 mg IM (using total and baseline corrected epinephrine concentrations)

Dependent	Epinephrine Conc	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(AUC _{0-t} /Doses)	Total	30	26	34
	Baseline Corrected	32	25	40

Test = ARS-1 1.0 mg IN, Reference = Epinephrine 0.3 mg IM.

Table 34 Comparative bioavailability of ARS-1 1.0 mg vs epinephrine 0.3 mg SC (using total and baseline corrected epinephrine concentrations)

Dependent	Epinephrine Conc	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(AUC _{0-t} /Doses)	Total	27	23	31
	Baseline Corrected	27	20	36

Test = ARS-1 1.0 mg IN, Reference = Epinephrine 0.3 mg SC.

Bioequivalence

The results show that the Ln(AUC_{0-t}) values and corresponding 90% confidence intervals were within the US FDA bioequivalence acceptance range of 80.0 – 125.0% for the ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM comparisons. The Ln (C_{max}) was very similar between ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM injection with the upper limit just outside of the acceptance range.

ARS-1 1.0 mg IN versus Epinephrine IM 0.3 mg

Compared to the Epinephrine 0.3 mg IM, ARS-1 1.0 mg IN resulted in a C_{max} value of 104% (90% CI, 85 – 129%) and an AUC_{0-t} value of 98% (90% CI, 86 – 112%) relative to the Epinephrine 0.3 mg IM. Comparative bioavailability of ARS-1 1.0 mg IN versus Epinephrine 0.3 mg IM resulted in a ratio % reference for Ln(AUC_{0-t}/Dose) of 30 (90% CI, 26 – 34%).

ARS-1 1.0 mg IN versus Epinephrine SC 0.3 mg

Compared to the Epinephrine 0.3 mg SC product, ARS-1 1.0 mg IN resulted in a C_{max} value of 113% (90% CI, 90 – 142%) and an AUC_{0-t} value of 88% (90% CI, 76 – 103%) relative to the Epinephrine 0.3 mg SC. Comparative bioavailability of ARS-1 1.0 mg IN versus Epinephrine 0.3 mg SC resulted in a ratio % reference for Ln(AUC_{0-t}/Dose) of 27 (90% CI, 23 – 31%).

ARS-1 1.0 mg IN versus Epinephrine 0.5 mg IM

Compared to the Epinephrine 0.5 mg IM, ARS-1 1.0 mg IN resulted in a C_{max} value of 68% (90% CI, 55 – 85%) and an AUC_{0-t} value of 58% (90% CI, 48 – 69%) relative to the Epinephrine 0.5 mg IM.

ARS-1 1.0 mg IN versus ARS-1 1.0 mg IN with Rhinitis

Administration of ARS-1 1.0 mg IN in the normal stated resulted in a C_{max} value of 133% (90% CI, 109 – 162%) and an AUC_{0-t} value of 77% (90% CI, 66 – 89%) relative to administration in the rhinitis state.

EPI 07. A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 or EpiPen to Healthy Volunteers.

Primary objectives were to assess the comparative bioavailability of epinephrine after intranasal (IN) administration of ARS-1 (1.0 milligram (mg) with EpiPen (0.3 mg intramuscular [IM] injection of epinephrine) after both one and two doses in healthy volunteers under fasted conditions, to evaluate

the comparative pharmacodynamic (PD) response based on pulse and blood pressure (BP) using an automated blood pressure measuring device between treatment groups.

Secondary objectives were to assess the relative bioavailability of two doses of ARS-1 (1.0 mg intranasal) given as in the right and left nares, as compared to two doses in the left nares, to evaluate the safety and tolerability of ARS-1 and EpiPen in healthy volunteers.

Blood samples (4 mL each) were collected at predose each treatment period (at -10 and -5 minutes) and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240, 360 and 480 minutes after dosing. PD measurements included pulse and BP (systolic and diastolic pressure) on Day 0 through Day 4.

Pharmacokinetic Assessments

The following PK parameters for epinephrine were calculated using noncompartmental analysis: C_{max}, t_{max}, AUC(0-t), for the first 60 minutes [AUC(0-60min)], and partial AUC values for each time point for the first 20 minutes after administration of study medication [AUC(0-2min), AUC(0-4min), AUC(0-6min), AUC(0-8min), AUC(0-10min), AUC(0-12.5min), AUC(0-15min), AUC(0-20min)].

Exploratory PK analyses included an analysis of baseline-corrected PK data as well as an assessment of time to reach a plasma concentration of 100 picograms/millilitre (pg/mL). In addition, an exploratory PK/PD analyses of epinephrine plasma concentrations versus relevant core laboratory cardiovascular safety parameters was investigated.

PK sampling time points were based upon the initial study drug administration for the three study arms that required a second dosing after ten minutes. Actual times by hour/minutes/seconds were recorded.

Pharmacokinetic Results

Pharmacokinetic Parameters

The PK parameters were calculated without the subtraction of the pre-dose epinephrine concentrations. Exploratory analyses were performed on baseline corrected concentrations and the results demonstrated no meaningful differences in the comparative results relative to uncorrected results.

Table 35 Summary statistic of epinephrine PK parameters by treatment

Treatment	N	Median t _{max} (minutes)	C _{max} (geo. mean) (%CV)	pAUC ₀₋₁₅ (min*pg/mL) (%CV)	pAUC ₀₋₆₀ (min*pg/mL) (%CV)	AUC _{last} (geo. Mean) (min*pg/mL) (%CV)	AUC _{last} (median) (min*pg/mL)	F _{rel} (geo.mean) (%CV)
ARS-1 1.0 mg IN	35	20.0	245 (93.7)	6460 (88.3)	8560 (84.8)	23300 (87.5)	23500	0.252 (93.5)
ARS-1 1.0 mg IN twice (L/R)	35	20.0	536 (102)	13500 (95.6)	16900 (94.4)	39700 (92.3)	46300	0.235 (94.5)
ARS-1 1.0 mg IN twice (L/L)	36	20.0	873 (147)	19100 (131)	23500 (124)	47300 (107)	64800	0.287 (86.5)
EpiPen 0.3 mg	35	24.0	311 (68.2)	8270 (60.2)	10300 (56.3)	27000 (51.2)	27100	--
EpiPen 0.3 mg twice (L/R)	36	25.5	538 (68.6)	13900 (66.1)	18400 (56.3)	48100 (44.1)	47500	--

Source: Appendix 16.1.13 Pharmacokinetic Report, [In-Text Table 2](#) and [Appendix Table 3](#)

Table 36 Epinephrine partial AUCs, sorted by treatment – total epinephrine values

Treatment	N	AUC 0-2min	AUC 0-4min	AUC 0-6min	AUC 0-8min	AUC 0-10min	AUC 0-12.5min	AUC 0-15min	AUC 0-20min	AUC 0-30min	AUC 0-45min	AUC 0-60min
		Geometric Mean (% CV)										
ARS-1 1.0 mg IN	35	55.3 (78.9)	143 (87.1)	257 (92.8)	399 (94.0)	608 (94.7)	939 (96.5)	1270 (95.2)	2060 (90.0)	3910 (89.2)	6460 (88.3)	8560 (84.8)
ARS-1 1.0 mg IN twice (L/R)	35	65.9 (93.2)	184 (95.7)	350 (99.8)	567 (108)	1030 (109)	1790 (114)	2520 (113)	4490 (102)	8780 (9702)	13500 (95.6)	16900 (94.4)
ARS-1 1.0 mg IN twice (L/L)	36	67.8 (81.1)	182 (85.0)	358 (93.3)	589 (104)	1030 (115)	1910 (130)	2960 (139)	6010 (146)	12500 (146)	19100 (131)	23500 (124)
EpiPen 0.3 mg	35	77.0 (119)	242 (126)	480 (128)	757 (126)	1100 (115)	1560 (103)	1950 (96.5)	2900 (83.0)	5260 (69.1)	8270 (60.2)	10300 (56.3)
EpiPen 0.3 mg twice (L/R)	36	83.6 (131)	252 (169)	496 (182)	768 (178)	1110 (160)	1650 (138)	2310 (121)	4120 (98.4)	8270 (80.5)	13900 (66.1)	18400 (56.3)

Source: Appendix 16.1.13 Pharmacokinetic Report, In-Text Table 2

Comparative Bioavailability and Bioequivalence

Although the mean concentration-time profile suggests a double peak for both treatments, this was not consistently observed in the concentration-time data for individual subjects and there was considerable variability in the time to reach maximum epinephrine concentrations.

The mean C_{max} after ARS-1 1.0 mg IN was slightly lower than what was observed after EpiPen 0.3 mg, at 245 and 311 pg/mL, respectively. The mean C_{max} was approximately proportional between ARS-1 1.0 mg IN and ARS-1 1.0 mg IN twice (L/R), while the mean C_{max} following ARS-1 1.0 mg IN twice (L/L) was approximately 3.5-times greater than what was observed following ARS-1 1.0 mg IN.

Peak plasma epinephrine levels were achieved faster following ARS-1 1.0 mg IN. The median t_{max} for all doses of ARS-1 1.0 mg IN was 20 minutes; the median t_{max} for EpiPen 0.3 mg was 24 minutes, and the median t_{max} for EpiPen 0.3 mg twice was 25.5 minutes. ARS-1 vs EpiPen 0.3 mg IM: Based on partial AUCs, exposure to epinephrine was lower after ARS-1 1.0 mg IN through approximately 30 min post dose compared to EpiPen 0.3 mg IM.

However, based on AUCs based on data at later times (45 to 480 min), the differences between these treatments were less pronounced; the geometric mean AUC_{last} was 23300 min*pg/mL after ARS-1 1.0 mg IN and 27000 min*pg/mL after EpiPen 0.3 mg IM.

Table 37 Comparative bioavailability of ARS-1 1.0 mg IN and EpiPen 0.3 mg

Calculations Using Total Epinephrine Plasma Concentrations			
Dependent	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(C _{max})	80.06	63.35	101.16
Ln(AUC _{0-2min})	73.65	55.85	97.11
Ln(AUC _{0-4min})	59.96	44.49	80.82
Ln(AUC _{0-6min})	54.34	40.03	73.76
Ln(AUC _{0-8min})	53.55	39.31	72.95
Ln(AUC _{0-10min})	56.63	42.22	75.96
Ln(AUC _{0-12.5min})	61.94	46.84	81.91
Ln(AUC _{0-15min})	66.66	50.86	87.37
Ln(AUC _{0-20min})	72.59	56.62	93.05
Ln(AUC _{0-30min})	75.77	60.48	94.93
Ln(AUC _{0-45min})	79.34	64.17	98.09
Ln(AUC _{0-60min})	84.25	68.57	103.51
Ln(AUC _{60-360min})	107.14	90.45	126.91
Ln(AUC _{0-t})	88.35	71.82	108.69

Source: Appendix 16.1.13 Pharmacokinetic Report, In-Text Table 3

ARS-1 1.0 mg IN twice (L/R) vs ARS-1 1.0 mg IN twice (L/L): Based on partial AUCs, exposure was similar after ARS-1 1.0 mg IN twice (L/R) and ARS-1 1.0 mg IN twice (L/L). However, parameters based on data collected after the second administration (after 10 min) suggested higher exposure for the (L/L) treatment. The geometric mean AUClast was 39700 min*pg/mL after ARS-1 1.0 mg IN twice (L/R) and 47300 min*pg/mL after ARS-1 1.0 mg IN twice (L/L).

EpiPen 0.3 mg vs EpiPen 0.3 mg twice: The geometric mean AUClast was 27000 min*pg/mL after EpiPen 0.3 mg IM and 48100 h*pg/mL after EpiPen 0.3 mg IM twice. Overall, exposure after EpiPen 0.3 mg IM twice was less than 2-fold higher than that after EpiPen 0.3 mg IM. mg was similar for the 3 treatments; the mean Frel was 0.252 after ARS-1 1.0 mg IN, 0.235 after ARS-1 1.0 mg IN twice (L/R), and 0.287 after ARS-1 1.0 mg IN twice (L/L).

ARS-1 1.0 mg IN versus EpiPen 0.3 mg: From the comparison of ARS-1 1.0 mg IN to EpiPen 0.3 mg after single doses (Table 38), the geometric mean ratio (ARS-1/EpiPen) was 80.06% for C_{max} and ranged from 53.55 to 107.14% for AUCs. Hence, C_{max} was 20% lower for 1.0 mg ARS-1 compared to 0.3 mg EpiPen and partial AUCs at early time points were up to 46% lower. However, the differences between treatments were less pronounced at later time points. AUC₀₋₆₀ and AUC_{0-t} were 16% and 12% lower and AUC₆₀₋₃₆₀ was 7% higher for 1.0 mg ARS-1 relative to 0.3 mg EpiPen.

ARS-1.0 mg twice (L/R) versus EpiPen 0.3 mg twice. From the comparison of 1.0 mg ARS-1 twice (L/R) to EpiPen 0.3 mg twice (L/R) (Table 39), the geometric mean ratio (ARS-1/EpiPen) was 98.13% for C_{max} and ranged from 70.49 to 108.73% for AUCs. C_{max} was comparable between treatments and partial AUCs at early time points were up to 30% lower for ARS-1 1.0 mg IN twice (L/R). However, as noted previously in the discussion of the concentration-time data and PK parameters, the differences between these treatments were less pronounced after the second dose was administered and the partial AUCs through 12.5 to 30 min were approximately 4 to 8% higher for ARS-1 1.0 mg IN twice (L/R).

ARS-1.0 mg twice (L/L) versus EpiPen 0.3 mg twice. From the comparison of 1.0 mg ARS-1 twice (L/L) to 0.3 mg EpiPen twice (L/R) (Table 40), the geometric mean ratio (ARS-1/EpiPen) was 162.04% for C_{max} and ranged from 71.78 to 150.48% for AUCs. Although C_{max} was 62% higher for ARS-1 1.0 mg IN twice (L/L), partial AUCs prior to the second dose were up to 28% lower. After the second dose, exposure was up to 50% higher for ARS-1 1.0 mg IN twice (L/L) compared to EpiPen 0.3 mg twice (L/R). Systemic exposure based on AUC₆₀₋₃₆₀ and AUC_{0-t} was similar for both treatments (and not significantly different based on the 90% confidence intervals within 80 to 125%).

Table 38 Comparative bioavailability of ARS-1 1.0 mg IN twice (L/R) and EpiPen 0.3 mg twice (L/R)

Calculations Using Total Epinephrine Plasma Concentrations			
Dependent	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(C _{max})	98.13	77.74	123.87
Ln(AUC _{0-2min})	79.74	60.57	104.98
Ln(AUC _{0-4min})	72.92	54.19	98.11
Ln(AUC _{0-6min})	70.49	52.02	95.51
Ln(AUC _{0-8min})	73.72	54.21	100.25
Ln(AUC _{0-10min})	91.75	68.50	122.87
Ln(AUC _{0-12.5min})	108.23	81.96	142.92
Ln(AUC _{0-15min})	108.73	83.07	142.32
Ln(AUC _{0-20min})	107.75	84.15	137.96
Ln(AUC _{0-30min})	103.89	83.01	130.04
Ln(AUC _{0-45min})	95.09	76.99	117.46

Calculations Using Total Epinephrine Plasma Concentrations			
Dependent	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(AUC _{0-60min})	90.47	73.70	111.05
Ln(AUC _{60-360min})	90.00	76.04	106.51
Ln(AUC _{0-t})	82.73	67.32	101.66

Source: Appendix 16.1.13 Pharmacokinetic Report, [In-Text Table 4](#)

Table 39 Comparative bioavailability of ARS-1 1.0 mg IN twice (L/R) and EpiPen 0.3 mg twice (L/R)

Calculations Using Total Epinephrine Plasma Concentrations			
Dependent	Ratio % Reference	Lower 90% CI	Upper 90% CI
Ln(C _{max})	162.04	128.67	204.08
Ln(AUC _{0-2min})	81.12	61.76	106.54
Ln(AUC _{0-4min})	71.93	53.59	96.53
Ln(AUC _{0-6min})	71.78	53.12	97.01
Ln(AUC _{0-8min})	76.21	56.19	103.35
Ln(AUC _{0-10min})	92.53	69.27	123.59
Ln(AUC _{0-12.5min})	116.01	88.08	152.80
Ln(AUC _{0-15min})	128.37	98.32	167.61
Ln(AUC _{0-20min})	146.06	114.34	186.57
Ln(AUC _{0-30min})	150.48	120.50	187.93
Ln(AUC _{0-45min})	137.19	111.30	169.10
Ln(AUC _{0-60min})	128.12	104.58	156.95
Ln(AUC _{60-360min})	95.37	80.71	112.69
Ln(AUC _{0-t})	99.16	80.85	121.62

Source: Appendix 16.1.13 Pharmacokinetic Report, [In-Text Table 5](#)

Dose proportionality assessments were based on dose normalised exposure parameters; a Test/Reference ratio of 100% indicates a proportional change in exposure with a change in dose.

For ARS-1 1.0 mg IN administered as single dose and ARS-1 1.0 mg IN twice (L/R), C_{max} and AUC₀₋₆₀ increased in an approximately proportional manner for the 2-fold increase in dose; for AUC₀₋₆₀, the 90% confidence intervals were within 80.00 to 125.00%, meeting the strict criteria for proportionality as defined in the PK SAP. The increase in AUC_{0-t} was slightly less than dose-proportional.

For ARS-1 1.0 mg IN administered as single dose and ARS-1 1.0 mg IN twice (L/L), C_{max} and AUC₀₋₆₀ increased in a greater than proportional manner for the 2-fold increase in dose. The increase in AUC_{0-t} was dose-proportional and the 90% confidence intervals were within 80.00 to 125.00%, meeting the strict criteria for proportionality as defined in the PK SAP. For EpiPen 0.3 mg administration as single dose and EpiPen 0.3 mg twice (L/R), C_{max}, AUC₀₋₆₀, and AUC_{0-t} increased in a slightly less than proportional manner.

Table 40 Dose proportionality of epinephrine after administration of ARS-1 1.0 mg IN twice (L/R), ARS-1 1.0 mg IN twice (L/L) and EpiPen 0.3 mg twice (L/R) to single doses

Test vs. Ref	Dependent Variable	LSMean ^a Test	LSMean ^a Ref	GeoMean ^b Test	GeoMean ^b Ref	Ratio (%) ^c (Test/Ref)	90% CI ^d Lower	90% CI ^d Upper
ARS-1 1.0 mg IN Twice (L/R) vs. Single	C _{max} /D	5.47	5.38	237	217	109.26	86.46	138.06
	AUC _{0-60 min} /D	8.92	8.93	7460	7540	98.99	80.56	121.62
	AUC _{0-t} /D	9.78	9.95	17700	20900	84.75	68.89	104.26
ARS-1 1.0 mg IN Twice (L/L) vs. Single	C _{max} /D	5.97	5.38	391	217	180.42	142.93	227.74
	AUC _{0-60 min} /D	9.27	8.93	10600	7540	140.18	114.20	172.08
	AUC _{0-t} /D	9.96	9.95	21300	20900	101.58	82.66	124.83
	C _{max} /D	6.72	6.83	827	928	89.14	70.62	112.51
EpiPen Twice (L/R) vs. Single	AUC _{0-60 min} /D	10.2	10.3	28200	30600	92.18	75.10	113.15
	AUC _{0-t} /D	11.2	11.3	73400	81100	90.51	73.65	111.22

Source: Appendix 16.1.13 Pharmacokinetic Report, In-Text Table 6

Exploratory Pharmacokinetic Analysis

The following exploratory pharmacokinetic analyses were conducted: Time to reach and time above 100 pg/mL, Baseline Corrected Pharmacokinetic Parameter Calculation

Time to Reach and Time Above 100 pg/mL

Prior research (Clutter-1980) has indicated that the direct pharmacological responses to epinephrine are reliably elicited once the epinephrine plasma concentrations reach the threshold plasma concentration of 100 pg/mL. As such, an exploratory analysis was conducted to determine time to reach the 100 pg/mL epinephrine concentration for each treatment group.

The median time to reach 100 pg/mL was 8.15 minutes after ARS-1 1.0 mg IN, 6.02 minutes following ARS-1 1.0 mg IN twice (L/R), 5.32 minutes following ARS-1 1.0 mg IN twice (L/L), 3.66 minutes following EpiPen 0.3 mg and 4.31 minutes following EpiPen 0.3 mg, twice.

The median time above 100 pg/mL was 56.6 minutes after ARS-1 1.0 mg IN, 124 minutes following ARS-1 1.0 mg IN twice (L/R), 120 minutes following ARS-1 1.0 mg IN twice (L/L), 57.8 minutes following EpiPen 0.3 mg and 96.6 minutes following EpiPen 0.3 mg, twice.

The highest maximum time to reach 100 pg/mL (29.8 minutes) was observed following EpiPen 0.3 mg, twice (L/R). The shortest maximum time to reach 100 pg/mL (15.7 minutes) was observed following ARS-1 1.0 mg IN twice (L/R).

Comparative Bioavailability and Bioequivalence– Baseline Corrected Values

All key pharmacokinetic parameters and analyses were consistent between total epinephrine values and baseline corrected values. While the baseline corrected values give the same overall results, some statistical power is lost with the baseline correction. The primary analysis of the study was based on uncorrected plasma levels, which takes into account normal variability and fluctuations of endogenous epinephrine.

EPI 12: A Four-Period, Four-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self-Administration of Adrenaline with Intranasal ARS-1, EpiPen, and Symjepi in Subjects with Type I Systemic Allergies

This was a Phase 1, single-dose, four-treatment, four-period, randomised crossover study that consisted of a screening and training period, baseline period, and an open-label randomised treatment period. The bioavailability of a single dose of IN ARS-1 (1 mg; 0.25% DDM), IN ARS-1 (1 mg; 0.35% DDM), EpiPen (0.3 mg adrenaline auto-injector) and Symjepi (0.3 mg adrenaline pre-filled syringe) was assessed after subjects self-administer the products in a clinical setting.

The primary objectives of EPI 12 were as follows: 1) to assess the comparative bioavailability of adrenaline after self-administration of ARS-1 (1 mg; 0.25% DDM), ARS-1 (1 mg; 0.35% DDM), EpiPen (0.3 mg adrenaline auto-injector) and Symjepi (0.3 mg adrenaline pre-filled syringe) after self-administration by subjects who have Type I allergy conditions; and 2) to evaluate the comparative PD response based on PR and SBP using an automated blood pressure measuring device.

Secondary objectives were as follows: 1) to assess the dosing error rates between the three devices with self-administration after the first and second use of ARS-1; 2) to evaluate the impact on pharmacokinetics of critical dosing errors by subjects who self-administer the four products; and 3) to evaluate the safety and tolerability of ARS-1 (1 mg; 0.25% DDM), ARS-1 (1 mg; 0.35% DDM), EpiPen (0.3 mg) and Symjepi (0.3 mg) when subjects self-administer the four products.

Pharmacokinetic Measurements: Blood samples (4 mL each) were collected at -10 and -5 minutes (± 1 minute) after sitting relaxed for at least 20 minutes and before the subject starts the simulation and self-administration; and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, and 240 minutes after dosing.

The following PK parameters for adrenaline were calculated: C_{max}, T_{max}, AUC_{0-xmin}: Area under the plasma concentration-time curve from time-zero to x min post dose, where x is every post-dose time point through 60 min (i.e. 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, and 60 min); AUC_{60-240min}, AUC_{0-120min}, AUC_{0-240min}, AUC_{last}. The PK parameters were calculated without the subtraction of the pre-dose adrenaline concentrations.

Pharmacokinetic Results

Due to potential carryover effect of the ARS-1 formulation and enhanced absorption for subsequent nasal administrations, the PK data (and possibly PD data) acquired in this study may not provide for accurate conclusions for ARS-1 (0.25% DDM) and ARS-1 (0.35% DDM). The treatment sequences used in this study have the ARS-1 treatments separated by 3 periods, with administration in Period 1 and Period 4, in an attempt at minimizing carryover effects. However, post hoc analysis of previous ARS-1 studies has suggested that carryover persists and is often substantial. To eliminate any potential carryover effect, unless otherwise indicated, the ARS-1 analysis focused on Period 1 data.

Plasma Concentrations and Noncompartmental Analysis.

Summary statistics of PK parameters sorted by treatment (primary population) are presented in Table 41. Summary statistics of adrenaline partial AUCs, sorted by treatment (primary population) are presented in Table 42.

Table 41 Pharmacokinetic Parameters of Total Adrenaline – Effect of Treatment

Treatment	N	t _{max} (min) median (range)	C _{max} (pg/mL)		AUC _{last} (min*pg/mL)	
			mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
Primary Population						
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	34.5 (2.00 - 120)	187 (54.6)	161	16800 (68.0)	14600
EpiPen 0.3 mg	29	15.0 (3.00 - 154)	458 (52.3)	389	23400 (38.7)	21800
Symjepi 0.3 mg	34	30.0 (4.00 - 90.0)	391 (52.8)	334	22600 (36.6)	19900
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	21.0 (6.00 - 90.0)	207 (106)	152	15600 (84.3)	11100
Secondary Population						
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	34.5 (2.00- 120)	187 (54.6)	161	16800 (68.0)	14600
EpiPen 0.3 mg	36	8.00 (3.00 - 154)	629 (68.6)	493	24400 (38.4)	22600
Symjepi 0.3 mg	36	30.0 (4.00 - 90.0)	438 (64.6)	359	23500 (39.1)	20600
ARS-1 1.0 mg IN 0.35% DDM Period 1	18	21.5 (6.00 - 90.0)	228 (74.8)	162	18200 (91.8)	12200

Source: EPI 12 PK Report, In-Text Table 2, Appendix Tables 3c and 3d

Table 42 Adrenaline Partial AUCs – Effect of 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
Primary Population															
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	76.1 (65.2)	59.7	164 (66.4)	127	262 (69.9)	204	375 (64.1)	308	510 (57.3)	436	721 (52.9)	629	977 (52.6)	854
EpiPen 0.3 mg	29	166 (80)	124	551 (85.9)	380	1050 (80.2)	709	1530 (71.5)	1080	1990 (64.4)	1450	2530 (58.6)	1910	3090 (57.1)	2370
Symjepi 0.3 mg	34	148 (93)	108	390 (91.9)	280	672 (83.7)	478	977 (77)	703	1290 (72.5)	937	1680 (70.3)	1240	2080 (69.4)	1540
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	118 (103)	78.8	267 (87.1)	190	463 (79.3)	323	697 (79.7)	467	949 (80.5)	626	1280 (78.7)	854	1620 (77.3)	1100
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
Primary Population															
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	1550 (51)	1350	2840 (44.9)	2530	4870 (43.8)	4360	6580 (47.1)	5860	11700 (60.6)	10300	17100 (65.8)	15100	10500 (83.4)	8850
EpiPen 0.3 mg	29	4360 (59.1)	3350	7140 (56.8)	5660	10900 (53.8)	9030	13500 (52.2)	11500	18600 (46.1)	16700	23600 (37.7)	22100	10100 (42.8)	9320
Symjepi 0.3 mg	34	3050 (67.8)	2290	5650 (61.3)	4400	9710 (53.5)	8100	12400 (49.3)	10600	18100 (38.1)	16900	23400 (30.9)	22400	11000 (34.2)	10300
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	2280 (75.1)	1580	3460 (69.3)	2540	5210 (65.7)	4000	7170 (63.7)	5730	12200 (78)	9580	17200 (73.4)	13900	10000 (88.4)	7420

Source: EPI 12 PK Report, Appendix Table 4c

Comparative Bioavailability

Statistical analysis of the PK parameters for ARS-1 vs EpiPen are presented in Table 43; ARS-1 vs Symjepi are presented in Table 44, and ARS-1 0.35% DDM vs ARS-1 0.25% DDM are presented in Table 45.

Table 43 Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Adrenaline after Administration of EpiPen 0.3 mg (Reference, ARS-1 0.25 % DDM, and ARS-1 0.35 % DDM

Test vs. Reference	Dependent Variable	Primary				Secondary			
		Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c	Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c
ARS-1 1.0 mg, 0.25% DDM (Period 1 only) vs EpiPen 0.3 mg	C _{max}	43.35	31.70	59.28	<0.0001	34.46	25.29	46.96	<0.0001
	AUC _{0-2min}	40.53	29.27	56.12	<0.0001	32.94	24.17	44.87	<0.0001
	AUC _{0-4min}	27.81	19.96	38.76	<0.0001	20.59	14.69	28.87	<0.0001
	AUC _{0-6min}	24.28	17.48	33.74	<0.0001	18.04	12.79	25.45	<0.0001
	AUC _{0-8min}	25.09	18.14	34.71	<0.0001	19.21	13.72	26.91	<0.0001
	AUC _{0-10min}	27.19	19.61	37.71	<0.0001	21.40	15.36	29.82	<0.0001
	AUC _{0-12.5min}	31.37	22.46	43.82	<0.0001	25.22	18.13	35.08	<0.0001
	AUC _{0-15min}	35.78	25.40	50.41	<0.0001	29.19	20.95	40.66	<0.0001
	AUC _{0-20min}	42.19	29.67	59.99	0.0001	34.99	25.10	48.78	<0.0001
	AUC _{0-30min}	49.37	35.05	69.55	0.0011	42.05	30.66	57.67	<0.0001
	AUC _{0-45min}	56.78	41.90	76.96	0.0029	50.41	38.27	66.41	<0.0001
	AUC _{0-60min}	59.93	45.74	78.53	0.0025	55.08	43.16	70.28	0.0001
	AUC _{0-120min}	69.11	56.00	85.28	0.0048	66.33	54.64	80.53	0.0008
	AUC _{0-240min}	75.46	62.38	91.28	0.0164	73.86	61.86	88.19	0.0058
	AUC _{60-240min}	99.24	78.53	125.40	0.9566	111.33	87.58	141.52	0.4583
	AUC _{last}	69.96	50.77	96.41	0.0677	69.39	52.17	92.29	0.0362
ARS-1 1.0 mg, 0.35% DDM (Period 1 only) vs EpiPen 0.3 mg	C _{max}	36.46	26.76	49.68	<0.0001	31.61	23.19	43.07	<0.0001
	AUC _{0-2min}	64.51	46.74	89.04	0.0267	51.98	38.15	70.82	0.0008
	AUC _{0-4min}	51.27	36.91	71.21	0.0012	38.63	27.56	54.15	<0.0001
	AUC _{0-6min}	46.09	33.28	63.83	0.0002	34.07	24.15	48.05	<0.0001
	AUC _{0-8min}	42.93	31.13	59.20	<0.0001	32.36	23.11	45.33	<0.0001
	AUC _{0-10min}	41.91	30.31	57.94	<0.0001	32.29	23.18	45.00	<0.0001
	AUC _{0-12.5min}	42.51	30.53	59.18	<0.0001	33.45	24.05	46.53	<0.0001
	AUC _{0-15min}	43.15	30.74	60.58	0.0001	34.67	24.88	48.30	<0.0001
	AUC _{0-20min}	42.62	30.09	60.37	0.0001	35.68	25.59	49.73	<0.0001
	AUC _{0-30min}	39.19	27.93	55.01	<0.0001	35.20	25.67	48.27	<0.0001
	AUC _{0-45min}	36.56	27.07	49.38	<0.0001	35.37	26.85	46.60	<0.0001
	AUC _{0-60min}	42.15	32.05	55.43	<0.0001	41.75	32.54	53.57	<0.0001
	AUC _{0-120min}	50.21	40.57	62.15	<0.0001	52.23	42.83	63.68	<0.0001
	AUC _{0-240min}	56.44	46.54	68.44	<0.0001	59.31	49.48	71.09	<0.0001
	AUC _{60-240min}	73.88	58.28	93.66	0.0372	84.76	66.33	108.30	0.2644
	AUC _{last}	48.43	35.28	66.49	0.0003	50.25	37.78	66.83	0.0001

Source: EPI 12 PK Report: in-text Table 7.

a: Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref); b 90% CI; c p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as p < 0.05

Table 44 Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Adrenaline after Administration of Symjepi 0.3 mg (Reference, Treatment C), ARS-1 0.25 % DDM (Treatment A), and ARS-1 0.35 % DDM (Treatment D)

Test vs. Reference	Dependent Variable	Primary				Secondary			
		Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c	Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c
ARS-1 1.0 mg, 0.25% DDM (Period 1 only), vs Symjepi 0.3 mg	C _{max}	50.78	37.82	68.18	0.0003	47.29	34.70	64.44	0.0001
	AUC _{0-2min}	49.27	36.30	66.87	0.0003	47.37	34.77	64.55	0.0001
	AUC _{0-4min}	40.03	29.33	54.64	<0.0001	36.98	26.39	51.84	<0.0001
	AUC _{0-6min}	38.24	28.11	52.02	<0.0001	34.82	24.68	49.11	<0.0001
	AUC _{0-8min}	40.75	30.08	55.22	<0.0001	37.11	26.49	51.97	<0.0001
	AUC _{0-10min}	44.60	32.84	60.59	<0.0001	40.81	29.29	56.86	<0.0001
	AUC _{0-12.5min}	50.92	37.23	69.65	0.0007	46.85	33.68	65.17	0.0003
	AUC _{0-15min}	57.42	41.64	79.18	0.0055	53.07	38.09	73.94	0.0022
	AUC _{0-20min}	63.88	45.91	88.88	0.0270	59.42	42.62	82.83	0.0110
	AUC _{0-30min}	64.75	46.93	89.35	0.0278	60.88	44.40	83.49	0.0108
	AUC _{0-45min}	63.68	47.86	84.71	0.0105	60.84	46.18	80.15	0.0037
	AUC _{0-60min}	65.21	50.60	84.04	0.0066	62.97	49.35	80.35	0.0023
	AUC _{0-120min}	68.55	56.27	83.50	0.0022	67.34	55.47	81.76	0.0011
	AUC _{0-240min}	74.52	62.33	89.10	0.0079	73.71	61.73	88.00	0.0055
	AUC _{60-240min}	90.29	72.49	112.45	0.4397	93.48	73.53	118.82	0.6406
ARS-1 1.0 mg, 0.35% DDM (Period 1 only), vs Symjepi 0.3 mg	AUC _{last}	76.94	56.84	104.15	0.1533	76.14	57.25	101.27	0.1157
	C _{max}	42.71	31.35	58.19	<0.0001	43.37	31.83	59.11	<0.0001
	AUC _{0-2min}	78.43	56.82	108.24	0.2125	74.77	54.87	101.87	0.1216
	AUC _{0-4min}	73.79	53.13	102.49	0.1275	69.37	49.49	97.24	0.0754
	AUC _{0-6min}	72.57	52.40	100.51	0.1053	65.72	46.60	92.70	0.0457
	AUC _{0-8min}	69.72	50.56	96.16	0.0658	62.51	44.63	87.55	0.0230
	AUC _{0-10min}	68.74	49.72	95.04	0.0580	61.59	44.20	85.81	0.0174
	AUC _{0-12.5min}	69.00	49.56	96.07	0.0659	62.14	44.68	86.44	0.0189
	AUC _{0-15min}	69.24	49.33	97.20	0.0753	63.03	45.24	87.82	0.0233
	AUC _{0-20min}	64.53	45.55	91.41	0.0398	60.58	43.45	84.44	0.0142
	AUC _{0-30min}	51.40	36.62	72.14	0.0017	50.96	37.16	69.88	0.0007
	AUC _{0-45min}	41.00	30.24	55.61	<0.0001	42.69	32.31	56.40	<0.0001
	AUC _{0-60min}	45.86	34.74	60.54	<0.0001	47.74	37.11	61.41	<0.0001
	AUC _{0-120min}	49.81	40.12	61.83	<0.0001	53.02	43.39	64.79	<0.0001
	AUC _{0-240min}	55.73	45.84	67.77	<0.0001	59.19	49.28	71.08	<0.0001
	AUC _{60-240min}	67.22	52.85	85.49	0.0077	71.17	55.55	91.17	0.0252
	AUC _{last}	53.26	38.80	73.12	0.0015	55.14	41.46	73.34	0.0009

Source: EPI 12 PK Report: [in-text Table 8](#),

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

Table 45 Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Adrenaline after Administration of ARS-1 0.25 % DDM (Treatment A) and ARS-1 0.35 % DDM (Treatment D)

Test vs. Reference	Dependent Variable	Primary				Secondary			
		Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c	Ratio (%) ^a (Test/Ref)	90% CI ^b Lower	90% CI ^b Upper	p-value ^c
ARS-1 1.0 mg, 0.25% DDM (Period 1 only) vs ARS-1 1.0 mg, 0.35% DDM (Period 1 only)	C _{max}	118.90	79.78	177.21	0.4713	109.02	72.70	163.50	0.7234
	AUC _{0-2min}	62.82	41.48	95.13	0.0662	63.36	42.26	95.00	0.0646
	AUC _{0-4min}	54.25	35.54	82.82	0.0188	53.31	34.26	82.95	0.0205
	AUC _{0-6min}	52.69	34.65	80.12	0.0132	52.97	33.77	83.10	0.0215
	AUC _{0-8min}	58.45	38.65	88.39	0.0341	59.36	38.19	92.28	0.0527
	AUC _{0-10min}	64.89	42.77	98.44	0.0881	66.26	42.92	102.30	0.1187
	AUC _{0-12.5min}	73.80	48.20	113.00	0.2381	75.39	48.94	116.13	0.2794
	AUC _{0-15min}	82.92	53.58	128.34	0.4765	84.20	54.54	129.97	0.5111
	AUC _{0-20min}	98.99	63.21	155.04	0.9701	98.09	63.49	151.53	0.9412
	AUC _{0-30min}	125.97	81.39	194.99	0.3807	119.47	79.01	180.65	0.4756
	AUC _{0-45min}	155.29	105.28	229.06	0.0634	142.52	99.28	204.60	0.1068
	AUC _{0-60min}	142.20	100.12	201.96	0.0989	131.91	95.41	182.37	0.1585
	AUC _{0-120min}	137.63	104.74	180.85	0.0554	127.01	98.15	164.35	0.1265
	AUC _{0-240min}	133.71	104.44	171.18	0.0541	124.53	98.39	157.61	0.1251
	AUC _{60-240min}	134.32	99.13	182.00	0.1099	131.35	95.50	180.65	0.1582
	AUC _{last}	144.46	95.95	217.48	0.1383	138.09	95.06	200.60	0.1541

Source: EPI 12 PK Report: [in-text Table 9](#).

a: Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref); b 90% CI; c p-value for the difference in the treatment_{id} estimates; Significant difference defined *a priori* as $p < 0.05$

Pharmacokinetics by Critical Dosing Errors

No critical dosing errors (CDEs) occurring during self-administration of ARS-1. Ten CDEs were observed with EpiPen and six CDEs were observed with Symjepi. The most commonly observed CDE was the subject not holding the pen or plunger down for the stipulated time of 3 seconds for EpiPen (n=10) or 2 seconds for Symjepi (n=5).

