Amsterdam, 25 March 2021
EMA/204348/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Neffy

International non-proprietary name: epinephrine

Procedure No. EMEA/H/C/005584/0000

Note

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

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List of abbreviations

Al	Aluminium
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BDL	Below the limit of detection
BE	Bioequivalence
BET	Bacterial endotoxin test
BZK	Benzalkoium chloride
CEP	Certificate of Suitability of the Ph. Eur.
CFU	Colony Forming Unit
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical reference substance
DDM	Dodecylmaltoside
DMF	Drug Master File = Active Substance Master File
DSC	Differential Scanning Calorimetry
EC	European Community
ECD	Electrochemical detection
EDMF	European Drug Master File
EDTA	Edetate Disodium
EDQM	European Directorate for the Quality of Medicines
FID	Flame ionisation detection
FT-IR	Fourrier transmission infra red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
HDPE	High Density Polyethylene
ICH	International Conference on Harmonisation
IR	Infra-red
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass spectroscopy
NF	National Formulary
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PFS	Pre-filled syringe
PVC	Polyvinyl chloride
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
QOS	Quality Overall Summary
RH	Relative Humidity

RRt	Relative retention time
Rt	Retention time
RT	Room temperature
SPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeasts and Moulds Count
USP	United States Pharmacopoeia
UV	Ultra violet
XRPD	X-ray powder diffraction
WFI	Water for injection

Adrenaline and Epinephrine are used interchangeably in this report, as in the dossier.

N.B. - NOT ALL ABBREVIATIONS ARE USED IN THIS REPORT

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Neffy nasal spray solution in the emergency treatment of allergic reactions, including anaphylaxis, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Multidisciplinary Quality and Clinical

1. The inclusion of antimicrobial preservatives and antioxidants in a medicinal product needs special justification.

2. To support the paediatric indication, the formulation and the delivery device need to be suitable for the intended paediatric population.

Efficacy

3. The applicant has not provided sufficient support for the key assumption that absorption from the nasal mucosa is comparable in healthy volunteers and in patients with acute anaphylaxis.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

Questions to be posed to additional experts
Not applicable.

Inspection issues

GMP inspection(s)
Not applicable.

GCP inspection(s)
Not applicable.

New active substance status
Not applicable. Product contains known active substance.

Similarity with authorised orphan medicinal products
N/A

Derogation(s) from market exclusivity
N/A

2. Executive summary

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).

A recent consensus document has defined anaphylaxis as a 'serious allergic reaction that is rapid in onset and may cause death', and proposed diagnostic criteria for use in clinical care. By these criteria, a diagnosis of anaphylaxis can be made if there is involvement of the respiratory or cardiovascular systems during an allergic reaction; or if a less severe reaction occurs in the setting of previously diagnosed allergy and likely exposure to the relevant allergen.

2.1.2. Epidemiology and risk factors, screening tools/prevention

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).

Anaphylaxis is the most severe form of allergic reaction, or hypersensitivity reaction, is almost always unexpected, and can be life-threatening (Tang, 2009).

It is an acute life-threatening allergic reaction that is rapid in onset, may rapidly progress to cardiovascular and respiratory arrest, and generally treated with epinephrine immediately (Lieberman, 2015).

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).

Fatal outcome is rare, even for people with known venom or food allergy, fatal anaphylaxis constitutes less than 1% of total mortality risk (Turner, 2017). Estimated mortality 1.4%-6% from perioperative anaphylaxis with 2% morbidity of brain damage reported (Lieberman, 2015). Food allergens associated with 30% of fatal cases of anaphylaxis (Lieberman, 2010).

Major risk factors include:

- prior history of anaphylaxis
- atopy (personal and/or family history)
- exposure to possible triggers
- systemic mastocytosis
- monoclonal mast cell activating syndrome

2.1.3. Biologic features, aetiology and pathogenesis

The most common cause of the anaphylaxis is food, such as nuts, sea food, milk, eggs, seeds. Medications are the second most common cause of anaphylaxis, including antibiotics, NSAIDs, chemotherapy drugs, neuromuscular blocking agents, monoclonal antibodies, vaccines etc. Insect stings such as from bees, vespids or fire ants are also known to cause anaphylaxis. Exercise can be an immediate or co-trigger for anaphylaxis.

The mechanism responsible for most cases of human anaphylaxis involves immunoglobulin E (IgE). Possible alternative mechanisms remain incompletely understood. Environmental exposures and complex genetic factors may also have important roles.

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, potentially leading to cardiovascular collapse (Peavy, 2008).

2.1.4. Clinical presentation, diagnosis

Anaphylaxis is usually characterised by a defined exposure to a potential cause, followed usually within seconds to minutes but rarely up to hours later, by rapid onset, evolution, and ultimate resolution of symptoms and signs.

Anaphylaxis may be mild and resolve spontaneously due to endogenous production of compensatory mediators (eg, epinephrine, angiotensin II, endothelin, and others) or it may be severe and progress within minutes to respiratory or cardiovascular compromise and death. At the onset of an anaphylactic episode, it is not possible to predict severity of the reaction.

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.

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).

2.1.5. 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 is supported by both pharmacologic and physiologic experiments in multiple animal studies, as well as reports from clinical experiences. Its use has been adopted as the standard-of-care, first-line treatment of anaphylaxis (Lieberman-2015, Simons-2011).

While no controlled efficacy study has ever been conducted for the treatment of subjects at risk of anaphylaxis, adrenaline is the first line treatment for severe allergic reactions that may lead to anaphylaxis and is approved in all countries worldwide. Despite there have been no prospective controlled studies, there is no doubt of adrenaline's efficacy and it is considered the only first-line medication in the management of anaphylaxis (Campbell-2014, Kemp-2008, Lieberman-2015, Brown-2020). All other treatments of anaphylaxis, including discontinuation of any suspected allergen, H1 antihistamines such as diphenhydramine or chlorpheniramine; H2 antagonists such as cimetidine or ranitidine; inhaled beta-agonists such as albuterol are considered either supportive or second line, and therefore adjunctive in nature. Further, while some prospective studies for vaccines or other preventative medications to reduce the intensity of the reaction, these have either been preventative indications and not well controlled studies or have exclude people at risk of anaphylaxis given the ethical concerns in enrolling a population at risk of anaphylaxis in a controlled study.

2.2. About the product

Adrenaline is a sympathomimetic catecholamine with α and β adrenergic agonist activity.

Chemically, adrenaline has two correct INN names: (-)-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol; or 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl].

Neffy is a novel formulation of adrenaline that includes a proprietary functional excipient called dodecylmaltoside (DDM). Dodecylmaltoside is an approved excipient in the United States, formulated at low concentrations to improve the bioavailability of drugs administered by the intranasal (IN) route. DDM alters mucosal viscosity and membrane fluidity to loosen cell-cell junctions and enhance paracellular movement through the nasal epithelium, behaving as a permeation enhancer when combined with certain medications intended for intranasal administration.

The Neffy (adrenaline) nasal spray formulation was found to have an optimal bioavailability with the addition of DDM.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Given the clinical history of adrenaline, pharmacology data is derived from literature and additional nonclinical pharmacology studies were not conducted with Neffy. This approach is justified as per the CHMP Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95) and due to the fact that new studies are unlikely to further the scientific knowledge of the pharmacologic profile of adrenaline.

The pharmacokinetic profile of different formulations (two aqueous and one non-aqueous) of IN adrenaline with and without DDM were assessed in four non-GLP studies using rats and dogs. Single dose pharmacokinetic profiles of 3 different adrenaline formulations, with different DDM concentrations, were compared to commercially available IV and IM adrenalin in Sprague-Dawley male rats and to IV adrenalin in Beagle dogs. Pharmacokinetic profiles of 11 different adrenaline

formulations with and without DDM were compared in Sprague-Dawley rats. As a part of the pharmacokinetic study metabolism of adrenaline by cytochrome P450 enzymes was studied using Supersomes.

The applicant received Scientific advice from the CHMP on 26 April 2019 (EMEA/H/SA/4077/1/2019/SME/III). The Scientific advice pertained to non-clinical and clinical aspects of the dossier: *Acceptability of the overall strategy of the non-clinical programme*; *Appropriateness of PK/PD studies*; *Acceptability of the dose, primary endpoint, inclusion and exclusion criteria.*

- CHMP agreed to the non-clinical development consisting of non-clinical studies conducted with the Intravail A3 excipient and published literature for the active substance.
- CHMP stated that the risk of accidental eye exposure and associated potential safety concerns should be thoroughly discussed in the MAA, in the light of the characteristics of the associated device.
- CHMP agreed that the study design for the proposed EPI03 PK study in healthy volunteers is adequate to demonstrate comparative bioavailability and PD of IN administration of adrenaline with IM of adrenaline.
- For efficacy, CHMP considered that the most important parameters that need to be at least as high for ARS-1 as for the IM formulations are early partial AUCs, that should be calculated on each early blood samples until 20 minutes, i.e. starting at 2 minutes and every 2 minutes until 10 minutes. Tmax is also relevant and should be the same or smaller than with the IM or SC route for the same adrenaline dose, but cannot replace early partial AUCs.
- For safety, Cmax and total AUC are deemed the most relevant parameters, and a slightly higher Cmax and/or total AUC could be acceptable provided that the safety parameters and PD parameters do not indicate any trend toward a less favourable tolerance than the IM autoinjectors.
- CHMP strongly supported the continuous monitoring of heart rate and blood pressure up to 12 minutes post treatment as safety parameters in EPI-03.
- CHMP did not agree that the results of the EPI-04 study can be compared to the EPI-03 study to confirm that the exposures when subjects have nasal oedema and congestion are within the range of exposures observed from either IM or SC injections of adrenaline.
- Overall, CHMP agreed that the proposed amended programme is adequate for a MAA for the IN formulation, with the caveat that a warning will have to be mentioned that the efficacy and safety in allergic rhinitis patients and patients with nasal congestion have not been demonstrated, or with the restriction of the target population to patients without nasal congestion.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Manufacturer's Authorisations and/or GMP certificates have been provided for all manufacturing sites or are available in EudraGMP database. Presented GMP Certificate for Casen Recordati S.L. covers only primary packaging. However valid GMP certificate, with proper operation scope, is available in EudraGMP database. For manufacturing facility, reference to FDA database has been instead of manufacturing authorisation, not currently issued in the paper version. The presented confirmation is valid, however scope of authorised manufacturing is not fully clear. No document confirming manufacturing conditions for sprayer manufacturer has been presented.

For API manufacturing site valid QP declaration has been presented. QP declaration has been issued on behalf Casen Recordati S.L. - the manufacturing site responsible for batch release.

GLP

Pivotal safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity studies were performed according to OECD GLP principles. Quality assurance and GLP compliance statements were included in all GLP-conform study reports.

GCP

The Applicant submitted confirmation that all clinical studies (EPI 01, EPI 02, EPI 03, EPI 04, EPI 06, EPI 07 and EPI JP01) meet the ethical requirements of Directive 2001/20/EC.

The Investigators agreed to conduct the study in compliance with the study protocol, with the International Standard of Good Clinical Practice (ICH E6 - GCP) procedures and with all applicable government regulations.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

N/A

Accelerated assessment

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that neither a significant change in the efficacy of anaphylaxis treatment nor a substantial improvement in treatment safety was demonstrated.

Conditional marketing authorisation

N/A

Marketing authorisation under exceptional circumstances

N/A

Additional data exclusivity/ marketing protection

N/A

Orphan designation

N/A

Similarity with orphan medicinal products

N/A

Derogation(s) from orphan market exclusivity

N/A

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 P0432/2020 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-CI -00274 9 -PIP0 1- 19.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as nasal spray in aqueous solution containing 1.0 mg in 100 µL of adrenaline as active substance.

Other ingredients are: sodium chloride, dodecylmaltoside (DDM, Intravail A3), disodium ethylenediaminetetraacetic acid dihydrate, benzalkonium chloride, sodium metabisulphite, hydrochloric acid, sodium hydroxide and water for injection.

The product is available in Type I glass vials and closed with a grey butyl rubber stopper and then assembled into an Aptar 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.

3.1.2. Active Substance

General Information
The drug substance adrenaline in the application is the subject of EDQM Certificate of Suitability R1-CEP 2013-266-Rev 00.

No general information section has been included in the dossier.

Manufacture, process controls and characterisation
The drug product manufacturer performs release testing of the adrenaline drug substance received from API manufacturer prior to use.

Drug substance manufacturer has provided Certificate of Suitability: R1-CEP 2013-266-Rev 00.

The evaluation of the manufacturing route of the drug substance has been completed during the process of issuing the certificate of suitability.

According to the CEP, the quality of the drug substance is controlled by the current version of the Ph.Eur. monograph of adrenaline (No.2303), only if it is supplemented by the tests mentioned on the CEP:

Test for residual solvents by gas chromatography:

Methanol	not more than 2000 ppm

Test for elemental impurity by inductively coupled plasma mass spectrometry:

Palladium	not more than 1 ppm

The additional methods are annexed to the CEP. In the last step of the synthesis water is used as solvent.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Drug substance specification has been provided by the applicant in section 3.2.4.1

Specification parameter	Test method
Description	73.4009
Identification A (FTIR)	USP <197A> Ph. Eur. 2.2.24
Identification B (HPLC)	73.8486
Loss on drying	USP <731>
Residue on ignition	USP <281> Ph. Eur. 2.4.14
Assay (HPLC)	73.8486
Enantiomeric Purity - D-adrenaline (HPLC)	73.8488
Impurities (HPLC)	73.8487
Residual solvents (HS-GC)	USP <467> Ph. Eur. 2.4.24
Palladium (ICP MS)	73.015[1]
Microbial Limits Testing (MLT): Total Aerobic Microbial Count Total Combined Yeasts/Molds Count	USP <61> Ph. Eur. 2.6.12

Extensive description of analytical methods and their validation has been provided. Batch analysis of three drug substance batches has been provided, with their parameters within the specification limits. Other concerns have been raised towards the fact, that the Applicant follows other than European Pharmacopoeia methods, while the drug substance quality is covered by CEP.

There are no specific issues towards container closure or stability of the drug substance, as it is covered by CEP. Re-test period of the API is declared to be 60 months.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The applied product is adrenaline nasal spray is an aqueous solution filled in unit dose 400 µL Type I glass vials and closed with a grey butyl rubber stopper and then assembled into an Aptar 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. The 125 µL overfill ensures full volumetric delivery of 100 µL upon actuation. After a single actuation, the unit dose system is then considered depleted and discarded.

The qualitative composition of Neffy is presented in Table 1.

Table 1 Qualitative composition of Neffy

Ingredient	Reference	Function
Water for Injection (WFI)	USP/Ph.Eur.	Solvent
L-Adrenaline	USP/Ph.Eur.	Active
Dodecylmaltoside (DDM)	Internal Specifications	Permeation Enhancer
Benzalkonium Chloride	USP/NF/Ph.Eur.	Preservative
Sodium Chloride	USP/BP/Ph.Eur./JP	Tonicity Agent
Disodium EDTA Dihydrate	USP/Ph.Eur./JP/CHP	Chelating Agent
Sodium Metabisulfite	USP/Ph.Eur./JP/CHP	Antioxidant
Hydrochloric Acid (1N)	USP/Ph.Eur.	Acidifying Agent
0.1 N Hydrochloric Acid	USP/Ph.Eur.	pH Adjustment
0.1 N Sodium Hydroxide	USP/Ph.Eur.	pH Adjustment

Definition: Adj. = Adjust; EDTA = ethylenediaminetetraacetic acid

Formulation development

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

The active pharmaceutical ingredient (API) in ARS-1 is adrenaline which exists as white to nearly white microcrystalline powder or granules. The drug substance is sourced from one manufacturer.

Adrenaline is soluble in aqueous solutions of mineral acids and slightly acidic water (pH 4.0); very slightly soluble in pH 7.0 water, ethanol (96%) and methanol, and practically insoluble in acetone, chloroform, methylene chloride, and ether. It is a crystalline substance. Its solubility in the formulation is a critical quality attribute (CQA). As the drug product is a true solution, and the drug substance is readily soluble in the formulation, particle size is not a critical parameter. In addition it has been confirmed that API batches are of the same polymorphic form.

Forced degradation studies have been conducted with adrenaline drug substance. It was found that adrenaline is a relatively unstable compound and is susceptible to decomposition in the solid and aqueous states which must be taken in account during the pharmaceutical development of the nasal product. The drug product was developed using the QbD approach. A quality target product profile (QTPP) was established; from the QTPP the drug product Critical Quality Attributes (CQAs) were identified. A risk assessment has been provided for drug substance and formulation attributes, but no Design of Experiments (DoE) studies are presented and no design space is claimed.

The comprehensive formulation development is provided, which is supported by clinical development.

The selection of excipients was based on approved adrenaline injection products as well as nasal spray products developed utilising DDM as a permeation enhancer. DDM has been used as a permeation enhancer in products for nasal administration approved in the US at the same concentration. DDM is considered by the applicant as novel excipient in EU. The applicant has stated that no unexpected loss in assay or significant increases in degradants indicative of an incompatibility was observed at room temperature, accelerated storage conditions and forced degradation conditions. However, no such data have been presented. An additional problem is connected with use of Sodium metabisulfite (SMB) as

an antioxidant, as SMB is known to react with adrenaline resulting in impurity adrenaline sulfonic acid (Ph. Eur. Impurity F). The main problem is use of preservative – benzalkonium chloride, as the drug product is single dose one.

The development of ARS-1 adrenaline nasal spray was performed as the intranasal route offers a less invasive and lower risk approach to administration of adrenaline. 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 to develop a control strategy.

The 1.0 mg (10 mg/mL) formulation utilised in EPI-02 was identified as the optimal formulation for further clinical studies and was the basis for subsequent drug product development.

Issues related to the use of antioxidant (sodium metabisulfite) and antimicrobial preservative (benzalkonium chloride) are raised as major objections on formulation development. Furthermore, acceptability of formulation (choice of excipients, the palatability and sensation of the drug product on administration) and pharmaceutical form for paediatric population (particularly, selected device and intended delivered volume should be suitable for the size of nostrils of the target age group) should be discussed.

Manufacturing Process Development

Changes in the manufacturing process have been clearly summarised.

The critical process parameters for the ARS-1 manufacturing process have been established during development and scaleup of the process. The process has been validated at commercial scale.

Container Closure System Development

The spray pump, a commercially available unit, is an easy-to-use delivery system and is small enough to carry around in a pocket or purse. The target 125 µL (± 10 µL) fill volume of the 0.4 mL vial conforms to the specifications which ensures a reproducible 100 µL dose (as demonstrated by pump delivery as part of routine product release testing) and enables a single dose of drug to be filled and the Type I borosilicate clear glass stoppered vial provides an impermeable barrier to contaminant ingress from the environment.

The opaque polypropylene vial holder protects the product from light. This system enables the product to have an adequate shelf-life at room temperature.

The compatibility of the adrenaline drug product solution with the container closure (glass bottle and rubber stopper) was investigated by extractables and leachable substances studies. It was concluded there is no safety concern from any potential leachables from the container closure system in adrenaline nasal spray. Also an elemental impurities risk assessment for the product was performed in accordance with ICH Q3D Guideline – all results were below the control level (30% of PDE).

To confirm the suitability of the container closure system with drug product, a series of performance studies were performed. Reliability assessments were conducted to demonstrate the performance of ARS-1 adrenaline nasal spray 10mg/mL nasal spray device-drug combination product to ensure consistent and reproducible performance in a commercial environment with cGMP produced final products. Furthermore, assessments for ARS-1 adrenaline nasal spray 10mg/mL device-drug combination for robustness were conducted under extreme shipping conditions (vibration and dropping). Devices used for this assessment were pooled from the 3 registration batches. Obtained results demonstrated that dose is delivered reproducibly and robustly. ARS has tested over a substantial number ARS-1 adrenaline nasal sprayers in reliability, release and stability testing with only

one (1) vial identified as having a crack and not delivering the full dose. Root cause was investigated, and correction actions introduced.

However, this part of development has not been performed fully in line with guideline EMEA/CHMP/QWP/49313/2005 Corr. 'Guideline on the pharmaceutical quality of inhalation and nasal drug products'.

The microbiological properties of the product are controlled in accordance with the requirements of the Ph.Eur. and USP. Antimicrobial efficacy tests were conducted with benzalkonium chloride at 100%, 60%, 50%, 40% and 20% of the target concentration with all other formulation components kept the same. All tested concentrations of benzalkonium chloride 20%, 40%, 50%, 60%, and 100% of the target concentration comply with Ph.Eur. and USP acceptance criteria. However, in addition to the fact that use of a preservative system in single dose product is questionable, the amount of benzalkonium chloride is significant.

Adrenaline nasal spray is not reconstituted with any diluents.

Manufacture of the product and process controls

Batch size have been defined. Composition of production scale batch has been clearly presented.

Manufacturing process flowchart is presented. Manufacturing process and process control are generally described in sufficient level of detail but no information on holding time is given and equipment has not been specified. Therefore, only small amendments are needed. The manufacturing process has been validated on the production scale batches, but presented process validation data requires explanation, as only part of vials have been assembled and, in addition, one process validation batch was discarded due to problems during filling process. If these points are not adequately addressed, the robustness of the process validation could be disputed, leading to a Major Objection.