Mean C_{max} and AUC_{last} were higher after EpiPen 0.3 mg followed by Symjepi 0.3 mg and ARS-1 1.0 mg IN. Media T_{max} was the fastest for EpiPen 0.3 mg, followed by ARS-1 1.0 mg IN 0.35%, DDM, Symjepi, and ARS-1 1.0 mg IN 0.25% IN DDM. ARS-1 1.0 mg IN exposure was lower compared to EpiPen and Symjepi at every timepoint tested. No dosing errors were defined during the ARS-1 administration. Ten and dosing errors were identified for EpiPen and Symjepi, respectively.

Influence of food

No study for the assessment of food influence on PK of adrenaline has been conducted by the applicant as it will be administrated IN and food intake is not perceived to influence PK of the drug.

2.6.2.1.4. Distribution

Adrenaline is an endogenous hormone that is distributed widely throughout the body (Dietz-1990).

2.6.2.1.5. Metabolism

Adrenaline is extensively metabolised in-vivo with only a small amount excreted unchanged. The primary metabolite in humans is vanillylmandelic acid, an inactive metabolite, by monoamine oxidase and catechol-O-methyltransferase that are abundantly expressed in the liver, kidneys, and other extra-neuronal tissues. The tissues with the highest contribution to removal of circulating exogenous adrenaline are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%). Adrenaline is not metabolised by enzymes known to be in the nasal mucosa (Hogan-2020, Dhamankar-2013, Oliveira-2016).

In nonclinical studies, an *in vitro* metabolism study showed that adrenaline is rapidly metabolised by cytochrome P450 isoforms CYP1A2, CYP2C9, and CYP3A4 (Study Number CYP0986-R23). The results showed that adrenaline degraded under the experimental condition as the compound is well known to be sensitive to oxygen and temperature. While adrenaline degraded rapidly there was no apparent effect by inhibitors, which indicated that the degradation of the adrenaline was likely not due to the CYP enzymes and due to the experimental system. No formation of noradrenaline was observed (theoretically possible from CYP3A4) in any of the time point samples for all three enzyme isoforms tested alone and in presence of CYP enzyme isoform selective chemical inhibitors.

The metabolism of adrenaline is well established. No clinical study was performed by the applicant which is acceptable.

No study researching the inter-conversion, pharmacokinetics of metabolites, consequences of possible genetic polymorphism was performed by the applicant.

2.6.2.1.6. Elimination

Most of adrenaline is excreted as metabolites in urine. Elimination is mainly via metabolism of the liver and sympathetic nerve endings, with a small amount excreted unchanged in the urine (Dalal-2020, Simon-1998).

2.6.2.1.7. Dose proportionality and time dependencies

Table 46 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 (51.1)	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 0.3 mg SC	35	45 (4 – 180)	246 (61.6)	214	30200 (34.9)	28400
ARS-1 1.0 mg IN* (Japanese only)	36	12.5 (4 – 45)	364 (62.1)	306	30600 (45.4)	27100
ARS-1 2.0 mg IN** (self-administration)	42	30 (10 – 240)	448 (67.1)	342	50365 (55.5)	41077
ARS-1 2.0 mg IN*** (paediatrics)	16	25 (2.5 – 120)	540 (70.7)	433	35500 (76.3)	27800
ARS-1 2.0 mg IN**** (with rhinitis)	33	6 (2-90)	309 (66.2)	260	23500 (69.1)	19700
Source: Integrated analysis Tables 39, 42, 45, 47, 48, 49 *Data from EPI JPN01, **Data from EPI 17, ***Data from EPI 10, ****Data from EPI 16 Results for <i>Primary populations</i>						

Table 47 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](#)

According to the integrated analysis, exposure of ARS-1 increased in dose proportional manner after single dose administration 1 mg vs 2 mg.

In studies with repeat administration of Eurneffy 2 mg, exposure was dose proportional and similar between administration in each (L/R) and one nostril (R/R).

2.6.2.1.8. Intra- and inter-individual variability

Table 48 Inter-individual variability for PK parameter across pivotal studies.

Study	Treatment	Mean C _{max} (pg/mL) (%CV)	Mean AUC _{last} (min*pg/mL) (%CV)	Median t _{max} (min)(range)
EPI 15	ARS-1 2.0 mg	481 (76.0)	43500 (69.4)	30.0 (6.00-150)
	ARS-1 2.0 mg (L/R)	805 (69.2)	72500 (61.4)	30.0 (6.0-150)
	ARS-1 2.0 mg (R/R)	946 (74.0)	85000 (61.6)	30.0 (12.0-150)
EPI 16	ARS-1 2.0 mg	491 (65.2)	37100 (66.1)	20.0 (2.00-120)
	ARS-1 2.0 mg with rhinitis	309 (66.2)	23500 (69.1)	6.0 (2.0-90.0)
EPI 17	ARS-1 2.0 mg	448 (67.1)	50365 (55.5)	30.0 (10.0-240)
	ARS-1 2.0 mg (with nasal drip)	334 (55.2)	35292 (42.7)	30.0 (6.0-60.0)
EPI 10	ARS-1 0.65 mg (15-<30kg)	534 (58.7)	21900 (49.7)	12.5 (2.50-30.0)
	ARS-1 1.0 mg (15-<30kg)	NA	NA	NA
	ARS-1 1.0 mg (≥30kg)	253 (66.2)	14000 (53.0)	20.0 (7.5-120)
	ARS-1 2.0 mg (≥30kg)	540 (70.7)	35500 (76.3)	25.0 (2.5-120)

The between-subject variability of PK parameters is observed to be moderate to high of about 50 – 95% for C_{max} and 40 – 77% for AUC.

Adrenaline is generally recognised as a highly variable drug, with a CV% exceeding 30%, regardless of the product or route of administration.

2.6.2.1.9. Special populations

- Race

No clinical research was conducted to compare race differences in PK. However, populational analysis by ethnic bridging analysis was performed.

Relative BA for Japanese patients is 2.3, 2.17 and 1.0, for IM, EpiPen and ARS-1 respectively compared to US population. Absorption after IM and EpiPen administration is different between Japanese and US patients but do not differ for ARS-1 IN administration between those two groups of patients. Two-fold greater exposure after IM/EpiPen administration in Japanese patients could be explained by the fact of smaller muscle weight and greater volume of distribution relative to the total muscle mass.

- Weight

ARS-1 IN dosed once or twice was not shown to be statistically significantly affected by body weight, with P values >0.05 (Table 49). There was no consistent relationship between BMI and drug exposure (a mix of negative and positive regression slope amongst the various formulations was observed).

Table 49 Linear Regression of Ln(C_{max}) 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 50 Linear Regression of Ln(C_{max}) and Ln(AUC_{0-240min}) vs BMI (kg / m²) 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

Neither body weight nor BMI were found to be a covariate of PK parameters (C_{max} and AUC₀₋₂₄₀) after ARS-1 once or twice administration

- Elderly

Eurneffy was not tested in the elderly population. Based on the POP PK model (POP PK Report) age was not a significant covariate for nasal absorption of the drug adrenaline from the nasal mucosa with Eurneffy formulation. It seems that in the case of elderly subjects the expected Eurneffy action should be similar. Appropriate wording is included in SmPC.

- Children

EPI 10. A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Paediatric Subjects with Systemic Allergies

Primary objectives: to assess the PKs of epinephrine after IN administration of 0.65 milligram (mg,) 1.0 mg, or 2.0 mg dose of ARS- 1 in paediatric allergy subjects; to evaluate the PD response based on PR and BP using an automated blood pressure monitoring (ABPM) device after IN administration of 0.65 mg, 1.0 mg, or 2.0 mg dose of ARS-1 in paediatric allergy subjects.

Secondary objectives:

to evaluate the impact of nasal congestion and rhinitis on the PKs of ARS-1 in paediatric subjects and to evaluate the safety and tolerability of ARS-1 in paediatric allergy subjects

Pharmacokinetic (PK) Assessments: Blood samples were collected at pre-dose each treatment period (at -10 and -5 minutes) and at 2.5, 5, 7.5,10, 12.5, 15, 20, 30, 45, 60, 90, and 120 minutes after dosing.

Pharmacokinetic Assessments

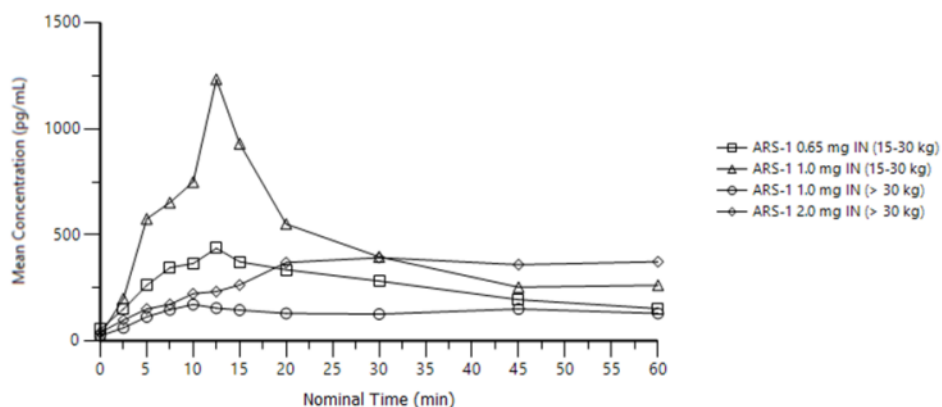
The PK parameters were calculated without the subtraction of the pre-dose epinephrine concentrations. The rationale for using epinephrine plasma levels without subtraction of the baseline values was based

on both clinical and PK considerations. First, the endogenous levels of epinephrine change based on both the diurnal cycle and due to stimuli. Second, clinically, the absolute plasma levels (e.g., 100 pg/mL) are considered more important to illicit an efficacious response.

Results

Plasma Concentrations

Figure 28 Mean Epinephrine Concentration-Time Profiles Truncated to 60 Minutes, by Treatment – Linear Scale



Pharmacokinetic Parameters

Noncompartmental Analysis

Summary statistics of PK parameters sorted by treatment are presented in Table 51. Summary statistics of epinephrine partial AUCs, sorted by treatment, are presented in Table 52.

Table 51 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

Treatment	N	t _{max} (min) median (range)	C _{max} (pg/mL)		AUC _{last} (min*pg/mL)	
			mean (%CV)	Geo. mean	mean (%CV)	Geo. mean
15 – 30 kg						
ARS-1 0.65 mg	11	12.5 (2.50 – 30.0)	534 (58.7)	475	21900 (49.7)	19400
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A
> 30 kg						
ARS-1 1.0 mg	25	20.0 (7.50 – 120)	253 (66.2)	203	14000 (53.0)	12000
ARS-1 2.0 mg	16	25.0 (2.50 – 120)	540 (70.7)	433	35500 (76.3)	27800

Table 52 Epinephrine Partial AUCs, Sorted by Treatment

Treatment	N	pAUC (min*pg/mL)											
		AUC _{0-2.5min}		AUC _{0-5min}		AUC _{0-7.5min}		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
15 – 30 kg													
ARS-1 0.65 mg	11	259 (61.3)	207	776 (52.7)	655	1540 (49.1)	1360	2430 (51.5)	2170	3430 (55.6)	3080	4440 (57.8)	3990
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
> 30 kg													
ARS-1 1.0 mg	25	115 (80.4)	86.3	351 (83.8)	250	689 (83.7)	496	1090 (84.5)	795	1500 (85.1)	1100	1880 (84.5)	1400
ARS-1 2.0 mg	16	175 (165)	99.9	489 (128)	293	894 (97.5)	603	1390 (81.1)	988	1960 (78.3)	1420	2580 (78.6)	1890
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		
15 – 30 kg													
ARS-1 0.65 mg	11	6220 (58.0)	5600	9320 (54.2)	8360	12900 (50.7)	11500	15500 (50.6)	13800	21900 (49.7)	19400		
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		
> 30 kg													
ARS-1 1.0 mg	25	2570 (78.1)	2000	3860 (62.7)	3200	5960 (52.2)	5100	8070 (52.4)	6880	14000 (53.0)	12000		
ARS-1 2.0 mg	16	4140 (78.3)	3150	7890 (77.1)	6230	13500 (76.2)	10900	19000 (79.7)	15100	35500 (76.3)	27800		

A slight increase in epinephrine absorption was observed in children >30kg after ARS-1 2.0 mg administration more than what was expected in POP modelling and observed in adults.

Epinephrine levels were dose proportional between 1.0 and 2.0 mg dosing in children >30 kg. Media t_{max} was 20.0 and 25.0 minutes after administration of 1.0 mg and 2.0 mg of epinephrine IN in children >30 kg. Mean C_{max} was 253 pg/mL after administration of ARS-1 1.0 mg and 540 pg/ml after ARS-1 2.0 mg administration in children above 30 kg. Mean AUC last was 14000 min*pg/mL and 35500 min*pg/mL, after 1.0 and 2.0 mg intranasal administration of ARS-1 in children >30 kgs.

Neither body weight nor BMI were found to be a covariate of PK parameters (C_{max} and AUC₀₋₂₄₀) after ARS-1 once or twice administration. In the paediatric population, the slightly increase in the absorption was observed in children >30kg after ARS-1 2.0 mg administration. Epinephrine levels were dose proportional between 1.0 and 2.0 mg dosing in children >30 kg.

2.6.2.1.10. Pharmacokinetic interaction studies

No PK interaction study was performed during clinical development of the product.

2.6.2.2. Pharmacodynamics

Mechanism of action

Adrenaline is a sympathomimetic catecholamine with α and β adrenergic agonist activity. Its therapeutic efficacy comes from its direct agonism of α and β adrenergic receptors leading to a reversal of the pathological response to the histamine cascade.

Primary and Secondary pharmacology

Pivotal studies

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

Objectives

Pharmacodynamic measurements included SBP, DBP, and PR after each dosing arm. Nasal irritation assessments were conducted for right (R) and left (L) nares before and after dosing of IN and IM study drugs and included assessment of nasal irritation, mucosal erythema, mucosal oedema, nasal discharge, mucosal crusting, and mucosal epistaxis. Nasal conditions were assessed at baseline and pre-dose of each dosing period using Total Nasal Symptom Score (TNSS).

Pharmacodynamic Assessments

The following PD parameters were calculated for change from baseline SBP, DPB, and HR: Emax, TEmax, AUEC0-xmin: Area under the effect time curve from time zero to x min post dose, 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

Systolic blood pressure (primary population)

Part 1

Mean Change from Baseline vs. Time:

All three treatments resulted in an increase from baseline SBP. This increase persisted for 30 minutes following ARS-1, 45 minutes following IM Epinephrine, and five minutes following EpiPen. In general, ARS-1 resulted in the greatest increase from baseline SBP. For all treatments, SBP returned to normal by approximately 120 minutes.

Pharmacodynamic Parameters:

Mean SPB Emax values were highest following ARS-1 (23.6 mmHg), followed by EpiPen (15.6 mmHg), and IM Epinephrine (12.0 mmHg). Overall exposure as measured by mean AUEclast was highest following ARS-1 (834 min* mmHg), followed by EpiPen (459 min* mmHg), and IM Epinephrine (222 min* mmHg). The longest median TEmax was observed following ARS-1 (25.0 minutes) followed by IM Epinephrine (20.0 minutes) and EpiPen (10.0 minutes).

Table 53 Pharmacodynamic Parameters for SBP Change from Baseline – Part 1 (Primary Population)

Treatment	N	t _{E_{max}} (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 2.0 mg	42	25.0 (1.00 – 116)	23.6 (64.8)	834 (84.9)	16.4 (232)	41.7 (208)	86.3 (147)	145 (115)	204 (100)	264 (93.0)	429 (92.6)	550 (94.6)	966 (101)
EpiPen 0.3 mg	35	10.0 (1.00 – 116)	15.6 (59.4)	459 (91.7)	21.3 (179)	52.0 (136)	73.4 (135)	92.9 (139)	105 (150)	118 (160)	165 (155)	188 (176)	420 (166)
Epinephrine IM 0.3 mg	41	20.0 (1.00 – 116)	12.0 (81.5)	222 (257)	2.6 (985)	2.54 (2230)	-1.99 (-4620)	-4.00 (-3300)	-7.38 (-2310)	-13.5 (-1580)	-3.87 (-8670)	-3.53 (-13000)	634 (105)

Comparison Between Treatments: In general, mean Emax and AUEClast were significantly higher following ARS-1 relative to both EpiPen and IM Epinephrine.

In the study's first phase, ARS at a dose of 2 mg was shown to have a stronger effect on SBP than injectable adrenaline 0.3 mg (both I.M. and subcutaneous EpiPen forms). Emax for ARS was almost twice as high as for the injectable forms. Similarly, the AUEC0-15 parameter, a key parameter for the clinical management of anaphylaxis, was virtually identical when comparing ARS with EpiPen and significantly higher when compared with the classic form.

Part 2

Mean Change from Baseline vs. Time:

All three treatments resulted in an increase from baseline SBP until 30 minutes following administration, after which there was a return towards baseline. Through 120 minutes postdose, change from baseline SBP was higher for both ARS-1 treatments compared to EpiPen.

Pharmacodynamic Parameters:

Mean SBP Emax values were highest following ARS-1 (R/R) (28.6 mmHg), followed by ARS-1 (L/R) (28.5 mmHg), and EpiPen (L/R) (19.2 mmHg). Overall exposure as measured by mean AUEClast was highest following ARS-1 (R/R) (1500 min*mmHg), followed by ARS-1 (L/R) (1430 min*mmHg), and EpiPen (L/R) (691 min*mmHg). The longest median TEmax was observed following ARS-1 (L/R) (29.0 minutes), followed by ARS-1 (R/R) (28.5 minutes), and EpiPen (L/R) (14.0 minutes).

Table 54 Pharmacodynamic Parameters for SBP Change from Baseline – Part 2 (Primary Population)

Treatment	N	t _{E_{max}} (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 2.0 mg (L/R)	36	29.0 (2.00 – 116)	28.5 (48)	1430 (66)	16.1 (206)	44.5 (153)	97.7 (107)	165 (87.8)	249 (76.3)	346 (68.5)	630 (58.2)	864 (57.8)	1390 (66.7)
ARS-1 2.0 mg (R/R)	38	28.5 (6.00 – 85.0)	28.6 (45.9)	1500 (76)	18.2 (175)	47.3 (153)	101 (116)	178 (92.7)	269 (80.9)	366 (72.0)	663 (65.1)	916 (67.6)	1740 (71.6)
EpiPen 0.3 mg (L/R)	37	14.0 (1.00 – 85.0)	19.2 (44.9)	691 (88.5)	22.0 (132)	60.1 (105)	104 (107)	146 (110)	184 (112)	225 (109)	342 (112)	428 (120)	731 (91.6)

Comparison Between Treatments: In general, both Emax and AUEClast were significantly higher after both ARS-1 (R/R) and ARS-1 (L/R) relative to EpiPen. The Emax and AUEClast between ARS-1 (R/R) and ARS-1 (L/R) were not significantly different from each other.

The results of the comparison in SBP between ARS-1 administered twice to both the same nostril and two different nostrils do not differ from each other and also from EpiPen epinephrine administered twice. The AUEC for the early response phase (0-15) is almost identical for all forms of the drug analysed.

Diastolic blood pressure (primary population)

Part 1

Mean Change from Baseline vs. Time:

All three treatments resulted in a decrease from baseline DBP. This decrease persisted for 60 minutes following ARS-1, 45 minutes following IM Epinephrine, and 30 minutes following EpiPen, after which there was an increase towards baseline. The degree of decrease was minimal with ARS-1 relative to EpiPen and IM Epinephrine

Pharmacodynamic Parameters: Mean DBP Emax values were highest following ARS-1 (8.10 mmHg), followed by EpiPen (5.83 mmHg), and IM Epinephrine (5.63 mmHg). Based on the mean AUEClast, there was a negative change in DBP after EpiPen (- 26.3 min*mmHg) and IM Epinephrine (- 63.0 min*mmHg), but not after ARS-1 (180 min*mmHg). The longest median TEmax was observed following EpiPen (14.0 minutes), followed by ARS-1 (13.0 minutes), and IM Epinephrine (9.0 minutes).

Table 55 Pharmacodynamic Parameters for DBP Change from Baseline – Part 1 (Primary Population)

Treatment	N	tEmax (min) median (range)	Emax (mmHg) Mean (%CV)	AUEClast (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 2.0 mg	42	13.0 (1.00 – 117)	8.10 (64.3)	180 (175)	9.14 (186)	14.7 (254)	13.8 (417)	10.9 (715)	8.20 (1250)	4.1 (3030)	-8.15 (-2480)	-38.3 (-740)	-33.7 (-938)
EpiPen 0.3 mg	35	14.0 (1.00 – 115)	5.83 (107)	-26.3 (-1220)	-3.55 (-599)	-19.8 (-240)	-43.3 (-166)	-68.0 (-140)	-93.4 (-125)	-120 (-114)	-197 (-96.3)	-266 (-97.6)	88.2 (889)
Epinephrine IM 0.3 mg	41	9.00 (1.00 – 115)	5.63 (141)	-63.0 (-519)	0.534 (5330)	-9.54 (-486)	-25.5 (-245)	-44.0 (-188)	-64.0 (-172)	-86.6 (-164)	-167 (-124)	-251 (-115)	202 (216)

Comparison Between Treatments: Mean DBP Emax values were significantly different following ARS-1 relative to IM Epinephrine, but not significantly different from EpiPen. Mean DBP AUECs after ARS-1 were significantly different relative to both EpiPen and IM Epinephrine injection.

Part 2

Mean Change from Baseline vs. Time:

Diastolic blood pressure fluctuated through the entire 120 minutes following both ARS-1 (R/R) and ARS-1 (L/R), with a minimal overall decrease in DBP at the end of the 120 min observation period. However, after administration of EpiPen, there was a decrease in mean from baseline DBP until about 30 min after which there was an increase in the from baseline DBP until 120 min. In general, the overall mean decreases in DBP were smaller after the ARS-1 (R/R) (-0.731 mmHg) and ARS-1 (L/R) (-1.32 mmHg) compared to EpiPen (- 5.93 mmHg).

Pharmacodynamic Parameters:

Mean DBP Emax values were highest following ARS-1 (L/R) (9.92 mmHg), followed by ARS-1 (R/R) (9.37 mmHg), and EpiPen (L/R) (6.43 mmHg). Overall exposure as measured by mean AUEClast was highest following ARS-1 (L/R) (289 min*mmHg), followed by ARS-1 (R/R) (271 min*mmHg), and

EpiPen (L/R) (6.22 min*mmHg). The longest median TEmax was observed following ARS-1 (L/R) (19.0 minutes), followed by ARS-1 (R/R) (11.5 minutes), and EpiPen (L/R) (5.00 minutes).

Table 56 Pharmacodynamic Parameters for DBP Change from Baseline – Part 2 (Primary Population)

Treatment	N	tEmax (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 2.0 mg (L/R)	36	19.0 (1.00 – 115)	9.92 (67.8)	289 (136)	4.84 (537)	11.8 (354)	18.9 (295)	26.1 (304)	32.3 (318)	39.7 (320)	60.6 (360)	73.1 (432)	336 (120)
ARS-1 2.0 mg (R/R)	38	11.5 (1.00 – 118)	9.37 (85.2)	271 (202)	6.05 (280)	10.1 (371)	15.0 (104)	18.3 (464)	22.4 (514)	23.3 (636)	21.3 (1160)	28.0 (1310)	356 (160)
EpiPen 0.3 mg (L/R)	37	5.00 (1.00 – 115)	6.43 (92.7)	6.22 (5080)	3.21 (652)	-2.68 (-1690)	-21.1 (-315)	-43.7 (-205)	-72.5 (-152)	-103 (-127)	-181 (-116)	-237 (-120)	88.0 (238)

Comparison Between Treatments: In general, mean DBP Emax AUEClast were significantly higher following both ARS-1 (R/R) and ARS-1 (L/R) relative to EpiPen (L/R). There were no significant differences between ARS-1 (R/R) and ARS-1 (L/R).

Pulse rate (primary population)

Part 1

Mean Change from Baseline vs. Time: All treatments resulted in increases from baseline PR in the first five minutes post-administration. There was a return towards baseline after both IM Epinephrine and EpiPen, while the elevation persisted throughout the 120 minutes following ARS-1.

Pharmacodynamic Parameters: Mean PR Emax values were highest following ARS-1 (17.3 bpm), followed by EpiPen (11.7 bpm), and IM Epinephrine (9.73 bpm). Overall exposure as measured by mean AUEClast was highest following ARS-1 (893 min*bpm), followed by EpiPen (414 min*bpm), and IM Epinephrine (386 min*bpm). The longest median TEmax was observed following IM Epinephrine (29.0 minutes), followed by ARS-1 (19.0 minutes), and EpiPen (11.0 minutes).

Table 57 Pharmacodynamic Parameters for PR Change from Baseline – Part 1 (Primary Population)

Treatment	N	tEmax (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 2.0 mg	42	19 (1.00 – 116)	17.3 (62.7)	893 (93.5)	17.8 (149)	53.3 (127)	94.4 (103)	133 (90.5)	171 (84.8)	213 (80.8)	330 (83.7)	450 (88.4)	885 (90.2)
EpiPen 0.3 mg	35	11.0 (2.00 – 115)	11.7 (64.9)	414 (96.7)	16.8 (183)	47.5 (141)	64.7 (134)	78.5 (136)	92.8 (142)	110 (138)	171 (125)	225 (122)	572 (74.7)
Epinephrine IM 0.3 mg	41	29.0 (1.00 – 117)	9.73 (88.0)	386 (119)	0.0998 (23400)	9.54 (579)	14.3 (588)	15.5 (707)	17.3 (770)	23.9 (678)	48.2 (519)	81.0 (423)	580 (57.8)

Comparison Between Treatments: In general, Emax and AUEClast were significantly higher following ARS-1 relative to EpiPen and IM Epinephrine.

Part 2

Mean Change from Baseline vs. Time: All three treatments resulted in an increase from baseline PR. This increase persisted for 10 minutes following administration of EpiPen (L/R) and for 45 minutes following administration of both ARS-1 (R/R) and ARS-1 (L/R). At later timepoints, PR was inconsistent

and fluctuated through 120 mins for all treatments. Overall, ARS-1 (R/R) and ARS-1 (L/L) resulted in more pronounced increases from baseline relative to EpiPen.

Pharmacodynamic Parameters: Mean PR Emax values were highest following ARS-1 (R/R) (22.4 bpm), followed by ARS-1 (L/L) (21.0 bpm) and EpiPen (L/R) (17.3 bpm).

Table 58 Pharmacodynamic Parameters for PR Change from Baseline – Part 2 (Primary Population)

Treatment	N	t _{max} (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 2.0 mg (L/R)	36	34.5 (1.00 – 116)	21.0 (57.1)	1270 (75.3)	13.9 (188)	46.9 (125)	92.2 (105)	145 (94.7)	204 (89.7)	269 (86.6)	470 (87.6)	662 (87.5)	1580 (73.9)
ARS-1 2.0 mg (R/R)	38	40.0 (1.00 – 116)	22.4 (43.2)	1430 (61.4)	13.8 (132)	45.7 (100)	99.7 (80.1)	165 (70.5)	233 (64.7)	295 (62.0)	504 (60.8)	717 (61.1)	1680 (57.7)
EpiPen 0.3 mg (L/R)	37	26.0 (1.00 – 116)	17.3 (52.4)	1000 (65.1)	18.7 (150)	61.3 (99.6)	109 (82.6)	153 (79.8)	193 (80.6)	234 (79.5)	398 (73.1)	555 (69.5)	1180 (43.1)

Pharmacokinetic-pharmacodynamic results

Part 1

Systolic Blood Pressure (Primary Population)

Change from baseline SBP versus epinephrine concentration: The strongest correlation between change from baseline SBP and epinephrine concentration was observed following ARS-1 ($r^2 = 0.3902$), followed by EpiPen ($r^2 = 0.2426$), and IM Epinephrine ($r^2 = 0.1417$).

Linear mixed effect analysis: There was no significant relationship between Emax and Cmax for any of the three treatments. Significant relationships were observed between pAUEC and pAUCs for ARS-1 and between AUEC0-120 and AUC0-120 for all three treatments. A significant positive relationship was observed between TEmax and Tmax for ARS-1, but not for EpiPen or IM Epinephrine.

Diastolic Blood Pressure (Primary Population)

Change from baseline DBP versus epinephrine concentration: All correlations between change from baseline DPP and epinephrine concentrations were inverse, and all correlations were considered weak, ranging from - 0.2475 (EpiPen) to -0.1704 (IM Epinephrine). Linear mixed effect analysis: There was no significant relationship between Emax and Cmax for any of the treatments. A significant relationship between AUEC0-120 and AUC0-120 was observed for all three treatments. A significant positive relationship was observed between TEmax and Tmax for ARS-1, but not for EpiPen or IM Epinephrine.

Pulse Rate

Change from baseline PR versus epinephrine concentration: The strongest correlation between change from baseline PR and epinephrine concentration was observed following ARS-1 ($r^2 = 0.5334$), followed by EpiPen ($r^2 = 0.2788$), and IM Epinephrine ($r^2 = 0.2191$).

Part 2

Systolic Blood Pressure (Primary Population)

Change from baseline SBP versus epinephrine concentration: The strongest correlation between change from baseline SBP and epinephrine concentration was observed following ARS-1(R/L) ($r^2 = 0.3532$), followed by ARS-1(R/R) ($r^2 = 0.3097$), and EpiPen (L/R) ($r^2 = 0.1719$).

Diastolic Blood Pressure (Primary Population)

Change from baseline DBP versus epinephrine concentration: All correlations between change from baseline DPP and epinephrine concentrations were inverse, and all correlations were considered weak, ranging from - 0.0847 (ARS-1 (R/L)) to -0.143 (ARS-1 (R/R)).

Pulse Rate (Primary Population)

Change from baseline PR versus epinephrine concentration: The strongest correlation between change from baseline PR and epinephrine concentration was observed following ARS-1 ($r^2 = 0.5334$), followed by EpiPen ($r^2 = 0.2788$), and IM Epinephrine ($r^2 = 0.2191$).

All three treatments resulted in an increase from baseline SBP. This increase persisted for 30 minutes following ARS-1, 45 minutes following IM Epinephrine, and five minutes following EpiPen. In general, ARS-1 resulted in the strongest increase of SBP. For all treatments, SBP returned to normal by approximately 120 minutes. Mean SPB Emax values were highest following ARS-1 (23.6 mmHg), followed by EpiPen (15.6 mmHg), and IM Epinephrine (12.0 mmHg).