Benzalkonium chloride, sodium chloride, disodium edetate dihydrate, sodium metabisulfite, hydrochloric acid, sodium hydroxide and water for injections are included in the Ph.Eur. Their quality corresponds to appropriate Ph.Eur monographs.

A non-compendial excipient, defined by the applicant as novel excipient, Intravail A3 (dodecyl maltoside or DDM), is a proprietary functional excipient.

The analytical procedures and their validation for DDM, as well as appropriate analytical data have been also presented. Nevertheless, several questions are raised regarding specification, analytical methods and validation data of DDM applied by finished product manufacturer (all as OC).

No excipients of human or animal origin are used in the manufacture of adrenaline nasal spray.

Product specification, analytical procedures, batch analysis

Table 2 Release and shelf-life specifications

Specification parameter	Test method
Appearance of Container	73.7320
Appearance of Container – Device	
Color of Solution (L*a*b*)	73.8568
Identity (UV)	73.8418
Identity (HPLC)	73.8418
Adrenaline Assay (HPLC)	73.8418
Enantiomeric Purity (HPLC) - D-Adrenaline	73.8434
Dodecylmaltoside (DDM) Assay (HPLC)	73.8417
Benzalkonium Chloride Assay (UPLC)	73.8432

Disodium Edetate Assay (HPLC)	73.8431
Related Substances - Noradrenaline (Impurity B)	73.8418
Related Substances - Adrenalone (Impurity C)	
Related Substances - Adrenaline Sulfonic Acid (Impurity F)	
Impurities – Other Individual Unspecified	
Total Unspecified Impurities	
Total Impurities	
pH	73.4011
Osmolality	USP <785> Ph.Eur. 2.2.35
Uniformity of Dosage Units (as Uniformity of Mass) - Tier I / II	USP<905> Ph.Eur. 2.9.40
Dose Delivered	73.8507
Droplet Size Distribution of Spray	73.8509
Pump Delivery	73.8507
Spray Pattern	73.8508
Actuation Force	73.8509
Particulate Matter	USP<788> Ph.Eur. 2.9.19 (Method 2)
Microbial Limits Testing (MLT): Total Aerobic Microbial Count	USP <61>/<62>/<60> Ph.Eur. 2.6.12 / 2.6.13
Total Combined Yeasts/Molds Count	
E. coli	
S. aureus	
P. aeruginosa	
B. cepacia	

Specification parameter	Test method
Appearance of Container	73.7320
Appearance of Container – Device	
Color of Solution (L*a*b*)	73.8568
Adrenaline Assay (HPLC)	73.8418
Enantiomeric Purity (HPLC) - D-Adrenaline	73.8434
Dodecylmaltoside (DDM) Assay (HPLC)	73.8417
Benzalkonium Chloride Assay (UPLC)	73.8432
Disodium Edetate Assay (HPLC)	73.8431
Related Substances - Noradrenaline (Impurity B)	73.8418
Related Substances - Adrenalone (Impurity C)	
Related Substances - Adrenaline Sulfonic Acid (Impurity F)	
Impurities – Other Individual Unspecified	
Total Unspecified Impurities	
Total Impurities	
pH	73.4011

Osmolality	USP <785> Ph.Eur. 2.2.35
Uniformity of Dosage Units (as Uniformity of Mass) - Tier I / II	USP<905> Ph.Eur. 2.9.40
Dose Delivered	73.8507
Droplet Size Distribution of Spray	73.8509
Pump Delivery	73.8507
Spray Pattern	73.8508
Actuation Force	73.8509
Particulate Matter	USP<788> Ph.Eur. 2.9.19 (Method 2)
Microbial Limits Testing (MLT): Total Aerobic Microbial Count	USP <61>/<62>/<60> Ph.Eur. 2.6.12 / 2.6.13
Total Combined Yeasts/Molds Count	
E. coli	
S. aureus	
P. aeruginosa	
B. cepacia	

The limits of specification in general comply with the ones reported in section 3.2.P.5.4 and 3.2.P.8. However, there are some issues that needs to be addressed concerning product description, related substances, and excipient control. The proposed finished specifications cannot be accepted at this stage since several questions are raised.

Since the amendments in drug product specification limits are considered necessary, the respective batch analysis data demonstrating compliance with the revised release specification are requested. A discussion on mutagenic impurities in line with ICH M7 has not been provided and it has been requested.

Analytical procedures

Summaries of the analytical methods used to assess the quality of the adrenaline nasal spray finished product are provided in Module 3, Section 3.2.P.5.2.Appearance of the assembled device of the adrenaline nasal spray product is evaluated prior to the visual assessment of the individual components. Colour of solution for adrenaline nasal spray is determined by measurement of sample solutions using a colorimeter. Confirmation of identity of adrenaline drug substance is accomplished by measuring the ultraviolet (UV) absorption spectra of the test solution and a standard solution utilizing a photodiode array (PDA) detector. Confirmation of identity of the adrenaline drug substance in a sample is accomplished by HPLC method. The procedure for the identification and determination of assay and related substances of adrenaline in adrenaline nasal spray utilises Reversed Phase High Performance Liquid Chromatography (RP-HPLC) coupled with ultraviolet (UV) detection. The determination of enantiomeric purity of the active L-(-)-Epinephrine in adrenaline nasal spray by reversed-phase HPLC coupled with UV detection.

<u>DODECYLMALTOSIDE (DDM) ASSAY (HPLC)</u>

This method provides a procedure for the determination of Assay of n-Dodecyl-β-D-Maltoside (DDM) in Adrenaline Nasal Spray. The test method utilises reversed-phase HPLC equipped with a Hypersil BDS C18, 250 x 4.0 mm, 5 µm coupled with a Refractive Index Detector.

Determination of other formulation excipients is performed by HPLC.

BENZALKONIUM CHLORIDE ASSAY (UPLC)

This method provides a procedure for the identification and quantification of benzalkonium chloride (BZK) in Adrenaline Nasal Spray. This method utilises reverse phase chromatography, with ultraviolet detection at 209 nm.

DISODIUM EDETATE ASSAY (HPLC)

This method provides a procedure for assay of edetate disodium (EDTA) in Adrenaline Nasal Spray. The test method utilises reversed-phase HPLC coupled with Ultra-Violet (UV) detection at 258 nm. Procedure for the identification and determination of assay and related substances in adrenaline nasal spray using HPLC. A potentiometric determination of pH is performed using a suitable pH meter with electrode. _Osmolarity performed according to harmonised methods in USP and Ph. Eur._Uniformity of dosage units performed according to harmonised methods in USP and Ph. Eur. Droplet size distribution of spray is determined with units tested on a calibrated automated actuator that has been presented and locked with the specified parameters. Dose weight of adrenaline nasal spray in a unit dose container determined by automated actuation for any testing that requires the dose weight to be calculated, including, but not limited to, dose delivered, single actuation content, delivered dose uniformity, uniformity of dosage units, and deliverable volume. Droplet size distribution of adrenaline nasal spray in a unit dose container, as well as the actuation force of the unit dose vial holder is tested on a calibrated automated actuator that has been presented and locked with specific parameters and measurements are taken. Particulate matter is determined according to harmonised methods for method 2, microscopic particle count test in USP and Ph. Eur. Microbial limits testing is performed according to harmonised methods in USP and Ph. Eur.

Validation of the analytical methods has been provided in extensive detail, covering all required parameters.

The ICP-MS, used in the determination of elemental impurities in line with ICH Q3D, has been adequately validated.

The risk evaluation of Neffy nasal spray for potential presence of nitrosamine impurities has been performed. No risk of nitrosamine impurities has been identified.

It should be noted that since a score of questions were raised towards pharmaceutical development, depending on the applicant's responses, additional questions relating the control of the finished product may be raised at a later stage of the MAA.

Container closure

Adrenaline nasal spray solution is filled into primary packaging which consists of Type I borosilicate glass micro vials

The filled vials are then assembled into the nasal actuator supplied . The vial/stopper provides a fully closed container-closure system which is held within the nasal actuator and container holder with the rubber seal from the stopper intact.

The proposed type of container closure system is suitable for intended product. Compliance to Ph. Eur. is stated for vials and rubber stoppers.

Nevertheless, questions are raised regarding IR spectra of rubber plunger, methods descriptions of device functionality tests, and declarations of compliance of unit dose device components with relevant standards (e.g., pharmacopoeial).

Stability of the product

Stability of the drug product has been demonstrated on four clinical and registration batches.

Stability studies have also been performed on registration batches in inverted position.

The applicant has provided information on forced degradation, photostability, and extreme storage conditions.

Stability results on registration lots for more than 12 months at the long-term 25°C/60% RH storage condition and 6 months at accelerated 40°C/75% RH storage condition demonstrated acceptable stability. Additionally, extrapolation by statistical analysis at the room temperature (25°C/60% RH) condition demonstrates that there is more than a 95% confidence that the product will remain within specifications for at least a 24-month shelf life as summarised in Section 2.3.P.8.1.3.

Based on the stability data accrued to date, a shelf life of 24 months is proposed. Given that the product remained within specification, the proposed labelling will state the following:

This medicinal product does not require any special storage conditions.
Store in the original packaging to protect the nasal sprayer from damage.
Do not freeze. If accidentally frozen, allow to thaw at least 1 hour prior to use.

Since the content of the active substance varies by more than 5% of the initial value in the accelerated stability studies, additional interim stability studies should be performed and shelf life should be based on the outcome of stability testing at the intermediate condition, as well as at the long-term condition.

The photostability study is not sufficiently described to allow a definitive conclusion to be drawn on the suitability of commercial packaging for protection against light. The further data is requested.

The applicant is requested to reconsider the other statement “Store in the original packaging to protect the nasal sprayer from damage” because it not related to finished product stability.

Biosimilarity

Not applicable

Post approval change management protocol(s)

Not applicable

Adventitious agents

Not applicable

GMO

Not applicable

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

A major objection is raised in relation to the presence of preservative and antioxidant in the composition of single dose drug product and to use of the applied product in paediatric population.

The level of other information provided to support the application is generally satisfactory. A number of other concerns are raised in relation to general properties and control of the active substance as well as the drug product manufacturing, excipients, control of the drug product and stability.

3.2. Non clinical aspects

3.2.1. Pharmacology

No 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 primary 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 and due to the fact that new studies are unlikely to further address the scientific knowledge of the pharmacologic profile of adrenaline.

3.2.2. Pharmacokinetics

A reduced non-clinical programme concerning pharmacokinetics has been conducted by the applicant.

No distribution, excretion and pharmacokinetic drug interactions studies have been performed by the applicant. However, taking into account the clinical history of adrenaline the proposed non-clinical development programme concerning pharmacokinetics can be considered acceptable.

No discussion on the absorption of adrenaline from the nasal mucosa during acute anaphylaxis is provided. The applicant is requested to present what is known in the literature regarding nasal mucosal perfusion during anaphylaxis. Furthermore, a discussion on the possible effects on absorption of adrenaline and the clinical relevance is expected (OC).

DDM has been included in the formulation to increase the bioavailability through IN route and a concentration dependant positive effect would have been expected. 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 DDM administered intranasally in rats exhibited the greatest absorption amongst the three formulations. The results of Study WIL-285503 demonstrated that the optimal ARS-1 formulation containing DDM exhibited a relative bioavailability of 80.2% compared to adrenaline injection administered intramuscularly.

However, absorption results in male rats (study no: WIL-285501) indicate that the use of lower amounts of DDM decreases AUC, C_{max} and bioavailability comparing to an IN formulation in which DDM is not added. applicant should justify why DDM at lower concentrations exhibit such an effect (OC).

The applicant performed the study to compare the pharmacokinetic profile of 3 different formulations of ARS-1 in Beagle dogs. However, no information regarding validation of the method of analysis for the ARS-1 concentration in dog plasma could be identified in the dossier. The applicant is invited to clarify (OC).

The applicant has provided relative bioavailability results for the comparison with both IV and IM adrenaline although it is generally acceptable to non-IV formulations. Bioavailability relative to IV formulation should be referred to as the absolute bioavailability. Due to this discrepancy, it should be clarified how the bioavailability calculations were performed (OC).

The applicant has evaluated 11 different vehicles following IN adrenaline administration in male rats and concluded that formulations without DDM showed a poorer or slower absorption than with DDT. According to the pharmacokinetic results from study 2555-003, formulation without DDM (ADR-1-WOE) had a higher C_{max}, equal t_{max} and a higher $AUC_{0\text{-}240min}$ comparing to a formulation with DDM (ADR-1) which is not in line with the conclusion made. The applicant should comment on this discrepancy (OC).

Absorption studies have been performed only in male animals. The applicant should justify why female animals were not involved in the study (OC).

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-eq/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 BZK did not appear to be important components for absorption of adrenaline in the formulation.

An *in vitro* metabolism study was conducted to demonstrate that nasal mucosa does not significantly impact the metabolism of adrenaline. 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.

3.2.3. 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

Adrenaline exposures from ARS-1 are within the normal physiological range that occur e.g. during physical exercise or fear reaction in humans.

The applicant conducted a single dose toxicity study 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 0.8mg was not associated with any mortality or relevant clinical observations. However, statistically significant relative to body weight increase in brain weight was observed at Day 2. Moreover, absolute and relative increase in pituitary weight were noted at Day 15. The applicant is invited to present results of a microscopic evaluation of these organs (OC).

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, 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, reproductive and developmental toxicity data were provided from the literature. Adrenaline is an endogenous substance and is intended to be use in the acute treatment of severe allergic reactions. As per the CHMP Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95), nonclinical investigations are normally not required when there is sufficient well-documented clinical experience. This is considered acceptable for the current application, given the clinical use history of adrenaline as well as availability of clinical data obtained with ARS-1.

DDM

Dodecylmaltoside 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.

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 dodecyl maltoside 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 dodecyl maltoside, 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.

Based on results of the study aimed to investigate the potential toxicity of dodecyl maltoside 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 MTD via intravenous infusion was identified at 400 mg/kg based on occurrence of 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 considered to be 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 considered to be 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 albino Dunkin Hartley Guinea pigs and New Zealand White Rabbit, 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.

Calculated DDM safety margins based on a rat NOAEL of 80 mcg/day and a dog NOAEL of 330 mcg/day are 74-144 fold and 55-28 fold, respectively.

3.2.4. Ecotoxicity/environmental risk assessment

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

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

3.2.5. Discussion on non-clinical aspects

No pharmacology studies have been conducted by the applicant. However, the absence of the pharmacology data is justified due to the fact that new studies are unlikely to further address the scientific knowledge of the pharmacologic profile of adrenaline.

A reduced non-clinical programme concerning pharmacokinetics has been conducted by the applicant. No distribution, excretion and pharmacokinetic drug interactions studies have been performed by the applicant.

No discussion on the absorption of adrenaline from the nasal mucosa during acute anaphylaxis is provided. The applicant is requested to present what is known in the literature regarding nasal mucosal perfusion during anaphylaxis. Furthermore, a discussion on the possible effects on absorption of adrenaline and the clinical relevance is expected (OC).

Four studies have been performed to evaluate the pharmacokinetic profile of different formulations of ARS-1 (aqueous and non-aqueous) with and without DDM. The results of the studies showed that ARS-1 with DDM administered intranasally in rats exhibited the greatest absorption amongst the three formulations and exhibited a relative bioavailability of 80.2% compared to adrenaline injection administered intramuscularly.

However, absorption results in male rats (study no: WIL-285501) indicate that the use of lower amounts of DDM decreases AUC, C_{max} and bioavailability comparing to an IN formulation in which DDM is not added. The applicant should justify why DDM at lower concentrations exhibit such an effect (OC).

The applicant performed the study to compare the pharmacokinetic profile of 3 different formulations of ARS-1 in Beagle dogs. However, no information regarding validation of the method of analysis for the ARS-1 concentration in dog plasma could be identified in the dossier. The applicant is invited to clarify (OC).

The applicant has provided relative bioavailability results for the comparison with both IV and IM adrenaline although it is generally acceptable to non-IV formulations. Bioavailability relative to IV formulation should be referred to as the absolute bioavailability. Due to this discrepancy, it should be clarified how the bioavailability calculations were performed (OC).

The applicant has evaluated 11 different vehicles following IN adrenaline administration in male rats and concluded that formulations without DDM showed a poorer or slower absorption than with DDT. According to the pharmacokinetic results from study 2555-003, formulation without DDM (ADR-1-WOE) had a higher C_{max}, equal t_{max} and a higher $AUC_{0\text{-}240min}$ comparing to a formulation with DDM (ADR-1) which is not in line with the conclusion made. The applicant should comment on this discrepancy (OC).

Absorption studies have been performed only in male animals. The applicant should justify why female animals were not involved in the study (OC).

An *in vitro* metabolism study was conducted to demonstrate that nasal mucosa does not significantly impact the metabolism of adrenaline. The study showed that adrenaline was degraded not due to the CYP enzymes but due to the experimental system.

The single-dose toxicity study was conducted in rats, ocular tolerability study was performed in rabbits. Repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and development toxicity and local tolerance studies have been conducted to evaluate the toxicological profile of DDM.

A single dose toxicity study was conducted to evaluate the toxicity and toxicokinetics of ARS-1 in the rat model. Although no relevant clinical findings or any mortality were observed, statistically significant relative to body weight increase in brain weight was observed at Day 2. Moreover, absolute and relative increase in pituitary weight were noted at Day 15. A microscopic evaluation of these organs should be presented by the applicant (OC).

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.

No significant findings on ophthalmological examination were shown in ocular tolerability study.

Repeat-dose toxicology, genotoxicity, reproductive and developmental toxicity data were provided from the literature.

Since dodecylmaltoside is 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.

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 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. Dodecylmaltoside did not show any evidence of genotoxic activity or carcinogenicity.

3.2.6. Conclusion on non-clinical aspects

The pharmacokinetics and safety have been adequately discussed from a non-clinical perspective. However, several other concerns preclude a marketing authorisation at this time.

3.3. Clinical aspects

Table 3 Tabular overview of clinical studies

Type of Study	Study Identifier	Objective of the study	Study design and type of control	Test product (s): dose regimen	Total N	Patients	Study status
PK	EPI 01	To assess the comparative bioavailability of a pilot buffered formulation of epinephrine and EpiPen	Phase 1, randomised, open-label, single-dose, 2-treatment crossover study	ARS-1 IN, 0.3 mg EpiPen, 0.3 mg	12	Healthy subjects	Completed CSR
PK	EPI 02	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	3	Healthy subjects	Completed CSR
				Part 2: ARS-1 IN, 1 mg Epinephrine IM, 0.3 mg	12		
				Part 3 ARS-1 IN, 1 mg Epinephrine IM, 0.3 mg	12		

PK	EPI 03	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
PK	EPI 04	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
PK	EPI 06	To assess the comparative bioavailability of five concentrations of ARS-1 in healthy volunteers under fasted conditions	Phase 1, randomised, 5-period, 5-treatment crossover study	ARS-1 IN: 0.5 mg, single dose 0.65 mg, single dose 0.8 mg, single dose 1 mg, single dose 1.3 mg, single dose	12	Healthy subjects	Completed CSR
PK	EPI 07	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
PK	JP 01	To assess the PK and PD of epinephrine of ARS-1 dosed once to evaluate the impact of nasal oedema and congestion; comparative bioavailability with epinephrine IM and EpiPen	Phase 1, partially randomised, four-treatment study	ARS-1 IN, 1 mg Epinephrine IM, 0.3 mg EpiPen, 0.3 mg	36	Allergy Patients	Completed CSR
PK	EPI 09	To assess the PK and PD of epinephrine after self-administration of ARS-1,, EpiPen and a prefilled syringe (Symjepi) in subjects with Type I allergy conditions; evaluation of dosing errors	Phase 1, randomised, single-dose, 3-treatment, 3-period, 6 sequence crossover study	ARS-1 IN, 1 mg EpiPen 0.3 mg Symjepi IM, 0.3 mg	60 - 75	Allergy Patients	Ongoing Safety Interim Provided Abbreviations: CSR,

3.3.1. Pharmacokinetics

Introduction

ARS Pharmaceuticals investigated Neffy for the treatment of anaphylaxis as an alternative, more convenient to use out-of-hospital product than the current standard of care, adrenaline injection, which is administered intramuscularly or subcutaneously using an auto-injector at the time of occurrence of anaphylaxis.

Methods

- Analytical methods

The applicant has submitted validation report (1004490) for determination of epinephrine in human acidified K2-EDTA plasma by LC-MS-MS. 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.

Bioanalysis - Determination of Epinephrine in Human Acidified K2-EDTA Plasma by LC-MS-MS report (4006428) during EPI 02 study, was submitted by the applicant. Bioanalytical assessment was made according to the above (1004490) validation report. QC samples, standard curves, incurred samples reproducibility were acceptable. No restarts and reinjections were needed. No deviations was observed. One run, run2 was rejected due to the unacceptable QCs.

Bioanalysis - Determination of Epinephrine in Human Acidified K2-EDTA Plasma by LC-MS-MS report (4007994) during EPI 06 study, was submitted by the applicant. Bioanalytical assessment was made according to the above (1004490) validation report. 1156 were assessed. QC samples, standard curves, incurred samples reproducibility were acceptable. Four of the sixteen total runs within this study required at least one restart and/or reinjection. No deviations was observed. One run, run2, was rejected due to exceeding established extract stability.