The results of the comparison in SBP between ARS-1 administered twice to both the same nostril and two different nostrils do not differ from each other and also from EpiPen epinephrine administered twice. The AUEC for the early response phase (0-15) is almost identical for all forms of the drug analysed.

All three treatments resulted in a decrease from baseline DBP. This decrease persisted for 60 minutes following ARS-1, 45 minutes following IM Epinephrine, and 30 minutes following EpiPen, after which there was an increase towards baseline. The degree of decrease was minimal with ARS-1 relative to EpiPen and IM Epinephrine. The probable reason for such effect is a strong direct activation of β_2 adrenergic receptors in muscles.

All treatments resulted in increases from baseline PR in the first five minutes post-administration. There was a return towards baseline after both IM Epinephrine and EpiPen, while the elevation persisted throughout the 120 minutes following ARS-1. In general, Emax and AUEClast were significantly higher following ARS-1 relative to EpiPen and IM Epinephrine. All three treatments resulted in an increase from baseline PR.

In sum, the study results indicate that the ARS-1 administered at a dose of 2 mg I.N. (once or twice, including the administration to the same nostril) produce the same pharmacodynamic effect as injectable adrenaline. The influence on the SBP and P.R. was similar for all tested forms. The opposite effect on the DBP may result from direct muscular β_2 receptors activation. Based on the results, it seems that ARS-1 at a dose of 2 mg give similar pharmacodynamic effects as injectable forms, which are essential for anaphylaxis treatment.

EPI 16. A Four-Treatment, Partially Randomized, Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis (EPI 16).

Pharmacodynamic Assessments:

The following PD parameters were calculated for change from baseline SBP, DPB, and HR: Emax, TEmax, AUEC0-xmin: Area under the effect time curve from time zero to x min post dose, 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), AUEC0-120, AUEClast.

PD Results

Systolic Blood Pressure

Table 59 Pharmacodynamic Parameters for SBP Change from Baseline – Primary Population

Treatment	N	t _E max (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 2.0 mg	36	26.0 (1.00–120).	20.8 (80.6)	695 (115)	4.98 (626)	17.9 (404)	43.4 (282)	79.2 (225)	122 (196)	175 (175)	316 (161)	402 (165)	612 (212)
ARS-1 2.0 mg with rhinitis	33	19.0 (1.00-120)	15.0 (84.5)	377 (145)	21.4 (208)	26.4 (278)	38.5 (273)	55.6 (255)	65.9 (273)	76.0 (287)	94.6 (362)	85.4 (522)	301 (296)
Epinephrine IM 0.3 mg	31	19.0 (1.00-123)	13.4 (70.9)	395 (188)	5.59 (531)	8.48 (744)	15.7 (615)	25.3 (505)	31.8 (515)	38.6 (525)	67.6 (505)	96.6 (489)	126 (767)
Epinephrine IM 0.5 mg	32	30.0 (1.00-120)	15.2 (62.3)	615 (110)	9.56 (359)	14.1 (535)	17.2 (664)	23.1 (639)	34.1 (540)	51.3 (440)	99.4 (383)	155 (352)	-34.0 (3100)

Diastolic Blood Pressure

Table 60 Pharmacodynamic Parameters for DBP Change from Baseline – Primary Population

Treatment	N	t _E max (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 2.0 mg	36	25.0 (1.00-120)	10.0 (77.2)	156 (283)	10.3 (223)	15.2 (330)	17.6 (427)	18.8 (537)	21.2 (638)	28.4 (609)	24.0 (1140)	-3.07 (-11600)	-16.2 (-4590)
ARS-1 2.0 mg with rhinitis	33	26.0 (1.00-119)	7.15 (95.8)	47.7 (1040)	2.46 (1030)	-3.44 (-1400)	-11.7 (-611)	-19.0 (529)	-30.2 (-419)	-41.6 (-354)	-82.4 (-276)	-138 (-236)	-270 (-319)
Epinephrine IM 0.3 mg	31	14.0 (1.00-123)	5.26 (141)	-94.5 (-543)	-3.83 (-630)	-20.3 (-237)	-40.9 (-185)	-63.5 (-166)	-85.6 (-156)	-113 (-143)	-206 (-117)	-286 (-116)	-579 (-141)
Epinephrine IM 0.5 mg	32	26.0 (1.00-120)	5.69 (104)	-65.7 (-668)	-2.33 (-988)	-14.0 (-349)	-32.0 (-224)	-48.8 (-197)	-69.2 (-174)	-91.5 (-160)	-179 (-135)	-262 (-125)	-675 (-115)

Pulse Rate

Summary statistics for change from baseline PR by treatment are presented in Table 61.

Table 61 Pharmacodynamic Parameters for PR Change from Baseline – Primary Population

Treatment	N	t _E max (min) median (range)	E _{max} (bpm) Mean (%CV)	AUEC _{last} (min*bpm) (Mean (%CV))	AUEC min*bpm								
					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 2.0 mg	36	25.0 (1.00-178)	18.5 (75.9)	886 (108)	14.7 (254)	44.4 (153)	79.4 (119)	114 (109)	146 (110)	182 (111)	300 (116)	418 (120)	731 (124)
ARS-1 2.0 mg with rhinitis	33	4.00 (1.00-119)	10.8 (114)	220 (179)	12.7 (341)	6.61 (1200)	3.46 (3510)	-3.36 (-4900)	-18.0 (-1120)	-31.2 (765)	-70.9 (-505)	-119 (-405)	-179 (-542)
Epinephrine IM 0.3 mg	31	44.0 (2.00-120)	11.1 (73.3)	433 (109)	-6.39 (-325)	-4.05 (-1200)	6.87 (1050)	12.5 (811)	14.5 (908)	16.7 (970)	64.3 (390)	125 (276)	292 (258)
Epinephrine IM 0.5 mg	32	19.5 (1.00-122)	13.6 (54.0)	560 (93.9)	3.22 (639)	22.7 (225)	36.8 (217)	52.9 (215)	73.9 (200)	97.6 (177)	170 (143)	246 (136)	331 (189)

Pharmacokinetic-Pharmacodynamic Analyses

Systolic Blood Pressure

Summary results of the SBP PK-PD analysis (primary population) using a linear mixed-effect model with PK parameters as the regressor are presented Table 62.

Table 62 Linear Mixed Effects Analysis of PK and PD Change from Baseline SBP Parameters, by Treatment

Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
ARS-1 2.0 mg	SBP E _{max} (mmHg)	C _{max} (pg/mL)	0.0199	0.1213	0.0213
IM Epinephrine 0.5 mg	SBP E _{max} (mmHg)	C _{max} (pg/mL)	0.0040	-0.0094	0.4031
IM Epinephrine 0.3 mg	SBP E _{max} (mmHg)	C _{max} (pg/mL)	-0.0135	0.0172	0.2267
ARS-1 2.0 mg with rhinitis	SBP E _{max} (mmHg)	C _{max} (pg/mL)	0.0054	-0.0242	0.6257
ARS-1 2.0 mg	SBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0133	0.0039	0.2936
IM Epinephrine 0.5 mg	SBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0118	0.0626	0.0938
IM Epinephrine 0.3 mg	SBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	-0.0170	0.0097	0.2645
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0067	-0.0250	0.6431
ARS-1 2.0 mg	SBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0185	0.0550	0.0904
IM Epinephrine 0.5 mg	SBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0112	0.0499	0.1194
IM Epinephrine 0.3 mg	SBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	-0.0222	0.0488	0.1219
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0137	0.0038	0.2978
ARS-1 2.0 mg	SBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0200	0.0765	0.0565
IM Epinephrine 0.5 mg	SBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0110	0.0398	0.1450
IM Epinephrine 0.3 mg	SBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	-0.0185	0.0357	0.1572
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0134	0.0085	0.2674
ARS-1 2.0 mg	SBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0211	0.0611	0.0791
IM Epinephrine 0.5 mg	SBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0085	0.0004	0.3229
IM Epinephrine 0.3 mg	SBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	-0.0146	1.0000	<0.0001
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0152	0.0170	0.2222
ARS-1 2.0 mg	SBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0261	1.0000	<0.0001
IM Epinephrine 0.5 mg	SBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0073	-0.0144	0.4544
IM Epinephrine 0.3 mg	SBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	-0.0207	0.0378	0.1508
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0167	0.0147	0.2335
ARS-1 2.0 mg	SBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0242	0.0644	0.0736
Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
IM Epinephrine 0.5 mg	SBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0068	-0.0194	0.5173
IM Epinephrine 0.3 mg	SBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	-0.0234	1.0000	<0.0001
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0129	1.0000	<0.0001
ARS-1 2.0 mg	SBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0147	0.0055	0.2823
IM Epinephrine 0.5 mg	SBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0185	0.0812	0.0660
IM Epinephrine 0.3 mg	SBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	-0.0441	0.1591	0.0151
ARS-1 2.0 mg with rhinitis	SBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	-0.0025	-0.0311	0.8542
ARS-1 2.0 mg	SBP T _{E_{max}} (min)	T _{max} (min)	0.0701	-0.0252	0.7117
IM Epinephrine 0.5 mg	SBP T _{E_{max}} (min)	T _{max} (min)	0.0115	-0.0341	0.9188
IM Epinephrine 0.3 mg	SBP T _{E_{max}} (min)	T _{max} (min)	-0.3287	0.0130	0.2472
ARS-1 2.0 mg with rhinitis	SBP T _{E_{max}} (min)	T _{max} (min)	0.0722	-0.0303	0.8089

Diastolic Blood Pressure

Summary results of the DBP PK-PD analysis (primary population) using a linear mixed-effect model with PK parameters as the regressor are presented in Table 63.

Table 63 Linear Mixed Effects Analysis of PK and PD Change from Baseline DBP Parameters, by Treatment

Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
ARS-I 2.0 mg	DBP E _{max} (mmHg)	C _{max} (pg/mL)	0.0012	-0.0269	0.7767
IM Epinephrine 0.5 mg	DBP E _{max} (mmHg)	C _{max} (pg/mL)	-0.0009	-0.0308	0.7493
IM Epinephrine 0.3 mg	DBP E _{max} (mmHg)	C _{max} (pg/mL)	-0.0096	0.0083	0.2723
ARS-I 2.0 mg with rhinitis	DBP E _{max} (mmHg)	C _{max} (pg/mL)	-0.0096	0.0613	0.0886
ARS-I 2.0 mg	DBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0012	-0.0289	0.8947
IM Epinephrine 0.5 mg	DBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0038	-0.0109	0.4179
IM Epinephrine 0.3 mg	DBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	-0.0176	0.0479	0.1241
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	-0.0078	-0.0097	0.4112
ARS-I 2.0 mg	DBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0013	-0.0283	0.8463
IM Epinephrine 0.5 mg	DBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0031	-0.0179	0.4974
IM Epinephrine 0.3 mg	DBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	-0.0182	0.0567	0.1048
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	-0.0154	0.0657	0.0811
ARS-I 2.0 mg	DBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0000	-0.0294	0.9964
IM Epinephrine 0.5 mg	DBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0026	-0.0244	0.5964
IM Epinephrine 0.3 mg	DBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	-0.0143	0.0273	0.1851
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	-0.0166	0.0914	0.0485
ARS-I 2.0 mg	DBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	-0.0007	-0.0291	0.9215
IM Epinephrine 0.5 mg	DBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	-0.0032	-0.0230	0.5723
IM Epinephrine 0.3 mg	DBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	-0.0132	0.0220	0.2058
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	-0.0149	0.0711	0.0728
ARS-I 2.0 mg	DBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	-0.0010	-0.0289	0.8961
IM Epinephrine 0.5 mg	DBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	-0.0101	0.0623	0.0942
IM Epinephrine 0.3 mg	DBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	-0.0135	0.0268	0.1870
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	-0.0180	1.0000	<0.0001
ARS-I 2.0 mg	DBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	-0.0043	-0.0191	0.5622
Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
IM Epinephrine 0.5 mg	DBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	-0.0117	1.0000	<0.0001
IM Epinephrine 0.3 mg	DBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	-0.0093	1.0000	<0.0001
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	-0.0205	0.1041	0.0376
ARS-I 2.0 mg	DBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	-0.0045	-0.0168	0.5213
IM Epinephrine 0.5 mg	DBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	-0.0219	1.0000	<0.0001
IM Epinephrine 0.3 mg	DBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0047	-0.0298	0.7187
ARS-I 2.0 mg with rhinitis	DBP AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	-0.0341	0.3188	0.0004
ARS-I 2.0 mg	DBP T _{Emax} (min)	T _{max} (min)	0.3317	0.0066	0.2747
IM Epinephrine 0.5 mg	DBP T _{Emax} (min)	T _{max} (min)	-0.1360	0.0038	0.2998
IM Epinephrine 0.3 mg	DBP T _{Emax} (min)	T _{max} (min)	-0.0662	-0.0333	0.8559
ARS-I 2.0 mg with rhinitis	DBP T _{Emax} (min)	T _{max} (min)	0.2003	-0.0234	0.6078

Pulse Rate

Summary results of the PR PK-PD analysis (primary population) using a linear mixed-effect model with PK parameters as the regressor are presented in the table below.

Table 64 Linear Mixed Effects Analysis of PK and PD Change from Baseline PR Parameters, by Treatment

Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
ARS-1 2.0 mg	PR E _{max} (mmHg)	C _{max} (pg/mL)	0.0138	0.0735	0.0602
IM Epinephrine 0.5 mg	PR E _{max} (mmHg)	C _{max} (pg/mL)	0.0037	0.0015	0.3152
IM Epinephrine 0.3 mg	PR E _{max} (mmHg)	C _{max} (pg/mL)	0.0130	0.0308	0.1729
ARS-1 2.0 mg with rhinitis	PR E _{max} (mmHg)	C _{max} (pg/mL)	0.0204	0.0864	0.0536
ARS-1 2.0 mg	PR AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0017	-0.0288	0.8859
IM Epinephrine 0.5 mg	PR AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0120	0.1863	0.0089
IM Epinephrine 0.3 mg	PR AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0262	0.1435	0.0203
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-10min} (min*mmHg)	AUC _{0-10min} (min*pg/mL)	0.0170	0.0075	0.2737
ARS-1 2.0 mg	PR AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0052	-0.0182	0.5443
IM Epinephrine 0.5 mg	PR AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0124	0.1794	0.0102
IM Epinephrine 0.3 mg	PR AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0214	0.1054	0.0419
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-15min} (min*mmHg)	AUC _{0-15min} (min*pg/mL)	0.0137	-0.0054	0.3702
ARS-1 2.0 mg	PR AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0079	1.0000	<0.0001
IM Epinephrine 0.5 mg	PR AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0125	0.1342	0.0243
IM Epinephrine 0.3 mg	PR AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0174	0.0639	0.0915
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-20min} (min*mmHg)	AUC _{0-20min} (min*pg/mL)	0.0120	-0.0079	0.3932
ARS-1 2.0 mg	PR AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0121	0.0378	0.1326
IM Epinephrine 0.5 mg	PR AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0131	0.1171	0.0335
IM Epinephrine 0.3 mg	PR AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0169	0.0580	0.1022
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-30min} (min*mmHg)	AUC _{0-30min} (min*pg/mL)	0.0133	-0.0010	0.3327
ARS-1 2.0 mg	PR AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0240	0.1686	0.0075
IM Epinephrine 0.5 mg	PR AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0104	0.0741	0.0754
IM Epinephrine 0.3 mg	PR AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0194	0.0825	0.0644
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-45min} (min*mmHg)	AUC _{0-45min} (min*pg/mL)	0.0185	0.0204	0.2064
ARS-1 2.0 mg	PR AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0309	0.2416	0.0014
Treatment	Dependent ^a Variable	Independent ^b Variable	Slope ^c	Adj r ² ^d	p-value ^e
IM Epinephrine 0.5 mg	PR AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0070	0.0126	0.2492
IM Epinephrine 0.3 mg	PR AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0172	1.0000	<0.0001
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-60min} (min*mmHg)	AUC _{0-60min} (min*pg/mL)	0.0236	0.0496	0.1124
ARS-1 2.0 mg	PR AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0239	0.1950	0.0041
IM Epinephrine 0.5 mg	PR AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0056	0.0026	0.3075
IM Epinephrine 0.3 mg	PR AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0154	0.0075	0.2771
ARS-1 2.0 mg with rhinitis	PR AUEC _{0-120min} (min*mmHg)	AUC _{0-120min} (min*pg/mL)	0.0223	0.0691	0.0758
ARS-1 2.0 mg	PR T _{Emax} (min)	T _{max} (min)	0.1617	-0.0212	0.6041
IM Epinephrine 0.5 mg	PR T _{Emax} (min)	T _{max} (min)	-0.0691	-0.0189	0.5104
IM Epinephrine 0.3 mg	PR T _{Emax} (min)	T _{max} (min)	0.4423	0.0452	0.1306
ARS-1 2.0 mg with rhinitis	PR T _{Emax} (min)	T _{max} (min)	0.1190	-0.0250	0.6430

Gender analysis

There were 16 female subjects and 20 male subjects enrolled in this clinical trial. As expected, the mean weight was higher for male subjects (77.5 kg vs. 68.7 kg) for male subjects as compared to female subjects, with BMI being similar between the two groups (25.5 vs. 25.2).

For SBP the median T_{Emax} for Eurneffy under normal conditions was more rapid for male subjects compared to female subjects (19.5 min vs. 29 min) as well as after NAC induction (9.5 min vs. 29.5 min). For female subjects SBP T_{Emax} was similar with Eurneffy with or without NAC induction, while for male subjects SBP T_{Emax} was more rapid after NAC induction (9.5 min vs. 19.5 min). For the IM groups under normal conditions the SBP T_{Emax} was more rapid in male subjects with the 0.3 mg dose (19 min vs. 22.5 min) but similar with the 0.5 mg dose. The mean E_{max} for SBP was similar or higher for Eurneffy as compared to IM injection in all groups and similar between genders.

For Pulse Rate (PR) median T_{Emax} was similar between genders for Eurneffy under normal conditions. After NAC induction PR median T_{Emax} with Eurneffy was more rapid for male subjects (2 min vs.

22.5 min). For female subjects the PR median TEmax was similar between normal conditions and after NAC induction, but for male subjects the median PR TEmax was significantly faster after NAC (2 min vs. 22.5 min) as compared to normal conditions. For IM injection the PR median TEmax was similar between genders at both the 0.3 mg and 0.5 mg dose. The mean Emax for PR was higher for Eurneffy then IM injection (0.3 mg or 0.5 mg) under normal conditions. After NAC induction the PR mean Emax for Eurneffy declined in both treatment groups (male and female) in a similar way for both male and female subjects but was still similar to 0.3 mg IM injection. There was no meaningful difference between male and female subjects for PR mean Emax between genders in any of the treatment groups.

Table 65 EPI 16 Demographics

	Female				Male			
	Age (year)	Height (cm)	Weight (kg)	BMI	Age (year)	Height (cm)	Weight (kg)	BMI
N	16	16	16	16	20	20	20	20
Mean	38.8	165.1	68.7	25.2	37.0	174.4	77.5	25.5
SD	8.6	5.7	11.3	3.8	8.2	7.8	8.6	2.5
Minimum	20.0	152.9	52.6	19.3	23.0	159.3	60.2	20.3
Median	38.5	165.8	66.9	24.7	38.0	173.7	79.1	25.6
Maximum	52.0	176.6	97.8	31.4	52.0	190.8	89.2	30.0

Table 66 EPI 16 Pharmacodynamic Parameters by Gender

	Treatment	Female							Male					
		N	Mean	SD	Max	Median	Min	N	Mean	SD	Max	Median	Min	
SBP														
TEmax	neffy 2.0 mg	16	31.8	26.8	120.0	29.0	1.0	20.0	25.9	27.3	120.0	19.5	1.0	
	neffy 2.0 mg IN with Rhinitis	16	43.3	36.1	120.0	29.5	1.0	18.0	20.8	28.8	90.0	9.5	1.0	
	IM 0.3 mg	16	34.3	32.5	123.0	22.5	1.0	19.0	26.9	31.3	119.0	19.0	1.0	
	IM 0.5 mg	16	47.6	42.1	119.0	29.5	1.0	19.0	36.1	33.7	120.0	30.0	1.0	
Emax	neffy 2.0 mg	16	23.7	19.6	88.0	19.0	1.0	20.0	18.4	14.1	40.0	18.0	-24.0	
	neffy 2.0 mg IN with Rhinitis	16	13.7	6.7	28.0	14.0	0.0	18.0	16.2	16.1	68.0	13.0	-12.0	
	IM 0.3 mg	16	11.4	8.6	28.0	11.5	-3.0	19.0	15.6	10.5	41.0	17.0	-3.0	
	IM 0.5 mg	16	15.4	11.5	45.0	16.0	-9.0	19.0	15.1	7.8	29.0	15.0	-2.0	
AUEC	neffy 2.0 mg	16	835	976	3028	696	-699	19	577	616	1511	536	-734	
	neffy 2.0 mg IN with Rhinitis	15	333	394	1221	264	-168	16	453	666	1502	123	-584	
	IM 0.3 mg	14	282	762	1881	42	-597	18	517	695	2137	145	-213	
	IM 0.5 mg	15	534	647	2342	402	-247	18	589	722	1984	405	-403	
DBP														
TEmax	neffy 2.0 mg	16	25.3	33.5	120.0	17.5	1.0	20.0	46.1	48.6	120.0	27.0	1.0	
	neffy 2.0 mg IN with Rhinitis	16	31.5	36.5	119.0	25.5	1.0	18.0	51.1	45.3	119.0	37.0	1.0	
	IM 0.3 mg	16	35.8	44.9	123.0	25.0	1.0	19.0	28.9	36.0	119.0	10.0	1.0	
	IM 0.5 mg	16	36.2	41.1	120.0	23.0	1.0	19.0	48.7	50.7	119.0	25.0	1.0	
Emax	neffy 2.0 mg	16	11.8	9.2	30.0	10.0	0.0	20.0	8.7	6.2	21.0	7.5	-4.0	
	neffy 2.0 mg IN with Rhinitis	16	6.1	6.0	17.0	7.5	-4.0	18.0	8.2	7.0	20.0	8.5	-5.0	
	IM 0.3 mg	16	6.4	7.8	29.0	5.5	-4.0	19.0	5.8	7.8	26.0	4.0	-4.0	
	IM 0.5 mg	16	5.4	6.5	21.0	4.5	-3.0	19.0	6.1	6.0	17.0	6.0	-5.0	
AUEC	neffy 2.0 mg	15	245	494	1619	39	-446	18	81	389	941	92	-888	

	Treatment	Female						Male					
		N	Mean	SD	Max	Median	Min	N	Mean	SD	Max	Median	Min
	neffy 2.0 mg IN with Rhinitis	14	100	439	1465	-10	-333	16	-4	534	720	9	-1520
	IM 0.3 mg	13	-52	547	722	2	-1501	15	-34	522	1083	-32	-1134
	IM 0.5 mg	11	-28	453	938	-87	-902	17	-87	421	706	2	-1050
PR													
TEmax	neffy 2.0 mg	16	41.4	40.5	120.0	25.5	2.0	20.0	43.1	47.8	178.0	22.5	1.0
	neffy 2.0 mg IN with Rhinitis	16	22.6	23.3	89.0	22.5	1.0	18.0	18.1	31.5	119.0	2.0	1.0
	IM 0.3 mg	16	41.0	31.2	120.0	44.0	2.0	19.0	44.2	36.1	119.0	44.0	5.0
	IM 0.5 mg	16	34.3	34.3	122.0	22.5	1.0	19.0	36.6	37.6	120.0	19.0	5.0
Emax	neffy 2.0 mg	16	20.1	14.7	58.0	16.0	4.0	20.0	17.3	13.7	54.0	14.0	-4.0
	neffy 2.0 mg IN with Rhinitis	16	12.8	13.7	53.0	13.0	-8.0	18.0	9.4	10.8	29.0	8.5	-13.0
	IM 0.3 mg	16	10.8	8.6	27.0	11.5	-6.0	19.0	11.2	7.2	24.0	11.0	-4.0
	IM 0.5 mg	16	13.1	4.8	23.0	12.0	7.0	19.0	13.7	9.4	37.0	13.0	-1.0
AUEC	neffy 2.0 mg	16	1047	977	2966	771	-194	19	751	947	3179	561	-541
	neffy 2.0 mg IN with Rhinitis	14	293	517	1188	239	-673	15	192	268	958	96	-10
	IM 0.3 mg	14	502	485	1391	513	-267	18	380	415	1335	253	-231
	IM 0.5 mg	16	678	448	1607	691	-74	18	504	579	2226	336	-315

The primary objectives of this study were 1) to compare ARS-1 2.0 mg under normal conditions to ARS-1 2.0 mg when the subject experiencing rhinitis, a worst-case situation for intranasal delivery, and 2) to IM Adrenaline 0.3 mg (reference listed drug) and IM Adrenaline 0.5 mg, both of which have worldwide approval for the treatment of severe allergic reactions and anaphylaxis.

ARS-1 2.0 mg resulted in greater overall exposure with more rapid tmax relative to IM Adrenaline 0.3 mg. ARS-1 2.0 mg also resulted in pharmacodynamic effects that were greater than IM Adrenaline 0.3 mg and comparable to IM Adrenaline 0.5 mg.

The EPI 16 study was designed as a three-way crossover study conducted in the normal state, comparing Eurneffy 2 mg, IM adrenaline 0.3 mg, and IM adrenaline 0.5 mg.

The results from this study indicate that Eurneffy 2 mg, when administered to individuals with rhinitis, leads to adrenaline exposure that is not statistically different from that of IM injection. This similarity was observed as early as 2 minutes post-dose and persisted through the first 20 minutes post-dose. The pharmacodynamic responses, including systolic blood pressure, diastolic blood pressure, and heart rate, showed that for at least the first 30 minutes after dosing, Eurneffy produced PD responses that were comparable to those of IM adrenaline injection.

However, only the classical injectable form of adrenaline was used in the EPI16 study (the EpiPen group was not included). Nevertheless, the results of clinical studies suggest that the PD response may also depend on the specific injectable form of adrenaline. From a clinical perspective, the absence of significant differences from the classical injectable form still provides reasonable evidence of an expected similar response to Eurneffy and injectable forms, even in patients with rhinitis.

In EPI 16 study in total 16 female and 20 male subjects were included. However, results of SBP, DBP and PR from inconsistent number of male subjects were provided (AUEC results for SBP, DBP and PR were provided for lower number of subjects compared to TEmax and Emax for SBP, DBP and PR). The applicant should clarify (OC).

The differences in the observed PD responses when Eurneffy is administered under NAC-induced rhinitis conditions seem to be more related to the ongoing systemic Type I allergic reaction induced by NAC, rather than a substantial divergence in the response to Eurneffy compared to injectable forms.

EPI 17. A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self- Administration of Epinephrine with Intranasal ARS-1 as compared to IM injection in Subjects with Type I Allergies.

Objectives

The primary objectives of this study were as follows:

- to assess the comparative bioavailability of epinephrine after self-administration of ARS-1 (2.0 mg IN epinephrine) or study staff-administered intramuscular (IM) injection in subjects who have Type I allergy conditions
- to evaluate the comparative PD response based on systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) using an automated blood pressure monitoring (ABPM) device between the two treatment groups

The secondary endpoints of this study were as follows:

- the dosing error rates with ARS-1 after self-administration
- the pharmacokinetics of ARS-1 following significant dosing errors by subjects who self-administer with ARS-1
- the safety and tolerability of ARS-1 and IM injection

Pharmacodynamic Assessments

Pharmacodynamic measurements included SBP, DBP, and PR using an ABPM device on Day 0 through Day 1. through 120 minutes post-dose while the subject remains in a sitting position.

Blood pressure (BP) and PR measurements were taken at baseline, -10 (± 2 min) and -5 (± 2 min) minutes prior to instructing or 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.

Emax, TEmax, AUEC0-xmin: Area under the effect time curve from time zero to x min post dose, 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), AUEC0-120, AUEClast.

Pharmacodynamic Results

Systolic Blood Pressure

ARS-1 2.0 mg resulted in an increase from baseline SBP that persisted throughout the entire 120-minute sampling period. Epinephrine 0.3 mg IM resulted in an initial increase from baseline SBP that persisted for approximately 10-minutes post-dose, at which point SBP returned to baseline and, eventually, to below baseline.

Pharmacodynamic Parameters

Emax: In the primary population, ARS-1 2.0 mg resulted in a mean peak effect of (SBP Emax) of 21 mmHg, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 13 mmHg. Similar values were observed in the secondary population.

TE_{max}: In both the primary and secondary populations, ARS-1 2.0 mg resulted in a median time to maximum effect (TE_{max}) of 18 minutes and Epinephrine 0.3 mg IM resulted in a median time to maximum effect of 16 minutes.

AUEC_{last}: In the primary population, ARS-1 2.0 mg resulted in a mean overall effect (AUEC_{last}) of 934 min*mmHg) and Adrenaline 0.3 mg IM resulted in a mean overall effect of 199 min*mmHg). Similar values were observed in the secondary population.

Table 67 Pharmacodynamic Parameters for SBP Change from Baseline – Primary Population

Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (mmHg) Mean (%CV)	AUEC _{last} (min*mmHg) (Mean (%CV)	pAUEC 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 2.0 mg	32	18 (1 – 117)	21 (46.0)	934 (111.1)	46 (97.3)	73 (127.9)	106 (147.1)	148 (150.8)	194 (146.8)	237 (145.2)	370 (131.1)	500 (125.7)	1001 (72.8)
Epinephrine 0.3 mg IM	42	16 (1 – 117)	13 (60.2)	199 (263.5)	15 (220.2)	15 (419.2)	10 (946.9)	7 (1838.7)	8 (2066.3)	6 (3302.9)	-2 (-20273.2)	-5 (-8841.2)	253 (310.8)

Diastolic Blood Pressure

Both treatments resulted in an initial increase from baseline DBP, with ARS-1 2.0 mg resulting in a more pronounced increase. By the 10-minute timepoint, both treatments resulted in a return to baseline; however, Epinephrine 0.3 mg IM resulted in a markedly greater decrease from baseline that persisted throughout the 120-minute sampling period.

Pharmacodynamic Parameters

E_{max}: In the primary population, ARS-1 2.0 mg resulted in a mean peak effect of (DBP E_{max}) of 9 mmHg, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 8 mmHg. Similar values were observed in the secondary population.

TE_{max}: In both the primary and secondary populations, both treatments resulted in a median time to maximum effect (TE_{max}) of 5 minutes.

AUEC_{last}: In the primary population, ARS-1 2.0 mg resulted in a mean overall effect (AUEC_{last}) of 171 min*mmHg) and Epinephrine 0.3 mg IM resulted in a mean overall effect of 50 min*mmHg). Similar values were observed in the secondary population.

Table 68 Pharmacodynamic Parameters for DBP Change from Baseline – Primary Population

Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (mmHg) Mean (%CV)	AUEC _{last} (min*mmHg) (Mean (%CV)	pAUEC 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 2.0 mg	32	5 (1 – 117)	9 (55.6)	171 (238.4)	17 (142.6)	27 (227.0)	27 (394.4)	29 (486.4)	29 (624.4)	26 (850.6)	16 (1863.9)	8 (4397.3)	284 (161.6)
Epinephrine 0.3 mg IM	42	5 (1 – 117)	8 (71.8)	50 (533.1)	11 (277.9)	13 (478.0)	13 (660.7)	7 (1465.7)	-4 (-3242.0)	-23 (-621.5)	-88 (-220.4)	-154 (-167.7)	-183 (-341.4)

Pulse Rate

Mean Change from Baseline vs. Time: Both treatments resulted in an initial increase from baseline PR. This increase persisted throughout the entire sampling period following ARS-1 2.0 mg; however, following Epinephrine 0.3 mg IM, PR returned to near-baseline levels by approximately 15-minutes post-dose.

Pharmacodynamic Parameters

E_{max}: In the primary population, ARS-1 2.0 mg resulted in a mean peak effect of (PR E_{max}) of

13 bpm, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 10 bpm. Similar values were observed in the secondary population.

TE_{max}: In the primary population, ARS-1 2.0 mg resulted in a median time to maximum effect

(TE_{max}) of 22 minutes and Epinephrine 0.3 mg IM resulted in a median time to maximum effect of 13 minutes. In the secondary population, the median TE_{max} remained the same following Epinephrine 0.3 mg IM and was 18 minutes following ARS-1 2.0 mg.

AUEC_{last}: In the primary population, ARS-1 2.0 mg resulted in a mean overall effect (AUEC_{last}) of 565 min*bpm) and Epinephrine 0.3 mg IM resulted in a mean overall effect of 297 min*bpm). Similar values were observed in the secondary population.

Table 69 Pharmacodynamic Parameters for PR Change from Baseline – Primary Population

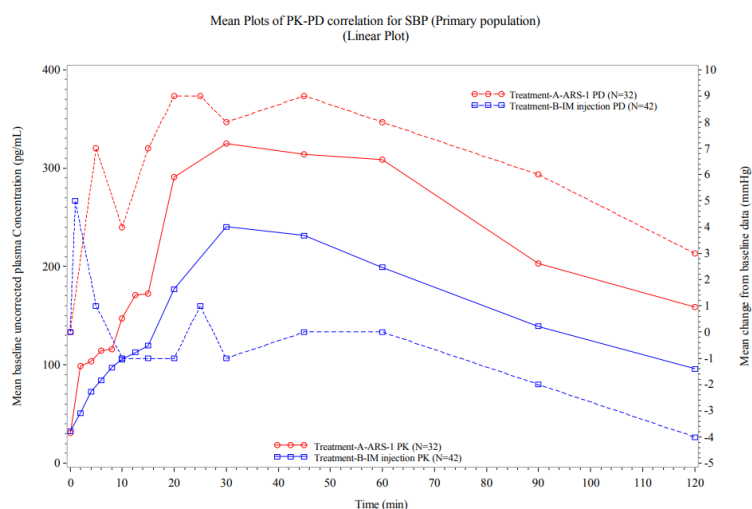
Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (bpm) Mean (%CV)	AUEC _{last} (min*mmHg) (Mean (%CV)	pAUEC min*bpm								
					AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120
					Mean (%CV)								
ARS-1 2.0 mg	32	22 (1 – 117)	13 (56.6)	565 (89.0)	25 (122.9)	51 (126.8)	78 (130.2)	98 (137.5)	116 (142.4)	131 (148.8)	178 (169.8)	238 (173.3)	962 (48.2)
Epinephrine 0.3 mg IM	42	13 (1 – 117)	10 (69.1)	297 (24.7)	10 (223.1)	29 (157.7)	54 (125.0)	70 (122.7)	76 (133.9)	78 (150.7)	87 (213.8)	102 (257.3)	181 (279.9)

Pharmacokinetic-Pharmacodynamic Analyses

Systolic Blood Pressure

Double y-axis plots of mean PK concentrations and mean SBP change from baseline versus time are presented in Figure 29.

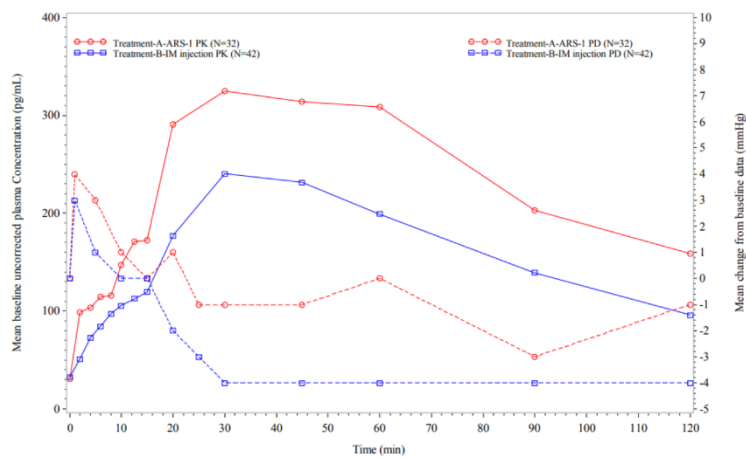
Figure 29 Mean PK Concentration and Mean SBP Change from Baseline vs. Time – Primary Population



Diastolic Blood Pressure

Double y-axis plots of mean PK concentrations and mean DBP change from baseline versus time are presented in Figure 30.

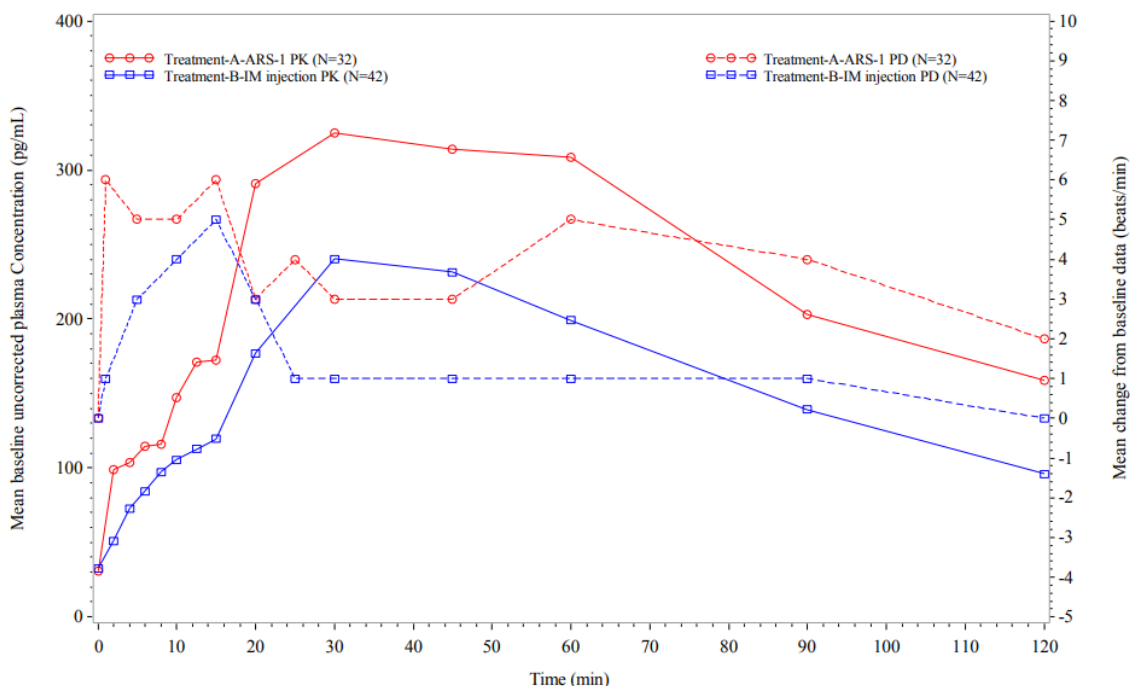
Figure 30 Mean PK Concentration and Mean DBP Change from Baseline vs. Time – Primary Population



Pulse Rate

Double y-axis plots of mean PK concentrations and mean PR change from baseline versus time are presented in Figure 30.

Figure 31 Mean PK Concentration and Mean PR Change from Baseline vs. Time – Primary Population



During the study all 42 subjects were able to successfully administer ARS-1. About 23.8% of subjects experienced some degree of nasal drip.

ARS-1 2.0 mg resulted in an increase from baseline SBP that persisted throughout the entire 120-minute sampling period. Adrenaline 0.3 mg IM resulted in an initial increase from baseline SBP that persisted for approximately 10-minutes post-dose, at which point SBP returned to baseline and, eventually, to below baseline. Both treatments resulted in an initial increase from baseline DBP, with ARS-1 2.0 mg resulting in a more pronounced increase. By the 10-minute time-point, both treatments

resulted in a return to baseline; however, Adrenaline 0.3 mg IM resulted in a markedly greater decrease from baseline that persisted throughout the 120-minute sampling period.

Both treatments resulted in an initial increase from baseline PR. This increase persisted throughout the entire sampling period following ARS-1 2.0 mg; however, following Adrenaline 0.3 mg IM, PR returned to near baseline levels by approximately 15-minutes post-dose. The epinephrine concentration and change from baseline SBP appeared to be well-correlated for both treatments across the full 120-minute timeframe. DBP appeared well-correlated with epinephrine concentration immediately post-dose, followed by a rapid decoupling where epinephrine concentrations continued to rise while DBP decreased. The epinephrine concentration and change from baseline PR appeared well-correlated for the first 20 minutes post-dose.

The results of the study indicate that the self-administration of the ARS-1 produces sufficient pharmacodynamic response, needed to anaphylaxis treatment.

EPI 10. A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Paediatric Subjects with Systemic Allergies

Pharmacodynamic (PD) Assessments: Pharmacodynamic measurements included PR and SBP and DBP predose and at each timepoint in the schedule of events using an automated blood pressure cuff.

Pharmacodynamic Assessments

Pharmacodynamic measurements including BP (systolic, SBP; diastolic, DBP) and PR were collected at the following times: 2 predose measurements, collected 5 min apart (at -10 and -5 min) 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min after dosing.

Summary of Statistical Analysis Systolic Blood Pressure

Summary statistics for SBP change from baseline, by timepoint and treatment, are presented in Table 70.

Table 70 Summary Statistics of Systolic Blood Pressure (mmHg) by Time Point and Change from Baseline

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
Day 0 Pre-dose	N	12	3	26	16	57
	Mean (SD)	102.42 (5.435)	N/A	109.00 (7.746)	112.50 (8.579)	108.26 (8.444)
	Median	102.00	N/A	108.00	114.50	108.00
	Min, Max	96.0,114.0	N/A	93.0,125.0	93.0,123.0	90.0,125.0
5 min post dose	N	12	3	26	16	57
	Mean (SD)	103.83 (7.566)	N/A	108.31 (8.303)	108.13 (9.926)	107.25 (8.547)
	Median	103.00	N/A	108.50	109.00	107.00
	Min, Max	90.0,118.0	N/A	83.0,123.0	92.0,120.0	83.0,123.0
5 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	1.42 (5.299)	N/A	-0.69 (6.793)	-4.38 (6.163)	-1.02 (6.635)
	Median	2.50	N/A	-2.00	-6.50	-1.00
	Min, Max	-8.0,8.0	N/A	-10.0,15.0	-13.0,10.0	-13.0,15.0
10 min post dose	N	12	3	26	16	57
	Mean (SD)	107.58 (10.113)	N/A	107.15 (10.306)	113.19 (8.879)	109.05 (9.871)
	Median	104.50	N/A	106.50	115.00	108.00
	Min, Max	97.0,128.0	N/A	87.0,126.0	94.0,126.0	87.0,128.0
10 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	5.17 (8.009)	N/A	-1.85 (10.318)	0.69 (8.739)	0.79 (9.636)
	Median	2.50	N/A	-3.00	-1.50	0.00
	Min, Max	-2.0,27.0	N/A	-24.0,20.0	-13.0,17.0	-24.0,27.0
15 min post dose	N	12	3	26	16	57
	Mean (SD)	107.17 (7.566)	N/A	109.27 (8.426)	114.44 (12.997)	110.56 (9.968)
	Median	109.00	N/A	110.50	116.00	110.00
	Min, Max	90.0,118.0	N/A	89.0,125.0	90.0,136.0	89.0,136.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
15 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	4.75 (7.111)	N/A	0.27 (8.254)	1.94 (10.142)	2.30 (8.742)
	Median	4.50	N/A	-1.50	4.00	1.00
	Min, Max	-8.0,14.0	N/A	-15.0,21.0	-17.0,16.0	-17.0,21.0
20 min post dose	N	12	3	26	16	57
	Mean (SD)	106.25 (6.969)	N/A	110.31 (8.293)	114.81 (10.407)	110.95 (9.038)
	Median	106.50	N/A	112.00	114.00	112.00
	Min, Max	95.0,120.0	N/A	89.0,121.0	98.0,131.0	89.0,131.0
20 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	3.83 (4.489)	N/A	1.31 (6.763)	2.31 (9.958)	2.68 (7.581)
	Median	3.50	N/A	1.50	3.00	3.00
	Min, Max	-2.0,11.0	N/A	-12.0,12.0	-17.0,21.0	-17.0,21.0
25 min post dose	N	12	3	26	16	57
	Mean (SD)	107.08 (8.436)	N/A	108.35 (9.230)	117.00 (6.563)	110.60 (9.045)
	Median	105.50	N/A	112.00	117.50	112.00
	Min, Max	97.0,128.0	N/A	84.0,124.0	105.0,128.0	84.0,128.0
25 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	4.67 (4.418)	N/A	-0.65 (7.294)	4.50 (9.661)	2.33 (7.861)
	Median	4.50	N/A	-0.50	3.50	3.00
	Min, Max	-3.0,14.0	N/A	-22.0,12.0	-18.0,25.0	-22.0,25.0
30 min post dose	N	12	3	26	16	57
	Mean (SD)	108.08 (9.587)	N/A	109.04 (10.074)	117.13 (8.024)	111.35 (9.990)
	Median	110.00	N/A	109.00	117.50	111.00
	Min, Max	89.0,122.0	N/A	84.0,129.0	106.0,132.0	84.0,132.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
30 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	5.67 (7.726)	N/A	0.04 (8.374)	4.63 (8.024)	3.09 (8.446)
	Median	7.50	N/A	-1.00	4.00	4.00
	Min, Max	-9.0,17.0	N/A	-12.0,16.0	-10.0,17.0	-12.0,17.0
45 min post dose	N	12	3	26	16	57
	Mcan (SD)	107.08 (9.482)	N/A	109.15 (9.238)	115.94 (10.535)	110.68 (10.006)
	Median	106.00	N/A	108.00	117.00	110.00
	Min, Max	93.0,128.0	N/A	96.0,134.0	98.0,135.0	93.0,135.0
45 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	4.67 (5.499)	N/A	0.15 (7.943)	3.44 (8.254)	2.42 (7.627)
	Median	5.50	N/A	1.00	2.00	3.00
	Min, Max	-5.0,14.0	N/A	-20.0,15.0	-9.0,18.0	-20.0,18.0
60 min post dose	N	12	3	26	16	57
	Mcan (SD)	102.75 (7.545)	N/A	107.27 (10.854)	114.13 (12.997)	108.21 (11.296)
	Median	100.50	N/A	106.50	116.00	107.00
	Min, Max	90.0,115.0	N/A	92.0,139.0	94.0,143.0	90.0,143.0
60 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.33 (5.975)	N/A	-1.73 (10.038)	1.63 (8.846)	-0.05 (8.760)
	Median	0.50	N/A	-1.00	2.00	0.00
	Min, Max	-8.0,8.0	N/A	-33.0,20.0	-12.0,23.0	-33.0,23.0
90 min post dose	N	12	3	26	16	57
	Mean (SD)	102.75 (8.646)	N/A	107.77 (10.626)	111.38 (14.913)	107.89 (11.827)
	Median	103.50	N/A	107.50	110.50	107.00
	Min, Max	83.0,117.0	N/A	87.0,131.0	89.0,137.0	83.0,137.0

Diastolic Blood Pressure

Summary statistics for DBP change from baseline, by timepoint and treatment, are presented in the table below.

Table 71 Summary Statistics of Diastolic Blood Pressure (mmHg) by Time Point and Change from Baseline

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
Day 0 Pre-dose	N	12	3	26	16	57
	Mean (SD)	65.58 (7.845)	N/A	69.00 (5.879)	68.88(6.571)	68.26(6.490)
	Median	63.50	N/A	69.50	69.00	68.00
	Min, Max	56.0,82.0	N/A	55.0,80.0	59.0,81.0	55.0,82.0
5 min post dose	N	12	3	26	16	57
	Mean (SD)	65.50 (5.697)	N/A	67.62 (7.161)	66.00(9.331)	66.49(7.354)
	Median	64.00	N/A	66.50	66.50	66.00
	Min, Max	58.0,76.0	N/A	55.0,83.0	47.0,79.0	47.0,83.0
5 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-0.08 (8.857)	N/A	-1.38 (6.616)	-2.88(5.965)	-1.77(6.889)
	Median	2.50	N/A	-2.50	-2.50	-2.00
	Min, Max	-24.0,10.0	N/A	-14.0,16.0	-15.0,7.0	-24.0,16.0
10 min post dose	N	12	3	26	16	57
	Mean (SD)	66.25 (11.194)	N/A	65.31 (7.662)	68.56(9.818)	66.72(9.053)
	Median	64.50	N/A	67.00	68.00	67.00
	Min, Max	53.0,92.0	N/A	46.0,79.0	47.0,86.0	46.0,92.0
10 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.67 (12.844)	N/A	-3.69 (7.999)	-0.31(6.364)	-1.54(8.860)
	Median	1.50	N/A	-3.00	0.50	0.00
	Min, Max	-29.0,28.0	N/A	-28.0,9.0	-12.0,9.0	-29.0,28.0
15 min post dose	N	12	3	26	16	57
	Mean (SD)	66.33 (7.958)	N/A	69.38 (6.113)	69.19(8.479)	68.77(7.529)
	Median	65.50	N/A	70.00	70.00	69.00
	Min, Max	54.0,80.0	N/A	54.0,83.0	46.0,84.0	46.0,85.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
15 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.75 (8.833)	N/A	0.38 (5.672)	0.31(6.580)	0.51(6.941)
	Median	0.50	N/A	0.00	2.50	1.00
	Min, Max	-18.0,13.0	N/A	-12.0,12.0	-13.0,9.0	-18.0,13.0
20 min post dose	N	12	3	26	16	57
	Mean (SD)	62.92 (7.440)	N/A	67.92 (6.542)	67.75(9.169)	66.74(7.898)
	Median	62.50	N/A	66.50	66.00	66.00
	Min, Max	50.0,77.0	N/A	54.0,82.0	53.0,87.0	50.0,87.0
20 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-2.67 (8.804)	N/A	-1.08 (5.130)	-1.13(6.702)	-1.53(6.623)
	Median	-2.00	N/A	-1.00	-1.00	-1.00
	Min, Max	-21.0,8.0	N/A	-9.0,14.0	-15.0,9.0	-21.0,14.0
25 min post dose	N	12	3	26	16	57
	Mean (SD)	65.75 (7.677)	N/A	64.92 (7.715)	70.44(9.522)	66.79(8.370)
	Median	65.00	N/A	65.00	68.50	67.00
	Min, Max	50.0,77.0	N/A	48.0,77.0	59.0,99.0	48.0,99.0
25 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.17 (9.074)	N/A	-4.08 (7.348)	1.56(8.270)	-1.47(8.175)
	Median	2.50	N/A	-3.00	3.50	-1.00
	Min, Max	-19.0,11.0	N/A	-26.0,7.0	-14.0,21.0	-26.0,21.0
30 min post dose	N	12	3	26	16	57
	Mean (SD)	65.42 (9.728)	N/A	66.54 (8.719)	68.81(6.555)	66.81(8.438)
	Median	66.00	N/A	66.00	69.00	66.00
	Min, Max	50.0,82.0	N/A	48.0,82.0	58.0,78.0	48.0,82.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
30 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-0.17 (11.968)	N/A	-2.46 (7.680)	-0.06(7.188)	-1.46(8.734)
	Median	1.50	N/A	-2.50	0.00	0.00
	Min, Max	-31.0,19.0	N/A	-17.0,14.0	-14.0,13.0	-31.0,19.0
45 min post dose	N	12	3	26	16	57
	Mean (SD)	63.58 (5.534)	N/A	65.27 (6.142)	68.44(6.532)	66.04(6.228)
	Median	63.00	N/A	65.50	68.50	66.00
	Min, Max	54.0,74.0	N/A	55.0,77.0	57.0,81.0	54.0,81.0
45 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-2.00 (6.238)	N/A	-3.73 (6.220)	-0.44(5.059)	-2.23(5.846)
	Median	-2.00	N/A	-1.00	0.00	-1.00
	Min, Max	-13.0,10.0	N/A	-19.0,4.0	-10.0,8.0	-19.0,10.0
60 min post dose	N	12	3	26	16	57
	Mean (SD)	61.92 (7.267)	N/A	65.54 (6.819)	66.94(7.434)	65.32(7.071)
	Median	61.00	N/A	66.00	67.00	66.00
	Min, Max	52.0,74.0	N/A	49.0,76.0	55.0,82.0	49.0,82.0
60 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-3.67 (10.021)	N/A	-3.46 (7.716)	-1.94(6.382)	-2.95(7.726)
	Median	-1.00	N/A	-2.00	-2.00	-2.00
	Min, Max	-28.0,9.0	N/A	-27.0,6.0	-13.0,8.0	-28.0,9.0
90 min post dose	N	12	3	26	16	57
	Mean (SD)	64.17 (6.913)	N/A	65.46 (8.636)	66.75(8.933)	65.65(8.079)
	Median	63.50	N/A	65.50	69.00	66.00
	Min, Max	53.0,80.0	N/A	43.0,77.0	48.0,79.0	43.0,80.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
90 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-1.42 (11.285)	N/A	-3.54 (8.315)	-2.13(6.937)	-2.61(8.470)
	Median	-1.50	N/A	-2.00	-2.00	-2.00
	Min, Max	-21.0,24.0	N/A	-26.0,13.0	-21.0,8.0	-26.0,24.0
120 min post dose	N	12	3	26	16	57
	Mean (SD)	68.08 (8.501)	N/A	66.35 (7.392)	68.19(7.808)	67.09(7.548)
	Median	65.50	N/A	65.50	69.00	66.00
	Min, Max	54.0,87.0	N/A	53.0,80.0	53.0,86.0	53.0,87.0
120 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	2.50 (10.639)	N/A	-2.65 (7.413)	-0.69(7.964)	-1.18(8.300)
	Median	3.50	N/A	-1.00	-1.00	-1.00
	Min, Max	-18.0,24.0	N/A	-19.0,8.0	-18.0,12.0	-19.0,24.0
Discharge	N	12	3	26	16	57
	Mean (SD)	66.33 (7.608)	N/A	66.77 (6.930)	68.88(9.926)	67.23(8.205)
	Median	65.00	N/A	68.00	67.50	67.00
	Min, Max	54.0,81.0	N/A	53.0,80.0	55.0,94.0	50.0,94.0
Discharge Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.75 (4.864)	N/A	-2.23 (7.140)	0.00(6.782)	-1.04(6.652)
	Median	0.50	N/A	-2.00	0.00	0.00
	Min, Max	-8.0,7.0	N/A	-21.0,16.0	-12.0,16.0	-21.0,16.0

Pulse Rate

Summary statistics for PR change from baseline, by timepoint and treatment, are presented in Table 72.

Table 72 Summary Statistics of Pulse Rate (bpm) by Time Point and Change from Baseline

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
Day 0 Pre-dose	N	12	3	26	16	57
	Mean (SD)	91.50 (8.639)	N/A	77.31(12.454)	73.25(10.253)	79.75(12.999)
	Mcdian	93.50	N/A	78.00	72.50	80.00
	Min, Max	75.0,106.0	N/A	55.0,100.0	55.0,94.0	55.0,106.0
5 min post dose	N	12	3	26	16	57
	Mean (SD)	95.50 (13.971)	N/A	77.31(12.827)	75.69(9.075)	81.86(14.652)
	Median	94.50	N/A	76.00	75.50	78.00
	Min, Max	69.0,123.0	N/A	57.0,110.0	57.0,99.0	57.0,123.0
5 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	4.00 (13.457)	N/A	0.00(10.438)	2.44(9.316)	2.11(10.768)
	Median	8.50	N/A	2.50	-1.50	3.00
	Min, Max	-27.0,19.0	N/A	-34.0,19.0	-9.0,22.0	-34.0,22.0
10 min post dose	N	12	3	26	16	57
	Mean (SD)	96.17 (17.729)	N/A	80.92(14.037)	78.13(11.592)	84.40(15.991)
	Median	93.00	N/A	78.00	75.50	81.00
	Min, Max	59.0,123.0	N/A	60.0,116.0	56.0,105.0	56.0,123.0
10 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	4.67 (16.008)	N/A	3.62(10.774)	4.88(7.830)	4.65(11.128)
	Median	6.00	N/A	-0.50	1.50	3.00
	Min, Max	-37.0,26.0	N/A	-16.0,26.0	-5.0,21.0	-37.0,26.0
15 min post dose	N	12	3	26	16	57
	Mean (SD)	99.00 (20.104)	N/A	82.96(16.333)	78.69(11.336)	86.11(17.684)
	Mcdian	96.00	N/A	81.50	79.00	82.00
	Min, Max	73.0,150.0	N/A	53.0,118.0	55.0,100.0	53.0,150.0
Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
15 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	7.50 (19.732)	N/A	5.65(12.541)	5.44(10.341)	6.35(13.396)
	Median	5.50	N/A	4.00	6.00	5.00
	Min, Max	-23.0,58.0	N/A	-10.0,42.0	-15.0,29.0	-23.0,58.0
20 min post dose	N	12	3	26	16	57
	Mean (SD)	92.00 (11.832)	N/A	80.54(13.877)	79.50(14.450)	83.79(14.783)
	Median	93.00	N/A	83.00	78.50	84.00
	Min, Max	72.0,111.0	N/A	57.0,113.0	55.0,111.0	55.0,117.0
20 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	0.50 (11.366)	N/A	3.23(6.301)	6.25(13.772)	4.04(10.149)
	Median	2.00	N/A	4.50	2.00	4.00
	Min, Max	-23.0,16.0	N/A	-9.0,13.0	-10.0,45.0	-23.0,45.0
25 min post dose	N	12	3	26	16	57
	Mean (SD)	92.75 (11.910)	N/A	80.88(13.095)	78.94(12.678)	83.63(13.660)
	Median	96.50	N/A	82.50	78.00	84.00
	Min, Max	73.0,108.0	N/A	57.0,113.0	54.0,108.0	54.0,113.0
25 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	1.25 (11.616)	N/A	3.58(6.338)	5.69(10.830)	3.88(9.026)
	Median	3.00	N/A	3.00	4.50	3.00
	Min, Max	-23.0,15.0	N/A	-9.0,14.0	-6.0,42.0	-23.0,42.0
30 min post dose	N	12	3	26	16	57
	Mean (SD)	90.25 (10.181)	N/A	79.46(13.981)	77.44(13.875)	82.30(14.378)
	Median	89.00	N/A	79.00	75.50	82.00
	Min, Max	73.0,114.0	N/A	58.0,112.0	53.0,111.0	53.0,114.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
30 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-1.25 (9.255)	N/A	2.15(9.341)	4.19(11.912)	2.54(10.181)
	Median	3.00	N/A	3.50	1.50	3.00
	Min, Max	-23.0,8.0	N/A	-18.0,23.0	-7.0,45.0	-23.0,45.0
45 min post dose	N	12	3	26	16	57
	Mean (SD)	86.08 (9.848)	N/A	79.27(15.361)	78.56(16.480)	80.96(14.793)
	Median	87.50	N/A	80.50	76.00	82.00
	Min, Max	66.0,99.0	N/A	52.0,112.0	52.0,112.0	52.0,112.0
45 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-5.42 (11.453)	N/A	1.96(8.838)	5.31(14.046)	1.21(11.568)
	Median	-7.00	N/A	1.00	1.50	1.00
	Min, Max	-23.0,16.0	N/A	-14.0,19.0	-14.0,46.0	-23.0,46.0
60 min post dose	N	12	3	26	16	57
	Mean (SD)	91.00 (11.724)	N/A	79.65(15.579)	78.81(13.742)	83.09(15.386)
	Median	91.00	N/A	80.00	78.00	83.00
	Min, Max	66.0,108.0	N/A	54.0,118.0	51.0,111.0	51.0,118.0
60 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-0.50 (12.362)	N/A	2.35(6.847)	5.56(12.072)	3.33(10.235)
	Median	2.00	N/A	1.00	4.00	3.00
	Min, Max	-30.0,15.0	N/A	-9.0,18.0	-6.0,45.0	-30.0,45.0
90 min post dose	N	12	3	26	16	57
	Mean (SD)	84.58 (13.420)	N/A	78.73(16.511)	77.19(14.242)	80.74(15.710)
	Median	87.00	N/A	80.50	80.00	84.00
	Min, Max	56.0,103.0	N/A	51.0,111.0	49.0,98.0	49.0,112.0

Treatment	Statistic	Weight/ Treatment				Total
		15 – 30 kg		>30 kg		
		ARS-1 0.65 mg	ARS-1 1.0 mg	ARS-1 1.0mg	ARS-1 2.0mg	
90 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-6.92 (16.941)	N/A	1.42(8.594)	3.94(10.043)	0.98(11.881)
	Median	-6.00	N/A	0.00	0.00	0.00
	Min, Max	-40.0,22.0	N/A	-12.0,28.0	-7.0,25.0	-40.0,28.0
120 min post dose	N	12	3	26	16	57
	Mean (SD)	89.42 (10.509)	N/A	79.23(14.630)	76.69(12.300)	81.63(14.432)
	Median	88.00	N/A	77.00	76.50	79.00
	Min, Max	67.0,109.0	N/A	57.0,112.0	48.0,103.0	48.0,112.0
120 min post dose Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-2.08 (12.788)	N/A	1.92(9.187)	3.44(8.959)	1.88(10.087)
	Median	0.50	N/A	3.00	3.50	2.00
	Min, Max	-29.0,15.0	N/A	-25.0,20.0	-12.0,23.0	-29.0,23.0
Discharge	N	12	3	26	16	57
	Mean (SD)	88.33 (10.094)	N/A	80.96(13.890)	74.63(11.690)	81.05(12.958)
	Median	89.50	N/A	80.50	76.00	82.00
	Min, Max	72.0,108.0	N/A	54.0,110.0	49.0,90.0	49.0,110.0
Discharge Change from BL	N	12	N/A	26	16	57
	Mean (SD)	-3.17 (11.424)	N/A	3.65(12.188)	1.38(12.055)	1.30(12.033)
	Median	-2.50	N/A	3.50	0.50	2.00
	Min, Max	-23.0,13.0	N/A	-16.0,40.0	-20.0,24.0	-23.0,40.0

Pharmacodynamic Parameters

Systolic Blood Pressure

Summary statistics for change from baseline SBP by treatment are presented in Table 73.

Table 73 Pharmacodynamic Parameters for SBP Change from Baseline

Treatment	N	t _{E_{max}} (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)								
15 – 30 kg													
ARS-1 0.65 mg	11	30.5 (10 – 120)	12.25 (43.5)	285.3 (150.8)	3.68 (332.5)	17.44 (214.0)	40.08 (157.4)	63.0 (127.4)	84.75 (113.4)	110.6 (103.1)	187.9 (101.3)	226.9 (99.1)	286.9 (149.7)
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
> 30 kg													
ARS-1 1.0 mg	25	20 (0 – 120)	8.23 (85.3)	-100.3 (-806.8)	-1.65 (-976.3)	-7.49 (-714.5)	-10.75 (-828.3)	-7.22 (-1575.4)	-5.32 (-2553.4)	-6.85 (-2374.4)	-5.81 (4287.7)	-17.25 (-2051.1)	-99.71 (-808.50)
ARS-1 2.0 mg	16	25 (0 – 90)	11.9 (68.6)	116.5 (756.8)	-10.39 (-142.8)	-20.7 (-217.1)	-13.4 (-604.1)	-2.54 (-4773.6)	14.3 (1123.3)	36.625 (530.5)	97.06 (299.4)	134.2 (282.6)	110.8 (793.7)

Diastolic Blood Pressure

Summary statistics for change from baseline DBP by treatment are presented in Table 74.

Table 74 Pharmacodynamic Parameters for DBP Change from Baseline

Treatment	N	t _{E_{max}} (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)								
15 – 30 kg													
ARS-1 0.65 mg	11	25 (0 – 120)	10.6 (80.3)	-128.5 (-740.0)	-0.35 (-6211.8)	-1.01 (-6946.7)	1.21 (10036.1)	-2.50 (-6417.8)	-8.83 (-2211.2)	-8.50 (-2789.9)	-23.3 (-1547.8)	-65.3 (-700.5)	-127.7 (-743.1)
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
> 30 kg													
ARS-1 1.0 mg	25	15.5 (0 – 122)	4.92 (91.2)	-352.6 (187.5)	-3.65 (-431.8)	-16.2 (-291.8)	-24.3 (-301.0)	-25.4 (-342.1)	-37.9 (-270.3)	-54.3 (-235.3)	-100.7 (-202.1)	-153.8 (-182.8)	-353.1 (-186.8)
ARS-1 2.0 mg	16	17.5 (0 – 120)	7 (76.0)	-154.2 (-374.8)	-6.90 (-214.4)	-15.3 (-251.6)	-15.3 (-408.2)	-16.7 (-534.3)	-15.7 (-657.3)	-11.64 (-1035.0)	-15.6 (-1253.2)	-33.4 (-799.8)	-135.9 (-419.4)

Pulse Rate

Summary statistics for change from baseline PR by treatment are presented in Table 75.

Table 75 Pharmacodynamic Parameters for PR Change from Baseline

Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (bpm) Mean (%CV)	AUEC _{last} (min* bpm) (Mean (%CV))	AUEC min* bpm								
					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)								
15 – 30 kg													
ARS-1 0.65 mg	11	10.5 (0 – 91)	17.7 (83.8)	-267.9 (-470.6)	9.93 (324.4)	30.99 (326.6)	51.8 (312.0)	72.3 (279.1)	78.2 (312.5)	76.7 (371.5)	26.6 (1493.7)	-17.4 (-3081.1)	-271.0 (-464.2)
ARS-1 1.0 mg	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
> 30 kg													
ARS-1 1.0 mg	25	18 (0 – 124)	13.8 (72.4)	259.1 (283.6)	-0.128 (-20311.2)	8.72 (832.2)	31.44 (370.6)	53.7 (284.0)	70.1 (249.2)	85.0 (238.2)	113.6 (265.7)	148.1 (260.8)	258.8 (282.4)
ARS-1 2.0 mg	16	32.5 (0 – 90)	15.4 (75.0)	589.8 (185.0)	6.17 (376.6)	24.6 (247.1)	50.0 (193.2)	79.5 (170.0)	109.2 (164.4)	133.7 (167.6)	204.7 (189.1)	285.8 (196.0)	538.1 (191.5)

Study EPI 18

A Five-Treatment, Five-Period, Randomized, Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Repeat Administration of Eurneffy and Intramuscular Epinephrine Injection in Type I Allergy Patients with Seasonal Rhinitis

Pharmacodynamic Parameters –Primary Analysis

Systolic Blood Pressure

Under normal nasal conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean SBP Emax of 29 mmHg and a mean AUEClast of 1211 min*mmHg and IM 0.3 mg twice resulted in mean Emax of 14 mmHg and a mean AUEClast of 473 min*mmHg. Median tEmax values were 19 minutes for Eurneffy 2.0 mg twice (R/L) and 38 minutes for IM 0.3 mg twice.

Under rhinitis conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean SBP Emax of 18 mmHg and mean AUEClast of 589 min*mmHg and Eurneffy 2.0 mg twice (R/R) resulted in a mean Emax of 21 mmHg and mean AUEClast of 932 min*mmHg. Under rhinitis conditions, IM 0.3 mg twice resulted in mean Emax of 13 mmHg and a mean AUEClast of 376 min*mmHg. Median tEmax values were 16 minutes for Eurneffy 2.0 mg twice (R/L), 26 minutes for Eurneffy 2.0 mg twice (R/R), and 30 minutes for IM 0.3 mg twice.

Least Squares Analysis – Primary Analysis

Under normal nasal conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater increases in SBP, beginning at 15 minutes post-dose and persisting through 60 minutes post-dose. Under rhinitis conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater increases in SBP at 5-, 10-, 25-, and 30-minutes post-dose; and Eurneffy 2.0 mg twice (R/R) resulted in significantly greater increases in SBP at 30-minutes post-dose.

Diastolic Blood Pressure

Under normal nasal conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean DBP Emax of 10 mmHg and a mean AUEClast of 214 min*mmHg and IM 0.3 mg twice resulted in mean Emax of 6 mmHg and a mean AUEClast of 20 min*mmHg. Median tEmax values were 15 minutes for Eurneffy 2.0 mg twice (R/L) and 10 minutes for IM 0.3 mg twice.

Under rhinitis conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean DBP Emax of 6 mmHg and mean AUEClast of 60 min*mmHg and Eurneffy 2.0 mg twice (R/R) resulted in a mean Emax of 7 mmHg and mean AUEClast of 169 min*mmHg. Under rhinitis conditions, IM 0.3 mg twice resulted in mean Emax of 6 mmHg and a mean AUEClast of 78 min*mmHg. Median tEmax values were 10 minutes for Eurneffy 2.0 mg twice (R/L), 20 minutes for Eurneffy 2.0 mg twice (R/R), and 13 minutes for IM 0.3 mg twice.

Least Squares Analysis – Primary Analysis

For both normal and rhinitis conditions, there were no persistent and meaningful differences between Eurneffy 2.0 mg twice (R/L or R/R) and IM 0.3 mg twice.

Pulse Rate

Under normal nasal conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean PR Emax of 24 bpm and a mean AUEClast of 1219 min*bpm and IM 0.3 mg twice resulted in mean Emax of 14 bpm and a mean AUEClast of 876 min*bpm. Median tEmax values were 16 minutes for Eurneffy 2.0 mg twice (R/L) and 45 minutes for IM 0.3 mg twice.