Bioanalysis - Determination of Epinephrine in Human Acidified K2-EDTA Plasma by LC-MS-MS report (4008284) during EPI 07 study, was submitted by the applicant. Bioanalytical assessment was made according to the above (1004490) validation report. QC samples, standard curves, incurred samples reproducibility were acceptable. Eleven of the forty total runs within this study required at least one restart and/or reinjection. No deviations was observed. Two runs, run 4 and 38 was rejected due to the unacceptable QCs and was then successfully repeated at run 18 and 39, respectively.

Bioanalysis - Determination of Epinephrine in Human Acidified K2-EDTA Plasma by LC-MS-MS report (4009114) during EPI JP01 study, was submitted by the applicant. Bioanalytical assessment was made according to the above (1004490) validation report. 2860 samples were assessed. QC samples, standard curves, incurred samples reproducibility were acceptable. Seven of the 37 total runs within this study required at least one restart and/or reinjection. No deviations was observed. Two runs, run 27 and 30 was rejected due to the unacceptable QC and was then successfully repeated at run 34 and 35, respectively.

Bioanalysis reports from studies EPI 01, EPI 03 and EPI 04 could not be found in the dossier and should be provided by the applicant.

- Pharmacokinetic data analysis

EPI 03, EPI 04, EPI 06: The following PK parameters for epinephrine were calculated using non-compartmental analysis: Maximum plasma concentration (Cmax), Time to maximum plasma concentration (tmax), area under the curve (AUC) to the final time with a concentration equal to or greater than the lower limit of quantitation [AUC(0-t)], for the first 60 minutes [AUC(0-60min)], and

partial AUC (pAUC) values for the first 20 minutes after administration of study drug [AUC(0-10min), AUC(0-15min), AUC(0-20min)].

Individual PK parameters for epinephrine in plasma were calculated from concentration-time data using noncompartmental methods, as outlined below. The program was a validated Phoenix WinNonlin program (Certara Company), version 8.1 or higher.

EPI 01, 02: The following pharmacokinetic parameters for epinephrine were calculated using non-compartmental analysis: maximum plasma concentration (Cmax), time to Cmax (Tmax), area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation (AUC0–t) and to infinity (AUCinf), elimination rate constant (λz), and half-life (t½), and, for epinephrine only, clearance (CL/F) and volume of distribution (Vz/F) uncorrected for bioavailability (F). The database was created in accordance with US regulation 21 CFR Part 11 and was WinNonlin-compliant. The program used was a validated Phoenix WinNonlin program, version 6.4 (Certara Company).

EPI 07: The following PK parameters for epinephrine were calculated using noncompartmental analysis: Cmax, tmax, area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation [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)]. Pharmacokinetic plasma concentration-time data were analyzed using noncompartmental methods in Phoenix WinNonlin (Version 8.1 of higher, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight Knowledgebase Server (PKSO; Version 4.0.4 or higher, Certara, L.P.)

EPI JP01: The following PK parameters for epinephrine were calculated using noncompartmental analysis: Cmax, tmax, AUC0-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); calculated using the linear trapezoidal rule, allowing for extrapolation/interpolation to the upper time if applicable (depending on sample time deviations at the scheduled 2, 4, 6, etc. sample times and the time duration over which quantifiable concentrations are observed), AUC0-120: Area under the plasma concentration time curve from time zero to 120 min post dose; calculated using the linear trapezoidal rule, allowing for extrapolation/interpolation as necessary 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)], AUClast, Clast, Tlast, T100. Pharmacokinetic plasma concentration-time data were analyzed using noncompartmental methods in Phoenix WinNonlin (Version 8.1 or higher, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight Knowledgebase Server (PKSO; Version 4.0.4 or higher, Certara, L.P.).

CHMP comment
Non-compartmental analysis PK analyses were conducted using conventional software and methods. The methodology seems acceptable.

- Evaluation and Qualification of Models

Population PK Modeling (POP PK)

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 approved that AUC and Cmax are similar with adult values except for 1 mg in the 4-6 years old group for both Cmax and AUC and in the group 6-12 years of age for AUCs. Changes in the SBP and HR are similar for paediatric and adults population even for 1 mg dose for 4-6 years of age group.

Relative BA for Japanese patients are 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 is explained by the fact of smaller muscle weight and greater volume of distribution relative to the total muscle mass.

Physiologically Based Absorption Model Analysis

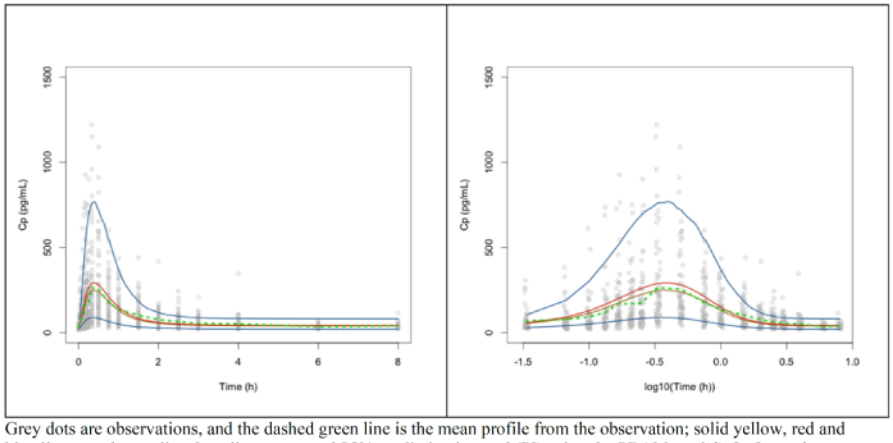
Results in Healthy Subjects

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

Mean concentrations for each individual trial and the predictions using the PBAM model in a virtual population of (n =1500) are displayed. Predicted and observed plasma AUC, Cmax and Tmax mean values and the predicted over observed ratios are shown in Table 4.

The model appropriately predicted the mean PK behavior in all the three studies as well as the variability. Moreover, as shown in the right panel of Figure 1 Comparison of epinephrine plasma profiles in healthy adults from study EPI-03 with the PBAM Model Predictions(log-X scale), the model adequately predicts the absorption behavior.

Figure 1 Comparison of epinephrine plasma profiles in healthy adults from study EPI-03 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% prediction interval (PI) using the PBAM model). Left panel: normal scale. Right panel: log-X

Table 4 Mean simulated and observed Cmax and AUC0-t and ratios, and median Tmax values for Neffy following a single 1 mg I.N. dose to healthy adult volunteers

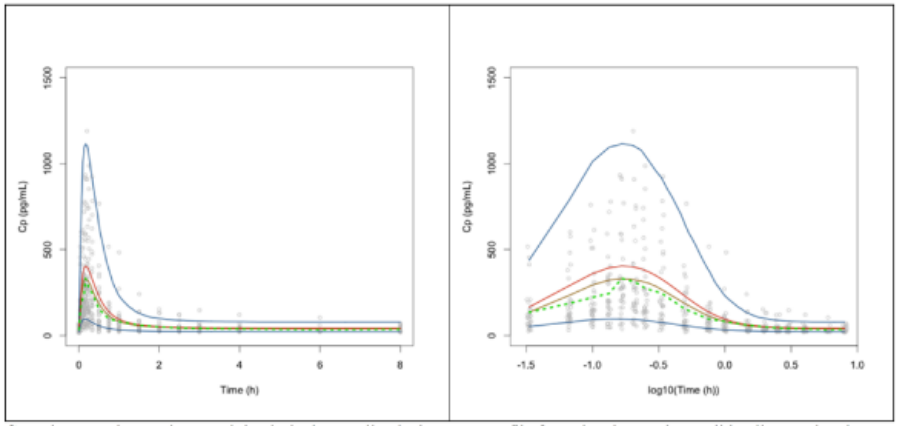
	Median Tmax (min)	Mean Cmax (pg/ml)	ratio	Mean AUC (pg.h/ml)	ratio
PBAM	23.7	296.8	-	574.0	-
EPI-03	20	352.7	0.84	475.4	1.21
EPI-04	20	285.5	1.04	446.5	1.29
EPI-07	20	328.9	0.9	488.6	1.17

Results in Subjects With Allergic Rhinitis

The simulated profiles were comparable to the clinical data and the predicted AUC, Cmax and Tmax 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 2. 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.

The model appropriately predicted the mean PK behavior in rhinitis patients as well as the variability. Moreover, as shown in the right panel of Figure 2 (log-X scale), the model adequately predicts the mean absorption behavior. Predicted and observed plasma AUC and Cmax mean values and Tmax median values as well as the predicted over observed ratios for AUC and Cmax are shown in Table 5.

Figure 2 Comparison of epinephrine plasma profiles in adults rhinitis patients from study EPI-04 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

Table 5 Mean simulated and observed Tmax, Cmax, and AUC0-t values and ratios for ARS-1 following a single 1 mg I.N. 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

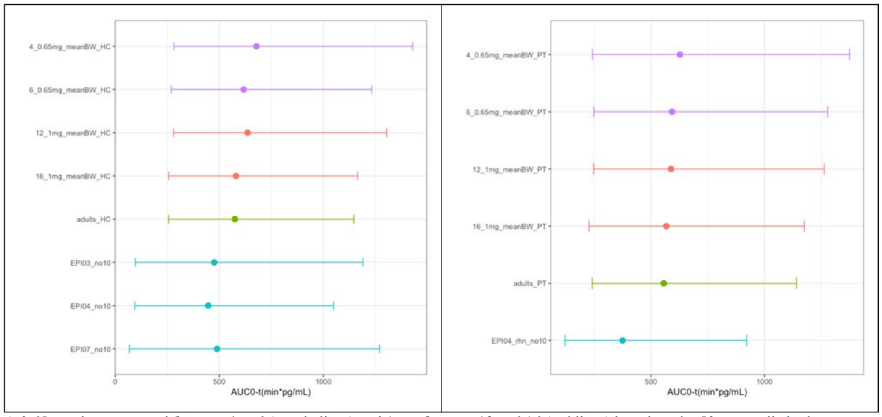
The paediatric PBAM model for ARS-1 was used to simulate epinephrine plasma profiles in paediatric patients of different ages (4 to < 17 years) receiving two different doses of ARS-1 depending on the body weight. A single 0.65 mg dose was used for children of 4- and 6-year-old children based on the median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

Table 6 Predicted Tmax, Cmax, and AUC for the Paediatric Model

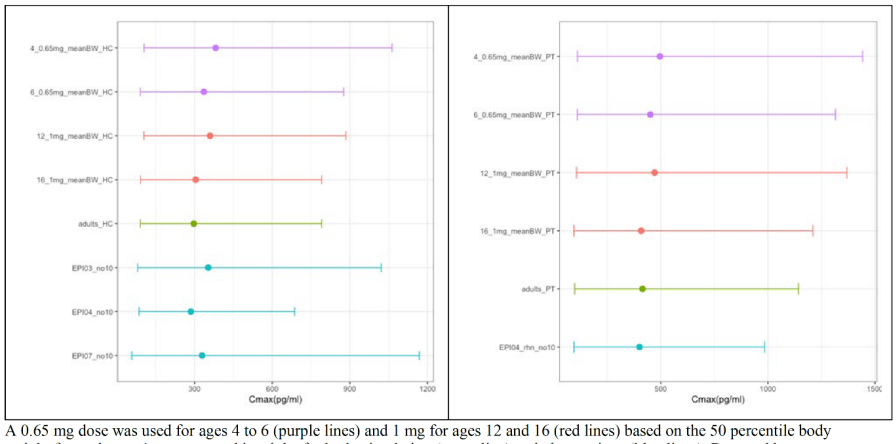
		Healthy Subjects				Rhinitis Patients			
		Mean	Median	Lower 95%CI	Upper 95%CI	Mean	Median	Lower 95%CI	Upper 95%CI
4 years 0.65 mg	T_{max} (min)	24.2	24.0	18.0	32.0	10.3	10.0	6.0	16.0
	C_{max} (pg/ml)	381.5	320.0	104.7	1063.0	496.0	397.8	111.4	1442.6
	AUC (pg.h/ml)	677.7	614.7	281.2	1428.4	627.5	561.7	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

Figure 3 Comparison of predicted AUC values in normal weight paediatric subjects of different ages and in adults using the PBAM model with the observed AUC in adults from the clinical trials.



A 0.65 mg dose was used for ages 4 to 6 (purple lines) and 1 mg for ages 12 and 16 (red lines) based on the 50 percentile body weight for each age; 1 mg was used in adults for both, simulation (green line) and observations (blue lines)). Dots and bars represent the mean and 95%CI, respectively. Left panel: simulations from adult healthy volunteers. Right panel: simulations from adult patients with allergic rhinitis.

Figure 4 Comparison of predicted Cmax values in normal weight paediatric subjects of different ages and in adults using the PBAM model with the observed Cmax in adults from the clinical trials.



A 0.65 mg dose was used for ages 4 to 6 (purple lines) and 1 mg for ages 12 and 16 (red lines) based on the 50 percentile body weight for each age; 1 mg was used in adults for both, simulation (green line) and observations (blue lines). Dots and bars represent the mean and 95%CI, respectively. Left panel: simulations from adult healthy volunteers. Right panel: simulations from adult patients with allergic rhinitis.

Paediatric Model – Extreme Scenarios

Figure 5 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)

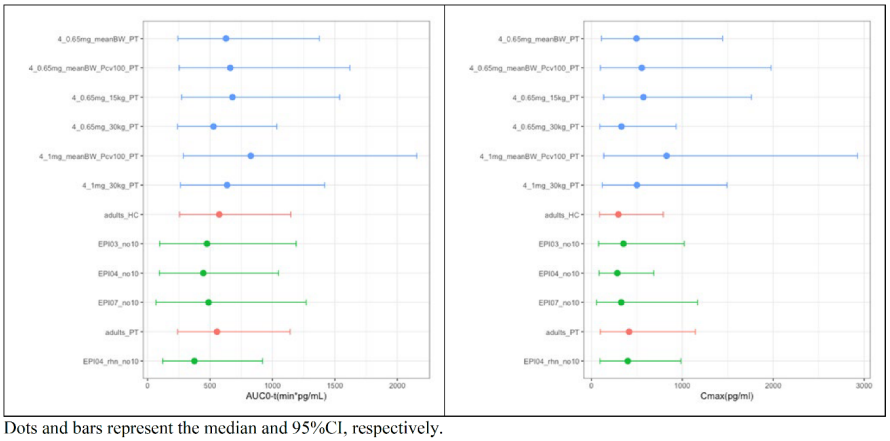
- 4 years old weighting 30kg and receiving the 0.65 mg dose (4_0.65mg_30kg_PT)

- 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 Cmax 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 raging study (EPI-02 Part I, 2,767 pg.h/mL and 2,470 pg/mL for mean AUC and Cmax, respectively). In study EPI-02 Part I ARS-1 exhibited a favorable 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 5 Comparison of predicted AUC (left panel) and Cmax (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.

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 as at the each of six years the physiological processes involved in epinephrine absorption from the nose and systemic PK are considered already mature, including the turbinates (i.e., main absorption site). Model predictions support the conclusion that the turbinates is the main physiological structure involved in the nasal absorption which is already mature in children older than 6 years, and therefore no significant differences are expected between this paediatric age group and adults. More uncertainty exists in children <6 years where additional scenarios were simulated to evaluate any possible safety concern due to the higher potential variability in the absorption in this age group. Simulation of the plasma concentration – time profiles after the proposed paediatric doses lead to overall plasma exposures within the expected values based on the adult clinical trials.

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 regardless of age, lending support for use in all paediatric age groups. Based on above considerations and the similar response predicted in children of different ages, including Cmax. Tmax 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.

CHMP comments

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 trail 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).

- Statistical methods

The standard statistical methods were used in the analysis of PK and PD data. The applied methods are considered acceptable for statistical analyses.

Absorption

- *Bioavailability*

EPI 01 - A Two-Period, Two-Treatment, Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine after Administration of ARS-1 and EpiPen to Healthy Volunteers.

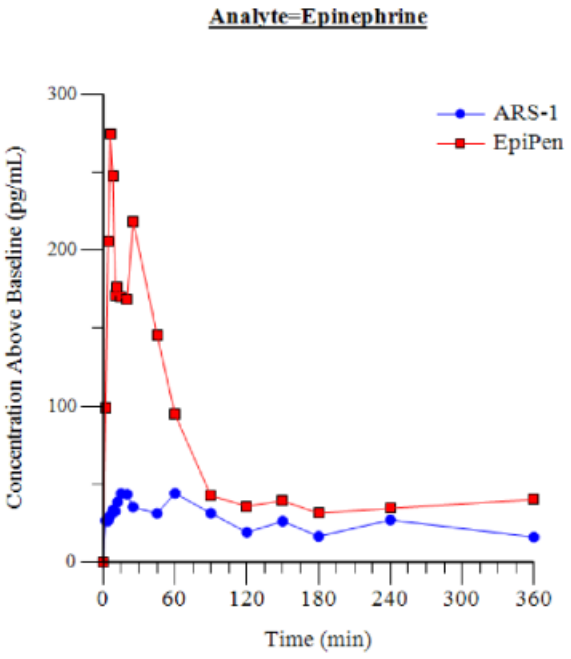
This was a Phase 1, open-label, randomised, single-dose, two-treatment, crossover study that consisted of a screening period, baseline period, and an open-label treatment period.

The primary objective of this study was to assess the comparative bioavailability of epinephrine after intranasal (IN) administration as ARS-1 and intramuscular (IM) administration as EpiPen (epinephrine injection) in healthy volunteers under fasted conditions. The secondary objective of this study was to evaluate the safety and tolerability of ARS-1 in healthy volunteers.

Pharmacokinetic results

The mean epinephrine concentration above baseline versus time curve is shown in Figure 6.

Figure 6 Mean Epinephrine Concentrations above Baseline (pg/mL) vs. Time (min) Sorted by Treatment (EPI 01).



Both the mean Cmax and AUC0–t of epinephrine were lower for ARS-1 relative to that of EpiPen: 83 versus 333 pg/mL and 8932 versus 19878 min*pg/mL, respectively. However, the Tmax values were similar (23 minutes for ARS-1 and 20 minutes for EpiPen).

Intranasal administration of epinephrine formulated as ARS-1 resulted in a bioavailability of approximately 25% based on Cmax and 35% based on AUC0-t compared to administration by the IM route with an EpiPen.

Table 7 ***Test for Bioequivalence (Cmax and AUC0–t) between ARS-1 (Test) and EpiPen (Reference)***

Analyte	Dependent	Ratio %Ref	CI 90% Lower	CI 90% Upper
Epinephrine	C_{max}	25	16	38
	AUC_{0-t}	35	20	60

CI = Confidence interval

Pharmacokinetic Conclusions

Intranasal administration of epinephrine using ARS-1 resulted in significantly lower exposure (Cmax and AUC0–t) of the parent compound epinephrine.

CHMP comments

The applicant has performed a two-period, two-treatment, randomised crossover study of the bioavailability and pharmacokinetics of epinephrine after administration of ARS-1 and EpiPen to healthy volunteers to assess the intranasal ARS-1 epinephrine bioequivalence with reference drug product - intramuscular (IM) administration as EpiPen. Twelve eligible subjects were randomised to receive 0.3 mg of ARS-1 or EpiPen. Samples were collected pre-dose and 360 minutes after dose regimen. Intranasal administration of epinephrine (0.3 mg ARS-1) resulted in lower exposure compared to reference drug product of epinephrine. Cmax and AUC0-t after intranasal ARS-1 compared to the IM EpiPen, was established to be 25 % and 45 %, respectively.

The formulation of ARS-1 used in this study was markedly different than the formulation used in subsequent pharmacokinetic (PK) studies. The dose was lower (0.3 mg) and the strong buffer (10 mM sodium acetate) used in the formulation for this pilot study has retarded drug absorption and gave a poor PK profile relative to the final ARS-1 formulation.

EPI 02. A Pilot Three-Treatment Dose Escalation Followed by a Two-Period, Two-Treatment, Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Epinephrine after Administration of ARS -1 and IM Epinephrine to Healthy Volunteers.

This was a Phase 1, dose-escalation followed by two 12-subject open-label, randomised, single-dose, two-treatment, two-period, crossover studies that consisted of a screening period, baseline period, and an open-label treatment period.

The primary objective of Part 1 of the study was to determine the optimal dose of ARS-1 to be used in Part 2 and Part 3 of the study. The primary objective of Part 2 and Part 3 of the study was to assess the comparative bioavailability of epinephrine after intranasal (IN) administration as ARS-1 and intramuscular (IM) administration as epinephrine injection in healthy volunteers under fasted conditions. The secondary objective of this study was to evaluate the safety and tolerability of ARS-1 in healthy volunteers.

The following pharmacokinetic parameters for epinephrine were calculated using non-compartmental analysis: Cmax, Tmax, AUC0–t, AUCinf, λz, t½, and, for epinephrine only, clearance (CL/F) and volume of distribution (Vz/F) uncorrected for bioavailability (F).