Under rhinitis conditions, Eurneffy 2.0 mg twice (R/L) resulted in a mean PR Emax of 22 bpm and mean AUEClast of 979 min*bpm and Eurneffy 2.0 mg twice (R/R) resulted in a mean Emax of 22 bpm and mean AUEClast of 1353 min*bpm. Under rhinitis conditions, IM 0.3 mg twice resulted in mean Emax of 14 bpm and a mean AUEClast of 715 min*bpm. Median tEmax values were 11 minutes for Eurneffy 2.0 mg twice (R/L), 16 minutes for Eurneffy 2.0 mg twice (R/R), and 28 minutes for IM 0.3 mg twice.

Least Squares Analysis – Primary Analysis

Under normal nasal conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater increases in PR through 60 minutes post-dose.

Under rhinitis conditions, relative to IM 0.3 mg, Eurneffy 2.0 mg twice (R/L) resulted in significantly greater increases in PR through 60 minutes post-dose; and Eurneffy 2.0 mg twice (R/R) resulted in significantly greater increases in PR through 120 minutes post-dose.

Gender Analysis:

An analysis by gender for both pharmacokinetic (PK) results and pharmacodynamic (PD) outcomes from EPI 18 is provided below.

There were 24 female subjects and 18 male subjects enrolled in this clinical trial. The mean weight was higher for male subjects (85 kg vs. 71 kg) as compared to female subjects, with BMI being similar between the two groups (27 vs. 26).

Table 76 EPI 18 Summary of Demographic Data

	Female				Male			
	Age (year)	Height (cm)	Weight (kg)	BMI	Age (year)	Height (cm)	Weight (kg)	BMI
N	24	24	24	24	19	19	19	19
Mean	43	164	71	26	43	175	85	27
SD	10	7	15	4	11	7	12	3
Minimum	29	147	52	19	24	163	61	20
Median	41	163	68	26	45	175	84	28
Maximum	61	180	108	35	63	188	107	34

Pharmacodynamic parameters from EPI 18

For SBP the Eurneffy groups the median TE_{max} was generally similar for Eurneffy between genders for the normal group and contralateral (R/L) group, while in the ipsilateral (R/R) group the male subjects exhibited a slightly faster SBP TE_{max} (21 min vs. 30 min). For the IM groups the SBP TE_{max} was more rapid in male subjects under normal conditions but similar after NAC induction. The mean E_{max} for SBP was generally higher for Eurneffy as compared to IM injection in all groups and similar between genders.

For pulse rate (PR) median TE_{max} was similar between genders for Eurneffy under normal conditions. After NAC induction SBP median TE_{max} with Eurneffy was more rapid for female subjects (7.5 min vs. 13 min) with contralateral (R/L) dosing and more rapid for male subjects (15 min vs. 31 min) with ipsilateral (R/R) dosing. For IM injection the PR median TE_{max} was more rapid for female subjects under normal conditions (45 min vs. 60 min) and after NAC induction (20 min vs. 30 min). The mean E_{max} for PR was similar between genders for all treatment groups.

Table 77 EPI 18 Pharmacodynamic Parameters by Gender

	Treatment	Female						Male					
		N	Mean	SD	Max	Median	Min	N	Mean	SD	Max	Median	Min
SBP													
TEmax	neffy (R/L)	24	29.9	27	1.0	20.0	120.0	19.0	21.6	14	1.0	16.0	60.0
	IM (R/L)	24	38.5	35	1.0	45.0	120.0	18.0	40.8	31	2.0	31.0	119.0
	neffy with Rhinitis (R/L)	24	26.6	27	1.0	17.0	120.0	16.0	24.5	29	1.0	15.5	120.0
	neffy with Rhinitis (R/R)	24	39.0	30	1.0	29.5	120.0	17.0	18.1	11	1.0	21.0	30.0
	IM with Rhinitis (R/L)	23	33.6	31	2.0	25.0	91.0	19.0	38.4	34	1.0	30.0	121.0
Emax	neffy (R/L)	24	26.5	13	2.0	24.5	50.0	19.0	33.1	19	5.0	29.0	71.0
	IM (R/L)	24	13.6	9	-8.0	15.5	31.0	18.0	14.2	9	-5.0	13.5	39.0
	neffy with Rhinitis (R/L)	24	19.5	12	-3.0	17.5	39.0	16.0	15.4	13	-8.0	12.0	44.0
	neffy with Rhinitis (R/R)	24	23.5	10	8.0	25.0	45.0	17.0	18.1	10	2.0	15.0	38.0
	IM with Rhinitis (R/L)	23	11.1	8	0.0	10.0	26.0	19.0	14.5	9	-9.0	14.0	34.0
AUEC	neffy (R/L)	24	15111	1616	12310	15243	18111	19	15412	1786	12735	14924	19516
	IM (R/L)	24	13734	2796	2342	13979	16987	18	14492	1674	11496	14722	17537
	neffy with Rhinitis (R/L)	24	14313	1357	12401	13955	17695	16	14764	1504	11925	14352	17735
	neffy with Rhinitis (R/R)	24	14597	1405	12433	14247	17659	17	14939	1314	13146	14722	17725
	IM with Rhinitis (R/L)	23	14154	1307	12087	14169	16548	19	14165	1319	11842	14069	16532
DBP													
TEmax	neffy (R/L)	24	20.4	25	1.0	15.5	120.0	19.0	17.2	11	1.0	15.0	45.0
	IM (R/L)	24	22.2	34	1.0	10.0	121.0	18.0	24.6	37	1.0	12.5	121.0
	neffy with Rhinitis (R/L)	24	24.0	33	1.0	12.5	121.0	16.0	33.6	41	1.0	10.0	121.0
	neffy with Rhinitis (R/R)	24	34.0	34	1.0	22.5	120.0	17.0	22.7	31	1.0	10.0	120.0
	IM with Rhinitis (R/L)	23	18.4	22	1.0	11.0	86.0	19.0	42.8	49	1.0	21.0	121.0
Emax	neffy (R/L)	24	11.0	6	-1.0	12.0	24.0	19.0	9.4	6	-3.0	9.0	23.0
	IM (R/L)	24	6.2	6	-5.0	6.0	22.0	18.0	4.9	5	-1.0	3.5	14.0
	neffy with Rhinitis (R/L)	24	6.0	7	-10.0	6.0	20.0	16.0	7.2	6	0.0	5.5	19.0
	neffy with Rhinitis (R/R)	24	5.7	6	-2.0	5.0	17.0	17.0	8.2	6	-3.0	9.0	22.0
	IM with Rhinitis (R/L)	23	5.6	6	-12.0	6.0	17.0	19.0	6.3	8	-5.0	4.0	24.0
AUEC	neffy (R/L)	24	9201	979	7345	9316	11147	19	9021	768	7818	9010	10281
	IM (R/L)	24	8492	1597	1637	8807	9977	18	8409	990	6883	8625	10436
	neffy with Rhinitis (R/L)	24	8881	943	7464	8715	11333	16	9389	751	8051	9531	10676
	neffy with Rhinitis (R/R)	24	8847	1072	7388	8754	11341	17	9192	700	8078	9155	10355
	IM with Rhinitis (R/L)	23	8867	854	7169	8885	10717	19	8612	968	6754	840	10484
PR													
TEmax	neffy (R/L)	24	29.3	35	1.0	16.0	120.0	19.0	24.4	23	1.0	19.0	90.0

	Treatment	Female						Male					
		N	Mean	SD	Max	Median	Min	N	Mean	SD	Max	Median	Min
	IM (R/L)	24	48.1	40	1.0	45.0	121.0	18.0	62.7	40	6.0	60.0	121.0
	neffy with Rhinitis (R/L)	24	19.3	29	1.0	7.5	121.0	16.0	22.9	34	1.0	13.0	120.0
	neffy with Rhinitis (R/R)	24	48.0	47	1.0	31.0	121.0	17.0	18.4	17	1.0	15.0	58.0
	IM with Rhinitis (R/L)	23	29.8	28	5.0	20.0	120.0	19.0	35.4	26	1.0	30.0	90.0
Ema x	neffy (R/L)	24	25.0	12	8.0	23.0	57.0	19.0	22.1	11	6.0	18.0	46.0
	IM (R/L)	24	16.1	11	2.0	14.5	53.0	18.0	11.3	5	2.0	11.0	19.0
	neffy with Rhinitis (R/L)	24	22.0	10	3.0	23.0	38.0	16.0	21.2	10	8.0	20.0	44.0
	neffy with Rhinitis (R/R)	24	24.0	10	7.0	24.5	47.0	17.0	18.2	9	7.0	17.0	36.0
	IM with Rhinitis (R/L)	23	16.2	8	1.0	17.0	38.0	19.0	12.1	5	3.0	12.0	25.0
AUE C	neffy (R/L)	24	1264	762	212	1245	2883	19	1163	1086	87	711	3269
	IM (R/L)	24	1029	962	-361	874	4182	18	673	484	-403	639	1502
	neffy with Rhinitis (R/L)	24	1066	788	-28	813	2705	16	849	588	63	568	2484
	neffy with Rhinitis (R/R)	24	1609	890	93	1386	3075	17	991	729	148	826	2663
	IM with Rhinitis (R/L)	23	724	522	-134	611	2201	19	705	554	-56	635	2254

In Study EPI 18 in total 24 female and 19 male subjects were included. Under normal conditions, median C_{max} in females was higher compared to male (773.7 vs 644.1). Under rhinitis conditions when administered to the same nostril the difference between female and male was more pronounced (894.1 vs 513.1). However, after administration to different nostrils median C_{max} in female was lower compared to male (408.9 vs 530.9).

Similarly, AUC after administration of Eurneffy was higher in female compared to male, both under normal and rhinitis conditions. Of note, median AUC in female under rhinitis conditions after R/R administration was much higher compared to R/L administration (81467 vs 43145). These results also support recommendation to administer second dose of Eurneffy to the other nostril.

Comparable trends in differences between females and males were observed in SBP, DBP and PR. However, pronounced differences in PR between males and females under rhinitis conditions after R/R administration should be noted.

Supportive studies

EPI 04. A Five-Treatment, Partially Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine After Administration of ARS -1 or Epinephrine Injection in Subjects with Allergic Rhinitis.

Pharmacodynamic Assessments

PD measurements included BP, PR, and RR. Assessments were conducted prior to dosing, and at 15 (± 5 min), 30 (± 5 min) minutes, 1 (± 10 min), 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dosing.

Pharmacodynamic Results

Vital sign data (SBP, DBP and PR) up to 2 hours post dose were evaluated. The subjects were supine

and quiescent for 1-hour period to dosing and 2 hours post dose, and vital signs were taken at 15 and 30 minutes, and at 1 and 2 hours.

Systolic Blood Pressure

Summary statistics for SBP comparing ARS-1 1.0 mg IN to rhinitis status and to Epinephrine 0.3 mg IM, Epinephrine 0.3 mg SC, and Epinephrine 0.5 mg IM are presented by timepoint and change from baseline are presented in Table 78.

Table 78 Summary statistic of systolic blood pressure (mm Hg) by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Baseline	N	35	36	35	33	23
	Mean (SD)	113.3 (12.79)	112.0 (9.22)	111.0 (12.73)	116.4 (10.80)	112.6 (14.63)
	Median	113.0	112.0	110.0	116.0	114.0
	Min, Max	91, 157	98, 140	87, 139	93, 145	85, 145
15 min Post dose	N	35	36	35	33	23
	Mean (SD)	124.5 (13.99)	116.2 (12.49)	113.6 (13.45)	123.9 (13.14)	118.8 (13.69)
	Median	124.0	116.5	112.0	123.0	119.0
	Min, Max	93, 154	93, 141	91, 140	100, 156	95, 141
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	11.1* (12.76)	4.2* (9.16)	2.5 (7.65)	7.5* (11.40)	6.2 (7.50)
	Median	10.0	4.0	2.0	5.0	6.0
	Min, Max	-18, 36	-10, 29	-14, 21	-10, 37	-9, 22
30 min Post dose	N	35	36	35	33	23
	Mean (SD)	124.0 (11.11)	113.3 (13.08)	115.1 (13.39)	120.2 (12.86)	121.2 (16.47)
	Median	125.0	112.0	118.0	121.0	123.0
	Min, Max	100, 142	93, 141	86, 137	98, 151	92, 152
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	10.7 (10.96)	1.3 (10.29)	4.1 (8.25)	3.7 (11.40)	8.6* (10.43)
	Median	11.0	-0.5	5.0	2.0	9.0
	Min, Max	-17, 35	-13, 29	-16, 21	-14, 34	-10, 25
1-hour Post dose	N	35	36	35	33	23
	Mean (SD)	123.2 (13.57)	115.4 (10.58)	116.5 (12.68)	116.7 (12.91)	120.5 (15.01)
	Median	125.0	115.0	116.0	117.0	120.0

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Change from Baseline	Min, Max	96, 155	96, 137	86, 146	92, 145	90, 147
	N	35	36	35	33	23
	Mean (SD)	9.9 (14.55)	3.4 (8.44)	5.4* (10.26)	0.3 (11.93)	7.9 (9.52)
	Median	10.0	1.0	5.0	0.0	7.0
	Min, Max	-26, 50	-11, 20	-19, 33	-25, 27	-10, 25
2 hours Post dose	N	35	36	35	33	23
	Mean (SD)	118.0 (12.20)	113.0 (12.35)	112.6 (11.54)	117.5 (13.71)	117.7 (14.44)
	Median	118.0	112.5	111.0	114.0	121.0
	Min, Max	84, 140	90, 151	93, 142	93, 142	87, 139
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	4.7 (10.42)	1.0 (10.64)	1.6 (8.69)	1.1 (11.60)	5.1 (12.46)
	Median	5.0	0.5	3.0	-2.0	6.0
	Min, Max	-17, 26	-19, 34	-23, 19	-17, 31	-16, 25
4 hours Post dose	N	35	36	35	33	23
	Mean (SD)	117.1 (12.01)	114.8 (11.66)	115.6 (11.39)	116.9 (10.64)	118.0 (10.57)
	Median	115.0	115.0	116.0	118.0	121.0
	Min, Max	93, 141	90, 140	98, 142	96, 145	92, 132
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	3.7 (11.54)	2.8 (8.77)	4.5 (9.10)	0.5 (8.48)	5.3 (10.59)
	Median	4.0	1.5	4.0	0.0	8.0
	Min, Max	-22, 27	-16, 20	-18, 19	-19, 16	-14, 30
6 hours Post dose	N	35	36	35	33	23
	Mean (SD)	114.1 (13.14)	110.7 (12.93)	113.1 (10.96)	113.4 (10.35)	114.7 (13.33)
	Median	111.0	111.0	113.0	111.0	116.0
	Min, Max	90, 139	84, 134	87, 134	94, 137	90, 136

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	0.8 (10.77)	-1.3 (8.36)	2.1 (8.58)	-3.0 (7.49)	2.1 (10.72)
	Median	1.0	-3.0	2.0	-3.0	2.0
	Min, Max	-34, 18	-14, 16	-20, 17	-22, 10	-14, 22

Abbreviations: IN=intranasal, IM=intramuscular, Max = maximum, Min = minimum, SC=subcutaneous.

Notes: Baseline = assessment from scheduled visit prior to dosing of each dosing period; post-baseline summary is based on the results collected from scheduled timepoints.

* – greatest change from baseline for each treatment group.

Diastolic Blood Pressure

Summary statistics for DBP presented by timepoint and change from baseline are presented in Table 79.

Table 79 Summary of diastolic blood pressure (mm Hg) by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Baseline	N	35	36	35	33	23
	Mean (SD)	72.0 (9.61)	71.5 (9.58)	71.5 (9.91)	75.5 (9.54)	71.9 (10.69)
	Median	72.0	71.0	69.0	75.0	70.0
	Min, Max	52, 92	51, 92	50, 88	54, 95	52, 90
15 min Post dose	N	35	36	35	33	23
	Mean (SD)	75.6 (11.59)	72.7 (9.22)	71.8 (12.34)	74.8 (9.95)	69.6 (13.34)
	Median	74.0	72.5	71.0	73.0	66.0
	Min, Max	55, 95	54, 89	52, 93	56, 98	48, 105
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	3.6 (8.41)	1.2 (7.15)	0.3 (6.19)	-0.6 (7.75)	-2.3 (7.40)
	Median	3.0	1.0	0.0	-2.0	-2.0
	Min, Max	-13, 21	-14, 20	-10, 18	-14, 19	-23, 15
30 min Post dose	N	35	36	35	33	23
	Mean (SD)	75.3 (11.89)	69.3 (9.10)	69.3 (10.62)	71.7 (10.40)	67.0 (11.64)
	Median	77.0	68.5	68.0	70.0	67.0
	Min, Max	41, 97	54, 87	54, 88	56, 95	46, 89
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	3.3 (9.26)	-2.2 (6.55)	-2.2 (5.67)	-3.8 (8.36)	-5.0 (7.18)
	Median	5.0	-2.5	-3.0	-4.0	-5.0
	Min, Max	-18, 25	-15, 21	-13, 7	-19, 25	-20, 10
1-hour Post dose	N	35	36	35	33	23
	Mean (SD)	75.7 (8.81)	68.2 (8.23)	69.4 (10.23)	73.4 (8.91)	68.7 (12.64)
	Median	77.0	68.5	69.0	71.0	69.0
	Min, Max	60, 90	50, 84	43, 89	56, 96	50, 100

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	3.6 (7.92)	-3.3 (5.78)	-2.1 (6.06)	-2.1 (8.20)	-3.3 (8.58)
	Median	4.0	-3.0	-2.0	-2.0	-5.0
	Min, Max	-19, 20	-13, 21	-14, 13	-21, 17	-24, 12
2 hours Post dose	N	35	36	35	33	23
	Mean (SD)	75.4 (9.58)	70.1 (8.71)	72.0 (9.37)	73.4 (10.20)	71.0 (12.11)
	Median	77.0	70.0	71.0	71.0	70.0
	Min, Max	57, 93	50, 87	54, 96	51, 90	50, 90
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	3.4 (7.95)	-1.4 (7.81)	0.5 (7.31)	-2.1 (7.87)	-0.9 (7.61)
	Median	5.0	-1.0	1.0	-3.0	-2.0
	Min, Max	-18, 20	-22, 24	-20, 14	-15, 23	-16, 23
	Min, Max	54, 86	52, 87	53, 90	51, 87	52, 90

Abbreviations: IN=intranasal, IM=intramuscular, Max = maximum, Min = minimum, SC=subcutaneous.

Notes: Baseline = assessment from scheduled visit prior to dosing of each dosing period; post-baseline summary is based on the results collected from scheduled timepoints.

Pulse Rate

Summary statistics for SBP presented by timepoint and change from baseline are presented in Table 80.

During the first 120 minutes after dosing, subjects' PR were collected in the supine position. After this timepoint, they were active and able to move around.

Table 80 Summary statistic of pulse rate (beats/min) by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
Baseline	N	35	36	35	33	23
	Mean (SD)	66.3 (10.59)	67.2 (9.29)	66.1 (10.02)	69.2 (8.10)	65.0 (10.03)
	Median	66.0	66.5	66.0	70.0	66.0
	Min, Max	44, 85	47, 85	48, 97	51, 86	45, 82
15 min Post dose	N	35	36	35	33	23
	Mean (SD)	73.2 (11.70)	68.9 (9.39)	69.1 (11.44)	73.7 (11.01)	69.3 (9.29)
	Median	70.0	68.0	68.0	76.0	70.0
	Min, Max	51, 98	52, 86	53, 109	50, 100	50, 90
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	6.9 (8.32)	1.7 (6.15)	3.0 (5.82)	4.5* (7.84)	4.2 (5.26)
	Median	6.0	2.0	3.0	5.0	4.0
	Min, Max	-14, 28	-20, 16	-9, 17	-20, 17	-4, 17
30 min Post dose	N	35	36	35	33	23
	Mean (SD)	74.3 (11.45)	71.7 (11.41)	71.4 (11.24)	71.0 (11.05)	71.5 (10.65)
	Median	76.0	71.5	70.0	72.0	74.0
	Min, Max	53, 97	51, 100	55, 100	49, 99	49, 90
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	8.0* (9.67)	4.5* (7.42)	5.3 (9.50)	1.8 (7.56)	6.5 (7.57)
	Median	9.0	4.5	6.0	3.0	4.0
	Min, Max	-27, 28	-7, 25	-15, 38	-19, 15	-3, 30
1-hour Post dose	N	35	36	35	33	23
	Mean (SD)	74.1 (10.89)	71.0 (7.51)	72.0 (12.44)	68.0 (10.05)	73.8 (10.67)
	Median	73.0	72.0	70.0	68.0	77.0

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	ARS-1 1.0 mg IN with Rhinitis	Epinephrine 0.5 mg IM
	Min, Max	54, 100	55, 84	47, 109	52, 99	53, 95
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	7.8 (8.05)	3.8 (8.23)	5.9* (11.64)	-1.2 (8.96)	8.7* (8.30)
	Median	8.0	5.0	6.0	0.0	8.0
	Min, Max	-8, 30	-18, 21	-23, 35	-21, 13	-4, 27
2 hours Post dose	N	35	36	35	33	23
	Mean (SD)	68.6 (10.37)	68.4 (9.08)	68.1 (10.69)	67.9 (8.62)	70.3 (10.79)
	Median	68.0	70.0	68.0	68.0	70.0
	Min, Max	50, 96	51, 86	50, 102	49, 81	52, 95
Change from Baseline	N	35	36	35	33	23
	Mean (SD)	2.3 (6.66)	1.2 (7.99)	2.0 (10.09)	-1.3 (9.47)	5.3 (6.65)
	Median	2.0	2.0	3.0	-2.0	7.0
	Min, Max	-12, 15	-15, 16	-20, 28	-21, 20	-6, 15

Abbreviations: IN=intranasal, IM=intramuscular, Max = maximum, Min = minimum, SC=subcutaneous.

Notes: Baseline = assessment from scheduled visit prior to dosing of each dosing period; post-baseline summary is based on the results collected from scheduled timepoints.

* – greatest change from baseline for each treatment group

EPI 04 was a five-treatment, partially randomised crossover study of the bioavailability and pharmacokinetics of epinephrine after administration of ARS-1 (1.0 mg I.N.) in healthy subjects and in subjects with rhinitis or epinephrine injection (0.3, 0.5 mg I.M.).

Subjects who received ARS-1 1.0 mg IN showed higher PB and greater changes in BP within the first 30 minutes post treatment compared to Epinephrine IM and SC injections. Comparison of maximum change in SBP after administration of ARS-1 1.0 mg IN was statistically significantly higher than that of Epinephrine 0.3 mg IM.

However, a significant more rapid reduction in haemodynamic response (SBP and HR) was observed after ARS-1 administration in patients with induced rhinitis. The effect of the drug is significantly reduced 30 minutes after administration and almost disappears after 60 minutes. The PD effects of ARS in patients without rhinitis were longer and lasted up to 2 hours.

EPI 07. A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 or EpiPen to Healthy Volunteers.

Pharmacodynamic Assessments

PD measurements included pulse and BP (systolic and diastolic pressure) using an automated blood pressure measuring device. Pulse and BP measurements were taken at baseline, pre-dose (twice after at least 5 minutes of supine or semi-supine position, at least 5 minutes apart) 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. PD were evaluated with the PK blood samples up to 120 minutes post-dose.

Respiratory rate and temperature were assessed at prior to dosing, the 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.

Standard vital signs (BP, pulse rate, respiratory rate, and temperature) were assessed at 4 (± 30 min), and 6 (± 30 min) hour time points.

Pharmacodynamic Results

Systolic Blood Pressure

Summary statistics of SBP by time point, sorted by treatment are presented in Table 81.

Table 81 Summary statistic of systolic blood pressure (mmHg) by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
BL	N	35	36	35	36	36
	Mean (SD)	116.20 (10.266)	113.53 (9.176)	115.00 (10.803)	115.44 (10.582)	114.17 (10.565)
	Median	114.00	114.00	115.00	115.50	114.00
	Min, Max	100.0, 136.0	92.0, 132.0	95.0, 138.0	87.0, 140.0	95.0, 139.0
5 min post dose	N	35	36	35	36	36
	Mean (SD)	125.37 (12.200)	127.36 (14.013)	126.94 (15.492)	122.44 (14.193)	122.75 (15.754)
	Median	125.00	130.00	126.00	121.00	122.50
	Min, Max	106.0, 152.0	99.0, 151.0	102.0, 178.0	93.0, 152.0	79.0, 164.0
5 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	9.17 (9.028)	13.83 (11.052)	11.94 (11.697)	7.00 (10.190)	8.58 (15.062)
	Median	9.00	14.00	11.00	5.00	6.50
	Min, Max	-9.0, 28.0	-10.0, 36.0	-7.0, 43.0	-10.0, 40.0	-28.0, 40.0
10 min post dose	N	35	36	35	36	36
	Mean (SD)	128.00 (14.536)	138.22 (16.964)	134.74 (16.355)	123.36 (14.802)	125.83 (12.580)
	Median	128.00	142.00	132.00	121.50	123.50
	Min, Max	99.0, 150.0	106.0, 170.0	108.0, 178.0	98.0, 151.0	101.0, 148.0
10min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	11.80 (12.952)	24.69 (15.534)	19.74 (14.345)	7.92 (10.541)	11.67 (12.481)
	Median	11.00	26.00	19.00	6.50	10.00
	Min, Max	-15.0, 39.0	-1.0, 54.0	-7.0, 49.0	-10.0, 34.0	-14.0, 43.0
15 min post dose	N	35	36	35	36	36
	Mean (SD)	128.17 (14.462)	144.56 (20.082)	136.37 (16.477)	118.75 (14.514)	128.86 (12.878)
	Median	131.00	145.00	138.00	119.00	130.00

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
15 min post dose Change from BL	Min, Max	102.0, 152.0	99.0, 191.0	103.0, 163.0	91.0, 145.0	95.0, 151.0
	N	35	36	35	36	36
	Mean (SD)	11.97 (12.067)	31.03 (18.735)	21.37 (16.360)	3.31 (10.362)	14.69 (13.090)
	Median	10.00	33.50	22.00	3.50	12.00
	Min, Max	-10.0, 40.0	-1.0, 69.0	-10.0, 63.0	-16.0, 33.0	-20.0, 39.0
20 min post dose	N	35	36	35	36	36
	Mean (SD)	130.37 (17.138)	146.83 (21.427)	137.63 (15.960)	124.58 (16.770)	129.39 (15.480)
	Median	134.00	146.50	141.00	126.00	129.50
	Min, Max	101.0, 164.0	99.0, 195.0	102.0, 170.0	92.0, 157.0	86.0, 165.0
20 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	14.17 (15.311)	33.31 (18.966)	22.63 (15.752)	9.14 (11.427)	15.22 (12.518)
	Median	15.00	35.50	24.00	7.00	17.00
	Min, Max	-18.0, 44.0	-6.0, 66.0	-8.0, 55.0	-7.0, 37.0	-23.0, 32.0
25 min post dose	N	35	36	34	36	36
	Mean (SD)	128.86 (16.183)	144.44 (19.807)	137.00 (14.892)	122.81 (15.840)	128.97 (17.407)
	Median	134.00	146.00	136.50	122.00	128.50
	Min, Max	94.0, 156.0	102.0, 178.0	105.0, 162.0	89.0, 150.0	103.0, 189.0
25 min post dose Change from BL	N	35	36	34	36	36
	Mean (SD)	12.66 (12.744)	30.92 (17.426)	22.12 (14.284)	7.36 (10.916)	14.81 (14.899)
	Median	10.00	35.50	22.00	6.00	15.50
	Min, Max	-20.0, 37.0	-2.0, 64.0	-5.0, 45.0	-15.0, 38.0	-9.0, 72.0
30 min post dose	N	35	36	35	35	36
	Mean (SD)	126.26 (15.721)	140.11 (17.896)	135.46 (14.261)	120.11 (15.132)	125.67 (14.434)
	Median	130.00	139.00	139.00	123.00	126.50
	Min, Max	94.0, 153.0	100.0, 172.0	96.0, 160.0	87.0, 150.0	97.0, 151.0

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
30 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	10.06 (12.395)	26.58 (15.469)	20.46 (14.527)	4.57 (12.125)	11.50 (12.429)
	Median	10.00	25.00	23.00	6.00	11.00
	Min, Max	-12.0, 43.0	-5.0, 58.0	-15.0, 47.0	-21.0, 27.0	-17.0, 31.0
45 min post dose	N	35	36	35	35	36
	Mean (SD)	125.49 (15.629)	134.72 (17.124)	130.14 (13.456)	124.37 (13.701)	126.42 (14.719)
	Median	125.00	136.50	130.00	122.00	129.50
	Min, Max	99.0, 159.0	101.0, 167.0	103.0, 153.0	100.0, 155.0	98.0, 154.0
45 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	9.29 (11.357)	21.19 (15.928)	15.14 (13.386)	8.83 (9.011)	12.25 (14.758)
	Median	10.00	21.00	14.00	8.00	10.00
	Min, Max	-16.0, 34.0	-7.0, 54.0	-16.0, 41.0	-6.0, 28.0	-17.0, 47.0
60 min post dose	N	35	36	35	35	36
	Mean (SD)	125.91 (12.176)	129.69 (16.283)	128.17 (15.464)	119.14 (13.731)	125.19 (13.665)
	Median	127.00	126.50	126.00	121.00	128.50
	Min, Max	103.0, 150.0	98.0, 160.0	99.0, 161.0	97.0, 158.0	101.0, 151.0
60 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	9.71 (8.726)	16.17 (14.155)	13.17 (13.356)	3.60 (10.430)	11.03 (14.310)
	Median	10.00	13.00	12.00	3.00	12.00
	Min, Max	-7.0, 31.0	-6.0, 42.0	-20.0, 52.0	-12.0, 31.0	-21.0, 36.0
90 min post dose	N	35	36	35	35	36
	Mean (SD)	118.06 (12.712)	121.89 (13.955)	121.71 (14.016)	117.20 (14.640)	117.97 (12.914)
	Median	118.00	122.00	125.00	115.00	117.00
	Min, Max	96.0, 144.0	94.0, 151.0	97.0, 143.0	95.0, 158.0	95.0, 151.0
90 min post dose	N	35	36	35	35	36

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
Change from BL	Mean (SD)	1.86 (10.296)	8.36 (12.762)	6.71 (12.851)	1.66 (10.488)	3.81 (12.674)
	Median	2.00	6.50	8.00	1.00	2.00
	Min, Max	-14.0, 25.0	-16.0, 38.0	-23.0, 28.0	-12.0, 31.0	-18.0, 34.0
120 min post dose	N	35	36	35	35	36
	Mean (SD)	119.29 (13.179)	122.11 (13.625)	120.31 (14.531)	119.49 (10.801)	116.58 (10.552)
	Median	119.00	122.00	122.00	121.00	114.00
	Min, Max	93.0, 148.0	97.0, 151.0	92.0, 146.0	98.0, 142.0	99.0, 144.0
120 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	3.09 (11.046)	8.58 (12.477)	5.31 (12.981)	3.94 (8.724)	2.42 (10.890)
	Median	3.00	9.00	4.00	5.00	2.00
	Min, Max	-19.0, 21.0	-25.0, 36.0	-26.0, 29.0	-15.0, 19.0	-21.0, 29.0

Abbreviations: BL = baseline, Epi = epinephrine, IM = intramuscular, IN = intranasal, Max = maximum, Min = minimum, PD = post dose, SD = standard deviation.

Source: [Table 14.3.7](#); [Listing 16.2.9.1](#)

Diastolic Blood Pressure

Summary statistics of DBP by time point, sorted by treatment are presented in Table 82.