Pharmacokinetic Results:

Part 1

Mean plasma concentration-versus-time profiles of epinephrine sorted by dose are provided in Figure 7. There was a dose-proportional increase in the exposure of epinephrine after intranasal

administration of 0.5 mg, 1.0 mg, and 2.0 mg (Part 1). At the two highest doses tested the mean Tmax was 12–13 minutes.

Figure 7 Mean Epinephrine Concentrations (pg/mL) vs. Time Sorted by Dose (Linear Scale)

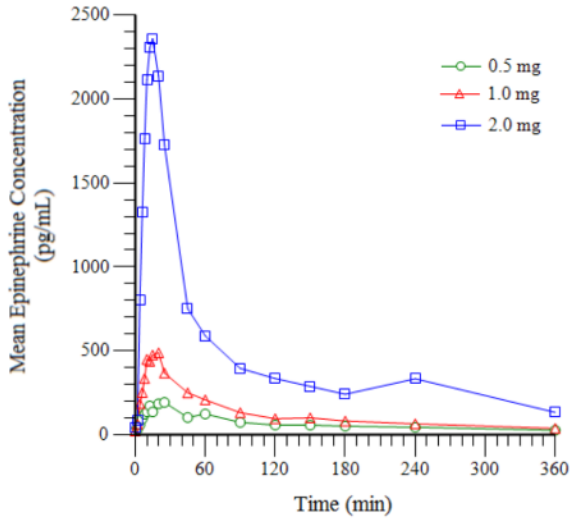


Table 8 Epinephrine Cmax and AUC0–t and Tmax for the Three Doses of ARS-1

	ARS-1 0.5 mg [N=3]			ARS-1 1.0 mg [N=3]			ARS-1 2.0 mg [N=3]		
Parameter	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/mL)	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/mL)	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/mL)
Mean	28.3	234	24000	12.7	586	43900	12.5	2470	166000
CV%	96.8	9.55	21.2	50.8	63	41.8	20	55.4	48.7

Part 2

Plasma Concentrations

Mean epinephrine concentration-versus-time curves for intramuscular (0.3 mg) and intranasal (1.0 mg) doses are shown in Figure 8. In Part 2, the pharmacokinetics of intranasal ARS-1 (1.0 mg) compared to intramuscular epinephrine injection (0.3 mg) was inferior to what was expected based on the data collected in Part 1. This discrepancy was attributable to error in the preparation of the ARS-1 formulation in the compounding pharmacy. Part 2 was repeated using two pH conditions of ARS-1 (A and B).

Figure 8 Mean Epinephrine Concentrations vs. Time Sorted Route (Linear Scale)

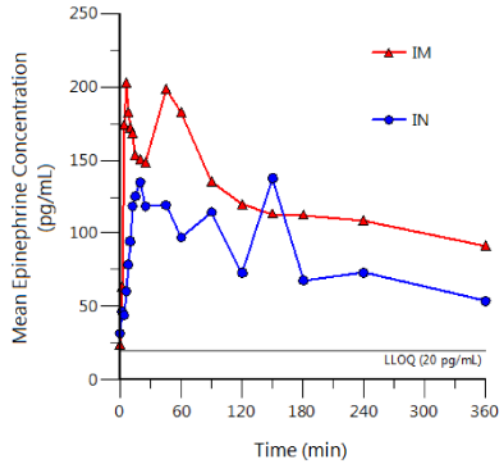


Table 9 Epinephrine Cmax and AUC0–t and Tmax without Baseline Correction.

Parameter	Intramuscular 0.3 mg [N=12]			ARS-1 Intranasal 1.0 mg [N=12]		
	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/ mL)	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/ mL)
Mean	-	301	43991	90	261	29225
CV%	-	61	17	86	56	41

Part 3

Plasma Concentrations

The mean epinephrine concentration-versus-time curves for the intranasal formulation and intramuscular route are shown in Figure 9 and Figure 10. In Part 3, intranasal administration of ARS-1 resulted in the same Tmax compared to 0.3 mg intramuscular epinephrine injection (geometric mean 25 minutes) and a comparable Cmax and AUC0–t. Moreover, comparable AUC values were observed through the first 20 minutes after administration of epinephrine. The range of plasma exposures for the intranasal route were less than the intramuscular dosing of epinephrine with CV% significantly lower for ARS-1. Intranasal ARS-1 provided a similar bioavailability profile to that of intramuscular injection.

Figure 9 Mean Epinephrine Concentrations vs. Time Sorted by Treatment (Linear Scale)

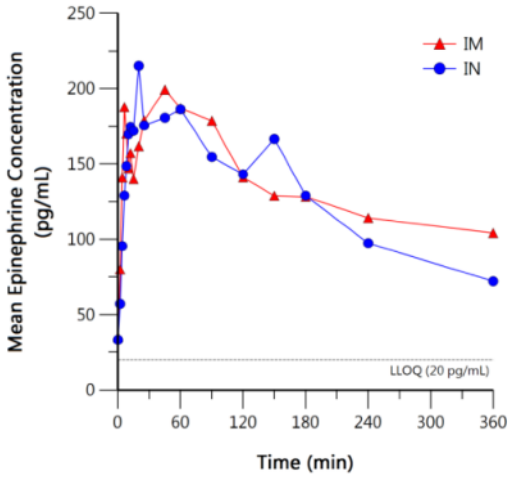


Figure 10 Mean Epinephrine Concentrations vs. Time Sorted by Treatment (Linear Scale): Initial 30 Minutes

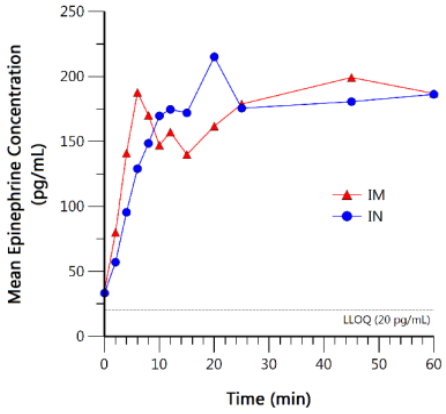


Table 10 Epinephrine Cmax, AUC0–t, and Tmax for the IN and IM Route

Parameter	ARS-1 Intranasal 1.0 mg (A/B)			Intramuscular 0.3 mg		
	C_{max} (pg/mL)	AUC_{0-t} (min*pg/mL)	T_{max} (min)	C_{max} (pg/mL)	AUC_{0-t} (min*pg/mL)	T_{max} (min)
N	12	12	12	12	12	12
Min	182	28102	6	64	16318	20
Max	484	70450	150	560	66792	61
Geo Mean	305	44221	25	236	45294	25
CV% Geo Mean	30	28	161	64	48	183

A comparison of the partial AUC out to 20 minutes after IN administration of ARS-1 with IM injection of epinephrine is presented in Table 11.

Table 11 Partial AUC-Time Data of ARS-1 Intranasal 1.0 mg (A/B) Compared to Intramuscular 0.3 mg Epinephrine Injection

Route	Mean (CV%) Partial AUC (min*pg/mL) out to:					
	2.5 min	5 min	7.5 min	10 min	15 min	20 min
IN	118 (51)	344 (69)	669 (74)	1060 (72)	1924 (68)	2892 (64)
IM	154 (75)	484 (72)	931 (73)	1335 (72)	2056 (67)	2811 (62)

Bioequivalence

Table 12 presents the bioequivalence data comparing the intranasal route (ARS-1) to the intramuscular route of administration of epinephrine.

Table 12 Intranasal Route vs. Intramuscular Administration

Dependent	Units	Ratio %Ref	CI 90 Lower	CI 90 Upper
C_{max}	pg/mL	129	90	185
AUC_{0-t}	min*pg/mL	98	78	122

CHMP comment

The applicant has performed a pilot, three-treatment dose escalation followed by a two-period, two-treatment, randomised crossover study of the bioavailability and pharmacokinetics of epinephrine after administration of ARS -1 and IM epinephrine to healthy volunteers.

First objective of the study was to determine optimal dose of IN ARS-1 for further Part 2 and Part 3 of the study. Single IN administration of ARS-1 of doses 0.5 mg, 1.0 mg, and 2.0 mg in healthy male volunteers resulted in dose proportional increase in plasma level of epinephrine between dose 1 and 2.

However, 2 mg of epinephrine caused no dose-proportional increase of Cmax and AUC0-t. The 1.0 mg of ARS-1 due to the optimal PK profile was chosen for following parts of the study.

The primary objectives of the Part 2 and 3 was to compare BA of epinephrine after intranasal ARS-1 and intramuscular injection. During Part 2 of the study PK of ARS-1 and IM epinephrine was inferior and this discrepancy was associated with an error during preparation of the ARS-1 formulation in the compounding pharmacy. The study was repeated.

Part 3 study researched the BQ between IN ARS-1 at dose 1.0 mg and IM injection of 0.3 mg of epinephrine. The Tmax was the same both formulation and was set to 12 minutes. Geometrical mean Cmax was 305 vs 236 pg/mL for IN vs IM administration respectively, and AUC0-t was 44,221 vs. 45,294 min*pg/mL for IN vs IM administration respectively.

In most studies, the Tmax for Neffy was 20 minutes. In the part 1 of the study (EPI-02), the time was 28.3, 12.7, 12.3 depending on the dose. The formulations used varied from the lowest concentration to the highest. The applicant is invited to comment on these changes in the Tmax in relation to the used dose. (OC)

The Cmax obtained for subsequent doses (0.5, 1.0 and 2.0 of ARS) is not proportionally related to the dose used. While this is not relevant in terms of the 1.0 mg dose selected, the substantial increase in the result for the higher dose is remarkable. The applicant is invited to comment this significant increase in Cmax after administration of higher doses. (OC)

- Bioequivalence

EPI 03. A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of ARS-1 and IM Epinephrine to Healthy Volunteers.

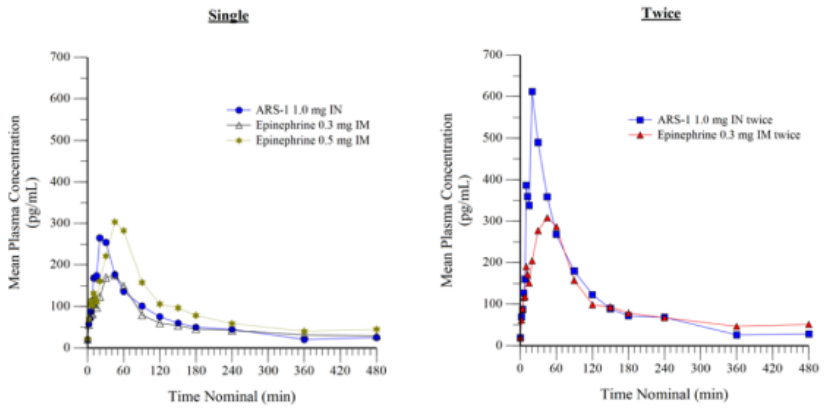
This was a Phase 1, randomised, single-dose, five-treatment, five-period, crossover study that consisted of a screening period, baseline period, and an open-label randomised treatment period. The bioavailability of both a single dose and repeat dose of IN ARS-1 was assessed as compared to a single and repeat dose of IM epinephrine injection.

Primary objective were: 1) To assess the comparative bioavailability of epinephrine after intranasal (IN) administration of ARS-1 with an IM injection of epinephrine after both one and two doses in healthy volunteers under fasted conditions; 2) To evaluate the comparative pharmacodynamic (PD) response based on heart rate (HR) determined from continuous electrocardiogram (ECG) and blood pressure (BP) determined from Ambulatory Blood Pressure Monitoring (ABPM) between administration of epinephrine by the IN and IM routes. Secondary objective was to evaluate the safety and tolerability of ARS-1 in healthy volunteers.

Pharmacokinetic results:

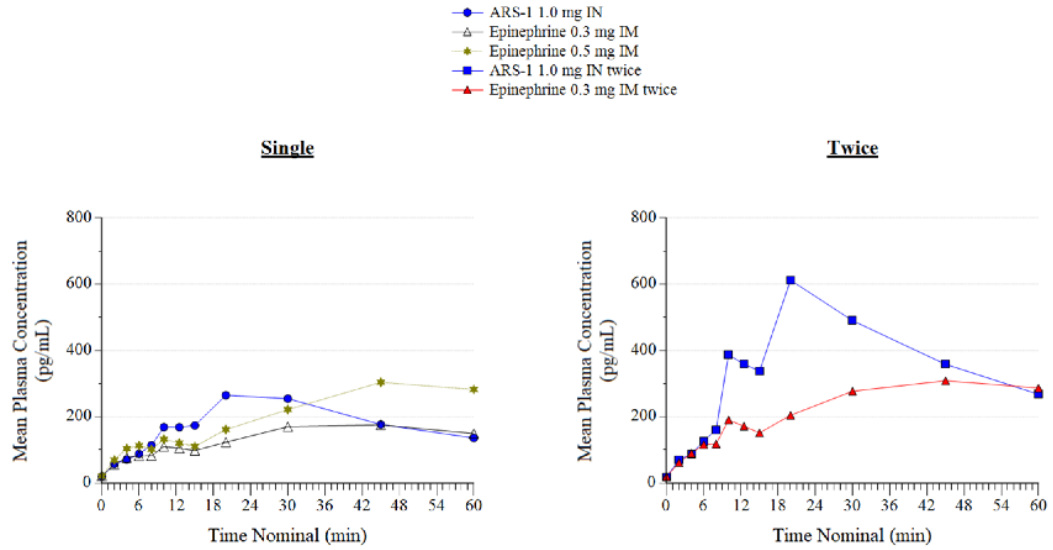
Mean plasma concentration versus time profiles of epinephrine, sorted by treatment and dosing regimen is presented in Figure 11.

Figure 11 Mean Plasma Concentration versus Time Profiles of Epinephrine, Sorted by Treatment and Dosing Regimen: Linear Scale



The initial first hour post dose mean plasma concentration-time profiles is presented in Figure 12.

Figure 12 Initial First Hour Post Dose: Mean Plasma Concentration versus Time Profiles of Epinephrine, Sorted by Treatment and Dosing Regimen: Linear Scale



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.

Cmax: Examination of the single-dose PK parameters revealed that administration of ARS-1 1.0 mg IN resulted in a higher Cmax value compared to Epinephrine 0.3 mg IM, with geometric mean values of 271 and 207 pg/mL, respectively, and a lower Cmax value compared to the Epinephrine 0.5 mg IM. Similar findings were found for the twice-dosing PK parameters with geometric mean values of 538 and 386 pg/mL for ARS-1 1.0 mg IN twice and Epinephrine 0.3 mg IM twice, respectively.

tmax: ARS-1 1.0 mg IN reached Cmax values sooner compared to the Epinephrine 0.3 mg IM and 0.5 mg IM with median tmax values of 20 and 45 minutes, respectively, for both the single and twice-dosing.

AUC0-t: The geometric mean AUC0-t values were similar between ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM whether administered as a single-dose (25,800 and 25,600 min·pg/mL for ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM, respectively) or dosed twice (43,000 and 45,300 min·pg/mL for ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM, respectively). The geometric mean AUC0-t value of Epinephrine 0.5 mg IM was in between single and twice dosings.

Partial AUC: In the vast majority of instances, the relative partial AUC values for ARS-1 1.0 mg IN were greater than those of the epinephrine 0.3 mg IM for both the single-dose and twice-dosed group. The partial AUC values for ARS-1 1.0 mg IN single-dose was similar to that of the epinephrine 0.5 mg IM.

Table 13 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

		Median	C_{max} (pg/mL)			$pAUC_{0-45}$ (min*pg/mL)			AUC_{0-t} (min*pg/mL)		
Treatment	N	t_{max} (minutes)	Mean (%CV)	Geo. mean (%CV)	Median	Mean (%CV)	Geo Mean (%CV)	Median	Mean	Geo. mean (%CV)	Median
ARS-1 1.0 mg IN	68	20.0	353 (75.4)	271 (85.9)	257	8640 (75.6)	6840 (76.7)	6750	30200 (59.4)	25800 (60.9)	23900
ARS-1 1.0 mg IN twice	70	20.0	739 (95.6)	538 94.2)	574	17400 (87.4)	13200 (86.2)	14000	52200 (68.6)	43000 (67.5)	43200
Epinephrine 0.3 mg IM	68	45.0	244 (58.4)	207 (62.9)	201	5840 (56.8)	4960 (65.9)	5150	27300 (39.9)	25600 (36.1)	24000
Epinephrine 0.3 mg IM, twice	70	45.0	436 (48.8)	386 (53.6)	386	9610 (59.4)	8160 (63.4)	8350	47500 (32.6)	45300 (31.1)	46300
Epinephrine 0.5 mg IM	69	45.0	378 (58.8)	327 (58.3)	311	8120 (65.4)	6790 (68.1)	6800	43800 (30.5)	41800 (30.9)	41700

Abbreviation: CV = coefficient of variation; Geo = geometric

Table 14 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	68	58.5 (83.9)	152 (90.2)	271 (87.5)	417 (87.9)	628 (86.7)	954 (84.8)	1280 (85.0)	2110 (84.1)	4160 (81.1)	6840 (76.7)	8870 (73.4)
ARS-1 1.0 mg IN Twice	70	69.1 (70.6)	185 (77.9)	347 (80.1)	565 (83.5)	984 (85.6)	1660 (89.1)	2340 (88.2)	4130 (88.8)	8200 (88.9)	13200 (86.2)	16900 (84.7)
Epinephrine 0.3 mg IM	68	57.6 (76.6)	152 (83.0)	268 (87.2)	389 (92.6)	531 (92.6)	725 (91.8)	911 (90.4)	1350 (83.4)	2640 (72.0)	4960 (65.9)	7210 (59.9)
Epinephrine 0.3 mg IM Twice	70	63.2 (85.4)	170 99.9)	307 (110)	459 (116)	691 (110)	1030 (105)	1340 (103)	2050 (93.1)	4170 (76.7)	8160 (63.4)	12400 (55.2)
Epinephrine 0.5 mg IM	69	62.1 (89.0)	165 (105)	291 (117)	474 (123)	594 (116)	841 (107)	1080 (101)	1640 (93.6)	3280 (82.3)	6790 (68.1)	10800 (59.9)

Comparative Bioavailability and Bioequivalence

Results of the comparative Cmax and AUCs of ARS-1 1.0 mg IN versus Epinephrine 0.3 mg IM (once and twice dosed) and epinephrine 0.5 mg IM calculated using total epinephrine concentrations are presented in Table 15, Table 16, and Table 17 respectively.

Table 15 Comparative Cmax and AUCs of ARS-1 1.0 mg IN.0 mg IN vs. Epinephrine 0.3 mg IM (Total Epinephrine Concentrations)

Calculated Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(C_{max})$	133	112	158
$Ln(AUC_{0-t})$	102	91	114
$Ln(AUC_{0-2min})$	103	87	122
$Ln(AUC_{0-4min})$	101	83	121
$Ln(AUC_{0-6min})$	102	84	123
$Ln(AUC_{0-8min})$	109	89	132
$Ln(AUC_{0-10min})$	120	98	146
$Ln(AUC_{0-12.5min})$	133	109	162
$Ln(AUC_{0-15min})$	142	117	173
$Ln(AUC_{0-20min})$	159	133	190
$Ln(AUC_{0-30min})$	161	137	190
$Ln(AUC_{0-45min})$	140	119	165
$Ln(AUC_{0-60min})$	125	107	146
$Ln(AUC_{60-360min})$	96	85	108

Test = ARS-1 1.0 mg IN.0 mg IN, Form Reference = Epinephrine 0.3 mg IM.

Table 16 Comparative Cmax and AUCs of ARS-1 1.0 mg IN vs. Epinephrine 0.3 mg IM Twice (Total Epinephrine Concentrations)

Calculated Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(C_{max})$	139	118	164
$Ln(AUC_{0-t})$	95	85	106
$Ln(AUC_{0-2min})$	109	94	128
$Ln(AUC_{0-4min})$	109	92	128
$Ln(AUC_{0-6min})$	113	95	134
$Ln(AUC_{0-8min})$	123	104	147
$Ln(AUC_{0-10min})$	143	121	168
$Ln(AUC_{0-12.5min})$	161	137	190
$Ln(AUC_{0-15min})$	175	149	207
$Ln(AUC_{0-20min})$	201	171	237
$Ln(AUC_{0-30min})$	197	167	232
$Ln(AUC_{0-45min})$	161	137	189
$Ln(AUC_{0-60min})$	136	117	158
$Ln(AUC_{60-360min})$	79	67	94

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

Table 17 Comparative Cmax and AUCs of ARS-1 1.0 mg IN vs. Epinephrine IM 0.5 mg (Total Epinephrine Concentrations)

Calculated Using Total Epinephrine Concentrations			
Dependent	**Ratio % Reference**	**Lower 90% CI**	**Upper 90% CI**
$Ln(C_{max})$	84	71	99
$Ln(AUC_{0-t})$	62	56	69
$Ln(AUC_{0-2min})$	94	81	110
$Ln(AUC_{0-4min})$	92	77	111
$Ln(AUC_{0-6min})$	93	77	114
$Ln(AUC_{0-8min})$	99	81	121
$Ln(AUC_{0-10min})$	106	87	131
$Ln(AUC_{0-12.5min})$	115	93	140
$Ln(AUC_{0-15min})$	120	98	147
$Ln(AUC_{0-20min})$	131	108	157
$Ln(AUC_{0-30min})$	129	108	153
$Ln(AUC_{0-45min})$	102	87	119
$Ln(AUC_{0-60min})$	83	71	96
$Ln(AUC_{60-360min})$	56	49	64

Test = ARS-1 1.0 mg IN, Form Reference = Epinephrine 0.5 mg IM.

Comparative Bioavailability: The relative bioavailability of the ARS-1 1.0 mg IN to that of the Epinephrine 0.3 mg IM resulted in a ratio % reference for Ln(AUC0-t/Dose) of 31% and 28%, calculated using the single-dose and twice-dosed data, respectively. These results demonstrate that administration of ARS-1 1.0 mg IN provide plasma exposures (AUC0-t) that are bioequivalent to

Epinephrine 0.3 mg IM given once (ratio 102%; 90% CI 91–114%) and twice (ratio 95%; 90% CI 85–106%).

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

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

Relative to epinephrine IM administration, administration of ASR-1 1.0 mg IN resulted in a faster time to an epinephrine plasma concentration of 100 pg/mL. The cumulative time that the epinephrine plasma concentrations were above 100 pg/mL was similar between ARS-1 1.0 mg IN and Epinephrine 0.3 mg IM, once or twice-dosed.

The mean time to reach 100 pg/mL was 10.7 minutes for ARS-1 1.0 mg IN and 7.22 minutes for ARS-1 1.0 mg IN twice. The mean times following IM epinephrine administration were 19.5 minutes for Epinephrine 0.3 mg IM, 12.3 minutes for Epinephrine 0.3 mg IM twice, and 15.2 minutes for Epinephrine 0.5 mg IM.

The mean time to above 100 pg/mL was 74.3 minutes for ARS-1 1 mg IN and 128 minutes for ARS- 1 1.0 mg IN twice. The mean times following IM epinephrine administration were 59.8 minutes for Epinephrine 0.3 mg IM, 137 minutes for Epinephrine 0.3 mg IM twice, and 119 minutes for Epinephrine 0.5 mg IM.

Following administration of ARS-1 1.0 mg IN, 60% of subjects reach the critical plasma concentration of 100 pg/mL. This number increased to 80% following administration of ARS-1 1.0 mg IN, twice. In contrast, 41% of subjects reached 100 pg/mL following administration of Epinephrine 0.3 mg IM. Sixty-nine percent and 52% of subjects reached 100 pg/mL following administration of Epinephrine 0.3 mg IM, twice, and Epinephrine 0.5 mg IM, respectively.

A higher proportion of subjects reached 100 pg/mL and 200 pg/mL plasma levels in the first 20 minutes following ARS-1 1.0 mg IN as compared to epinephrine IM. Compared to either the 0.3 mg or 0.5 mg epinephrine injections, a lower proportion of subjects failed to reach 200 pg/mL following administration of ARS-1.

CHMP comment

This was a Phase 1, randomised, single-dose, five treatment, five-period, crossover study. The bioavailability of both a single dose and repeat dose of ARS-1 1 mg IN was assessed as compared to a single and repeat dose of IM epinephrine injection. The intent of this study was to compare ARS-1 1 mg IN to Epinephrine 0.3 mg IM, with the expectation that these products would demonstrate comparable pharmacokinetics. Given that Epinephrine 0.5 mg IM is also approved for the treatment of severe allergic reactions and anaphylaxis, the 0.5 mg IM treatment arm as an additional safety comparator was also included.

The relative bioavailability of ARS-1 1 mg IN to that of 0.3 mg epinephrine IM injection resulted in a ratio % reference for Ln (AUC0-t/Dose) of 31% and 28%, calculated using the single dose and twice dosed data, respectively. The geometric mean AUC0-t values for ARS-1 1 mg IN and Epinephrine 0.3 mg IM demonstrated comparable bioavailability for both once and twice dosing. The tmax was significantly shorter, more rapid time to 100 pg/mL and greater partial AUC values over the initial hour post dose for ARS-1 1 mg IN compared to Epinephrine 0.3 mg IM, indicating a more rapid absorption of ARS-1 1 mg IN. The partial AUC values for 1 mg ARS-1 1 mg IN once were similar to those resulting from administration of Epinephrine 0.5 mg IM injection, which is an approved safe dose of epinephrine. The

geometric mean Cmax values for ARS-1 1 mg IN were higher than those of the Epinephrine 0.3 mg IM but were similar to that obtained from the approved 0.5 mg IM injection dose.

Intranasal administration of ARS-1 1 mg reached the epinephrine plasma concentration level of 100 pg/mL as fast, as the IM route of administration. The cumulative time the epinephrine plasma concentrations were above 100 pg/mL were similar for ARS-1 1 mg IN and Epinephrine 0.3 mg IM injection single or twice dosing. Based on the more rapid absorption with ARS-1 1 mg IN, a higher proportion of subjects reached 100 pg/mL and 200 pg/mL plasma levels with ARS-1 1 mg IN as compared to IM injection in the first 20 minutes. Compared to either the 0.3 mg or 0.5 mg epinephrine injections, a lower proportion of subjects failed to reach 200 pg/mL following administration of ARS-1 1 mg IN. These outcomes were consistent with both the total plasma concentration and with baseline corrected plasma values.

For single administration, adrenaline concentrations after I.M. and I.N. administration can be considered similar. However, for the second intranasal administration, the maximum levels obtained were significantly higher. Assuming that the effective level is 100 pg/mL, the observed 600 pg/mL after repeated intranasal administration of I.M. compared to 300 pg/mL after I.M. administration, appears to be an excessive level which raises safety concerns. The applicant is asked to comment on this issue. (OC)

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.

This was a Phase 1, single-dose, five-period study that consisted of a screening period, baseline period, and an open label treatment period. The first three treatments periods were a fully randomised in a crossover design with subjects randomised to receive ARS-1 1.0 mg IN in the left nostril, Epinephrine 0.3mg IM injection in the left anterolateral thigh, and Epinephrine 0.3mg SC injection in the left anterolateral thigh. The fourth treatment period was defined as dosing of ARS-1 1.0 mg IN after allergy challenge to induce allergic rhinitis symptoms. In the fifth treatment period subjects received a Epinephrine 0.5mg IM injection in the left anterolateral thigh. There was at least a 24-hour wash period between each treatment period. Subjects were observed in the clinical research the for 24 hours after the last dosing in the Treatment period 4 and for 8 hours after the last dosing in the Treatment period 5.

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 Results

Cmax: Under normal conditions, the pharmacokinetic profile of ARS-1 is comparable to Epinephrine 0.3 mg IM and 0.3 mg SC. The mean Cmax 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.

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

AUC0-t : The AUC0-t values followed a similar pattern as seen for Cmax 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 AUC0-t value (42500 min•pg/mL).

Partial AUC: 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 Cmax and partial AUC values. Beyond 10 minutes post dose, ARS-1 1.0 mg IN resulted in noticeably higher partial AUCs, yet the total AUC0-t values were comparable (ratio close to 100%) between the two products.

Table 18 Summary Statistics of Epinephrine Pharmacokinetic Parameters, by Treatment and Allergic Status – Total Epinephrine Values

Treatment	N	Median t_{max} (minutes)	C_{max} (geo. mean) (%CV)	$pAUC_{0-45}$ (min*pg/mL) (%CV)	$pAUC_{0-60}$ (min*pg/mL) (%CV	AUC_{0-t} (min*pg/mL) (%CV)	Comments
ARS-1 1.0 mg IN	35	20	243 (63.4%)	6490 (62.9%)	8570 (63.5)	25200 (53.8%)	IN Left Nostril
ARS-1 1.0 mg IN with Rhinitis	33	10	320 (78.0%)	6730 (80.8%)	7280 (78.7)	19200 (62.8%)	IN Left Nostril
Epinephrine 0.3 mg IM	36	45	232 (59.6%)	4420 (69.1%)	7030 (57.6)	25500 (32.9%)	IM Left Leg
Epinephrine 0.3 mg SC	35	45	214 (55.4%)	4180 (65.6%)	6640 (57.7)	28400 (36.7%)	SC Left Leg
Epinephrine 0.5 mg IM	23	45	347 (52.8%)	7330 (69.1%)	11300 (59.5)	42500 (38.7%)	IM Left Leg

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 Cmax and AUC0-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 Cmax and AUC0-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 Cmax and AUC0-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 Cmax and AUC0-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(AUC0-t/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(AUC0-t/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 Cmax earlier, with a median tmax of 10 minutes compared to the normal state, with a median tmax value of 20 minutes. The geometric mean Cmax value was greater for subjects with allergic rhinitis (320 pg/mL) as compared to the normal state (243 pg/mL).

The geometric mean AUC0-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.

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

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 (Table 19). 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 19 Summary Statistics of 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 (Table 20). 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 mean time 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 20 Summary Statistics 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.

CHMP comments

This was a Phase 1, single-dose, five-period study. The primary objective of this study was to assess the comparative bioavailability of epinephrine after IN administration of ARS-1 in subjects with induced allergic rhinitis and to evaluate the impact of nasal oedema and congestion on the absorption of epinephrine. Additional objectives of this study 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 in subjects after IN administration of epinephrine as compared to alternate routes of administration by IM and SC administration.

The present study demonstrates that allergic rhinitis results in a more rapid rate of epinephrine absorption following ARS-1 1 mg IN, with a median tmax of 20 minutes under normal conditions and 10 minutes under rhinitis conditions. Rhinitis also resulted in a slightly higher Cmax values (geometric mean 243 pg/mL versus 320 pg/mL under normal and rhinitis conditions, respectively), though it is important to note that the Cmax of ARS-1 1 mg IN with rhinitis is slightly less than the Cmax of the approved Epinephrine 0.5 mg IM (geometric mean 347 pg/mL).

While drug exposure during the first 30-minutes following ARS-1 administration (the crucial time period for efficacy) is higher under rhinitis conditions, the overall AUC0-t is lower relative to normal conditions (19200 min•pg/mL versus 25200 min•pg/mL), presumably because of more rapid absorption resulting in more rapid elimination. It should be noted that for all pharmacokinetic variables there were no meaningful differences between total epinephrine and baseline corrected results.

The results show that the Ln(AUC0-t) values and corresponding 90% confidence intervals were within the range of 80.0 – 125.0% for the ARS-1 1 mg IN and Epinephrine 0.3 mg IM comparisons. The Ln(Cmax) was very similar between ARS-1 1 mg IN and Epinephrine 0.3 mg IM injection with the upper limit just outside of the acceptance range.

ARS-1 1 mg IN reaches the 100 pg/mL level more rapidly than the other 3 epinephrine drug products, and a higher percentage of subjects reached 100 pg/mL and 200 pg/mL plasma levels within 10 minutes following ARS-1 as compared to IM injection. The cumulative time the plasma concentrations are above 100 pg/mL are similar for ARS-1 1 mg IN, Epinephrine 0.3 mg SC 0.3, and Epinephrine IM 0.3 mg. Intranasal administration during the allergic rhinitis state, appears to shorten both the time it takes to reach 100 pg/mL and the length of time it stays above this level. ARS-1 1 mg IN most closely paralleled

the data from the Epinephrine 0.3 mg IM dosing with regards to AUC and Cmax, however, ARS-1 was more rapidly absorbed (median tmax 20 minutes) as compared to Epinephrine 0.3 mg IM (median tmax of 45 minutes).

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.

This was a Phase 1, randomised, single-dose, five-treatment, five-period, crossover study that consisted of a screening period, baseline period, and an open-label randomised treatment period. The bioavailability of both a single dose and repeat dose of IN ARS-1 (1.0 mg) were assessed as compared to a single and repeat dose of EpiPen (0.3 mg IM epinephrine auto-injector)

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.

Pharmacokinetic Results

Plasma Concentrations

Mean plasma epinephrine concentration versus time profiles of epinephrine, sorted by treatment are presented in Figure 13 for single dosed groups and in Figure 14 for twice-dosed groups.

Figure 13 Mean Epinephrine Concentration-Time Profile after Administration of ARS-1 1.0 mg IN and EpiPen 0.3 mg Administered Once – Linear Scale

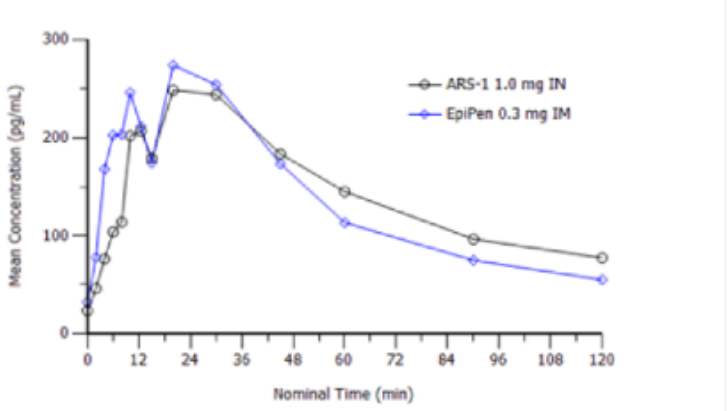
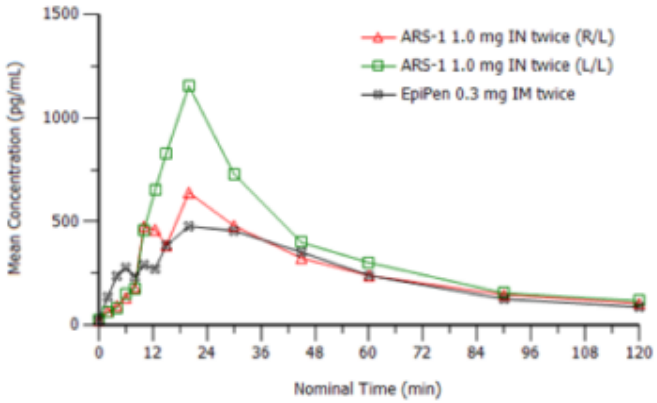


Figure 14 Mean Epinephrine Concentration-Time Profile after Administration of ARS-1 1.0 mg IN and EpiPen 0.3 mg Administered Twice – Linear Scale



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 21 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

Treatment	N	Median t_{max} (minutes)	C_{max} (geo. mean) (%CV)	$pAUC_{0-45}$ (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 22 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 Cmax 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 Cmax was approximately proportional between ARS-1 1.0 mg IN and ARS-1 1.0 mg IN twice (L/R), while the mean Cmax 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 tmax for all doses of ARS-1 1.0 mg IN was 20 minutes; the median tmax for EpiPen 0.3 mg was 24 minutes, and the median tmax 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 AUClast was 23300 min*pg/mL after ARS-1 1.0 mg IN and 27000 min*pg/mL after EpiPen 0.3 mg IM.

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, the geometric mean ratio (ARS-1/EpiPen) was 80.06% for Cmax and ranged from 53.55 to 107.14% for AUCs. Hence, Cmax 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 AUC0-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), the geometric mean ratio (ARS-1/EpiPen) was 98.13% for Cmax and ranged from 70.49 to 108.73% for AUCs. Cmax 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), the geometric mean ratio (ARS-1/EpiPen) was 162.04% for Cmax and ranged from 71.78 to 150.48% for AUCs. Although Cmax 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 AUC0-t was similar for both treatments (and not significantly different based on the 90% confidence intervals within 80 to 125%).

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), Cmax 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 AUC0-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), Cmax and AUC0-60 increased in a greater than proportional manner for the 2-fold increase in dose. The increase in AUC0-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), Cmax, AUC0-60, and AUC0-t increased in a slightly less than proportional manner.

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).

54% of subjects receiving ARS-1 1.0 mg IN once, 86% of subjects receiving ARS-1 1.0 mg IN twice (L/R), and 78% of subjects receiving ARS-1 1.0 mg IN twice (L/L) reached the plasma concentration of 100 pg/mL within 10 minutes of dosing. Eighty-one percent of subjects receiving EpiPen 0.3 mg once and 69% of subjects receiving EpiPen 0.3 mg twice (L/R) reached plasma concentrations of 100 pg/mL within 10 minutes. Seventy-seven (77%) of subjects receiving ARS-1 1.0 mg IN once, 97% of subjects receiving ARS-1 1.0 mg IN twice (L/R), and 94% of subjects receiving ARS-1 1.0 mg IN twice (L/L) reached100 pg/mL within 20 minutes of dosing. Ninety-two percent of subjects receiving EpiPen 0.3 mg once and 97% of subjects receiving EpiPen 0.3 mg twice (L/R) reached plasma concentrations of 100 pg/mL within 20 minutes.

CHMP comments:

This was a Phase 1, randomised, single-dose, five-treatment, five-period, crossover study.

The primary objectives of EPI07 study were as follows: 1) to assess the comparative bioavailability of epinephrine after IN administration of ARS-1 with EpiPen (0.3 mg IM injection of epinephrine) after both one and two doses in healthy volunteers under fasted conditions; and 2) to evaluate the comparative PD response-based pulse and BP using an automated blood pressure measuring device between treatment groups.

Secondary objectives were as follows: 1) to assess the relative bioavailability of two doses of ARS-1 1 mg IN given in the right and left nares, as compared to two doses in the left nares; 2) to evaluate the safety and tolerability of ARS-1 1 mg IN and EpiPen in healthy volunteers; and 3) to evaluate the distribution of tmax values across treatments.

Additional, exploratory objectives included: 1) a presentation of both mean and median data for select PK and PD parameters; 2) to determine the proportion of subjects who reach plasma epinephrine levels of 50 pg/mL, 100 pg/mL, and 200 pg/mL; and 3) to compare PK parameters between total epinephrine and baseline-corrected plasma levels.

The pharmacokinetic results of this study show that ARS-1 results in similar pharmacokinetic results as EpiPen and that both products have comparable pharmacokinetic parameters with both single and repeat dosing.

When administered as a single dose, ARS-1 1 mg demonstrates a slightly faster tmax relative to EpiPen (20.0 vs 24.0 minutes, respectively). ARS-1 as a single dose also demonstrates a slightly lower Cmax relative to EpiPen as a single dose (245 pg/mL vs 311 pg/mL).

A similar pattern for tmax was observed following two administrations of ARS-1 (both L/R and L/L) and EpiPen (L/R), with ARS-1 twice (both L/R and L/L) demonstrating a tmax of 20.0 minutes and EpiPen twice (L/R) demonstrating a tmax of 25.5 minutes). The Cmax values were similar between ARS-1 (L/R) and EpiPen (L/R) (536 pg/mL and 538 pg/mL, respectively).

The Cmax after ARS-1 was administered twice (L/R), as recommended, was within the bracket of maximum exposures obtained from two doses of EpiPen. The Cmax value following ARS-1 (L/L) was higher (873 pg/mL), however, there were no significant clinical outcomes or adverse effects as a result of this higher epinephrine exposure. The lack of significant clinical effects or adverse events following two doses to the same nostril demonstrates the safety and tolerability of ARS-1, even in the event of inadvertent administration twice to the same nostril.

EPI JP01. A Four-Treatment, Partially Randomized Crossover Study of the Pharmacokinetics of Adrenaline After Administration of ARS -1 or Adrenaline Injection in Subjects with Allergic Rhinitis.

This was a Phase 1, single-dose, four-period study that consisted of a screening period, baseline period, and an open-label treatment period.

Primary objectives were to assess the pharmacokinetics (PK) after intranasal (IN) administration of ARS-1 in subjects with normal nasal conditions and with induced allergic rhinitis and to evaluate the impact of nasal oedema and congestion on the absorption of adrenaline, to assess the PK of ARS-1 (0.3 mg epinephrine nasal spray suspension manufactured for ARS Pharmaceuticals Inc) when administered in subjects under normal conditions to adrenaline injection administered both by the IM via needle/syringe and EpiPen.

Secondary objectives were to evaluate the safety of ARS-1 in subjects after ARS-1 and adrenaline intramuscular (IM) via needle/syringe and EpiPen.

Pharmacokinetic results

Mean plasma epinephrine concentrations sorted by treatment over the complete sampling period (480 min) are shown in Figure 15 (linear scale). Mean epinephrine concentrations by treatment over the first 60 minutes are shown in Figure 16 (linear scale).