Table 82 Summary statistic of DBP (mm Hg) by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
BL	N	35	36	35	36	36
	Mean (SD)	72.29 (8.101)	71.50 (7.268)	71.00 (6.932)	71.42 (8.470)	70.61 (9.050)
	Median	71.00	72.00	71.00	71.50	71.00
	Min, Max	53.0, 88.0	57.0, 83.0	58.0, 84.0	54.0, 89.0	46.0, 91.0
5 min post dose	N	35	36	35	36	36
	Mean (SD)	79.17 (8.713)	75.94 (7.982)	75.54 (7.453)	71.08 (7.485)	69.19 (7.167)
	Median	79.00	75.00	77.00	70.50	69.00
	Min, Max	64.0, 100.0	59.0, 96.0	58.0, 87.0	55.0, 87.0	55.0, 86.0
5 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	6.89 (7.642)	4.44 (6.421)	4.54 (7.022)	-0.33 (6.132)	-1.42 (6.963)
	Median	6.00	4.50	5.00	0.00	0.00
	Min, Max	-6.0, 30.0	-6.0, 28.0	-10.0, 21.0	-11.0, 13.0	-19.0, 12.0
10 min post dose	N	35	36	35	36	36
	Mean (SD)	77.86 (8.307)	78.17 (9.013)	77.23 (8.479)	70.64 (8.271)	71.36 (7.717)
	Median	78.00	80.00	79.00	70.50	71.00
	Min, Max	65.0, 100.0	60.0, 98.0	55.0, 97.0	54.0, 87.0	55.0, 86.0
10min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	5.57 (7.732)	6.67 (7.460)	6.23 (6.353)	-0.78 (8.233)	0.75 (9.808)
	Median	7.00	5.00	4.00	-0.50	0.00
	Min, Max	-11.0, 26.0	-5.0, 25.0	-6.0, 23.0	-18.0, 12.0	-18.0, 26.0
15 min post dose	N	35	36	35	36	36
	Mean (SD)	75.23 (10.466)	76.42 (10.606)	76.69 (10.099)	68.83 (8.150)	68.31 (9.916)
	Median	75.00	76.00	78.00	69.00	70.50

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
	Min, Max	52.0, 94.0	52.0, 100.0	59.0, 100.0	52.0, 87.0	43.0, 88.0
15 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	2.94 (10.335)	4.92 (11.101)	5.69 (8.228)	-2.58 (5.793)	-2.31 (9.255)
	Median	3.00	4.00	6.00	-3.00	-1.00
	Min, Max	-21.0, 31.0	-26.0, 27.0	-8.0, 22.0	-16.0, 13.0	-24.0, 17.0
20 min post dose	N	35	36	35	36	36
	Mean (SD)	74.60 (9.690)	75.81 (9.692)	75.43 (8.462)	69.97 (9.497)	66.92 (9.967)
	Median	75.00	73.00	75.00	72.00	67.00
	Min, Max	50.0, 96.0	56.0, 94.0	54.0, 91.0	54.0, 93.0	41.0, 88.0
20 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	2.31 (8.567)	4.31 (8.454)	4.43 (7.520)	-1.44 (7.647)	-3.69 (8.501)
	Median	4.00	5.00	4.00	-2.00	-2.00
	Min, Max	-16.0, 22.0	-13.0, 20.0	-15.0, 21.0	-17.0, 13.0	-26.0, 11.0
25 min post dose	N	35	36	34	36	36
	Mean (SD)	75.57 (11.194)	75.25 (8.227)	75.56 (7.836)	67.31 (8.193)	68.19 (11.471)
	Median	76.00	74.50	75.50	68.50	67.00
	Min, Max	52.0, 100.0	56.0, 93.0	63.0, 91.0	45.0, 82.0	47.0, 99.0
25 min post dose Change from BL	N	35	36	34	36	36
	Mean (SD)	3.29 (9.260)	3.75 (7.546)	4.56 (6.514)	-4.11 (6.511)	-2.42 (10.432)
	Median	5.00	4.50	4.50	-4.00	-3.00
	Min, Max	-21.0, 22.0	-12.0, 19.0	-14.0, 18.0	-15.0, 9.0	-23.0, 23.0
30 min post dose	N	35	36	35	35	36
	Mean (SD)	73.94 (10.762)	75.17 (8.853)	75.00 (7.364)	68.20 (7.545)	66.92 (8.689)
	Median	72.00	75.50	75.00	69.00	67.00
	Min, Max	51.0, 98.0	59.0, 92.0	62.0, 94.0	51.0, 88.0	45.0, 84.0

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
30 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	1.66 (8.908)	3.67 (7.903)	4.00 (7.666)	-3.11 (6.443)	-3.69 (9.988)
	Median	3.00	3.00	4.00	-3.00	-4.00
	Min, Max	-15.0, 17.0	-12.0, 24.0	-10.0, 34.0	-20.0, 13.0	-27.0, 18.0
45 min post dose	N	35	36	35	35	36
	Mean (SD)	72.94 (8.758)	74.83 (8.614)	74.97 (8.126)	71.40 (8.458)	69.36 (8.118)
	Median	72.00	74.00	77.00	73.00	69.00
	Min, Max	54.0, 92.0	55.0, 90.0	57.0, 95.0	54.0, 90.0	50.0, 88.0
45 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	0.66 (7.017)	3.33 (6.080)	3.97 (8.053)	0.09 (7.717)	-1.25 (9.262)
	Median	0.00	3.50	4.00	2.00	-3.00
	Min, Max	-16.0, 12.0	-6.0, 19.0	-17.0, 20.0	-19.0, 15.0	-20.0, 22.0
60 min post dose	N	35	36	35	35	36
	Mean (SD)	73.20 (9.267)	74.42 (7.747)	74.80 (7.734)	70.51 (6.419)	68.69 (7.767)
	Median	72.00	74.50	74.00	71.00	69.50
	Min, Max	53.0, 91.0	54.0, 91.0	59.0, 94.0	57.0, 79.0	47.0, 82.0
60 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	0.91 (7.671)	2.92 (7.101)	3.80 (8.464)	-0.80 (7.627)	-1.92 (9.394)
	Median	1.00	2.50	4.00	-2.00	-0.50
	Min, Max	-19.0, 14.0	-11.0, 20.0	-11.0, 24.0	-16.0, 17.0	-22.0, 15.0
90 min post dose	N	35	36	35	35	36
	Mean (SD)	73.77 (10.181)	73.81 (9.671)	73.26 (8.179)	71.26 (8.853)	68.61 (6.867)
	Median	74.00	74.00	73.00	71.00	69.00
	Min, Max	53.0, 93.0	51.0, 94.0	60.0, 91.0	54.0, 96.0	51.0, 81.0
90 min post dose	N	35	36	35	35	36

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
Change from BL	Mean (SD)	1.49 (9.011)	2.31 (9.093)	2.26 (7.310)	-0.06 (8.585)	-2.00 (7.739)
	Median	3.00	2.50	4.00	2.00	-1.50
	Min, Max	-19.0, 23.0	-15.0, 24.0	-14.0, 19.0	-27.0, 13.0	-24.0, 13.0
120 min post dose	N	35	36	35	35	36
	Mean (SD)	75.49 (9.086)	72.89 (8.074)	75.20 (9.551)	73.23 (7.574)	72.22 (7.983)
	Median	74.00	73.50	78.00	73.00	73.50
	Min, Max	60.0, 97.0	50.0, 87.0	60.0, 99.0	55.0, 93.0	51.0, 84.0
120 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	3.20 (7.851)	1.39 (7.831)	4.20 (7.760)	1.91 (8.780)	1.61 (10.283)
	Median	3.00	2.00	4.00	2.00	0.50
	Min, Max	-12.0, 25.0	-18.0, 17.0	-14.0, 21.0	-16.0, 23.0	-23.0, 24.0

Abbreviations: BL – baseline, Epi – epinephrine, IM – intramuscular, IN – intranasal, Max – maximum, Min – minimum, PD – post dose, SD – standard deviation.
Source: [Table 14.3.7](#); [Listing 16.2.9.1](#)

Pulse Rate

Summary statistics of PR by time point, sorted by treatment are presented in Table 83.

Table 83 Summary statistic of pulse rate by time point and change from baseline, sorted by treatment

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R))
BL	N	35	36	35	36	36
	Mean (SD)	59.37(6.996)	59.72(8.534)	60.71(7.902)	60.97(8.157)	63.28(8.059)
	Median	59.00	60.50	60.00	63.00	62.50
	Min, Max	46.0,71.0	44.0,79.0	45.0,87.0	45.0,77.0	50.0,87.0
5 min post dose	N	35	36	35	36	36
	Mean (SD)	67.37(11.212)	71.03(10.363)	71.23(9.668)	69.58(10.238)	70.00(9.716)
	Median	66.00	70.00	72.00	66.50	69.50
	Min, Max	50.0,97.0	50.0,91.0	52.0,101.0	51.0,89.0	52.0,85.0
5 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	8.00(8.805)	11.31(8.039)	10.51(8.929)	8.61(7.765)	6.72(10.194)
	Median	7.00	12.50	10.00	7.50	7.00
	Min, Max	-9.0,38.0	-5.0,31.0	-11.0,33.0	-6.0,25.0	-22.0,34.0
10 min post dose	N	35	36	35	36	36
	Mean (SD)	70.37(9.997)	78.25(12.443)	75.31(11.842)	70.78(10.715)	71.89(11.740)
	Median	70.00	76.50	76.00	69.00	72.00
	Min, Max	52.0,98.0	56.0,109.0	56.0,98.0	54.0,94.0	50.0,109.0
10min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	11.00(8.317)	18.53(10.617)	14.60(11.536)	9.81(10.042)	8.61(11.970)
	Median	9.00	19.00	15.00	8.00	8.50
	Min, Max	1.0,39.0	-5.0,40.0	-7.0,36.0	-9.0,45.0	-27.0,46.0
15 min post dose	N	35	36	35	36	36
	Mean (SD)	71.54(12.042)	79.11(14.390)	76.83(11.242)	69.00(10.321)	73.69(9.600)
	Median	72.00	78.00	76.00	68.00	73.50

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
	Min, Max	53.0,106.0	56.0,108.0	55.0,100.0	54.0,100.0	57.0,96.0
15 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	12.17(10.453)	19.39(12.654)	16.11(10.377)	8.03(7.049)	10.42(9.664)
	Median	10.00	16.00	14.00	6.00	9.00
	Min, Max	-6.0,38.0	-5.0,46.0	-5.0,42.0	-1.0,36.0	-16.0,34.0
20 min post dose	N	35	36	35	36	36
	Mean (SD)	69.57(10.097)	77.92(13.756)	74.31(11.430)	69.75(10.742)	73.67(10.298)
	Median	68.00	75.50	73.00	68.00	74.50
	Min, Max	49.0,94.0	51.0,102.0	51.0,97.0	51.0,108.0	54.0,100.0
20 min post dose Change from BL	N	35	36	35	36	36
	Mean (SD)	10.20(8.058)	18.19(12.247)	13.60(11.327)	8.78(9.705)	10.39(10.434)
	Median	9.00	16.00	13.00	8.50	7.50
	Min, Max	-7.0,32.0	-2.0,44.0	-9.0,39.0	-7.0,44.0	-13.0,36.0
25 min post dose	N	35	36	34	36	36
	Mean (SD)	69.34(11.133)	78.31(13.916)	75.09(12.748)	68.39(11.360)	73.89(10.025)
	Median	71.00	79.50	74.50	67.00	74.00
	Min, Max	48.0,91.0	51.0,98.0	54.0,103.0	52.0,98.0	52.0,98.0
25 min post dose Change from BL	N	35	36	34	36	36
	Mean (SD)	9.97(8.900)	18.58(12.648)	14.35(12.730)	7.42(8.412)	10.61(10.341)
	Median	9.00	18.50	14.00	7.00	8.00
	Min, Max	-9.0,32.0	-6.0,45.0	-7.0,45.0	-6.0,34.0	-13.0,33.0
30 min post dose	N	35	36	35	35	36
	Mean (SD)	70.23(12.905)	80.08(14.600)	75.80(10.286)	70.23(9.197)	77.03(11.751)
	Median	69.00	80.00	75.00	70.00	76.00
	Min, Max	50.0,106.0	55.0,117.0	58.0,94.0	52.0,91.0	54.0,102.0

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
30 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	10.86(10.126)	20.36(12.971)	15.09(10.036)	9.29(8.259)	13.75(11.850)
	Median	8.00	22.00	16.00	9.00	12.50
	Min, Max	-3.0,38.0	-5.0,52.0	-6.0,33.0	-4.0,29.0	-18.0,36.0
45 min post dose	N	35	36	35	35	36
	Mean (SD)	71.74(10.528)	83.00(13.363)	78.63(11.293)	72.40(9.300)	80.33(10.907)
	Median	72.00	85.50	78.00	71.00	80.50
	Min, Max	54.0,96.0	52.0,112.0	57.0,105.0	56.0,98.0	58.0,103.0
45 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	12.37(9.280)	23.28(12.743)	17.91(11.330)	11.46(7.265)	17.06(9.378)
	Median	11.00	27.00	20.00	13.00	16.00
	Min, Max	-4.0,28.0	-3.0,47.0	-10.0,46.0	-4.0,31.0	0.0,41.0
60 min post dose	N	35	36	35	35	36
	Mean (SD)	70.03(11.485)	78.69(13.249)	74.14(9.296)	68.54(9.620)	76.86(10.508)
	Median	69.00	78.50	73.00	67.00	75.50
	Min, Max	50.0,97.0	56.0,106.0	57.0,97.0	52.0,89.0	58.0,97.0
60 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	10.66(9.725)	18.97(11.787)	13.43(9.705)	7.60(7.093)	13.58(10.976)
	Median	9.00	18.50	11.00	7.00	12.00
	Min, Max	-9.0,32.0	-5.0,41.0	-8.0,30.0	-5.0,23.0	-5.0,40.0
90 min post dose	N	35	36	35	35	36
	Mean (SD)	68.74(12.349)	76.83(13.712)	72.23(10.293)	67.46(9.034)	71.94(9.807)
	Median	67.00	78.50	70.00	67.00	72.50
	Min, Max	49.0,97.0	54.0,106.0	55.0,90.0	52.0,85.0	55.0,98.0
90 min post dose	N	35	36	35	35	36

Time Point	Statistic	Treatment				
		ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/R)	ARS-1 1.0 mg IN twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
Change from BL	Mean (SD)	9.37(11.428)	17.11(11.114)	11.51(9.528)	6.51(7.249)	8.67(9.255)
	Median	8.00	18.00	12.00	7.00	8.50
	Min, Max	-11.0,38.0	-5.0,41.0	-8.0,29.0	-9.0,30.0	-11.0,34.0
120 min post dose	N	35	36	35	35	36
	Mean (SD)	69.57(10.503)	75.50(11.305)	74.66(11.350)	67.31(9.084)	71.75(9.503)
	Median	71.00	74.00	76.00	65.00	72.50
	Min, Max	47.0,89.0	54.0,103.0	55.0,102.0	51.0,89.0	49.0,88.0
120 min post dose Change from BL	N	35	36	35	35	36
	Mean (SD)	10.20(9.155)	15.78(9.399)	13.94(10.994)	6.37(8.353)	8.47(9.167)
	Median	9.00	16.00	16.00	6.00	8.00
	Min, Max	-7.0,30.0	-4.0,30.0	-10.0,38.0	-5.0,23.0	-17.0,26.0

Abbreviations: BL – baseline, Epi – epinephrine, IM – intramuscular, IN – intranasal, Max – maximum, Min – minimum, PD – post dose, SD – standard deviation.

Source: [Table 14.3.7](#); [Listing 16.2.9.1](#)

Exploratory Pharmacokinetic-Pharmacodynamic Analysis

Double-Y Plots

- Relative to EpiPen, ARS-1 was more correlated with changes in SBP. Correlation coefficients ranged from 0.3143 to 0.5802 for ARS-1 and from -0.0132 to 0.3420 for EpiPen.
- There was no consistent correlation between change from baseline DBP and epinephrine concentration; the Pearson correlation coefficients for DBP ranged from -0.0776 after EpiPen 0.3 mg to 0.2695 after ARS-1 1.0 mg IN twice (L/L).
- Weak to moderate positive correlations were observed between ARS-1 and PR. Correlation coefficients ranged from 0.2321 to 0.5249 for ARS-1 and from 0.3723 to 0.4868 for EpiPen.

EPI 07 was a five-period, five-treatment, randomised crossover study of the pharmacokinetics of epinephrine after administration of intranasal ARS-1 or EpiPen to healthy volunteers. PD measurements included pulse and BP (systolic and diastolic pressure) using an automated blood pressure measuring device.

The mean SBP change from baseline was higher after ARS-1 1.0 mg IN than for EpiPen 0.3 mg, for both single dose and 2 administrations. The effect of epinephrine on SBP was most pronounced after ARS-1 1.0 mg IN twice compared to the other treatments; the mean SBP change from baseline was higher for (L/L) than for (L/R). There was a significant relationship between SBP change from baseline and epinephrine concentration for all treatments.

As in studies EPI 03 and EPI 04, I.N. epinephrine administration was associated with an increase in DBP while I.M. administration resulted in a decrease. This discrepancy in effect is not fully clear. However, the phenomenon appears to be permanent.

The effect of epinephrine on PR was more pronounced after ARS-1 1.0 mg IN twice compared to the other treatments; the mean PR change from baseline was higher for (L/L) than for (L/R). There was a significant relationship between PR change from baseline and epinephrine concentration for all treatments. In general, a significant relationship between the noncompartmental effect parameters for PR change from baseline and the epinephrine PK exposure parameters was observed for after ARS-1 1.0 mg IN (single dose), ARS-1 1.0 mg IN IN (L/L), EpiPen 1.0 mg (single dose), and EpiPen 1.0 mg twice.

EPI 12: A Four-Period, Four-Treatment, Randomized Crossover Study of the Pharmacokinetics, Pharmacodynamics and Dosing Errors After Self-Administration of Adrenaline with Intranasal ARS-1, EpiPen, and Symjepi in Subjects with Type I Systemic Allergies

Pharmacodynamic measurements

The following PD parameters were calculated for change from baseline SBP, DPB, and HR: Emax, TEmax, AUEC0-xmin, AUEC0-120min, AUEClast.

Pharmacodynamic Results

Pharmacodynamic Parameters

Summary statistics for change from baseline SBP, DBP, and PR by treatment are presented in Table 84, Table 85, Table 86.

Table 84 Pharmacodynamic Parameters for SBP Change from Baseline

Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (mmHg) Mean (%CV)	AUEC _{last} (min*mmHg g) (Mean (%CV)	pAUEC* 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)								
Primary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	21.58 (5.00 – 115)	15.6 (79.2)	664 (98.5)	20.6 (138)	53.9 (149)	77.4 (169)	107 (169)	143 (157)	169 (161)	225 (182)	264 (190)	389 (286)
EpiPen 0.3 mg	29	9.00 (5.00 – 115)	16.8 (68.4)	580 (99.7)	24.1 (139)	69.7 (143)	105 (141)	138 (137)	171 (134)	200 (135)	278 (141)	312 (164)	259 (354)
Symjepi 0.3 mg	34	16.0 (4.00 – 115)	14.1 (78.7)	479 (117)	21.1 (142)	47.2 (159)	61.1 (187)	79.8 (210)	106 (201)	129 (197)	161 (233)	162 (305)	124 (783)
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	14.0 (5.00 – 115)	13.6 (112)	428 (205)	19.9 (187)	55.2 (206)	76.9 (226)	92.9 (231)	107 (239)	114 (271)	144 (320)	148 (414)	107 (1070)
Secondary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	21.5 (5.00 – 115)	15.6 (79.2)	664 (98.5)	20.6 (138)	53.9 (149)	77.4 (169)	107 (169)	143 (157)	169 (161)	225 (182)	264 (190)	389 (286)
EpiPen 0.3 mg	36	9.00 (5.00 – 115)	17.8 (61.8)	575 (94.2)	28.5 (113)	82.2 (117)	124 (117)	159 (115)	197 (112)	228 (114)	304 (122)	335 (145)	267 (331)
Symjepi 0.3 mg	36	16.0 (4.00 – 115)	14.9 (76.2)	481 (114)	23.6 (132)	54 (145)	69.9 (168)	89.5 (188)	118 (183)	143 (180)	176 (212)	177 (276)	147 (645)
ARS-1 1.0 mg IN 0.35% DDM Period 1	18	11.5 (5.00 – 115)	14.1 (106)	436 (195)	22 (169)	59.9 (187)	85.5 (201)	106 (204)	123 (209)	131 (235)	163 (278)	173 (350)	119 (937)

Source: EPI 12 First Amendment to the PK Report: [Table 13](#), EPI 12 PK Report: [Appendix Tables: 11c, 11d](#)

Table 85 Pharmacodynamic Parameters for DBP Change from Baseline

Treatment	N	t _{E_{max}} (min) median (range)	E _{max} (mmHg) Mean (%CV)	AUEC _{last} (min*mmHg) (Mean (%CV)	pAUEC* min*mmHg								
					AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC
					0-5	0-10	0-15	0-20	0-25	0-30	0-45	0-60	0-120
Mean* (%CV)													
Primary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	28.0 (5.00 – 115)	8.11 (90.0)	232 (168)	7.08 (230)	18.2 (267)	24.1 (336)	21.3 (533)	17.9 (817)	12.9 (1380)	-18.8 (-1480)	-42.5 (-887)	26.6 (2690)
EpiPen 0.3 mg	29	28.0 (4.00 – 115)	4.03 (127)	-30.7 (-911)	-6.06 (- 245)	-21.7 (-203)	-35.6 (-194)	-49 (-184)	-66.3 (-174)	-88.6 (-160)	-150 (-136)	-202 (-127)	-330 (-154)
Symjepi 0.3 mg	34	16.0 (4.00 – 115)	5.68 (116)	72.4 (556)	1.12 (1610)	-1.04 (-4780)	-7.83 (-1020)	-18.2 (-606)	-28.6 (-486)	-44.5 (-373)	-111 (-220)	-161 (-205)	-228 (-268)
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	18.0 (5.00 – 115)	3.94 (125)	-31.5 (-660)	-1.36 (- 1320)	-9.82 (-541)	-24.1 (-340)	-35.5 (-287)	-47.9 (-259)	-56.2 (-256)	-93.1 (-228)	-154 (-188)	-358 (-154)
Secondary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	28.0 (5 .00 – 115)	8.11 (90.0)	232 (168)	7.08 (230)	18.2 (267)	24.1 (336)	21.3 (533)	17.9 (817)	12.9 (1380)	-18.8 (-1480)	-42.5 (-887)	26.6 (2690)
EpiPen 0.3 mg	36	21.5 (4.00 – 115)	4.39 (111)	-1.46 (-18700)	-4.85 (-297)	-18.3 (-228)	-31 (-212)	-41.5 (-208)	-54.6 (-203)	-73.8 (-186)	-126 (-159)	-169 (-150)	-274 (-180)
Symjepi 0.3 mg	36	18.0 (4.00 – 115)	5.78 (112)	83.8 (466)	0.922 (1920)	-1.13 (-4280)	-6.85 (-1140)	-16 (-673)	-25.1 (-540)	-40.1 (-405)	-103 (-232)	-149 (-216)	-200 (-302)
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	18.0 (5.00 – 115)	4.28 (117)	-22.4 (-908)	-0.868 (-2010)	-7.01 (-753)	-17.9 (-470)	-27.6 (-379)	-41 (-303)	-52.7 (-267)	-98.2 (-211)	-161 (-175)	-374 (-144)

Source: EPI 12 First Amendment to the PK Report: [Table 12](#), EPI 12 PK Report, [Appendix Tables: 10c, 10d](#)

Table 86 Pharmacodynamic Parameters for PR Change from Baseline

Treatment	N	t _{E_{max}} (min)	E _{max} (mmHg)	AUEC _{last} (min*mmHg)	pAUEC* min*mmHg								
		median (range)	Mean (%CV)	(Mean (%CV))	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC	AUEC
					0-5	0-10	0-15	0-20	0-25	0-30	0-45	0-60	0-120
Mean* (%CV)													
Primary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	28.0 (5.00 – 115)	7.78 (84.9)	376 (113)	-0.556 (- 3270)	-1.95 (- 2600)	8.68 (880)	14 (768)	13.4 (1050)	15.6 (1140)	12.1 (2390)	24.1 (1660)	39.1 (2220)
EpiPen 0.3 mg	29	9.00 (4.00 – 115)	8.90 (96.0)	227 (116)	9.74 (238)	23.4 (242)	28.8 (273)	36 (263)	38.8 (304)	41.6 (338)	53.3 (379)	53.2 (494)	8.7 (6030)
Symjepi 0.3 mg	34	18.0 (5.00 – 85.0)	8.32 (101)	252 (149)	7.21 (361)	15.3 (441)	15.6 (635)	19.9 (657)	28.2 (583)	37.7 (513)	54.5 (523)	65 (577)	-7.5 (-9620)
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	14.0 (5.00 – 115)	7.41 (116)	200 (129)	3.11 (789)	10.6 (687)	16.3 (735)	17.6 (954)	18.2 (1190)	18.3 (1400)	3.53 (10200)	-30.5 (-1520)	-229 (-409)
Secondary Population													
ARS-1 1.0 mg IN 0.25% DDM Period 1	18	28.0 (5 .00 – 115)	7.78 (84.9)	376 (113)	-0.556 (-3270)	-1.95 (-2600)	8.68 (880)	14 (768)	13.4 (1050)	15.6 (1140)	12.1 (2390)	24.1 (1660)	39.1 (2220)
EpiPen 0.3 mg	36	8.00 (4.00 – 115)	10.9 (88.8)	237 (105)	17.3 (162)	39.1 (164)	47.8 (181)	58.5 (176)	64.2 (193)	68.5 (212)	83.4 (243)	87.3 (295)	38 (1280)
Symjepi 0.3 mg	36	16.0 (5.00 – 85)	8.86 (96.3))	275 (138)	9.31 (288)	20.1 (343)	21.5 (466)	26.5 (493)	35.9 (456)	46.1 (416)	66.2 (424)	78.7 (468)	30.4 (2370)
ARS-1 1.0 mg IN 0.35% DDM Period 1	17	14.0 (5.00 – 115)	7.94 (109)	247 (127)	3.21 (740)	12.6 (567)	22.1 (537)	26.3 (636)	28.3 (757)	29.2 (866)	22.7 (1580)	-2.5 (-18500)	-161 (-592)

Source: EPI 12 First Amendment to the PK Report: [Table 14](#), EPI 12 PK Report: [Appendix Tables: 12c-2, 12d-2](#)

Relationship between plasma concentration and effect

Exposure Analysis

Linear regression of mean change from baseline SBP versus mean epinephrine concentration is presented in Table 87.

Table 87 Linear Regression of Mean Change from Baseline SBP vs Mean Epinephrine Concentration

			Dependent			
			Regression Mean ΔSBP vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	EPI 03	Slope	0.0401	0.0268	0.00578	0.0744
	EPI 03	Intercept	0.900	0.669	-3.72	5.52
	EPI 07	Slope	0.0635	0.00847	0.0213	0.106
	EPI 07	Intercept	0.808	0.727	-4.35	5.97
ARS-1 1.0 mg IN twice (L/L)	EPI 07	Slope	0.0435	0.0144	0.0113	0.0757
	EPI 07	Intercept	10.2	0.00973	3.22	17.1
ARS-1 1.0 mg IN twice (L/R)	EPI 03	Slope	0.0215	0.0520	-0.000235	0.0432
	EPI 03	Intercept	5.83	0.0326	0.602	11.1
	EPI 07	Slope	0.0243	0.135	-0.00940	0.0579
	EPI 07	Intercept	1.19	0.676	-5.12	7.49
ARS-1 2.0 mg IN	EPI 15	Slope	0.0433	0.000106	0.0302	0.0563
	EPI 15	Intercept	-2.64	0.0866	-5.78	0.494
	EPI 16	Slope	0.0428	0.00280	0.0203	0.0653
	EPI 16	Intercept	-3.63	0.107	-8.27	1.01
ARS-1 2.0 mg IN twice (L/R)	EPI 15	Slope	0.0265	4.66E-05	0.0195	0.0336
	EPI 15	Intercept	0.707	0.624	-2.55	3.96
ARS-1 2.0 mg IN twice (R/R)	EPI 15	Slope	0.0293	<0.00001	0.0236	0.0350
	EPI 15	Intercept	0.108	0.928	-2.60	2.82
Epinephrine 0.3 mg IM	EPI 03	Slope	0.0238	0.0161	0.00557	0.0420
	EPI 03	Intercept	-2.01	0.0604	-4.13	0.108
	EPI 15	Slope	0.00736	0.353	-0.0101	0.0249
	EPI 15	Intercept	-1.78	0.155	-4.42	0.862
	EPI 16	Slope	0.00800	0.223	-0.00616	0.0222
	EPI 16	Intercept	-0.253	0.781	-2.32	1.81
Epinephrine 0.3 mg IM twice (L/R)	EPI 03	Slope	0.00924	0.185	-0.00533	0.0238
	EPI 03	Intercept	0.396	0.764	-2.50	3.30
Epinephrine 0.5 mg IM	EPI 03	Slope	0.0214	0.00641	0.00768	0.0351
	EPI 03	Intercept	-0.887	0.429	-3.31	1.53
	EPI 16	Slope	0.00931	0.0704	-0.00101	0.0196
	EPI 16	Intercept	-0.160	0.874	-2.46	2.14

			Dependent			
			Regression Mean Δ SBP vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
EpiPen 0.3 mg	EPI 07	Slope	0.0274	0.0108	0.00826	0.0464
	EPI 07	Intercept	0.503	0.744	-2.93	3.94
	EPI 15	Slope	0.0180	5.15E-05	0.0132	0.0229
	EPI 15	Intercept	-1.81	0.00663	-2.93	-0.686
EpiPen 0.3 mg twice (L/R)	EPI 07	Slope	0.0320	6.59E-05	0.0222	0.0418
	EPI 07	Intercept	0.416	0.759	-2.60	3.44
	EPI 15	Slope	0.0218	0.000123	0.0151	0.0286
	EPI 15	Intercept	-2.53	0.0509	-5.08	0.0132

Linear regression of mean change from baseline HR versus mean epinephrine concentration is presented in Table 88.

Table 88 Linear Regression of Mean Change from Baseline Heart Rate vs Mean Epinephrine Concentration

			Dependent			
			Regression Mean ΔHR vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	EPI 03	Slope	0.0327	0.0114	0.00896	0.0564
	EPI 03	Intercept	2.61	0.0817	-0.388	5.61
	EPI 07	Slope	0.0432	0.0358	0.00368	0.0828
	EPI 07	Intercept	4.40	0.0690	-0.433	9.24
ARS-1 1.0 mg IN twice (L/L)	EPI 07	Slope	0.0211	0.0591	-0.00103	0.0433
	EPI 07	Intercept	8.26	0.00404	3.48	13.0
ARS-1 1.0 mg IN twice (L/R)	EPI 03	Slope	0.0210	0.000459	0.0116	0.0304
	EPI 03	Intercept	6.31	3.41E-05	4.23	8.39
	EPI 07	Slope	0.0296	0.0840	-0.00500	0.0642
	EPI 07	Intercept	6.07	0.0629	-0.415	12.6
ARS-1 2.0 mg IN	EPI 15	Slope	0.0193	0.0259	0.00308	0.0354
	EPI 15	Intercept	2.93	0.118	-0.954	6.81
	EPI 16	Slope	0.0243	0.00710	0.00900	0.0396
	EPI 16	Intercept	1.84	0.209	-1.31	4.99
ARS-1 2.0 mg IN twice (L/R)	EPI 15	Slope	0.0164	0.00915	0.00552	0.0272
	EPI 15	Intercept	4.19	0.0883	-0.815	9.19
ARS-1 2.0 mg IN twice (R/R)	EPI 15	Slope	0.0151	0.0175	0.00356	0.0267
	EPI 15	Intercept	5.11	0.0643	-0.397	10.6
Epinephrine 0.3 mg IM	EPI 03	Slope	0.0282	0.0306	0.00317	0.0532
	EPI 03	Intercept	-0.0189	0.988	-2.81	2.77
	EPI 15	Slope	0.00390	0.544	-0.0106	0.0184
	EPI 15	Intercept	0.742	0.448	-1.44	2.93
	EPI 16	Slope	0.0180	0.0649	-0.00145	0.0374
	EPI 16	Intercept	-0.710	0.572	-3.55	2.13

			Dependent			
			Regression Mean Δ HR vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
Epinephrine 0.3 mg IM twice (L/R)	EPI 03	Slope	0.0176	0.0439	0.000580	0.0347
	EPI 03	Intercept	3.61	0.0300	0.419	6.80
Epinephrine 0.5 mg IM	EPI 03	Slope	0.0282	0.00235	0.0124	0.0440
	EPI 03	Intercept	0.726	0.557	-1.91	3.36
	EPI 16	Slope	0.0109	0.0406	0.000616	0.0211
	EPI 16	Intercept	1.21	0.252	-1.08	3.49
EpiPen 0.3 mg	EPI 07	Slope	0.0243	0.0242	0.00409	0.0444
	EPI 07	Intercept	3.60	0.0517	-0.0329	7.23
	EPI 15	Slope	0.00892	0.0265	0.00139	0.0165
	EPI 15	Intercept	1.15	0.159	-0.579	2.89
EpiPen 0.3 mg twice (L/R)	EPI 07	Slope	0.0188	0.0507	-7.05E-05	0.0377
	EPI 07	Intercept	4.51	0.113	-1.33	10.4
	EPI 15	Slope	0.0135	0.0231	0.00248	0.0245
	EPI 15	Intercept	3.70	0.0729	-0.448	7.84

Linear regression of mean change from baseline DBP is presented in Table 89.

Table 89 Linear Regression of Mean Change from Baseline DBP vs Mean Epinephrine Concentration

			Dependent			
			Regression Mean ΔDBP vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	EPI 03	Slope	-0.0214	0.181	-0.0547	0.0119
	EPI 03	Intercept	4.58	0.0458	0.107	9.06
	EPI 07	Slope	0.00812	0.618	-0.0270	0.0433
	EPI 07	Intercept	1.05	0.564	-2.88	4.99
ARS-1 1.0 mg IN twice (L/L)	EPI 07	Slope	0.0124	0.161	-0.00586	0.0308
	EPI 07	Intercept	3.83	0.0398	0.217	7.45
ARS-1 1.0 mg IN twice (L/R)	EPI 03	Slope	-0.0134	0.0494	-0.0268	-4.07E-05
	EPI 03	Intercept	7.15	0.000726	3.92	10.4
	EPI 07	Slope	0.00448	0.689	-0.0197	0.0287
	EPI 07	Intercept	2.13	0.279	-2.02	6.29
ARS-1 2.0 mg IN	EPI 15	Slope	-0.00321	0.210	-0.00859	0.00217
	EPI 15	Intercept	0.164	0.760	-1.01	1.34
	EPI 16	Slope	0.00367	0.541	-0.00981	0.0171
	EPI 16	Intercept	-0.989	0.428	-3.77	1.79
ARS-1 2.0 mg IN twice (L/R)	EPI 15	Slope	0.00221	0.0432	8.36E-05	0.00434
	EPI 15	Intercept	-0.245	0.552	-1.14	0.653
ARS-1 2.0 mg IN twice (R/R)	EPI 15	Slope	0.000384	0.528	-0.000941	0.00171
	EPI 15	Intercept	0.479	0.0937	-0.0991	1.06
Epinephrine 0.3 mg IM	EPI 03	Slope	-0.0270	0.0226	-0.0493	-0.00477
	EPI 03	Intercept	-0.542	0.647	-3.13	2.04
	EPI 15	Slope	-0.0284	1.63E-05	-0.0362	-0.0207
	EPI 15	Intercept	0.278	0.570	-0.789	1.34
	EPI 16	Slope	-0.0345	0.000538	-0.0481	-0.0209
	EPI 16	Intercept	0.649	0.464	-1.33	2.63
Epinephrine 0.3 mg IM twice (L/R)	EPI 03	Slope	-0.0250	0.00114	-0.0370	-0.0129
	EPI 03	Intercept	1.24	0.272	-1.16	3.64
Epinephrine 0.5 mg IM	EPI 03	Slope	-0.0119	0.0713	-0.0250	0.00127

			Dependent			
			Regression Mean Δ DBP vs Epinephrine Concentration			
Tx	Study	Effect Level	Estimate	P value	Lower 95% CI	Upper 95% CI
	EPI 03	Intercept	-1.06	0.327	-3.38	1.26
	EPI 16	Slope	-0.0185	0.00197	-0.0276	-0.00938
	EPI 16	Intercept	-0.196	0.826	-2.23	1.84
EpiPen 0.3 mg	EPI 07	Slope	-0.00922	0.147	-0.0223	0.00384
	EPI 07	Intercept	0.583	0.560	-1.57	2.74
	EPI 15	Slope	-0.0169	0.00148	-0.0254	-0.00843
	EPI 15	Intercept	-0.456	0.575	-2.23	1.32
EpiPen 0.3 mg twice (L/R)	EPI 07	Slope	-0.00772	0.0201	-0.0139	-0.00149
	EPI 07	Intercept	0.471	0.565	-1.29	2.23
	EPI 15	Slope	-0.00863	0.00159	-0.0130	-0.00425
	EPI 15	Intercept	-0.469	0.497	-1.97	1.03

2.6.3. Discussion on clinical pharmacology

Four primary clinical pharmacology studies (EPI 10 (paediatric population), EPI 15 (healthy volunteers), EPI 16 (healthy volunteers), EPI 17 (self-administration in subjects with type I allergies)) were conducted to characterise the pharmacokinetics of intranasally administered adrenaline 2 mg, Eurneffy, and to contextualise its pharmacokinetics to other authorised adrenaline products administered via SC or IM route. Cross-over study design was considered appropriate. The studies also evaluated the comparative pharmacodynamic response. Haemodynamic endpoints were used as surrogate markers (blood pressure, systolic and diastolic; heart rate) predictive of clinical efficacy through activation of α - and β -adrenergic receptors. The use of surrogate pharmacodynamic endpoints were in accordance with the EMA in Scientific Advice (EMA/H/SA/4077/1/2019/SME/III).