Figure 15 Mean Epinephrine Concentration-Time Profiles after IN Administration of ARS-1 – 480 Minutes; Linear Scale

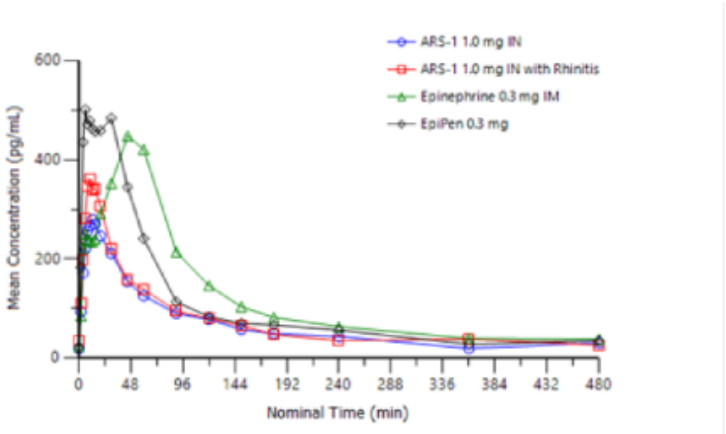
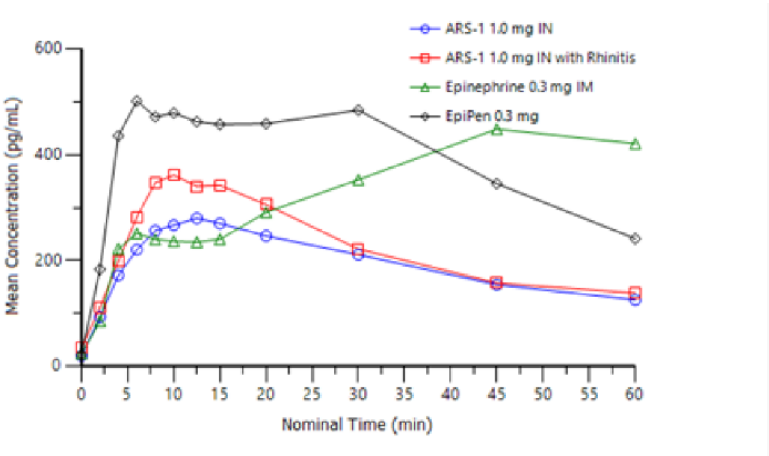


Figure 16 Mean Epinephrine Concentration-Time Profiles after IN Administration of ARS-1 – First 60 Minutes; Linear Scale



Pharmacokinetic Parameters

The PK parameters were calculated without the subtraction of the pre-dose epinephrine concentrations.

Summary statistics of PK parameters sorted by treatment are presented in Table 23 Summary statistics of epinephrine partial AUCs, sorted by treatment, are presented in Table 24.

Table 23 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

Treatment	N	Median t_{max} (min)	Median T_{100} (min)	Median $T_{>100}$ (min)	C_{max} (geo. mean) (%CV)	Key AUC Values (min*pg/mL)		
						$pAUC_{0-45}$ (%CV)	$pAUC_{0-60}$ (%CV	AUC_{last} (%CV)
ARS-1 1.0 mg IN	36	12.5	2.58	63.4	306 (66.1)	8080 (63.1)	9940 (61.7)	27100 (56.5)
ARS-1 1.0 mg IN with rhinitis	35	10.0	2.43	72.9	367 (79.8)	9040 (75.4)	11000 (73.4)	29400 (65.5)
Epinephrine 0.3 mg IM	35	45.0	2.67	138	518 (36.5)	12400 (46.1)	18900 (38.2)	55300 (21.7)
EpiPen 0.3 mg	30	10.0	1.39	97.8	608 (51.7)	17300 (50.4)	21800 (44.0)	48100 (24.1)

Source: PK Report: in-text Table 1

Table 24 Epinephrine Partial AUCs, Sorted by Treatment

Treatment	N	AUC_{0-2}	AUC_{0-4}	AUC_{0-6}	AUC_{0-8}	AUC_{0-10}	$AUC_{0-12.5}$	AUC_{0-15}	AUC_{0-20}	AUC_{0-30}	AUC_{0-45}	AUC_{0-60}	AUC_{0-120}
		Geometric Mean (min*pg/mL) (% CV)											
ARS-1 1.0 mg IN	36	91.6 (71.5)	307 (72.7)	623 (74.6)	1010 (74.1)	1440 (71.8)	2030 (68.5)	2620 (67.1)	3270 (65.9)	5690 (64.8)	8080 (63.1)	9940 (61.7)	15100 (57.8)
ARS-1 1.0 mg IN with rhinitis	35	116 (76.3)	366 (74.0)	777 (68.8)	1290 (73.1)	1840 (77.9)	2520 (79.5)	3200 (80.4)	4470 (82.0)	6630 (78.9)	9040 (75.4)	11000 (73.4)	16400 (69.7)
Epinephrine 0.3 mg IM	35	81.8 (96.2)	296 (114)	628 (114)	1000 (106)	1390 (96.5)	1890 (88.5)	2390 (83.4)	3570 (73.5)	6590 (59.1)	12400 (46.1)	18900 (38.2)	33700 (30.5)
EpiPen 0.3 mg	30	154 (96.4)	655 (88.5)	1470 (74.7)	2330 (67.2)	3190 (62.1)	4220 (60.3)	5190 (61.3)	7120 (63.5)	11300 (60.2)	17300 (50.4)	21800 (44.0)	30100 (36.3)

Source: PK Report: in-text Table 1

Relative to normal nasal conditions, rhinitis resulted in a slight increase in peak plasma levels. Geometric mean Cmax values were highest following administration of EpiPen 0.3 mg (608 pg/mL),

followed by Epinephrine 0.3 mg IM (518 pg/mL), ARS-1 1.0 mg IN with rhinitis (367 pg/mL) and ARS-1 1.0 mg IN (306 pg/mL).

The shortest tmax times were observed following ARS-1 1.0 mg IN, an effect that was amplified under rhinitis conditions. Median tmax values were shortest following EpiPen 0.3 mg (10 minutes), ARS-1 1.0 mg IN (12.5 and 10 minutes in the normal and rhinitis states, respectively). In contrast, median tmax values were 45 minutes following Epinephrine 0.3 mg IM.

Time to Reach and Time ≥100 pg/mL: The fastest time to reach 100 pg/mL was observed following administration of EpiPen 0.3 mg. The median time to reach 100 pg/mL were 1.39 min following EpiPen 0.3 mg, 2.43 min following ARS-1 1.0 mg IN with rhinitis, 2.58 min following ARS-1 1.0 mg IN, and 2.67 min following Epinephrine 0.3 mg IM. The median time for epinephrine concentrations exceeding 100 pg/mL (T>100) ranged from 63.4 min (ARS-1 1.0 mg IN) to 138 min (Epinephrine 0.3 mg IM).

AUC: The geometric mean AUCs for the first 30-minutes were similar between ARS-1 1.0 mg IN, ARS-1 1.0 mg IN with rhinitis, and Epinephrine 0.3 mg IM, however, the geometric mean AUCs for EpiPen 0.3 mg during the same time period were considerably higher (approximately 2-times higher for some intervals) compared to other treatments. The geometric mean AUClast ranged from 27100 min*pg/mL after ARS-1 1.0 mg IN (the geometric mean AUClast after ARS-1 1.0 mg IN with rhinitis was similar at 29400 min*pg/mL) to 55300 min*pg/mL after Epinephrine 0.3 mg IM.

Comparative Bioavailability:

ARS-1 1.0 mg IN vs. Epinephrine 0.3 mg IM:

Cmax was approximately 40% lower after ARS-1 1.0 mg IN and the geometric mean ratio (90% CI) was 59.06% (49.78-70.06%). Between 2 and 20 min, the partial AUCs were within 10% between these two treatments; during this time interval, the geometric mean ratios ranged from 98.34 to 110.29%. At later times, the AUCs (AUC0-30 to AUClast) were lower after ARS-1 1.0 mg IN compared to Epinephrine 0.3 mg IM; the geometric mean ratios ranged from 45.25 to 86.46%.

ARS-1 1.0 mg IN vs. EpiPen 0.3 mg: exposure to epinephrine was approximately 40 to 60% lower for ARS-1 1.0 mg IN compared to EpiPen 0.3 mg. The geometric mean ratio for Cmax was 48.66%; the geometric mean ratios for AUCs ranged from 39.86 to 59.39%.

ARS-1 1.0 mg IN vs. ARS-1 1.0 mg IN with rhinitis: rhinitis increased exposure to epinephrine by approximately 8 to 29%. The geometric mean ratio for Cmax was 120.66%; the geometric mean ratios for AUCs ranged from 108.51 to 128.81%. The difference was most apparent at early time points.

Non-compartmental Analysis

All key pharmacokinetic parameters and analyses were consistent between total epinephrine values and baseline corrected values. The primary analysis of the study was based on uncorrected plasma levels, which take into account the normal variability and fluctuations of endogenous epinephrine.

Table 25 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment – Baseline Corrected and Total Epinephrine Values

Treatment	N	Measurement	Median t_{max} (min)	Median T_{100} (min)	Median $T_{>100}$ (min)	C_{max} (geo. mean) (%CV)	Key AUC Values (min*pg/mL)		
							$pAUC_{0-45}$ (%CV)	$pAUC_{0-60}$ (%CV)	AUC_{last} (%CV)
ARS-1 1.0 mg IN	33	Total epinephrine	12.5	2.58	64.3	306 (66.1)	8080 (63.1)	9940 (61.7)	27100 (56.5)
		Baseline corrected	12.5	3.39	48.1	281 (73.8)	6890 (75.3)	8460 (75.6)	19200 (66.6)
ARS-1 1.0 mg IN with rhinitis	35	Total epinephrine	10.0	2.43	72.9	367 (79.8)	9040 (75.4)	11000 (73.4)	29400 (65.5)
		Baseline corrected	10.0	2.93	40.9	319 997.7)	6890 (113)	8140 (115)	14500 (120)
Epinephrine 0.3 mg IM	35	Total epinephrine	45.0	2.67	138	518 (36.5)	12400 (46.1)	18900 (38.2)	55300 (21.7)
		Baseline corrected	45.0	3.04	120	494 (37.9)	11300 (49.6)	17500 (40.2)	44400 (23.3)
EpiPen 0.3 mg	30	Total epinephrine	10.0	1.39	97.8	608 (51.7)	17300 (50.4)	21800 (44.0)	48100 (24.1)
		Baseline corrected	10.0	1.83	82.0	584 (54.1)	16200 (53.5)	20300 (47.0)	37300 (30.4)

Source: PK Report: in-text Table 1; Table 6; Table 7 (partial AUCs)

Table 26 Epinephrine Partial AUCs, Sorted by Treatment– Baseline Corrected and Total Epinephrine Values

Treatment	N	Measurement	AUC_{0-2}	AUC_{0-4}	AUC_{0-6}	AUC_{0-8}	AUC_{0-10}	$AUC_{0-12.5}$	AUC_{0-15}	AUC_{0-20}	AUC_{0-30}	AUC_{0-45}	AUC_{0-60}	AUC_{0-120}
			Geometric Mean (% CV)											
ARS-1 1.0 mg IN	36	Total	91.6 (71.5)	307 (72.7)	623 (74.6)	1010 (74.1)	1440 (71.8)	2030 (68.5)	2620 (67.1)	3270 (65.9)	5690 (64.8)	8080 (63.1)	9940 (61.7)	15100 (57.8)
		Baseline corrected	--	207 (123)	475 (104)	814 (94.1)	1200 (88.1)	1730 (81.5)	2260 (78.4)	3250 (76.2)	4970 (75.3)	6980 (75.3)	8640 (75.6)	12300 (74.4)
ARS-1 1.0 mg IN with rhinitis	35	Total	116 (76.3)	366 (74.0)	777 (68.8)	1290 (73.1)	1840 (77.9)	2520 (79.5)	3200 (80.4)	4470 (82.0)	6630 (78.9)	9040 (75.4)	11000 (73.4)	16400 (69.7)
		Baseline corrected	--	212 (122)	531 (106)	945 (107)	1390 (108)	1960 (106)	2510 (106)	3530 (109)	5190 (110)	6890 (113)	8140 (115)	11100 (120)
Epinephrine 0.3 mg IM	35	Total	81.8 (96.2)	296 (114)	628 (114)	1000 (106)	1390 (96.5)	1890 (88.5)	2390 (83.4)	3570 (73.5)	6590 (59.1)	12400 (46.1)	18900 (38.2)	33700 (30.5)
		Baseline corrected	--	--	436 (181)	763 (144)	1100 (123)	1530 (109)	1970 (99.8)	3020 (86.1)	5800 (66.4)	11300 (49.6)	17500 (40.2)	30800 (32.2)
EpiPen 0.3 mg	30	Total	154 (96.4)	655 (88.5)	1470 (74.7)	2330 (67.2)	3190 (62.1)	4220 (60.3)	5190 (61.3)	7120 (63.5)	11300 (60.2)	17300 (50.4)	21800 (44.0)	30100 (36.3)
		Baseline corrected	--	547 (112)	1320 (84.0)	2140 (72.9)	2950 (66.1)	3920 (63.9)	4830 (64.9)	6630 (67.3)	10600 (63.6)	16200 (53.5)	20300 (47.0)	27300 (39.9)

Source: PK Report: in-text Table 1; Table 7

CHMP comments

EPI JP01: This was a Phase 1, single-dose, four-period study. The primary objectives of this study were as follows: 1) to assess the pharmacokinetics (PK) of adrenaline after administration of ARS-1 1 mg IN in subjects with normal nasal conditions and with induced allergic rhinitis and to evaluate the impact of nasal oedema and congestion on the absorption of adrenaline; and 2) to assess the PK of ARS-1 1 mg IM when administered in subjects under normal conditions to adrenaline injection administered both by IM via needle/syringe and EpiPen.

The present study demonstrates that rhinitis resulted in both a slight increase in peak plasma levels and a reduced time to peak plasma levels. Relative to both Epinephrine 0.3 mg IM and EpiPen 0.3 mg, ARS-1 1 mg IN resulted in a shorter Tmax, an effect that was amplified under rhinitis conditions.

ARS-1 1 mg IN resulted in Cmax values that were approximately 40% lower than what was observed following Epinephrine 0.3 mg IM and 40 – 60% lower than what was observed following EpiPen 0.3 mg. During the first 30-minutes post-dose, partial AUCs were comparable between ARS-1 1 mg IN and Epinephrine 0.3 mg IM.

The results observed for ARS-1 were consistent with prior ARS-1 studies, however, results in Japanese from injection were significantly higher than previously observed with either EpiPen or IM injection in both the literature and prior ARS studies. This higher absorption from injection may be due to the lower body weight in Japanese (approximately a 12 Kg difference) as compared to non-Japanese in prior studies.

The applicant has not conducted studies on ARS-1 in the EU population. The applicant is asked to discuss whether the results obtained in other studies on the US population, can be extrapolated to the European population.(OC)

- Influence of food

CHMP comment

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.

Distribution

Adrenaline is an endogenous hormone that is distributed widely throughout the body (Dietz-1990). Given the clinical history of adrenaline, distribution data in support of this marketing application is derived from prior clinical use. The absence of the additional distribution data is justified per the CHMP Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95) and due to the fact that new studies are unlikely to further the scientific knowledge of the distribution of adrenaline.

CHMP comment

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

Elimination

- Excretion

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).

CHMP comment

The epinephrine is excreted as the metabolites in the urine. As the excretion of the epinephrine is well established in the literature due to the history of clinical treatment the studies aiming to assess elimination processes was not conducted.

In studies EPI 01 and EPI 02 the applicant claims that parameters like: elimination rate constant (λz) and half-life (T½), clearance (CL/F), volume of distribution (Vz/F) uncorrected for bioavailability (F) will be assessed, but finally no results and discussion occurs in chapter devoted. The applicant is asked to attach missing results (OC).

- 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.

CHMP comment

The metabolism of adrenaline as it is a endogenous hormone is well established. No clinical study researching the metabolism of adrenaline was performed by the applicant.

- Inter-conversion

CHMP comment

No study researching the inter-conversion of epinephrine was performed by the applicant.

- Pharmacokinetics of metabolites

CHMP comment

No PK study for metabolites of epinephrine was conducted.

- Consequences of possible genetic polymorphism

CHMP comment

No study researching consequences of possible genetic polymorphism was conducted.

- Dose proportionality

EPI 06. A five-period, five-treatment, randomized crossover study of the pharmacokinetics of epinephrine after administration of intranasal ARS-1 to healthy volunteers.

This was a Phase 1, five-period, five-treatment, randomised crossover study of the pharmacokinetics of epinephrine after administration of intranasal (IN) ARS-1 to healthy volunteers. The bioavailability of five concentrations of ARS-1 was assessed.

Primary objective was to assess the comparative bioavailability of five concentrations of ARS-1 in healthy volunteers under fasted conditions. Secondary objective was to evaluate the safety and tolerability of ARS-1 in healthy volunteers.

Exploratory objective was to identify a dose of ARS-1(Intranasal epinephrine) that gives about 50% of the exposure [based on area under the curve to the time of the last quantifiable concentration (AUClast)] and maximum plasma concentration (Cmax) as compared to the 1 milligram (mg) dose.

Pharmacokinetic Results

Plasma Concentrations

Mean plasma epinephrine concentrations sorted by treatment over the complete sampling period (480 min) are shown in Figure 17 (linear scale). Mean epinephrine concentrations by treatment over the first 120 minutes are shown in Figure 18 (linear scale).

Figure 17 Mean Epinephrine Concentration-Time Profiles after IN Administration of ARS-1 – 480 Minutes; Linear Scale

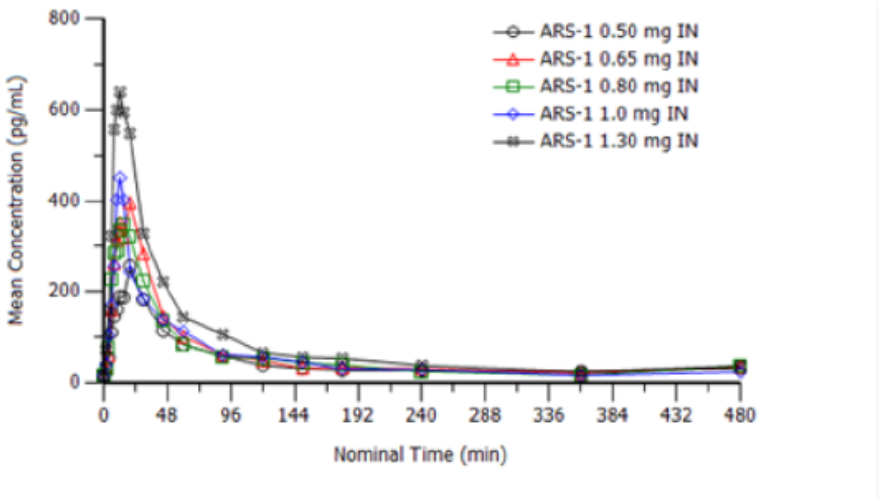
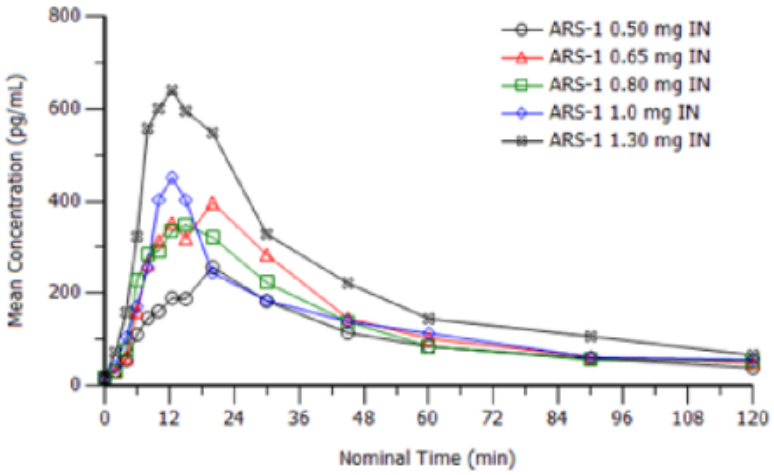


Figure 18 Mean Epinephrine Concentration-Time Profiles after IN Administration of ARS-1 – 120 Minutes; Linear Scale



Pharmacokinetic Parameters

The PK parameters were calculated without the subtraction of the pre-dose epinephrine concentrations.

After IN administration of ARS-1, maximum epinephrine concentrations were observed within a median tmax of 20 min for all dose levels; the median tmax ranged from 12.0 min after 1.0 mg to 20.0 min after 0.50 mg. Mean epinephrine plasma concentrations generally increased proportionally with increasing dose. Likewise, Cmax and AUCs increased with increasing dose, between the 0.5 and 1.3 mg doses. Geometric mean Cmax values ranged from 223 pg/mL after 0.50 mg to 545 pg/mL after 1.30 mg. Mean AUClast values ranged from 18,600 h*pg/mL after 0.50 mg to 32,900 h*pg/mL after

1.30 mg. The mean Cmax and AUCs were similar for the intermediate doses (0.65 mg and 0.8 mg), likely due to the similarity of the doses (incremental increases in dose of 20 to 30% between 0.50 and 1.30 mg) and the high degree of pharmacokinetic variability (CV up to 122%). The mean epinephrine concentrations were highest after the 1.30 mg dose throughout most of the PK sampling interval; there was some variability at later time points (360 and 480 min), likely due to fewer reported quantifiable epinephrine concentrations (>LLOQ).

Taking into consideration the dose level and the potency of each dose level, the mean bioavailability (Frel), (relative to the 1.0 mg dose) of the 0.50, 0.65, 0.80, and 1.30 mg products was 1.67, 1.94, 1.44, and 1.21, respectively. These results suggest higher systemic availability, on a per-mg basis, for the 0.50, 0.65, 0.80, and 1.30 mg products compared to the 1.0 mg product. However, these results need to be interpreted with caution due to the limited quantifiable data for the lower dose levels (through only 60 min for some subjects) and the variability in estimating Frel (CV from 68.0 to 110%).

Table 27 Summary Statistics of Epinephrine Pharmacokinetic Parameters by Treatment

Treatment	N	Median t_{max} (minutes)	C_{max} (geo. mean) (%CV)	$pAUC_{0-45}$ (min*pg/mL) (%CV)	$pAUC_{0-60}$ (min*pg/mL) (%CV	AUC_{last} (min*pg/mL) (%CV)	Mean F_{rel} (relative to 1.0 mg) (%CV)
ARS-1 0.50 mg IN	12	20.0	223 (74.6%)	6130 (69.9%)	7500 (66.7%)	18600 (88.9%)	1.67 (135%)
ARS-1 0.65 mg IN	11	15.0	374 (77.2%)	9540 (81.0%)	11200 (77.7%)	26800 (46.4%)	1.94 (95.4%)
ARS-1 0.80 mg IN	12	17.5	344 (126%)	7890 (114%)	9620 (105%)	24800 (66.8)	1.44 (109%)
ARS-1 1.0 mg IN	12	12.0	356 (102%)	8010 (97.3%)	9680 (90.9%)	21300 (78.3%)	--
ARS-1 1.30 mg IN	12	15.0	545 (101%)	12800 (80.4%)	15500 (71.3%)	32900 (66.3%)	1.21 (75.7%)

Table 28 Epinephrine Partial AUCs, Sorted by Treatment

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 0.50 mg IN	12	43.8 (58.0%)	124 (62.6%)	257 (75.0%)	445 (85.6%)	673 (88.5%)	1010 (87.0%)	1400 (87.1%)	2310 (85.8%)	4110 (77.8%)	6130 (69.9%)	7500 (66.7%)
ARS-1 0.65 mg IN	11	47.1 (80.6%)	140 (77.4%)	348 (73.9%)	701 (77.6%)	1150 (81.4%)	1790 (86.6%)	2450 (87.5%)	3940 (84.8%)	6740 (84.9%)	9540 (81.0%)	11200 (77.1%)
ARS-1 0.80 mg IN	12	45.2 (67.6%)	143 (76.4%)	344 (115%)	620 (151%)	940 (163%)	1410 (162%)	1930 (159%)	3150 (143%)	5410 (126%)	7890 (114%)	9620 (105%)
ARS-1 1.0 mg IN	12	53.2 (73.7%)	180 (78.4%)	395 (87.6%)	716 (91.3%)	1160 (95.9%)	1870 (103%)	2650 (106%)	3870 (105%)	5930 (103%)	8010 (97.3%)	9680 (90.9%)
ARS-1 1.30 mg IN	12	81.2 (49.8%)	269 (62.3%)	585 (81.1%)	1100 (97.6%)	1770 (106%)	2720 (109%)	3720 (109%)	5710 (105%)	9060 (95.9%)	12800 (80.4%)	15500 (71.3%)

Comparative Bioavailability

Ratios of the geometric mean exposure parameters (Cmax, AUCs) for the 0.50 mg compared to 1.0 mg ranged from 55.43% (AUC0-12.5min) to 89.53% (AUClast). Of the dose levels tested, the 0.50 mg dose yielded exposure closest to 50% of that for 1.0 mg, although most ratios were between approximately 60 and 85%. As noted for the PK parameters, the ratios for 0.65 and 0.80 mg compared to 1.0 mg were not markedly different, likely due to the closeness in the dose levels. For 0.65 mg, geometric mean ratios ranged from 71.01% (AUC0 4min) to 121.01% (AUClast); for 0.80 mg, the geometric mean ratios ranged from 65.33% (AUC0-15min) to 112.13% (AUClast). Geometric mean ratios for Cmax were 64.32% for 0.50 mg, 88.47% for 0.65 mg, 85.98% for 0.80 mg, and 137.18% for 1.30 mg. In general, the 30% increase in dose between 1.0 mg and 1.30 mg was reflected in the statistical analysis results, with geometric mean ratios of approximately 130%.

Estimates of slope in the dose proportionality assessment were 0.8090 for Cmax and 0.4293 for AUClast. The 90% confidence intervals were not fully contained within the critical region and the results were inconclusive.

CHMP comments

A five-period, five-treatment, randomised crossover study of the epinephrine PK after administration of intranasal ARS-1 to healthy volunteers was performed. The bioavailability of five concentrations – 0.5 mg, 0.65 mg, 0.8 mg, 1.0 mg and 1.3 mg, compared to 1 mg IN ARS-1 was assessed.

Study EPI 06 was a Phase 1, randomised, five-period, five-treatment crossover study of the pharmacokinetics of adrenaline following administration of Neffy to healthy volunteers. The primary objective of this study was to determine the concentrations of Neffy that would give blood levels that approximate a 0.15 mg and 0.5 mg IN adrenaline injection. The bioavailability of the following five adrenaline concentrations of Neffy was assessed: 0.50 mg, 0.65 mg, 0.80 mg, 1 mg, and 1.3 mg.

Following ARS-1, mean adrenaline plasma concentrations generally increased with dose, although mean adrenaline concentrations after 0.65 mg and 0.80 mg doses were not markedly different from each other. In addition, there was appreciable overlap of the mean concentration profiles for the 0.50 mg, 0.65 mg, 0.80 mg, and 1 mg doses at time points after 15 minutes.

Throughout most of the PK sampling interval the mean adrenaline concentrations were highest after the 1.30 mg dose, however there was some variability at later time points (360 and 480 min), likely due to fewer reported quantifiable adrenaline concentrations (> lower limit of quantification).

A median tmax of 20 minutes was observed for all dose levels of ARS-1. Median tmax values ranged from 12.0 minutes after 1 mg to 20.0 minutes after 0.50 mg. In general, exposure to adrenaline increased with the increasing doses of ARS-1. However, mean Cmax and AUCs values were similar for some treatments, most likely due to the narrow range between dose levels (incremental increases in dose of 20% to 30% between 0.50 mg and 1.30 mg) and the degree of PK variability (CV up to 122%). Geometric mean Cmax values ranged from 223 pg/mL after 0.50 mg to 545 pg/mL after 1.30 mg. Geometric mean AUClast values ranged from 18,600 min•pg/mL after 0.50 mg to 32,900 min•pg/mL after 1.30 mg.

Ratios of the geometric mean exposure parameters (Cmax, AUCs) for the 0.50 mg compared to 1 mg ranged from 55.43% (AUC0-12.5min) to 89.53% (AUClast). Of the dose levels tested, the 0.50 mg dose yielded exposure closest to 50% of that for 1 mg, although most ratios were between approximately 60 and 85%. As noted for the PK parameters, the ratios for 0.65 and 0.80 mg compared to 1 mg were not markedly different, likely due to the closeness in the dose levels. For 0.65 mg, geometric mean ratios ranged from 71.01% (AUC0-4min) to 121.01% (AUClast); for 0.80 mg, the geometric mean ratios ranged from 65.33% (AUC0-15min) to 112.13% (AUClast). Geometric mean ratios for Cmax were 64.32% for 0.50 mg, 88.47% for 0.65 mg, 85.98% for 0.80 mg, and 137.18% for 1.30 mg. In general, the 30% increase in dose between 1 mg and 1.30 mg was reflected in the statistical analysis results, with geometric mean ratios of approximately 130%.

- Time dependency

EPI 07

Table 29 Dose proportionality of epinephrine after administration of ARS-1 1.0 mg I.N. twice (L/R), ARS-1 1.0 mg I.N. 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
	$AUC_{0\text{-}60\ min}$/D	8.92	8.93	7460	7540	98.99	80.56	121.62
	$AUC_{0\text{-}t}$ /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
	$AUC_{0\text{-}60\ min}$/D	9.27	8.93	10600	7540	140.18	114.20	172.08
	$AUC_{0\text{-}t}$ /D	9.96	9.95	21300	20900	101.58	82.66	124.83
EpiPen Twice (L/R) vs. Single	C_{max}/D	6.72	6.83	827	928	89.14	70.62	112.51
	$AUC_{0\text{-}60\ min}$/D	10.2	10.3	28200	30600	92.18	75.10	113.15
	$AUC_{0\text{-}t}$ /D	11.2	11.3	73400	81100	90.51	73.65	111.22

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

CHMP comments

For ARS-1 1 mg administrated IN as a single dose and ARS-1 1.0 mg given IN twice (L/R), Cmax and $AUC_{0\text{-}60}$ increased proportionally according to 2-fold increase of dose (the 90% confidence intervals were within 80.00 to 125.00%).

For ARS-1 1 mg administrated IN as a single dose and ARS-1 1.0 mg given IN twice (L/L), Cmax and AUC0-60 increased greater that proportionally manner, according to 2-fold increase of dose. AUC0-t was dose-proportional (the 90% confidence intervals were within 80.00 to 125.00%).

Intra- and inter-individual variability

The variability of the assessed PK parameters is shown in Table 30.

Study number	Design	Subjects (N)	Arm treatment	PK parameters;	Mean Value (CV%)
EPI 02	Phase 1, randomised, open-label 3-treatment dose-escalation followed by 2 randomised, open-label, single-dose, 2-treatment, 2-period crossover studies	Healthy subjects (27)	ARS-1 0.5 mg	Cmax (pg/mL)	234 (9.55)
				T max (min)	28.3 (96.8)
				AUC0-t (min*pg/mL)	24000 (21.2)
			ARS 1.0 mg	Cmax (pg/mL)	586 (63)
				T max (min)	12.7 (50.8)
				AUC0-t (min*pg/mL)	43900 (41.8)
			ARS-1 2 mg	Cmax (pg/mL)	2470 (55.4)
				T max (min)	12.5 (20)
				AUC0-t (min*pg/mL)	166000 (48.7)
			ARS-1 IN 1.0 mg	Cmax (pg/mL)	305 (30)
				T max (min)	25 (161)
				AUC0-t (min*pg/mL)	44221 (28)
			IM 0.3 mg	Cmax (pg/mL)	236 (64)
				T max (min)	25 (183)
				AUC0-t (min*pg/mL)	45294 (48)
EPI 03	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	Healthy subjects (70)	ARS-1 IN, 1 mg	Cmax (pg/mL)	353 (75.4)
				AUC0-t (min*pg/mL)	30200 (59.4)
			ARS-1 IN, 1 mg, twice	Cmax (pg/mL)	739 (95.6)
				AUC0-t (min*pg/mL)	52200 (68.6)
			Epinephrine IM, 0.3 mg	Cmax (pg/mL)	244 (58.4)
				AUC0-t (min*pg/mL)	27300 (39.9)
			Epinephrine IM, 0.3 mg, twice	Cmax (pg/mL)	436 (48.8)
				AUC0-t (min*pg/mL)	47500 (32.6)
			Epinephrine IM, 0.5 mg	Cmax (pg/mL)	378 (58.8)
				AUC0-t (min*pg/mL)	43800 (30.5)
EPI 04	Phase 1, randomised, single-dose, 5-	Allergy Patients (36)	ARS-1 IN, 1 mg	Cmax (geo. mean)	243 (63.4)
				AUC0-t (min*pg/mL)	25200 (53.8)
			ARS-1 IN, 1 mg, Rhinitis	Cmax (geo. mean)	320 (78.0)
				AUC0-t (min*pg/mL)	19200 (62.8)

	period, partial cross-over study		Epinephrine IM, 0.3 mg	Cmax (geo. mean)	232 (59.6)
				AUC0-t (min*pg/mL)	25500 (32.9)
			Epinephrine SC, 0.3 mg	Cmax (geo. mean)	214 (55.4)
				AUC0-t (min*pg/mL)	28400 (36.7)
			Epinephrine IM, 0.5 mg	Cmax (geo. mean)	347 (52.8)
				AUC0-t (min*pg/mL)	42500 (38.7)
EPI 06	Phase 1, randomised, 5-period, 5-treatment crossover study	Healthy subjects (12)	ARS-1 IN: 0.5 mg, single dose	Cmax (geo. mean)	223 (74.6)
				AUC0-last (min*pg/mL)	18600 (88.9)
				Mean Frel (relative to 1.0 mg)	1.67 (135)
			0.65 mg, single dose	Cmax (geo. mean)	374 (77.2)
				AUC0-last (min*pg/mL)	26800 (46.4)
				Mean Frel (relative to 1.0 mg)	1.94 (95.4)
			0.8 mg, single dose	Cmax (geo. mean)	344 (126)
				AUC0-last (min*pg/mL)	24800 (66.8)
				Mean Frel (relative to 1.0 mg)	1.44 (109)
			1 mg, single dose	Cmax (geo. mean)	356 (102)
				AUC0-last (min*pg/mL)	21300 (78.3)
				Mean Frel (relative to 1.0 mg)	-
			1.3 mg, single dose	Cmax (geo. mean)	545 (101)
				AUC0-last (min*pg/mL)	32900 (66.3)
				Mean Frel (relative to 1.0 mg)	1.21 (75.7)
EPI 07	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	Healthy subjects (36)	ARS-1 IN, 1 mg (L nostril)	Cmax (geo. mean)	245 (93.7)
				AUC0-last (geo. Mean; min*pg/mL)	23300 (87.5)
				Frel (geo.mean) (%CV)	0.252 (93.5)
			ARS-1 IN, 1 mg, twice (L/R)	Cmax (geo. mean)	536 (102)
				AUC0-last (geo. Mean; min*pg/mL)	39700 (92.3)
				Frel (geo.mean) (%CV)	0.235 (94.5)
			ARS-1 IN, 1 mg, twice (L/L)	Cmax (geo. mean)	873 (147)
				AUC0-last (geo. Mean; min*pg/mL)	47300 (107)
				Frel (geo.mean) (%CV)	0.287 (86.5)
			EpiPen 0.3 mg (L thigh)	Cmax (geo. mean)	311 (68.2)
				AUC0-last (geo. Mean; min*pg/mL)	27000 (51.2)
				Frel (geo.mean) (%CV)	-
			EpiPen 0.3 mg, twice (L/R)	Cmax (geo. mean)	538 (68.6)
				AUC0-last (geo. Mean; min*pg/mL)	48100 (44.1)
				Frel (geo.mean) (%CV)	-
Jp 01	Phase 1, partially randomised, , four-treatment study	Allergy patients (36)	ARS-1 IN, 1 mg	Cmax (geo. mean)	306 (66.1)
				AUClast (min*pg/mL)	27100 (56.5)
			ARS-1 1.0 mg IN with rhinitis	Cmax (geo. mean)	367 (79.8)
				AUClast (min*pg/mL)	29400 (65.5)
			Epinephrine IM, 0.3 mg	Cmax (geo. mean)	518 (36.5)
				AUClast (min*pg/mL)	55300 (21.7)
			EpiPen, 0.3 mg	Cmax (geo. mean)	608 (51.7)
				AUClast (min*pg/mL)	48100 (24.1)

CHMP comment

Variability of individual pharmacokinetic parameters was assessed in studies: EPI02, 03, 04, 06, 07 and JP 01. In the conducted studies, it can be observed that the variability of PK parameters in subjects receiving ARS-1 I.N. is significantly higher than in those receiving I.M. with EpiPen administration. The applicant is asked to discuss the reasons for this increased variability.(OC)

Pharmacokinetics in target population

Given that randomised controlled studies in the treatment of patients at risk of anaphylaxis are considered unethical and no randomised, controlled, efficacy study has ever been conducted to date in

this population, ARS utilised haemodynamic endpoints as surrogate markers for the mechanism of action and efficacy. These markers are used to measure the effects of Neffy as predictive of its clinical efficacy.

CHMP comment

Randomised and controlled studies in the course of anaphylaxis are perceived as unethical. No clinical studies in target population was performed by the applicant.

Special populations

- Impaired renal function

CHMP comment

No studies revealing PK of epinephrine after IN administration in patients with renal impairment have been conducted. Epinephrine is eliminated by the liver, sympathetic nerve endings and kidneys.

- Impaired hepatic function

CHMP comment

No studies revealing PK of epinephrine after IN administration in patients with liver impairment have been conducted.

- Sex

CHMP comment

No studies revealing potential differences in PK of epinephrine after IN administration between sexes have been conducted. However, the literature data inform about sex differences in the muscle mass and in the nasal septal body and inferior turbinate sizes. In that context, the applicant is asked to discuss if any PK differences of epinephrine given intranasally may occur between the sexes. As for clinical studies, women and men were enrolled, the applicant is asked to present PK and PD analysis according to sex. (OC)

- Race

During the development of the study no clinical research was conducted to compare race differences in PK. However, populational analysis by ethnic bridging analysis was performed.

Relative Bioavailability for Japanese patients is 2.3, 2.17, and 1.0, respectively, for IM, EpiPen and Neffy respectively, suggesting that IM/EpiPen absorption is different in Japanese patients as compared to US populations but the same for Neffy in Japanese and US populations. Also, when covariate was used on F only without the Japanese data (US data only), then weight became a more important covariate.

Following that adjustment of F, weight (and not BMI) can explain the further difference in the MOFV on the Vd/Vc and Clearance. It is also relevant that the scaling factors for weight are 0.62 and 1.2 for clearance and volume of difference, respectively, which are similar to the typical allometric scaling of 0.75 and 1 used for scaling of Clearance and Volume of Distribution. Thus, taking relative bioavailability into account can explain most of the variability that is seen between Japanese and US populations.

Also, data from literature 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 (Al-Gindan-2014, Hill-2016, Hasunuma-2016) 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 is likely a significant contributor to the observation of two-fold increase in exposure following IM/EpiPen administration to the lower weight Japanese subjects (e.g., specifically that they would have smaller muscle and greater volume of distribution relative to the total muscle mass).

CHMP comment

Relative BA for Japanese patients are 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

EPI04

The effect of body weight on PK parameters AUC0-t and Cmax were explored using linear regression analysis for both total and baseline- corrected epinephrine concentrations.

Results are presented in Table 31 and Table 32, respectively.

Table 31 Effect of body weight on AUC0-t

Treatment	Measurement	Slope	P value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	Total epinephrine	-113	0.510	-460	233
	Baseline corrected	-89.3	0.555	-394	215
ARS-1 1.0 mg IN with Rhinitis	Total epinephrine	-85.4	0.697	-528	357
	Baseline corrected	-65.2	0.710	-419	289
Epinephrine 0.3 mg IM	Total epinephrine	-98.2	0.427	-346	150
	Baseline corrected	-24.2	0.816	-234	186
Epinephrine 0.3 mg SC	Total epinephrine	-290	0.0265	-544	-35.9
	Baseline corrected	-351	0.00365	-580	-123
Epinephrine 0.5 mg IM	Total epinephrine	-122	0.628	-636	393
	Baseline corrected	-124	0.606	-614	367

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, SC = subcutaneous.

Table 32 Effect of body weight on Cmax

Treatment	Measurement	Slope	P value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	Total epinephrine	0.230	0.915	-4.10	4.56
	Baseline corrected	0.246	0.905	-3.90	4.40
ARS-1 1.0 mg IN with Rhinitis	Total epinephrine	-3.77	0.321	-11.4	3.85
	Baseline corrected	-3.72	0.324	-11.3	3.85
Epinephrine 0.3 mg IM	Total epinephrine	-3.42	0.0893	-7.39	0.553
	Baseline corrected	-3.22	0.107	-7.17	0.734
Epinephrine 0.3 mg SC	Total epinephrine	-3.55	0.0612	-7.28	0.177
	Baseline corrected	-3.67	0.0480	-7.31	-0.034
Epinephrine 0.5 mg IM	Total epinephrine	0.407	0.891	-5.69	6.50
	Baseline corrected	0.369	0.900	-5.67	6.40

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, SC = subcutaneous.

CHMP comment

For epinephrine 0.3 mg administrated SC, increased in body weight caused a decrease in AUC0-t, however no statistical significance was reached (for total and baseline corrected values of epinephrine. Also in group receiving epinephrine 0.3 mg SC, increased body weight caused a decrease in Cmax (only baseline corrected values).

EPI JP01. Weight and BMI Adjusted Analysis

Regression analysis was performed to determine if weight or BMI had a significant effect on epinephrine exposure. There was no significant difference in exposure based on weight or BMI in the population evaluated in this study.

CHMP comment

The exposure did not differ based on weight and BMI in the population of this study.

- Elderly

CHMP comment

No PK studies in elderly patients were performed by the applicant.

- Children

No studies on paediatric population was performed by the applicant.

A single pharmacokinetic study (EPI 010) with ARS-1 will be conducted in adolescents and children. EPI 010 is open-label, randomised, parallel-group, single-dose study that will enrol up to 20 paediatric subjects in total (8–10 per age cohort, age cohorts 6 to 11 years and 12 to <16 years). For patients aged 16 years and older, the nasal passages, absorption nasal and metabolism of epinephrine are well understood and so this population is considered equivalent to adult in these respects. Epinephrine is dosed by weight with patients 15-<30 kg being dosed with 0.15 mg injection or 0.65 mg inhalation and patients 30+ kg dosed 0.3 mg injection or 1 mg inhalation. Proposed indication(s) in children: The emergency treatment of allergic reactions, including Anaphylaxis. Date of initiation 01/05/2020; Date of completion (last patient, last visit) 01/05/2021

CHMP comment

Pharmacokinetic studies in children after Neffy administration has not been conducted. However, the applicant has performed modelling extrapolations to support the use of IN epinephrine in children at 12 years of age and older.