In the pivotal studies, subjects with prior nasal fractures, severe nasal injuries, polyps, polyposis, recurrent epistaxis [>1 nosebleed per month], deviated septum, etc. were excluded from the participating population. The primary four clinical pharmacology studies are supported by five clinical studies that utilise a 1 mg dose Eurneffy in adult Type 1 allergy patients (EPI 04 and EPI JP01), healthy volunteers (EPI 03 and 07) and with self-administration by Type 1 allergy patients (EPI 12). Other supportive studies include pilot ranging studies such as EPI 02.

Of note, two studies (EPI 09 and EPI 13) were considered supportive for safety and not considered valid for PK and PD outcomes, due to study conduct errors. The EPI 09 study was repeated to provide results for self-administration of Eurneffy 1 mg in adults and EPI 17 to give results from self-administration of Eurneffy 2 mg in adults (EPI 12).

EPI18 study investigated PK and PD parameters after the administration of a repeat dose of Eurneffy (twice to the same nostril and to the opposite nostril) in patients with NAC (Nasal Allergen Challenge) using epinephrine IM at a dose of 0.3 mg as comparator (in normal conditions and in patients with NAC).

The initial dose-escalation pharmacokinetic (PK) studies with Eurneffy determined that an IN dose of 1 mg adrenaline in a volume of 100 μ L closely matched that of a 0.3 mg dose of adrenaline delivered by intramuscular (IM) administration. Subsequent studies also demonstrated that adrenaline absorption following repeat administrations of Eurneffy in the same nostril was potentiated by the prior Eurneffy administration, mainly when there were only 24 hours between Eurneffy doses. This “carry-over effect” is likely attributable to subtle alterations to the nasal mucosa that do not fully resolve within 24 hours,

resulting in enhanced intranasal absorption of subsequent doses. Given the rapid clearance of adrenaline, studies were typically conducted with a 24-hour wash-out before the applicant discovered the potential for a carry-over effect. Thus, repeated administration of Eurneffy to the same nostril appeared to enhance adrenaline exposure artificially. As a result of this carry-over effect, the pharmacokinetic results of EPI 01, EPI 02, EPI 06 and EPI 11 represent a level of adrenaline exposure that is artificially inflated and not representative of the exposure expected in a real-world treatment setting. Therefore, additional studies were conducted with adequate wash-out periods to avoid any impact of this carry-over effect (EPI 15, EPI 16, and EPI 17 as presented above). These studies were designed to assess the comparative bioavailability of a single dose of Eurneffy 2 mg relative to single IM doses of adrenaline via needle/syringe and/or adrenaline auto-injectors (AAIs).

Pharmacokinetics

Methods

The applicant has conducted Population Pharmacokinetic assessments (POP PK) and Physiologically Based Absorption Model (PBAM), to evaluate the data and extrapolate the PK and PD to other populations. The results of the POP PK model were consistent with the PBAM model. In paediatric allergy patients ≥ 30 kg Eurneffy 2 mg has a predicted C_{max} that is bracketed by IM adrenaline 0.3 mg injection on the lower end and by EpiPen on peak exposure. These simulations support that the overall exposure from Eurneffy 2 mg in the paediatric allergy patient population ≥ 30 kg will be in the efficacious and safe range as compared to approved injection products in this population.

The issue of higher adrenaline exposure in subjects weighing 30 kg after a double administration of the drug (extreme scenario) was discussed during the procedure.

Absorption, distribution and elimination

The applicant has investigated absorption after administration of the proposed dosage form, and results have been compared among products with different routes of administrations (i.e., IN, IM, SC including investigation of potential impact on absorption by rhinitis and possible misuse, when second dose is administrated into the same nostril.

Eurneffy 2 mg IN had comparatively higher partial AUCs than adrenaline 0.3 mg IM/ 0.5 mg IM up to first 12 minutes after administration, while till 10 minute it was lower respectively. In addition, studies with EpiPen 0.3 mg as reference product demonstrated that Eurneffy 2 mg IN had lower C_{max} and pAUCs up to 60 min after single dosing or repeated dose. While AUC_{last} was higher after ARS-1 2.0 mg IN, it is not considered clinically significant as exposure to adrenaline (C_{max} and AUC) during first minutes after administration are considered the most important for the effect.

In most cases, exposure after intranasal administration was higher than when the drug was injected.

In the treatment of anaphylactic disorders after the administration of epinephrine, the expected clinical effect occurs after 5-15 minutes, and if there is no sufficient clinical effect, another dose of the drug is administered. In case of unsatisfactory clinical response after the first dose, subsequent administration of ARS-1, either to the same nostril or to the other nostril, also resulted in higher exposure to repeat injectable adrenaline.

EPI 15 study showed that the use of ARS-1 2.0 mg C_{max} values was 38% lower than EpiPen and 26% higher than Epinephrine IM. Epinephrine exposure after ARS-1 2.0 mg administration was the highest (43500 min*pg/mL) compared to other formulations tested (EpiPen (30900 min*pg/mL), and Epinephrine injection IM (29000 min*pg/mL)). Total exposure measured by AUC_{last}, was 17% higher compared to EpiPen and 30% higher compared to Epinephrine IM injection.

EPI15 study tested a second administration of the drug after 10 minutes. The selected time point, which is 10 minutes in the EPI 15, aligns with the recommended timeframe of 5-15 minutes as suggested in both US and EU guidelines and is reflected in the agreed SmPC section 4.2.

EPI 16 study investigated the effect of induced rhinitis on adrenaline absorption after one dose of Eurneffy, as anaphylactic reactions are likely to occur with rhinitis. A higher increase in adrenaline concentration after intranasal administration was observed in subjects with induced rhinitis compared with classical injectable administration (Epinephrine IM 0.3 mg). The Cmax magnitude was lower (260 pg/mL) than under normal conditions (386 pg/mL). In addition, the total exposure (AUClast) after ARS-1 2.0 mg administration during rhinitis was lower (19700 min*pg/mL) compared to IM Epinephrine 0.3 mg (25900 min*pg/mL) and to Eurneffy under normal conditions (29400 min*pg/mL).

Gender effect

Since the non-clinical anaphylaxis model study in dogs show substantial gender differences in adrenaline absorption, the applicant was requested by CHMP to analyse and present the EPI 16 and EPI 18 studies results (PK and PD data) by gender.

In Study EPI 18, in total 24 female and 19 male subjects were included. Under normal conditions, median Cmax in females was higher compared to male (773.7 vs 644.1). Under rhinitis conditions when administered to the same nostril the difference between female and male was more pronounced (894.1 vs 513.1). However, after administration to different nostrils median Cmax in female was lower compared to male (408.9 vs 530.9). Similarly, AUC was higher in female compared to male, both under normal and rhinitis conditions following Eurneffy administration. Of note, median AUC and median Cmax (894.1 pg/ml) in female under rhinitis conditions after R/R administration was much higher compared to R/L administration (median AUC 81467 vs 43145). However, the significance of this finding is unknown. The maximum level of Cmax in females (2567.9 pg/ml) remain within that observed in Eurneffy in normal condition (R/L), in which Cmax is still higher than after IM administration. The higher exposure in female translates in a higher effect on change from baseline of SBP and PR compared to male subjects, but it is still lower to that observed in normal condition with Eurneffy. Moreover, for SBP and PR the TEmax in male treated with Eurneffy (R/R) in rhinitis conditions is faster than in female. Additionally pronounced differences in PR between males and females under rhinitis conditions after R/R administration should be noted. Taking all data into consideration, the CHMP considered that the PK differences in gender should not have an influence on efficacy and safety of Eurneffy.

Overall, the results of clinical studies suggest that the PD response may also depend on the specific injectable formulation of adrenaline used. It was confirmed that Eurneffy exhibited higher variability than injectable forms, particularly concerning the AUClast parameter. However, the variability of partial AUC and Cmax was similar among all adrenaline forms, including intranasal, and consistent across different conditions in which Eurneffy was administered, including cases of rhinitis and different doses (1 or 2 mg).

From a clinical perspective, the absence of clinically significant differences between Eurneffy and the classical injectable form provides reasonable evidence of an expected similar response between Eurneffy and injectable forms, both in patients with rhinitis and under normal conditions.

Administration- related errors

EPI17 study assessed correctness and the frequency of administration-related errors with Eurneffy. The administration of ARS-1 was not associated with incidents of application errors in contrast to EpiPen and adrenaline i.m. administered by professional staff.

No specific studied investigating metabolism of adrenaline interconversion, PK of metabolites or

consequences of possible genetic polymorphism were performed which is acceptable considering the well-established knowledge of adrenaline with other formulations. The PK and PD intra and inter-variability observed after ARS-1 IN is similar to IM or EpiPen administration.

Second administration (R/L versus R/R nostril)

It was demonstrated that the exposure to Eurneffy under rhinitis conditions and administered in the contralateral nostril (R/L) showed lower exposure than observed under normal conditions (R/L). The effect in rhinitis conditions (R/R) is closer to that observed with Eurneffy under normal conditions, whereas the effect in rhinitis conditions (R/L) is closer to that observed with IM administration. Further, the administration of Eurneffy in the same nostril or in the contralateral one under normal conditions did not differ in terms of PK/PD. Additionally, the human factor (HF) studies, showed that if participants used their non-dominant hand or actuated the spray contralaterally for the second dose, they had less of a secure grip on the spray device. Taking all into consideration, it should be concluded that the recommendation to use the same nostril for the second dose is justified. The SmPC section 4.2 adequately reflects this recommendation.

Pharmacodynamics

Chosen haemodynamic endpoints (i.e., mean changes from baseline SBP, DBP and HR) are considered relevant to characterise the mechanism of action. The lack of clinical studies with patients at risk of anaphylaxis is endorsed as considered unethical.

EPI 15 and EPI 16 studies indicated that Eurneffy 2 mg results in pharmacodynamic responses (SBP and HR/PR) comparable to EpiPen, but more rapid and robust than IM adrenaline injection with needle and syringe. The haemodynamic response (SBP and HR), observed with Eurneffy were comparable to EpiPen. SBP and HR results between ARS-1 administered twice to both the same nostril (R/R) and two different nostrils (L/R) were comparable to each other as well as to EpiPen 0.3 mg administered twice.

In conclusion, the applicant has demonstrated the positive correlation of change from baseline Emax on SBP and HR with epinephrine Cmax values in timely manner. However, there is a lower effect and more rapid drop in haemodynamic response following the use of ARS-1 in the presence of rhinitis is observed.

In all studies the linear regression of the mean change from baseline stratified by treatment for SBP and HR results showed that the PD effect was positively correlated with increasing mean epinephrine concentrations. Population (POP) PK and Pharmacologically Based Absorption Model (PBAM) analyses provided additional support based on the data from Eurneffy studies. The model predicts adrenaline plasma concentrations after Eurneffy 1 and 2 mg and can be extrapolated to children. The PBAM model also supports that nasal cavity size does not have significant impact on absorption. Overall, Eurneffy presents equivalent haemodynamic responses relative to the approved products, which supports comparable treatment of severe allergic reactions and anaphylaxis.

Special populations

In the paediatric population, a slight increase in absorption was observed in children >30kg after ARS-1 2.0 mg administration. Epinephrine levels were proportional between 1.0 and 2.0 mg dosing in children >30 kg.

Based on the POP PK model age was not a significant covariate for nasal absorption of adrenaline from the nasal mucosa Eurneffy formulation. The recommended posology in children with a body weight ≥ 30 kg is the same as adults.

In elderly subjects (patients agreed 65 years or older), no pharmacokinetic data are available after nasal administration of adrenaline. No dose adjustment is required.

Adequate information has been included in SmPC (section 4.2).

2.6.4. Conclusions on clinical pharmacology

The PK/PD programme is considered comprehensive. All issues were addressed satisfactorily, and results adequately reflected in SmPC.

2.6.5. Clinical efficacy

The application for nasal spray administration is based on literature data describing adrenaline's use as the first-line treatment of Type I allergic reactions; and pharmacodynamic data as a surrogate for efficacy.

Due to both ethical and practical limitations, it is not possible to conduct controlled clinical trials to assess the efficacy of adrenaline for the treatment of severe allergic reactions and anaphylaxis and a review of the literature has confirmed that no prospective, randomised controlled clinical trials have been conducted to substantiate the use of adrenaline for treatment of anaphylaxis (Sheikh-2008, Rubin-2014). Involvement of body organ systems in anaphylaxis varies among patients even in the same patient from one allergic reaction to another (Fisher-1995, Simons-2010a). Such unpredictability of clinical course could put patients in a risk of life-threatening, potentially fatal condition (Fisher-1987, Dinakar-2012, Lieberman-2015, Brown-2020, Pumphrey-2000).

Given the issues outlined above, the application for nasal spray administration is based on literature data describing background of adrenaline's use as the first-line treatment of Type I allergic reactions; and pharmacodynamic data as a surrogate for efficacy.

Adrenaline has been used over 110 years in various indications (treatment of anaphylaxis, severe allergy such as asthma, and shock) with about 60 years of use for the treatment of anaphylaxis. Adrenaline has been adopted as the standard-of-care, first-line treatment of anaphylaxis worldwide as stated in literature (Lieberman-2015, Simons-2011, Simons-2015, EAACI-2021). Therefore, there is extensive clinical experience of use of adrenaline for severe systemic allergic reactions, including anaphylaxis,

While dosing differs internationally, initial doses for persons 30 kg or greater body weight are typically 0.3 milligrams (mg) to 0.5 mg by injection, with repeat dosing, as necessary. Typically, total doses up to 1.0 mg by injection are sufficient to resolve most cases, with some events requiring even higher doses (Järvinen-2008, Noimark-2012).

In Europe, the usual dose of adrenaline for allergic reactions in adults is 0.3 mg by IM injection for patients with body weight greater than 25 – 30 kg. European Union treatment guidelines recommend that when using adrenaline auto-injectors, patients weighing between 7.5–25 kg should receive 0.15 mg dose, with patients being moved to 0.3 mg dose at 25–30 kg (Muraro-2022, Gloaguen-2017). In the absence of clinical improvement or if deterioration occurs, a second injection with an additional 0.3 mg dose may be administered 5 – 15 minutes after the first injection.

It has been well documented that the sooner administration of adrenaline can occur, the less severe the systemic allergic reaction may become and less likely it will be to develop into an anaphylaxis event or other severe outcomes and reduce the likelihood of hospital admission or death, as compared with adrenaline initial injection only after Emergency Department arrival. (Simons-2010b, Simons-2001).

A retrospective analysis of anaphylaxis related deaths over the course of 25-years found that of 77% of fatalities were in patients who did not receive adrenaline prior to experiencing cardiac arrest (Xu-

2014).

The use of a commercially made adrenaline autoinjector has been the current out-of-hospital standard of care and, in some situations, is prescribed to all patients who have experienced anaphylactic reactions or who are at risk of anaphylaxis. Previously, use of adrenaline IM injection (vial with needle and syringe) was more common.

In EU for community use, defined as caregiver administration or patient self-administration auto-injectors or prefilled syringes are the most typically used method of administration. (as 0.3 mg injection for all persons 30 kg (0.01 mg/kg) and above and as 0.5 mg auto-injector product for larger persons or when a 0.3 mg auto-injector has been used and failed to resolve an allergic event). For children aged 6 months and greater with body weight of > 15 kg, a 0.15 mg auto-injector dose is available for community use.

As mentioned earlier, heart rate and blood pressure are being used as easily measurable PD indicators of $\alpha 1$ - and $\beta 1$ adrenergic receptor agonism and, as such, serve as the pharmacodynamic surrogates of efficacy. However, both heart rate and blood pressure effects are mediated via $\alpha 1$ and $\beta 1$ adrenergic receptors, which are less sensitive than the $\beta 2$ adrenergic receptor. Effects such as bronchial smooth muscle relaxation and increased bronchodilation, coronary vasodilation, inhibit plasma exudation, and decreased mast cell mediator release are mediated by the $\beta 2$ receptors, therefore, cannot be directly measured, in subjects experiencing severe allergic reactions.

Effects of the $\alpha 1$ and $\beta 2$ can counteract each other with vasoconstriction effect from $\alpha 1$ and vasodilation effect from $\beta 2$. At low doses, $\beta 2$ receptor activation decreases peripheral resistance, however, once adrenaline concentrations increase enough to stimulate the $\alpha 1$ receptors, vasoconstriction become prominent and, thus reverse the $\beta 2$ mediated vasodilatation, resulting in a net increase in SBP. Therefore, once the SBP increase occurs by $\alpha 1$ mediated vasoconstriction at higher adrenaline plasma concentrations, it can be assumed that adrenaline concentration has reached the level where $\beta 2$ effects are activated.

Adrenaline efficacy is supported by surrogate pharmacodynamic data with Eurneffy as marker for efficacy. As discussed in earlier clinical pharmacology section, Eurneffy is within the range, yet typically more rapidly absorbed, of pharmacokinetics obtained from various different injection products and devices that are all known to be highly effective.

2.6.5.1. Dose-response

The initial dose-escalation pharmacokinetic (PK) studies with ARS-1 determined that 1 mg adrenaline in a volume of 100 μ L closely matched that of a 0.3 mg dose of adrenaline delivered by intramuscular (IM) administration. However, subsequent studies demonstrated the possibility that adrenaline absorption following subsequent administrations of ARS-1 was potentiated by “carryover effect”. This issue was addressed in EPI 11b, where repeated doses of ARS-1 to the same nostril are separated by at least 12 days, allowing time for the nasal mucosa to return to baseline before administering a second dose. The results of EPI 11b, combined with the first dose analysis conducted for Studies EPI 03 and EPI 07 informed the selection of the 2 mg dose for subsequent ARS-1 studies conducted in both adults and children.

Studies EPI 15, EPI 16, and EPI 17 were designed to assess the comparative bioavailability of a single and repeat dose of ARS-1 2 mg relative to single IM doses of adrenaline via needle/syringe and/or AAls without carryover effect and are the basis for approval.

Study EPI 11b was a Phase 1 randomised, crossover study conducted in two groups to evaluate the pharmacokinetics of adrenaline after administration of intranasal ARS-1 to healthy volunteers. The

primary objectives of this study were:

- Group 1: to assess the comparative bioavailability of four pharmacy compounded formulations of ARS-1 with 0.25% or 0.30% DDM and different adrenaline concentrations in healthy volunteers under fasted conditions
- Group 2: to assess the comparative bioavailability of two commercially manufactured formulations of ARS-1 with different manufacturing dates, as well as two pharmacy compounded formulations in healthy volunteers under fasted conditions.

Twenty-six healthy volunteer subjects (13 per Group) were randomised as follows:

Group 1:

- a single dose of Symjepi (adrenaline injection) 0.3 mg
- a single dose of ARS-1 1.3 mg with 0.25% DDM, pH 4.5
- a single dose of ARS-1 1.5 mg with 0.25% DDM pH 4.5
- a single dose of ARS-1 1.5 mg with 0.30% DDM, pH 4.5
- a single dose of ARS-1 1.8 mg with 0.30% DDM, pH 4.5

Group 2:

- a single dose of EpiPen (0.3 mg adrenaline injection)
- a single dose of ARS-1 1.0 mg with 0.25% DDM (Commercial Lot 190932)
- a single dose of ARS-1 1.0 mg with 0.25% DDM (Commercial Lot 202130)
- a single dose of ARS-1 1.5 mg with 0.30% DDM, Citrate Buffer at pH 4.5
- a single dose of ARS-1 2.0 mg with 0.30% DDM at pH 4.5

For all treatments, dosing was alternated for the intranasal administration between the left and right nostril to provide a minimum of 12-days between doses to the same nostril, eliminating the carryover effect observed in earlier studies.

No consistent trend was observed in the adrenaline concentration-time profiles in Group 1. Within Group 2, peak concentrations were observed within 10 min with EpiPen followed by ARS-1 2.0 mg with DDM 0.30%, ARS-1 1.5 mg with DDM 0.30%, ARS-1 1.0 mg with DDM 0.25% (Commercial Lot 202130), and ARS-1 1.0 mg with DDM 0.25% (Commercial Lot 190932). In general, the concentration-time profiles after administration of ARS-1 (Group 2) increased with dose though the mean concentration-time profiles were similar between the two commercial lots of ARS-1. These results combined with the first dose analysis from studies EPI 03 and EPI 07, informed the decision to select the 2 mg dose.

2.6.5.2. Main studies

Studies EPI 15, EPI 16, EPI 17 and EPI 10 were submitted as main studies in support of efficacy.

All of those listed are PK/PD studies. For the design, methods, conduct and outcomes of studies please refer to the Clinical pharmacology sections above. No formal surrogate markers for efficacy are defined for any of the studies, but the study reports state that given the predictable effect of epinephrine administration on PR and SBP, increases in both these measures can be considered reliable predictors of its efficacy as an anti-anaphylactic agent.

Special populations

Subjects between the ages of 4 and 55 years were included in the main ARS-1 studies, and a history of hypertension and cardiovascular disease, clinically significant gastrointestinal, renal, hepatic, neurologic, haematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, severe allergies or any other condition was mentioned among exclusion criteria. In summary, studies in special populations were not provided.

Table 90 Summary statistics to reach 100 pg/ml epinephrine plasma concentration, injection treatments

	Treatment					
	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN twice (L/L)	ARS-1 1.0 mg IN twice (L/R)	ARS-1 2.0 mg IN	ARS-1 2.0 mg IN twice (L/R)	ARS-1 2.0 mg IN twice (R/R)
Statistic	Time of Onset (min)					
N	85	7	34	70	39	39
Mean	11.4	14.9	10.4	8.92	10.3	9.59
SD	9.25	5.18	4.87	13.5	12.8	6.8
CV%	81.1	34.7	46.9	151	124	70.9
Min	0.606	8.48	1.86	0	0.383	0.262
Median	9.28	14.1	8.9	6.32	7.18	9.52
Max	54	24.3	26.5	111	72.6	41.3

Abbreviations: CV = coefficient of variation, IN = intranasal, L = left, max = maximum, min = minimum, R = right, SD = standard deviation

	Treatment					
	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM twice (L/R)	Epinephrine 0.3 mg SC	Epinephrine 0.5 mg IM	EpiPen 0.3 mg	EpiPen 0.3 mg twice (L/R)
Statistic	Time of Onset (min)					
N	166	70	33	122	76	78
Mean	16.5	12.4	23.6	14	4.34	4.96
SD	28	16.4	17.9	17.6	5.05	5.35
CV%	170	133	75.8	126	116	108
Min	0	0	0.966	0.178	0	0
Median	7.85	8.02	24.5	8.44	2.39	2.46
Max	323	116	81.6	142	23.6	29.8

Abbreviations: CV = coefficient of variation, IM = intramuscular, L = left, max = maximum, min = minimum, R = right, SD = standard deviation

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 studies

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The mechanism of action of adrenaline that leads to its therapeutic efficacy is well understood and comes 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. Conducting PK/PD clinical trials instead of randomised clinical trials in target population is considered appropriate for the proposed indication, i.e. treatment of Type I allergic reactions as randomised clinical trials would be unethical. Changes of blood pressure (α 1 effect) and heart rate (β 1 effect) are considered appropriate surrogate endpoints of adrenalin efficacy in treatment of Type I allergic reaction.

Data from the primary clinical trials for the 2 mg dose of Eurneffy in adults (EPI 15, EPI 16, and EPI 17 [self-administration]) and children 30 kg or greater (EPI 10) are presented to support approval of this application. Primary PK/PD studies in adults with a 1 mg dose of Eurneffy (EPI 03, EPI 04, EPI 07, EPI 12 [self-administration] and EPI JP01) as well as other pilot studies are supportive information.

Efficacy data and additional analyses

The results of the study EPI 11b combined with the first dose analysis from studies EPI 03 and EPI 07, informed the decision to select the 2 mg dose. Data from EPI 11b show considerable variation in exposure of different doses of Eurneffy (e.g. 1.5 mg dose shows higher exposure compared to 2 mg), however, exposure of 2 mg dose is bracketed by manually injectable and EpiPen formulations, therefore the choice of the 2 mg dosing is justified.

During the clinical programme, as anaphylactic reactions are likely to occur with rhinitis, the influence of the rhinitis on the PK and PD of the nasally administered (single and twice) adrenaline was studied in patients with NAC (Nasal Allergen Challenge) as well as in patients who have Type I allergy. Overall, the C_{max} magnitude and the total exposure AUC_{last} after Eurneffy 2.0 mg administration during rhinitis was lower than under normal conditions. In addition, PD response (PR and SBP) followed 0.3 mg injection was similar to Eurneffy under normal conditions with either once or twice dosing. For details see clinical pharmacology section.

To justify the SmPC recommendation to use the second dose of 10 minutes after the first dose, the applicant presented pooled data from studies EPI 15, 16, 17 showing that the first physiological response of IN adrenaline starts immediately after dosing and is higher than IM injection but

comparable to EpiPen. The analysis of PD response in the EPI 18 study additionally confirmed the proposed timing for the second dose. The analysis of PD response in the EPI 18 study additionally confirmed the proposed timing for the second dose.

Assessment of paediatric data on clinical efficacy

In the paediatric population, a slight increase in absorption was observed in children >30kg after ARS-1 2.0 mg administration. Epinephrine levels were proportional between 1.0 and 2.0 mg dosing in children >30 kg.

Based on the POP PK model age was not a significant covariate for nasal absorption of adrenaline from the nasal mucosa Eurneffy formulation.

Therefore, the recommended posology in children with a body weight ≥ 30 kg is the same as adults.

2.6.7. Conclusions on the clinical efficacy

Data from clinical studies using PD surrogate endpoints - blood pressure and heart rate - demonstrate the efficacy of IN adrenaline comparable to manual and autoinjector adrenaline products. The same dose can be administered in adults and children above 30 kgs. In case of not complete response a second administration can be done after 10 minutes of the initial administration, using a second device.

2.6.8. Clinical safety

The applicant conducted in total fourteen pharmacokinetic/safety studies with Eurneffy (ARS-1) in healthy volunteers (EPI 03, EPI 06, EPI 07, EPI 11, EPI 11b, and EPI 15), in patients with Type I allergies (EPI 09, EPI 12, EPI 13, and EPI 17), in patients with allergic rhinitis (EPI 04, EPI 16, and EPI JP 01), and paediatric patients with Type 1 allergies (EPI 10 - study is ongoing at the time of this MAA) with the commercial formulation of ARS-1, including formulations with variable concentrations of the dodecylmaltoside excipient (DDM) (0.25% - 0.35%), which bracket the commercial formulation concentration of DDM (0.275%).

2.6.8.1. Patient exposure

550 subjects were enrolled and received at least one dose of ARS-1. Due to the crossover design of each study, subjects received more than one exposure to ARS-1 per study, for a total of 1069 total exposures to ARS-1 across the fourteen studies. In addition, only 537 subjects were treated with ARS-1 as on some occasions the same subject was enrolled more than once.

In EPI 15 Study, 59 out of 59 subjects (100%) received at least one dose of study medication. Out of these, 54 unique subjects received one dose of study drug. Fifty subjects (84.7%) completed the study age 21 to 54 years as nine subjects withdrew prematurely. Of note, an additional cohort with 17 subjects was enrolled due to an error in processing PK samples at the clinical site, five of these 17 subjects were subjects from Cohort 1 who re-enrolled.

In Study EPI 16, 36 out of 36 subjects (100%) received at least one dose of study medication. Thirty-four subjects (94.4%) completed the study as two subjects withdrew prematurely. Subjects ranged in age from 20 to 52 years.

In Study EPI 17, 45 out of 45 subjects (100%) received at least one dose of medication. Forty-one subjects (91.1%) completed the study as four subjects were discontinued after the first dose following physician decision. Subjects ranged in age from 23 to 53 years.

As of the interim analysis cutoff date, in the ongoing EPI 10 paediatric study, a total of 57 subjects were enrolled. Subjects ranged in age from 4 to 17 years. Thirty-two subjects (56.1%) were male and 25 subjects (43.9%) were female. Forty-two subjects (73.7%) were White, 10 subjects (17.5%) were Black or African American, and 5 subjects (8.8%) were Asian. Three subjects (5.3%) were Hispanic or Latino and 54 subjects (94.7%) were not Hispanic or Latino.

A pooled number of subjects that received a 2 mg dose includes subjects that received two 1 mg doses spaced 10 minutes apart and separate information regarding the intended medical product dose of 2 mg is displayed below. Comparing both groups, no substantial differences on demographic profiles are observed (see table below) except for minimum age (20 vs 8 years).

Table 91 Demographic Profile of Patients in Controlled Trials by Pooled Treatment Safety Population – ARS Treatments

Demographics	Only single dose 2.0 mg (N=134) n(%) *	Pooled 2 mg (N=344) n(%) **
Age(Year)		
Mean (SD)	39.5(9.10)	37.0(10.64)
Median	40.0	37.0
Minimum,Maximum	20,54	8,55
Sex		
Male	82(61.2)	210(61.0)
Female	52(38.8)	134(39.0)
Race		
White	61(45.5)	144(41.9)
Black or African American	40(29.9)	124(36.0)
Asian	18(13.4)	38(11.0)
American Indian or Alaska Native	3(2.2)	9(2.6)
Native Hawaiian or Other Pacific Islander	2(1.5)	5(1.5)
Other	10(7.5)	24(7.0)
Ethnicity		
Hispanic or Latino	39(29.1)	96(27.9)
Not Hispanic or Latino	95(70.9)	248(72.1)

* from ISS Addendum #2 only single dose of 2 mg

** from Clinical Overview (), including two 1 mg doses spaced 10 minutes apart.

2.6.8.2. Adverse events

All abnormal changes from baseline were collected, graded with regards to severity or clinical significance, and assessed for causal relationship.

Study subjects were evaluated post-exposure to ARS-1 (with and without induced rhinitis), IM adrenaline, SC adrenaline, EpiPen, and Symjepi in clinical studies: EPI 03, EPI 04, EPI 06, EPI 07, EPI JP01, EPI 09, EPI 10 (interim results), EPI 11, EPI 11b, EPI 12, EPI 13, EPI 15, EPI 16, and EPI 17 in the pooled integrated summary of safety.

Treatment-emergent adverse events were pooled into 18 different types and dose levels:

- ARS-1 0.5 mg, 0.65 mg, 0.8 mg, 1 mg, 1.3 mg, 1.5 mg, 1.8 mg, 2 mg, and 4 mg
- ARS-1 1 mg and 2 mg with rhinitis IN
- Adrenaline 0.3 mg, 0.5 mg, and 0.6 mg IM
- Adrenaline 0.3 mg SC
- EpiPen 0.3 mg and 0.6 mg
- Symjepi 0.3 mg

Table 92 Summary of Treatment-Emergent Adverse Events by Treatment - Pooled Population for EPI 15, EPI 16, and EPI 17

	ARS-1 Nasal		Epinephrine IM		EpiPen	
	2 mg ¹ (N=134) n(%)	4 mg ² (N=42) n(%)	0.3 mg (n = 134) n(%)	0.5 mg (n = 35) n(%)	0.3 mg (n = 55) n(%)	0.6 mg (L/R) ³ (n = 42) n(%)
No. (%) of Subjects with at Least 1 TEAE	33 (24.6)	8 (19.0)	10 (7.5)	1 (2.9)	2 (3.6)	1 (2.4)
No. (%) of Subjects with at Least 1 SAE	0 (0.0)	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)	0 (0.0)	0 (0.0)	0 (0.0)
No. (%) of Subjects with Treatment Related TEAE	30 (22.4)	6 (14.3)	9 (6.7)	0 (0.0)	2 (3.6)	1 (2.4)
No. (%) of Subjects Who Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Common Adverse Events from Primary 2 mg Clinical Trials (Integrated Summary of Safety of EPI 15, EPI 16, and EPI 17)

In support of the intended commercial dose of, the 2 mg primary studies safety analysis pools data from studies EPI 15, EPI 16, and EPI 17 and compares the adverse events of single dose ARS-1 (2.0 mg) and repeat dose ARS-1 (4.0 mg) to the injectable epinephrine control arms. The analysis pools the subjects with and without rhinitis. The N size for the analysis is the number of subjects per each treatment received and not the number of exposures (i.e., unique subjects only).

This summary of adverse reactions from the 2 mg primary clinical Eurneffy studies includes a breakdown of events observed in the 2 mg treatment group that occurred in $\geq 10\%$ of subjects (most common adverse reactions); $\geq 1\%$ and $< 10\%$ of subjects and ≥ 2 subjects; and lastly, those events observed in $< 1\%$ and ≥ 2 subjects.

Most Common Adverse Reactions ($\geq 10\%$)

There were no adverse reactions observed in $\geq 10\%$ of subjects in the ARS-1 2 mg treatment group.

Other Adverse Reactions ($\geq 1\%$ and $< 10\%$)

Other common adverse reactions that occurred in more than ≥ 2 subjects and observed in $\geq 1\%$ and $< 10\%$ of subjects in the ARS-1 2 mg group were as follows: Nasal discomfort (9.7%)

Other Adverse Reactions ($< 1\%$)

Other adverse reactions that occurred in more than ≥ 2 subjects and observed in $< 1\%$ of subjects in the ARS-1 2 mg group were as follows: headache (6.0%), rhinorrhoea (3.0%), nausea (2.2%), throat irritation (1.5%), dizziness (1.5%).

A display of treatment-related adverse events and occurrence rates from the pooled primary 2 mg studies is presented by treatment in Table 93.

Table 93 Incidence of Treatment-Related Treatment-Emergent Adverse Events - Pooled Population for EPI 15, EPI 16, and EPI 17.

System Organ Class Preferred Term	ARS-1 Nasal		Epinephrine IM		EpiPen	
	2 mg ¹ (N=134) n(%)	4 mg ² (N=42) n(%)	0.3 mg (n = 134) n(%)	0.5 mg (n = 35) n(%)	0.3 mg (n = 55) n(%)	0.6 mg (L/R) ³ (n = 42) n(%)
Subjects with at least One Adverse Event	30 (22.4)	6 (14.3)	9 (6.7)	0 (0.0)	2 (3.6)	1 (2.4)
Respiratory, Thoracic and Mediastinal Disorders	18 (13.4)	3 (7.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Discomfort	13 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhea	4 (3.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Throat Irritation	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sneezing	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	10 (7.5)	4 (9.5)	5 (3.7)	0 (0.0)	1 (1.8)	0 (0.0)
Headache	8 (6.0)	3 (7.1)	3 (2.2)	0 (0.0)	1 (1.8)	0 (0.0)
Dizziness	2 (1.5)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	1 (2.4)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	3 (2.2)	1 (2.4)	6 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	3 (2.2)	0 (0.0)	4 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Mouth	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia Oral	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorders	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lacrimation Increased	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular Discomfort	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.8)	1 (2.4)
Feeling Jittery	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Injection Site Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Investigations	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	ARS-1 Nasal		Epinephrine IM		EpiPen	
	2 mg ¹ (N=134) n(%)	4 mg ² (N=42) n(%)	0.3 mg (n = 134) n(%)	0.5 mg (n = 35) n(%)	0.3 mg (n = 55) n(%)	0.6 mg (L/R) ³ (n = 42) n(%)
Body Temperature Decreased	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Rate Decreased	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood Pressure Decreased	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Temporomandibular Joint Syndrome	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	1 (0.7)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyerhidrosis	1 (0.7)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

In EP15 study, all TEAEs were considered mild, and none were life-threatening or resulted in death. No AEs were considered serious or resulted in discontinuation from the study. 7.1% of subjects experienced at least one adverse event in Part 1 of the study. 19.0% experienced at least one adverse event in Part 2 of the study.

While it is acknowledged that the overall number of TEAE was low there were two cases of vomiting following administration of ARS – 1 2.0 mg in two subjects (3.6%)

Abnormal ECG results were observed in the majority of subjects at baseline and following all treatments, but none of the observed abnormal ECG results were considered clinically relevant.

Study EPI 16

In EPI16 study, 28% of subjects experienced at least one treatment emergent adverse event.

25.0% and 2.9% of patients experienced a TEAE following ARS-1 2.0 mg and Epinephrine 0.5 mg IM, respectively. Of note, following ARS-1 2.0 mg administration 2.9% with rhinitis experienced a TEAE and 13.9% and 5.6 % of subjects experienced headache and dizziness, respectively,

There was a relevant difference in the incidence of AE between ARS-1 and epinephrine IM groups. Of note, there were no treatment-related TEAEs in patients in rhinitis following administration of ARS-1.

Study EPI 17

In EPI17 study, 53.3% of subjects experienced at least one treatment emergent adverse event. 50.0% experienced a total of 35 TEAEs following ARS-1 2.0 mg. Three events (vomiting, decreased heart rate, and dizziness) in two subjects were considered moderate, and one subject treated with Neffy 2mg experienced severe syncope and hypotension but resolved without sequela or medical intervention. This event was rated possibly related by the principal investigator, however the applicant considered these events were more related to the specific EPI17 study procedures (the clinical site used separate needle punctures for each blood draw and did not use a catheter as standard site procedure) and not

to the adrenaline treatment, given syncope and hypotension was not observed in any other applicant clinical trials.

These severe events (syncope and hypotension) were observed in both treatment arms, Eurneffy 2 mg and IM adrenaline injection 0.3 mg. Two subjects in the IM adrenaline injection 0.3 mg group experienced severe syncope, with one having hypotension and the other associated asthenia and blood pressure decreased.

All other TEAEs following ARS-1 2.0 mg were considered mild. 22.7% experienced a total of 29 TEAEs following Epinephrine 0.3 mg IM. Five events (vomiting, headache [2 reports], hypotension, and presyncope) in four subjects were considered moderate, and three events (asthenia, syncope, and blood pressure decreased) in two subjects were considered severe. All other TEAEs following Epinephrine 0.3 mg IM were considered mild. No TEAEs were considered serious or resulted in discontinuation from the study.

In EPI10, paediatric study, there was one moderate TEAE (nasal discomfort following administration of ARS-1 2.0 mg in a subject > 30 kg). All other TEAEs were considered mild, and none were life-threatening or resulted in death.

In subjects greater than 30 kg treatment emergent AEs (TEAE) occurring in ≥ 2 subjects following administration of ARS-1 1.0 mg included: nasal discomfort and rhinorrhoea (three subjects each, 11.5%) and sneezing, rhinalgia, oropharyngeal pain, nasal mucosal disorder, taste disorder, lacrimation increased, and ocular hyperaemia (two subject each, 7.7%).

Treatment emergent AEs occurring in ≥ 2 subjects following administration of ARS-1 2.0 mg included: nasal discomfort and IN paraesthesia (four subjects each, 25.0%); sneezing (3 subjects, 18.8%); and rhinorrhoea, rhinalgia, paraesthesia, fatigue, and feeling jittery (2 subjects each, 12.5%). There was one moderate TEAE (nasal discomfort following administration of ARS-1 2.0 mg in a subject > 30 kg). All other TEAEs were considered mild, and none were serious, life-threatening, or resulted in death.

2.6.8.3. Serious adverse events, deaths, and other significant events

No deaths have occurred in clinical studies conducted with Eurneffy and adrenaline injection. No SAEs and significant AEs have been reported in clinical studies with Eurneffy and adrenaline injection.

2.6.8.4. Laboratory findings

In clinical studies with ARS-1 and adrenaline injection, there has been no significant clinical laboratory evaluation findings related to the safety of the test article.

2.6.8.5. Discontinuation due to adverse events

There were no discontinuations due to adverse events in any of the studies.,

2.6.8.6. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Patients population

In total 537 subjects were exposed to Eurneffy with a total of 1069 total exposures to ARS-1 across the fourteen completed clinical studies. Of those subjects, 171 patients with type I allergies (EPI 09, EPI 12, EPI 13, and EPI 17), 102 patients with induced rhinitis (EPI 04, EPI 16, and EPI JP01) and 57 paediatric patients with type I allergies (EPI 10) received at least one dose of ARS-1.

All included patients were between 19 and 55 years of age. Patients included in Studies EPI 15, EPI 16 and EPI 17 were between 20 and 54 years of age. In total 134 patients were exposed to the dose of 2 mg of ARS -1 in the pivotal studies. Moreover, 42 patients received 2 administrations of 2mg ARS-1.

Pooled number of subjects that received a 2 mg dose includes subjects that received two 1 mg doses spaced 10 minutes apart and separate information regarding the intended medical product dose of 2 mg should be displayed. Nonetheless, comparing groups with and without two 1 mg doses included in the pooled 2 mg group, no substantial differences in demographic profiles are observed except for minimum age (20 vs. 8 years).

Additionally paediatric patients above 4 years of age were included in the EPI 10 study, which is ongoing.

Patients with renal and or hepatic impairment, women during pregnancy and breast feeding were not specifically studied. This is acceptable by CHMP. The studied population is considered representative. Effects of weight on adrenaline concentration following adrenaline injection versus intranasal formulation is discussed earlier in the clinical pharmacology section. Effects of weight might be a more important covariate as compared to either BMI or age. The majority of subjects being from North America, and a total of only 36 subjects from Japan. No subjects recruited in the studies from Europe and Rest of World, respectively however, since adrenaline is a well-known active substance in EU, this is acceptable. The overall size of the safety database can be considered sufficient taking into account a well – known safety profile of epinephrine.

Adverse events

Of note, there may be a reporting bias in the ARS-1 arms since subjects were asked if they felt any nasal discomfort, as well as nasal irritation or nasal pain since the latter were part of the study evaluation measures. However, discomfort, irritation, or pain of the injection groups were not solicited. Any reports in the injection groups were voluntarily reported.

Overall, in all completed studies conducted by the applicant, 24.6%, 19% of patients exposed to nasal adrenaline dose of 2 mg and 4mg experienced at least 1 TEAE, respectively.

2 mg dose administration

There were no adverse reactions observed in $\geq 10\%$ of subjects in the ARS -1 2mg treatment group.

The most common adverse reaction that was observed in the clinical studies in ≥ 2 subjects and observed in $\geq 1\%$ and $< 10\%$ in patients exposed to 2mg ARS-1 was nasal discomfort. Other reported AE included headache, rhinorrhoea, nausea, throat irritation and dizziness.

Moderate events after receiving a dose of ARS-1 consisted of 2 events of nasal oedema, and 1 event each of dyspnoea and presyncope; 1 event each of nasal discomfort, sneezing, heart rate decrease, dizziness, vomiting. Severe events after use of ARS-1 consisted of 1 event each of syncope and

hypotension (ARS-1 2 mg). Severe events for syncope and hypotension were observed both in ARS-1 2 mg and IM adrenaline injection 0.3 mg trial arms.

4 mg dose administration

Overall, there were no significant differences in rates of adverse events comparing a single dose and two repeated 2 mg doses (total dose – 4 mg). Furthermore, it is comparable to twice a dosing of i.m. adrenaline. In subjects receiving two doses the most common adverse events were headache (7.1%) and rhinorrhoea (4.8%).

Reported adverse events are coherent with adverse events observed in case of adrenaline systemic exposure described in literature, with exception of local nasal symptoms.

No differences in blood pressure-related AEs were observed between patients treated with ARS-1 and EpiPen. However, in total 9% of patients exposed to ARS-1 2mg experienced blood pressure increase. Moreover, 6.1% of patients exposed to ARS-1 2mg experienced palpitations. Majority of nasal-related AE were considered mild and did not require any treatment.

Assessment of paediatric data on clinical safety

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

In paediatric patients aged 4 to 17, there was one moderate TEAE (nasal discomfort following administration of ARS-1 2.0 mg in a subject > 30 kg). All other TEAEs were considered mild, and none were life-threatening or resulted in death. Overall, the safety profile in patients above 30kgs is similar to the one observed with adult data.

In summary, no cases of serious adverse events or deaths were reported during the overall clinical development programme. No subjects discontinued due to AEs in the overall clinical development programme. There have been no significant clinical laboratory evaluation findings related to the safety of the test article.

Results of ECG following administration of the treatment was provided only for Study EPI 15. However, since abnormal ECG results were observed in most of the subjects at baseline, the effect of ARS-1 administration is very difficult to interpret.

2.6.10. Conclusions on the clinical safety

Adrenaline has a well known and characterised safety profile following its use for many decades. The safety profile has been adequately characterised for the nasal formulation. No major safety concerns have been identified.

2.7. Risk Management Plan

2.7.1. Safety concerns

The following summary of safety concerns is agreed in the RMP:

Table 94 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 PhV activities are planned.

2.7.3. Risk minimisation measures

Table 95 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Medication error or mishandling of device	<i>Routine risk minimisation measures:</i> 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). <i>Additional risk minimisation measures:</i> • training device • training videos • digital educational material • IFU within Eurneffy device blister	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal:</i> Targeted questionnaire in case of medication errors. <i>Additional pharmacovigilance activities:</i> None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

Based on the new administration route and new device to be used in emergency situations, the PRAC is of the opinion that a separate entry in the EURD list for Eurneffy is needed, as it cannot follow the already existing entry for epinephrine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 17 January 2019.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. 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). Delay in clinical diagnosis and treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters-2015).

The prevalence of anaphylactic reactions in Europe and different subpopulations has been described in the literature with a relative variability observed. 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). In the US lifetime prevalence of an anaphylaxis event is up to 2%, with a mortality rate of approximately 1% (Kemp, 2007, Tang, 2009, Arnold, 2011).

The proposed indication for Eurneffy is 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. The recommended dose for patients ≥ 30 kg body weight is a single intranasal administration of 2.0 mg adrenaline which can be increased to a second dose in case of initial incomplete clinical response.

3.1.2. Available therapies and unmet medical need

Adrenaline is a non-specific adrenergic agonist that is the drug of choice for the treatment of severe allergic reactions and anaphylaxis, and its appropriate use in these circumstances is widely documented in the published literature. Its therapeutic efficacy comes from its direct agonism of α and β adrenergic receptors leading to a reversal of the pathological response to the histamine cascade. Adrenaline also effectively reverses the symptoms of rhinitis, urticaria, bronchospasm, and hypotension due to its pharmacological antagonist properties on smooth muscles, blood vessels, and other tissues.

Commercially available adrenaline autoinjectors are the current out-of-hospital practice standard of care to all patients having experienced anaphylactic reactions or at risk of anaphylaxis. When properly used, these devices can allow for early administration of adrenaline to stop or reduce the intensity of the systemic allergic reaction before refractory anaphylaxis develops.

There have been reports related to safety due to overdose, with IV adrenaline inducing rapid cardiovascular changes, and inadequate dilution (Pumphrey-2000, Andre-2019, Ring-2018). IV administration is only recommended for the treatment of severe events, including hypotension, under careful clinical monitoring (Brown-1998, Simons- 2010b, Wood-2013, Ring-2018, Lieberman-2015).

Published guidelines based on extensive clinical evidence support the efficacy and safety of IM administration of adrenaline at a dose of 0.01 mg/kg (maximum of 0.5 mg), or 0.15 mg (15 kg to 30 kg children) and 0.3 mg up to 0.5 mg in adults. Administration should be given without delay at the onset of symptoms related to a systemic allergic reaction (Pumphrey-2000) to effectively stop the allergic reaction.

Subcutaneous (SC) administration has been used, however literature data suggest that IM administration, including EpiPen, in the vastus lateralis muscle of the thigh produces a more rapid rate of increase in adrenaline plasma levels than SC or IM administration in the deltoid muscle of the arm.

3.1.3. Main clinical studies

The clinical development programme for adrenaline (ARS-1, Eurneffy) consists of clinical pharmacology studies conducted in healthy subjects and in allergic patients with chronic rhinitis.

The pivotal data supporting the indication consist of data from four cross-over Phase I PK/PD trials (EPI 15,16,17,10) in healthy volunteers and rhinitis patients comparing PK and PD parameters between Eurneffy 2 mg intranasal spray and several marketed epinephrine injections, i.e., Epinephrine 0.3 mg and 0.5 mg IM and EpiPen 0.3 mg IM. Treatments were dosed once or twice.

EPI18 assessed PK and PD parameters after the administration of a repeat dose of Eurneffy intranasally in patients with Nasal Allergen Challenge (NAC) compared with epinephrine IM at a dose of 0.3 mg (in normal conditions and in patients with NAC).

Adult data:

Studies EPI 15, EPI 16, and EPI 17 were designed to assess the comparative bioavailability of a single and repeat dose of ARS-1 2 mg relative to single IM doses of adrenaline via needle/syringe and/or AAI without carryover effect.

EPI 15 study assessed the effects of single and repeat (twice) dosing of Eurneffy 2 mg in adult healthy volunteers compared to 0.3 mg IM injection and 0.3 mg EpiPen single and repeat (twice).

EPI 16 Study compared the effects of administration of Eurneffy 2 mg in normal nasal conditions and during induced rhinitis in allergy patients compared to 0.3 mg IM and 0.5 mg IM injection by HCP.

EPI 17 Study assessed pharmacokinetics, pharmacodynamics and dosing Errors After Self-Administration of Epinephrine with Intranasal ARS-1 as compared to IM injection in Subjects with Type I Allergy).

EPI 18 study assessed PK and PD parameters after the administration of a repeat dose of Eurneffy intranasally (twice to the same nostril and to the opposite nostril) in patients with NAC (Nasal Allergen Challenge) compared with epinephrine IM at a dose of 0.3 mg (in normal conditions and in patients with NAC).

Primary PK/PD studies in adults with a 1 mg dose of Eurneffy (EPI 03, EPI 04, EPI 07, EPI 12 [self-administration] and EPI JP01) as well as other pilot studies and are presented in this MAA as supportive information due to significant carry-over effect identified during previous assessment.

Paediatric data:

EPI 10 A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Paediatric Subjects with Systemic Allergies.

3.2. *Favourable effects*

Data to support this application are based on surrogate pharmacodynamic endpoints.

The PK data from the clinical pharmacology studies demonstrate that Eurneffy pharmacokinetic profile is similar to the profile of IM dosing by an EpiPen or adrenaline injected with syringe and needle.

Adrenaline is well absorbed from nasal cavity and appears to distribute quickly into tissues.

In the EPI10 study, it was demonstrated that epinephrine levels were dose proportional between 1.0 and 2.0 mg dosing in in paediatric allergy subjects >30 kg. The pharmacokinetic results demonstrates that in children >30 kg, Eurneffy 2 mg results in adrenaline absorption that is comparable to that observed in adults and expected based on PBAM. Eurneffy elicited SBP and PR responses comparable to what is observed in adults.

EPI 15 study showed that of Cmax values after ARS-1 2.0 mg administration was 38% lower compared to EpiPen and 26% higher compared to Epinephrine IM. Total exposure measured by AUC last, was 17% higher compared to EpiPen and 30% higher compared to Epinephrine IM injection.

After single nasal dose Eurneffy 2 mg, the increase in SBP and PR were within the range of adrenaline injection treatments (injection 0.3 mg IM injection using a needle-syringe product and/or an auto-injector product) during the first 10 minutes post-dose and higher through 60 minutes post-dose.

After two nasal doses of Eurneffy 2mg, the total exposure (AUC last) after (R-R) administration was 45% higher compared to EpiPen and 14% higher compared to (L/R) administration. The SBP and PR responses was similar to two intramuscular doses of adrenaline injection (using an autoinjector).

EPI17 study was performed in subjects with history of Type I Allergy. No changes between Cmax was observed after ARS-1 2.0 mg and Epinephrine 0.3 mg IM administration. AUC0-t was greater after ARS-1 2.0 mg administration compared to Epinephrine 0.3 mg IM. On the other hand, it was demonstrated that the PD of adrenaline following self-administered one nasal dose of Eurneffy 2 mg to one intramuscular dose of adrenaline injection 0.3 mg (using a needle-syringe product) was similar to that observed in the study EPI 15.

EPI 16, and EPI 18 were performed in subjects after single and double administration, respectively, in subjects with allergy patients (in normal nasal conditions and followed nasal challenge).

In EPI 16 study it was demonstrated that PK parameters (C_{max} and AUC_{last}) following single epinephrine administration (2.0 mg) in subjects with induced allergic rhinitis (nasal challenge) was lower than in subjects with normal nasal conditions and comparable with injectable form (IM Epinephrine 0.3 mg).

In EPI 18 study the PK and PD of epinephrine after two doses of Eurneffy 2.0 mg under allergic rhinitis conditions (NAC) were compared to two doses under normal conditions. Additionally, the study tested the administration of the second dose of the drug to the same and the opposite nostril. Under normal and under rhinitis conditions mean epinephrine concentrations were greater for Eurneffy relative to Epinephrine IM 0.3 mg (regardless of whether the drug was administered to the same or the opposite nostril). Similarly, C_{max} values of epinephrine (with ipsi- and contralateral dosing) were higher than following IM 0.3 mg. The mean SBP, DBP, and PR change were greater for Eurneffy relative to IM 0.3 mg, regardless of nasal condition and of whether the drug was administered to the same or the opposite nostril.

Haemodynamic data indicate that administration of Eurneffy resulting in rapid stimulation of α and β adrenergic receptors leads to increased heart rate (HR) and systolic blood pressure (SBP) as the surrogate markers for efficacy in treating systemic allergic reactions. The mean haemodynamic effects of ARS-1 were typically greater than that observed with epinephrine injection.

3.3. Uncertainties and limitations about favourable effects

The main uncertainty is related to absence of RCTs in target population demonstrating efficacy of IN adrenaline, including paediatric population. The efficacy is demonstrated by using pharmacodynamic surrogate markers. Overall, there was high intra-individual variability in observed PK and PD values that potentially might lead to lower efficacy in certain individuals.

Studies in a population of patients with experimentally induced rhinitis have shown that administration of I.N. adrenaline in this patient population results in a slightly different PK/PD profile than in a population of subjects without rhinitis. A faster absorption of epinephrine was observed in people with rhinitis, however, the total exposure as well as the C_{max} levels reached were lower than in normal conditions. At the same time, a more rapid decline in blood concentrations was observed.

In the pivotal studies, subjects who had prior nasal fractures, severe nasal injuries, polyps, polyposis, recurrent epistaxis [>1 nosebleed per month], deviated septum, etc. were excluded from the participating population. In clinical practice, ARS-1 will also be able to be used in this group of patients. Nonetheless, the conducted studies have shown that in a diverse population varying in nasal cavity size, including paediatric and adult populations of different genders (women and men), no significant differences in PD were observed. At present, a different response to the drug in the described population is not expected.

The PK and PD parameters of epinephrine following Eurneffy administration were studied in EPI 10 study and were also analysed using popPK and PBAM. Paediatric data indicate that the PK parameters fall within the range of approved injectable products. However, greater and more rapid exposures relative to IM adrenaline 0.3 mg and slightly lower exposures compared to EpiPen are expected.

3.4. Unfavourable effects

Overall, no major safety concerns have been identified in the performed studies.

There was higher incidence of nasal discomfort and headache in patients exposed to ARS-1 compared to Epinephrine IM or EpiPen. In EPI 16 study relevant differences in the incidence of TEAE were

observed between patients with and without rhinitis exposed to ARS-1. 25.0% and 2.9% of patients experienced a TEAE following ARS-1 2.0 mg and Epinephrine 0.5 mg IM, respectively. Of note 2.9% with rhinitis experienced a TEAE following ARS-1 2.0 mg administration. 13.9% and 5.6 % of subjects experienced headache and dizziness, respectively, following ARS-1 2.0 mg administration. Of note, there were no treatment-related TEAEs in patients in rhinitis following administration of ARS-1.

Following repeated administration of 2mg of Eurneffy, the most common adverse reactions were throat irritation (18.8%), headache (17.6%), nasal discomfort (12.9%), and feeling jittery (10.6%).

In EPI 10 study, followed ARS-1 administration the most frequent TAEs were nasal discomfort, rhinalgia, nasal mucosal disorder, nasal paraesthesia, oropharyngeal pain and rhinorrhoea. All (beside one - nasal discomfort following administration of ARS-1 2.0 mg) TEAEs were considered mild, and none were life-threatening or resulted in death. Overall, the safety profile of Eurneffy in the paediatric population with weight above 30 kgs was similar to the one observed in adults.

3.5. Uncertainties and limitations about unfavourable effects

No patient above 55 years of age were included in the studies. Clinical safety studies did not include individuals with history of heart conditions or arterial hypertension.

3.6. Effects Table

Table 96 Effects Table for Eurneffy

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (PD surrogate results)						
SBP (systolic blood pressure)	SBP E _{max} (mean)	mmHg	ARS-1 2.0 mg I.N. (N - 42) - 23.6	EpiPen 0.3 mg I.M. (N – 42) - 18.2 Adrenaline IM - 0.3 mg (N - 42) 11.9	ARS-1 resulted in the greatest increase from baseline SBP. The mean E _{max} and AUEC _{last} were significantly higher following ARS-1 relative to both EpiPen and IM Epinephrine.	Epi15
HR (heart rate)	HR E _{max} (mean)	bpm	ARS-1 2.0 mg I.N. (N - 42)- 17.3	EpiPen 0.3 mg I.M. (N – 42)– 12.3 Adrenaline IM - 0.3 mg (N - 42) 9.71	The E _{max} and AUEC _{last} were significantly higher following ARS-1 relative to EpiPen and IM Epinephrine.	Epi15

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
DBP (systolic blood pressure)	DBP Emax (mean)	Mm Hg	ARS-1 2.0 mg I.N. (N - 42) - 8.1	EpiPen 0.3 mg I.M. (N - 42) - 5.62 Adrenaline IM - 0.3 mg (N - 42) - 5.48	Mean DBP Emax values were significantly different following ARS-1 relative to IM Epinephrine, but not significantly different from EpiPen.	Epi15
SBP (systolic blood pressure)	SBP Emax (mean)	mmHg	ARS-1 2.0 mg I.N. (N - 36) - 20.8 ARS-1 2.0 mg I.N. (rhinitis) (N-33) - 15.0	Adrenaline IM 0.3 mg (N-31) - 13.4 Adrenaline IM 0.5 mg (N-32) - 15.2	There were no differences in overall effect between ARS-1 2.0 mg (normal nasal conditions) and either dose of IM Epinephrine. The first 30 minutes post-dose, ARS-1 2.0 mg with rhinitis resulted in a peak effect (Emax) that was comparable to both IM Epinephrine 0.3 mg and 0.5 mg.	Epi 16
HR (heart rate)	HR E _{max} (mean)	bpm	ARS-1 2.0 mg I.N. (N - 36) - 18.5 ARS-1 2.0 mg I.N. (rhinitis) (N-33) - 10.8	Adrenaline IM 0.3 mg (N-31) - 11.1 Adrenaline IM 0.5 mg (N-32) - 13.6	Overall effect (AUEClast) following ARS-1 2.0 mg (normal nasal conditions) was significantly greater relative to both doses of IM Epinephrine. Rhinitis resulted in lower peak and overall effect.	Epi 16
DBP (systolic blood pressure)	DBP Emax (mean)	Mm Hg	ARS-1 2.0 mg I.N. (N - 36) - 10.0 ARS-1 2.0 mg I.N. (rhinitis) (N-33) - 7.15	Adrenaline IM 0.3 mg (N-31) - 5.26 Adrenaline IM 0.5 mg (N-32) - 5.69	Overall effect (AUEClast) following ARS-1 2.0 mg (normal nasal conditions) was greater relative to IM Epinephrine 0.3 mg, but not IM Epinephrine 0.5 mg. Rhinitis did not have a significant impact on any DBP PD parameters.	Epi 16
SBP (systolic blood pressure)	SBP Emax (mean)	mmHg	ARS-1 2.0 mg I.N. (N - 42) - 20.0	Adrenaline IM 0.3 mg (N-42) - 13.0	ARS-1 2.0 mg resulted in an increase of SBP that persisted throughout the 120-minute sampling period. Epinephrine 0.3 mg IM resulted in an initial increase of SBP that persisted for approximately 10-minutes post-dose, at which point SBP returned to baseline	Epi17

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
HR (heart rate)	HR E _{max} (mean)	bpm	ARS-1 2.0 mg I.N. (N - 42)– 13.0	Adrenaline IM 0.3 mg (N-42)–10.0	Both treatments resulted in an initial increase from baseline PR. This increase persisted throughout the sampling period following ARS-1 2.0 mg	Epi17
DBP (systolic blood pressure)	DBP E _{max} (mean)	Mm Hg	ARS-1 2.0 mg I.N. (N - 42)– 9.0	Adrenaline IM 0.3 mg (N-42)– 8.0	Both treatments resulted in an initial increase from baseline DBP, with ARS-1 2.0 mg resulting in a more pronounced increase. By the 10-minute timepoint, both treatments resulted in a return to baseline	Epi 17
SBP (systolic blood pressure)	SBP E _{max} (mean)	mmHg	ARS-1 0.65 mg (n-11)– 12.25 ARS-1 -1.0 mg (n-25)– 8.23 ARS-1 -2.0 mg (n-16)– 11.9 Age of subjects - 4 and <18 years	x	ARS-1 0.65 mg ARS-1 -1.0 mg ARS-1 -2.0 mg The mean E _{max} (mmHg) following the administration of ARS-1 was comparable in all analysed groups	EPI10
HR (heart rate)	HR E _{max} (mean)	bpm	ARS-1 0.65 mg (n-11)– 17.7 ARS-1 -1.0 mg (n-25, subjects >30 kg)– 13.8 ARS-1 -2.0 mg (n-16, subjects >30 kg)– 15.4 Age of subjects - 4 and <18 years		ARS-1 0.65 mg ARS-1 -1.0 mg ARS-1 -2.0 mg The mean E _{max} (bpm) following the administration of ARS-1 was comparable in all analysed groups	EPI10

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
DBP (systolic blood pressure)	DBP Emax (mean)	Mm Hg	ARS-1 0.65 mg (n-11)– 10.6 ARS-1 -1.0 mg (n-25)– 4.92 ARS-1 -2.0 mg (n-16)– 7.0 Age of subjects - 4 and <18 years		ARS-1 0.65 mg ARS-1 -1.0 mg ARS-1 -2.0 mg The mean Emax (mmHg) following the administration of ARS-1 was comparable in all analysed groups	EPI10
Unfavourable Effects						
Nasal discomfort		%	ARS-1 2 mg - 9.7%	Epinephrine IM – 0% EpiPen – 0%	ARS-1 – N=134 Epinephrine IM – n=90 EpiPen – N=97	Pooled EPI15+ EPI16+ EPI17
Head-ache		%	ARS-1 2 mg – 6%	Epinephrine IM 0.3mg – 2.2% Epinephrine IM 0.5mg – 0% EpiPen 0.3mg – 1.8% EpiPen 0.6mg – 0%	ARS-1 – N=134 Epinephrine 0.3 mgIM – n=55 Epinephrine 0.5 mgIM – n=35 EpiPen 0.3mg– N=55 EpiPen 0.6mg– N=42	Pooled EPI15+ EPI16+ EPI17
Nasal discomfort	Subjects >30 kg b.w.	%	ARS-1 (2 mg) – 25%	ARS-1 (1 mg) – 11.5%	ARS-1 (1mg)– N=26 ARS-1 (2mg) – N=16	EPI-10
Intra-nasal paraesthesia	Subjects >30 kg b.w.	%	ARS-1 (2 mg) – 25%	ARS-1 (1 mg) – 0%	ARS-1 (1mg)– N=26 ARS-1 (2mg) – N=16	EPI-10
Sneezing	Subjects >30 kg b.w.	%	ARS-1 (2 mg) – 18.8%	ARS-1 (1 mg) – 7.7%	ARS-1 (1mg)– N=26 ARS-1 (2mg) – N=16	EPI-10

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Fatigue	Subjects >30 kg b.w.	%	ARS-1 (2 mg) – 12.5%	ARS-1 (1 mg) – 0%	ARS-1 (1mg)– N=26 ARS-1 (2mg) – N=16	EPI-10
Feeling jittery	Subjects >30 kg b.w.	%	ARS-1 (2 mg) – 12.5%	ARS-1 (1 mg) – 0%	ARS-1 (1mg)– N=26 ARS-1 (2mg) – N=16	EPI-10

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The clinical pharmacology programme includes analysis of PK and PD parameters in healthy subjects followed single or double administration, including subjects with induced allergic rhinitis as well as paediatric subjects as studies in the target population would be considered unethical.

Efficacy and safety data from clinical trials are based on surrogate validated pharmacodynamic endpoints. The applicant utilised haemodynamic endpoints (blood pressure (systolic and diastolic) and heart rate) as surrogate markers predictive of clinical efficacy through activation of α - and β -adrenergic receptors.

The applicant conducted a GLP pharmacokinetics study to evaluate the pharmacokinetics of ARS-1 after administration with and without anaphylaxis conditions using Beagle dogs. More pronounced absorption of intranasal epinephrine was reported in animals with anaphylaxis at earlier timepoints compared to animals without anaphylaxis, suggesting that anaphylaxis increases the rate of epinephrine absorption. The provided non-clinical pharmacokinetic data show that intranasal ARS-1 can be administered during anaphylaxis and the pharmacokinetic parameters are not impaired during anaphylaxis event.

A comparison of PD responses following ARS-1 administrations (once or twice) was also performed. In addition, the changes in the PD of ARS-1 were also assessed following injections in subjects with induced rhinitis, including two consecutive injections of the drug into the same nostril as well as into two different nostrils.

The pivotal clinical pharmacology studies conducted with Eurneffy (EPI 15, EPI 16, EPI 17, EPI 10 and EPI 18) (as well as supportive studies) demonstrate the efficacy and safety of adrenaline by the nasal route of administration. The PK data from the clinical pharmacology studies demonstrate that Eurneffy has a pharmacokinetic profile similar to the PK profile of IM dosing by an EpiPen or adrenaline injected with syringe and needle.

Main uncertainties pertain to intra-individual variability in observed PK and PD values that potentially might lead to lower efficacy in certain individuals, however overall PK and PD values remained within the range of other adrenaline injectors.

Haemodynamic data indicate that Eurneffy resulting in rapid stimulation of α and β adrenergic

receptors leads to increased heart rate (HR) and systolic blood pressure (SBP) as the surrogate markers for efficacy in treating systemic allergic reactions. The mean haemodynamic effects of ARS-1 were greater than that observed with epinephrine injection but remained within the range of other adrenaline tested products.

Overall, no major concerning safety issues have been identified in the performed studies, one event of syncope and hypotension were observed after single 2 mg ARS-1 administration. There were no cases of death in clinical studies. The most frequently occurring adverse reactions observed in clinical studies of Eurneffy 2 mg and after a second 2 mg dose included nasal discomfort, blood pressure increased, headache, feeling jittery, throat irritation and palpitations.

3.7.2. Balance of benefits and risks

The available PK/PD and safety data indicate that epinephrine administered intranasally may be a useful alternative to treatment with intramuscular epinephrine injections. The data support an authorisation for nasal administration for 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.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

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, efficacy and safety the CHMP considers by consensus that the benefit-risk balance of Eurneffy is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- Risk Management Plan (RMP)

The 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 (MS), the MAH must agree on the content and format of the educational materials, including communication media, distribution modalities with the National Competent Authority.

The following materials with key elements should be provided to minimise the risk of medication errors 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/Care givers information pack

Physician educational material:

- The Summary of Product Characteristics
- Training device
- Healthcare professionals training material (Training videos)
 - o training device to familiarise with use of Eurneffy device
 - o Indications in which Eurneffy should be used.
 - o Detailed description of the administration procedures of Eurneffy
 - o Importance of seeking medical assistance when using Eurneffy
 - o Relevant information on the Eurneffy single dose device and how to use it
 - o Instructions on correct handling of Eurneffy device.
 - o Need to always carry a second device in case of second dose would be required
 - o Need to seek emergency medical assistance
 - o Patient's preparation for the procedure and subsequent monitoring

- o Management of early signs and symptoms of selected safety concerns, namely severe allergic reaction/anaphylaxis

Patient/Care givers information pack:

- Patient information leaflet
- Training device provided by physician as needed
- Patient/care givers digital information brochure (training Videos):
 - o Indication in which Eurneffy should be used including anaphylaxis/severe allergic reaction action plan
 - o Information on how to identify a serious allergic reaction
 - o A description of the correct use of Eurneffy and the need to seek emergency medical assistance when using Eurneffy
 - o Detailed description of the modalities used for the self-administration of Eurneffy,
 - o A description of the best course of action if second dose is needed.
 - o Need to always carry a second device in case of second dose would be required
 - o 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.

These conditions fully reflect the advice received from the PRAC.

New active substance status

Based on the review of available data, it is considered that adrenaline is not a new active substance, as it is a constituent of medicinal products previously authorised within the European Union.