CHMP overall comments on pharmacokinetics in special populations

No studies supporting revealing epinephrine PK given intranasally have been performed in the following special populations: patients with renal impairment, patients with hepatic function impairment, patients with different sexes, children and elderly. Weight has been revealed as a covariate of epinephrine exposure only after SC, not IN, administration. PK studies for assessment of epinephrine exposure in paediatric population was not conducted. The ongoing study EPI 10, was designed to support introduction of Neffy formulation for treatment of children between 4 and 16 years. The applicant has performed modelling extrapolations to justify the use of IN epinephrine in 12 years old children and older.

In the clinical studies, women and men were enrolled, the applicant is asked to present PK and PD analysis according to sex. (OC)

Interactions

In vitro, in vivo, in silico

Given the clinical history of adrenaline, pharmacokinetic drug interactions in support of this marketing application are derived from prior clinical use. The absence of the additional pharmacokinetic drug interactions data is justified per the Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications and due to the fact that new studies are unlikely to further the scientific knowledge of the pharmacokinetic drug interactions with adrenaline.

CHMP comment

No PK interaction study was performed during clinical development of the product, as the adrenaline PK interaction comes from prior clinical use of adrenaline and additional studies would not broad current scientific knowledge.

CHMP overall comments on Interactions

The applicant claims that dedicated trials for drug-drug interaction assessments are not necessary as they have been established for the reference product – prior used in clinical conditions epinephrine. This is acceptable.

- Exposure relevant for safety evaluation

Four studies were conducted with the commercial formulation of Neffy: EPI 03, EPI 04, EPI 07, and EPI JP01. These four studies were pooled for the Integrated Summary of Safety (ISS) analysis. A cumulative total dosing exposure was evaluated on a study population which consisted of 177 subjects that were enrolled in the EPI 03, EPI 04, EPI 07, and EPI JP01 clinical studies and received at least one dose of study drug. Due to the crossover design of each study, subjects received more than one exposure to Neffy per study, for a total of 383 total exposures to Neffy across the four studies. There were an addition 39 persons exposed to the commercial formulation of ARS-1 included in pilot studies EPI 02 and EPI 06. These subjects were not included in the pooled analysis. However, they are included in the summary of supportive clinical studies.

Three healthy volunteer pharmacokinetic/safety studies were completed with investigational formulations of Neffy: Studies EPI 01, EPI 02, and EPI 06. A summary of the exposure from the supportive studies in provided in Table 34. studies consists of 87 subjects. Of the 87 subjects, 39 subjects received the commercial formulation of Neffy. In addition, an interim analysis of the safety data from the ongoing patients with Type I allergies, study EPI 09, is included in this summary.

Table 33 Study subject drug exposure by cumulative dose safety population

Number of Dosed Subjects (%)										
ARS-1				Epinephrine				EpiPen		Placebo IM 0.3 mg
Nasal				IM			SC			
1 mg	2 mg (L/R)	2 mg (L/L)	1 mg with rhinitis	0.3 mg	0.5 mg	0.6 mg (L/R)	0.3 mg	0.3 mg	0.6 mg (L/R)	
174 (100.0)	105 (100.0)	36 (100.0)	68 (100.0)	140 (100.0)	92 (100.0)	70 (100.0)	35 (100.0)	72 (100.0)	36 (100.0)	70 (100.0)

Table 34 Study subject drug exposure by cumulative dose safety population from supportive clinical studies.

Number of Dosed Subjects										
	Neffy							Epinephrine	EpiPen	Symjepi
	Nasal							IM		IM
Study	0.3 mg	0.5 mg	0.65 mg	0.8 mg	1 mg	1.3 mg	2 mg	0.3 mg	0.3 mg	0.3 mg
EPI 01	12	-	-	-	-	-	-	-	12	-
EPI 02	-	3	-	-	27	-	3	24	-	-
EPI 06	-	12	12	12	12	12	-	-	-	-
EPI 09	-	-	-	-	53	-	-	-	54	54
Total	12	15	12	12	92	12	3	24	66	54

3.3.2. Pharmacodynamics

Introduction

The data to support this MAA, with legal basis for this application under Article 8(3), is efficacy and safety data from ARS clinical trials based on surrogate pharmacodynamic endpoints. Randomised, controlled clinical studies in the treatment of patients at risk of anaphylaxis are considered unethical and no such efficacy study has ever been conducted to date in patients at risk of serious allergic reactions and anaphylaxis. The applicant utilised haemodynamic endpoints as surrogate markers for the mechanism of action that are predictive of clinical efficacy through activation of α- and β-adrenergic receptors.

Mechanism of action

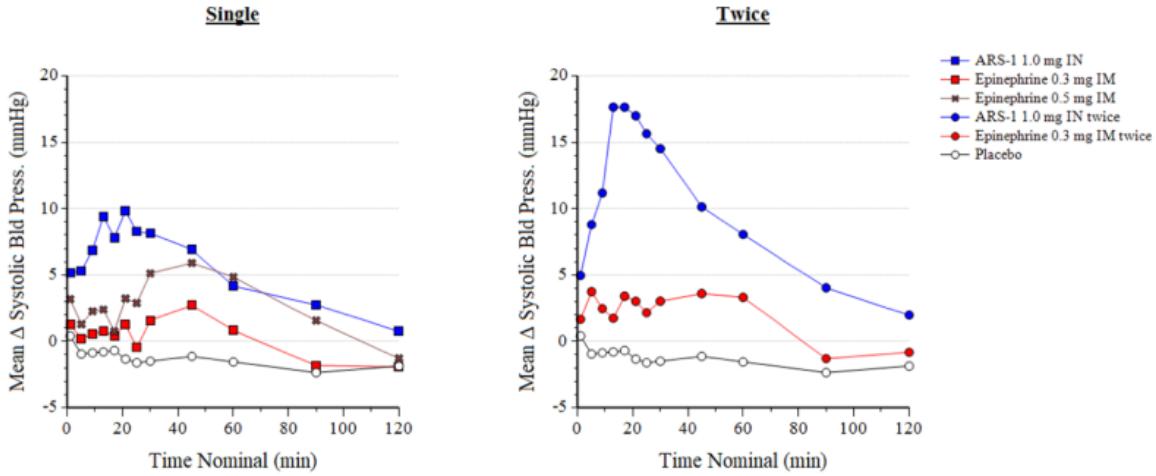
Adrenaline is a sympathomimetic catecholamine with α and β adrenergic agonist activity. Adrenaline is a non-specific adrenergic agonist that is the drug of choice for the treatment of severe allergic reactions and anaphylaxis. Its therapeutic efficacy comes from its direct agonism of α and β adrenergic receptors leading to a reversal of the pathological response to the histamine cascade.

Primary pharmacology

EPI 03. A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of ARS-1 and IM Epinephrine to Healthy Volunteers.

Systolic Blood Pressure

Figure 19 Mean Change from Baseline Systolic Blood Pressure vs. Time



Diastolic Blood Pressure

Summary statistics of DBP by time point, sorted by treatment are presented in Table 35.

Table 35 ***Summary Statistics of Diastolic Blood Pressure by Time Point, Sorted by Treatment***

Time Point	Statistic	Treatment					
		Placebo 0.3 mL IM	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
BL	N	68	68	70	68	70	69
	Mean (SD)	69.4 (7.57)	67.9 (7.78)	68.5 (7.43)	68.9 (6.84)	67.9 (7.72)	67.8 (7.68)
	Median	69.5	67.5	68.0	70.3	67.8	68.0
	Min, Max	52, 90	50, 89.5	49.5, 90	50, 83.5	47.5, 93	43, 91
1 min post dose	N	64	64	66	67	65	65
	Mean (SD)	68.9 (7.68)	73.2 (9.19)	76.0 (7.73)	69.6 (8.83)	69.8 (9.28)	69.3 (7.74)
	Median	70.0	72.0	75.5	70.0	69.0	69.0
	Min, Max	53, 97	58, 92	59, 94	43, 86	51, 103	46, 87
1 min post dose Change from BL	N	63	64	66	67	65	65
	Mean (SD)	-0.4 (4.12)	5.2 (6.74)	7.4 (6.88)	0.7 (6.48)	1.7 (6.62)	1.2 (4.72)
	Median	-1.0	5.0	7.5	0.0	1.5	1.0
	Min, Max	-9, 9	-8.5, 26	-12.5, 28.5	-16, 20	-20.5, 21.5	-9, 15.5
5 min post dose	N	67	67	66	66	67	68
	Mean (SD)	68.1 (7.92)	71.1 (8.35)	74.9 (7.81)	66.5 (7.38)	68.0 (9.73)	64.7 (8.66)
	Median	68.0	71.0	76.5	67.0	66.0	64.0
	Min, Max	53, 86	52, 90	56, 93	47, 84	47, 91	40, 85
5 min post dose Change from BL	N	65	67	66	66	67	68
	Mean (SD)	-0.6 (4.09)	3.1 (7.42)	6.1 (7.66)	-2.4 (5.62)	-0.0 (7.45)	-3.2 (6.23)
	Median	-0.5	3.5	5.8	-2.5	-1.0	-2.5
	Min, Max	-16.5, 12.5	-11, 21	-9.5, 24.5	-27, 9	-15.5, 21	-19.5, 14
9 min post dose	N	67	64	65	67	66	67
	Mean (SD)	67.8 (7.37)	71.0 (8.07)	73.8 (7.24)	65.8 (7.81)	66.0 (8.89)	65.4 (8.48)
	Median	67.0	72.0	74.0	67.0	66.0	64.0
	Min, Max	51, 88	54, 92	60, 89	48, 82	46, 94	44, 85

Time Point	Statistic	Treatment					
		Placebo 0.3 mL IM	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
9 min post dose Change from BL	N	66	64	65	67	66	67
	Mean (SD)	-1.1 (4.76)	2.9 (6.72)	4.9 (8.99)	-3.0 (6.35)	-2.1 (6.75)	-2.6 (5.60)
	Median	-0.8	3.5	4.5	-2.5	-1.5	-2.0
	Min, Max	-16.5, 9.5	-11, 18.5	-21, 24.5	-26, 10.5	-17, 15.5	-14, 12
13 min post dose	N	67	66	66	67	68	65
	Mean (SD)	68.9 (7.94)	69.6 (7.75)	73.8 (8.80)	64.6 (6.25)	64.6 (8.74)	64.2 (7.77)
	Median	70.0	70.5	74.0	65.0	63.5	63.0
	Min, Max	55, 94	53, 90	55, 101	51, 79	45, 95	49, 82
13 min post dose Change from BL	N	67	66	66	67	68	65
	Mean (SD)	-0.5 (4.46)	1.5 (7.55)	5.2 (8.94)	-4.6 (5.68)	-3.4 (6.04)	-3.5 (6.01)
	Median	-0.5	-0.3	4.3	-5.0	-3.5	-3.0
	Min, Max	-12.5, 13.5	-19.5, 21.5	-12, 25.5	-22, 15	-18, 9	-17.5, 10.5
17 min post dose	N	68	60	56	63	60	62
	Mean (SD)	68.7 (6.87)	69.2 (9.37)	72.4 (8.60)	64.6 (6.64)	63.1 (9.28)	63.6 (7.73)
	Median	68.5	70.5	72.0	66.0	62.0	62.0
	Min, Max	54, 86	51, 90	51, 89	46, 78	40, 93	46, 84
17 min post dose Change from BL	N	67	60	56	63	60	62
	Mean (SD)	-0.2 (4.64)	1.3 (8.13)	3.1 (8.84)	-3.8 (5.25)	-4.5 (7.74)	-3.8 (7.19)
	Median	-0.5	2.0	3.0	-4.5	-4.0	-3.8
	Min, Max	-11.5, 12	-12, 24.5	-14, 25.5	-14, 9.5	-18, 31.5	-23, 16.5
21 min post dose	N	66	64	64	66	69	66
	Mean (SD)	68.6 (7.93)	70.2 (7.89)	71.9 (11.58)	64.7 (8.52)	63.7 (8.69)	65.2 (8.15)
	Median	69.0	70.0	72.0	64.0	63.0	65.0
	Min, Max	52, 85	52, 91	49, 122	41, 84	43, 90	43, 84

Time Point	Statistic	Treatment					
		Placebo 0.3 mL IM	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
21 min post dose Change from BL	N	65	64	64	66	69	66
	Mean (SD)	-0.6 (4.58)	2.1 (8.57)	3.1 (10.65)	-4.3 (6.87)	-4.1 (5.86)	-2.9 (6.11)
	Median	0.0	2.5	2.8	-4.8	-5.0	-3.0
	Min, Max	-11.5, 8	-17, 30	-18.5, 50	-19, 15.5	-16, 12.5	-17.5, 11.5
25 min post dose	N	67	66	67	67	65	68
	Mean (SD)	69.4 (6.83)	67.9 (9.04)	71.8 (8.83)	63.4 (7.97)	62.7 (8.66)	63.9 (8.58)
	Median	70.0	69.5	72.0	64.0	62.0	63.0
	Min, Max	56, 86	47, 90	51, 93	45, 80	43, 94	44, 87
25 min post dose Change from BL	N	67	66	67	67	65	68
	Mean (SD)	0.4 (4.44)	0.0 (8.01)	3.1 (8.77)	-5.5 (5.69)	-5.5 (7.36)	-4.0 (7.47)
	Median	0.0	0.5	3.5	-5.5	-5.0	-4.3
	Min, Max	-13.5, 10.5	-18, 23	-13.5, 26.5	-19.5, 6.5	-20.5, 14.5	-23, 14
30 min post dose	N	68	65	67	62	69	62
	Mean (SD)	69.3 (8.04)	67.0 (8.05)	70.6 (8.60)	64.4 (9.34)	62.7 (8.95)	63.9 (8.81)
	Median	68.0	67.0	70.0	65.5	64.0	64.0
	Min, Max	54, 91	45, 87	53, 88	42, 92	41, 92	43, 98
30 min post dose Change from BL	N	67	65	67	62	69	62
	Mean (SD)	0.1 (4.17)	-1.2 (8.15)	2.1 (7.45)	-4.6 (6.78)	-5.4 (7.28)	-4.4 (8.35)
	Median	1.0	-0.5	1.5	-5.5	-6.0	-4.8
	Min, Max	-11.5, 11.5	-22.5, 18	-17.5, 18.5	-17.5, 13.5	-22.5, 22.5	-20.5, 25
45 min post dose	N	69	63	70	66	68	67
	Mean (SD)	68.8 (7.70)	66.9 (8.09)	69.8 (8.35)	64.5 (7.85)	61.8 (9.27)	63.4 (10.35)
	Median	70.0	67.0	70.0	64.0	61.5	62.0
	Min, Max	50, 88	40, 88	49, 88	46, 82	41, 96	48, 103

Time Point	Statistic	Treatment					
		Placebo 0.3 mL IM	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
45 min post dose Change from BL	N	67	63	70	66	68	67
	Mean (SD)	-0.2 (4.76)	-0.5 (6.96)	1.2 (7.92)	-4.5 (6.09)	-6.3 (6.37)	-4.3 (9.23)
	Median	0.5	-1.0	0.8	-4.0	-6.5	-5.5
	Min, Max	-10.5, 13.5	-16, 19	-15.5, 32.5	-21.5, 9.5	-23, 10	-17.5, 35.5
60 min post dose	N	70	66	65	64	69	67
	Mean (SD)	68.5 (8.12)	67.2 (8.36)	69.8 (8.49)	64.1 (9.32)	62.9 (8.72)	64.5 (8.78)
	Median	67.5	67.0	70.0	64.0	64.0	64.0
	Min, Max	50, 88	44, 93	50, 92	45, 97	43, 89	47, 94
60 min post dose Change from BL	N	68	66	65	64	69	67
	Mean (SD)	-0.7 (5.94)	-0.8 (7.79)	1.3 (7.74)	-4.7 (8.50)	-5.3 (7.04)	-3.1 (8.73)
	Median	-0.5	-0.5	2.0	-5.8	-5.0	-3.5
	Min, Max	-15.5, 15.5	-17.5, 15	-14, 24.5	-29, 26.5	-19, 12.5	-23, 24.5
90 min post dose	N	68	66	68	68	70	69
	Mean (SD)	68.0 (7.68)	70.2 (10.28)	68.3 (8.06)	64.9 (7.82)	63.7 (8.63)	63.6 (7.44)
	Median	67.5	69.0	69.0	65.0	64.0	65.0
	Min, Max	50, 86	50, 106	51, 81	46, 80	45, 91	44, 80
90 min post dose Change from BL	N	66	66	68	68	70	69
	Mean (SD)	-1.3 (5.70)	2.2 (8.86)	-0.3 (8.41)	-4.1 (6.68)	-4.2 (6.97)	-4.1 (7.09)
	Median	-0.8	1.5	-0.3	-3.5	-4.3	-3.5
	Min, Max	-19.5, 9.5	-17.5, 29	-32, 17.5	-26.5, 10	-22.5, 20.5	-24, 8.5
120 min post dose	N	70	66	70	68	70	69
	Mean (SD)	68.3 (7.35)	68.6 (8.20)	70.7 (9.29)	65.7 (8.38)	65.4 (8.95)	65.4 (7.46)
	Median	69.0	68.5	72.0	65.0	65.0	66.0
	Min, Max	48, 88	51, 89	49, 96	41, 86	42, 94	44, 83

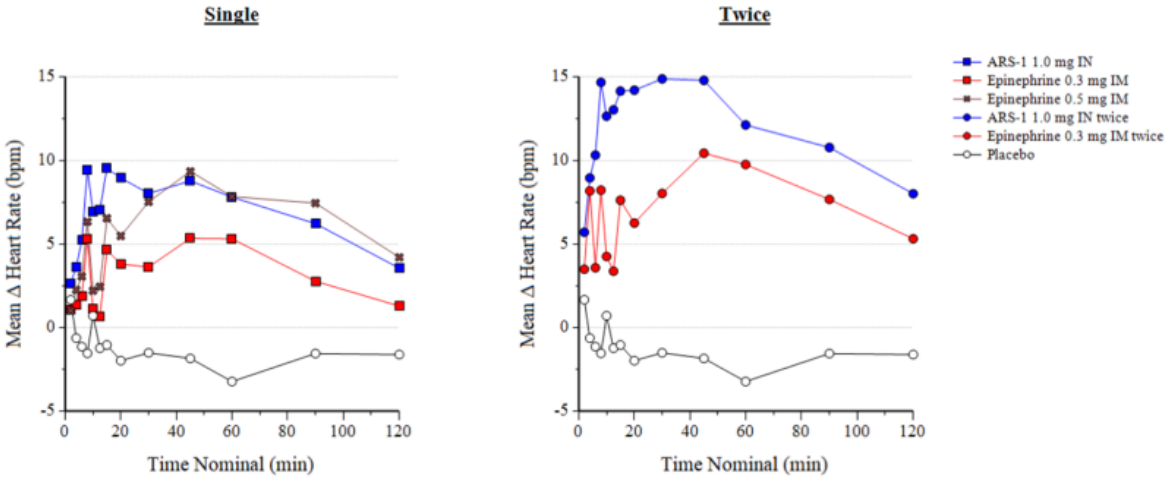
Time Point	Statistic	Treatment					
		Placebo 0.3 mL IM	ARS-1 1.0 mg IN	ARS-1 1.0 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
120 min post dose Change from BL	N	68	66	70	68	70	69
	Mean (SD)	-0.7 (5.62)	0.7 (6.72)	2.2 (8.12)	-3.2 (6.90)	-2.5 (7.72)	-2.3 (7.30)
	Median	-0.5	-0.3	1.8	-3.3	-2.5	-2.5
	Min, Max	-15.5, 17.5	-21.5, 16	-13, 42.5	-17, 19	-19.5, 22.5	-21.5, 16.5

Abbreviations: Max = maximum, Min = minimum, PD = post dose, SD = standard deviation.
Notes: Baseline is assessment from scheduled visit prior to dosing of each dosing period; post-baseline summary is based on the results collected from scheduled timepoints.

Heart Rate

Plots of the mean and mean (SD) change from baseline HR versus time, sorted by dosing regimen are presented in Figure 20.

Figure 20 Mean Change from Baseline Heart Rate vs. Time



Pharmacodynamic Parameters

Emax: Analysis of the mean maximum effect (Emax) on SBP demonstrated that, relative to Epinephrine 0.3 mg IM, ARS-11.0 mg IN resulted in a greater mean increase on SBP. This finding was observed for both ARS-1 1.0 mg IN (mean Emax = 17 mmHg) and ARS-1 1.0 mg IN twice (mean Emax = 25.6 mmHg). In contrast, mean Emax values following treatment with Epinephrine IM ranged from 11.1 mmHg (Epinephrine 0.3 mg IM, once) to 13.4 mmHg (Epinephrine 0.3 mg IM, twice). The Emax for HR demonstrated that, relative to Epinephrine 0.3 mg IM, treatment with ARS-1 1.0 mg IN resulted in a greater increase in mean Emax values (16 bpm versus 12.8 bpm for once dosed respectively, and 23.2 bpm versus 17 bpm for twice dosed respectively). The range of maximum and minimum changes in HR was similar across dose groups.

tEmax: Review of the median time to maximum effect (tEmax) values indicated that for SBP, ARS- 1 1.0 mg IN had the shortest tEmax value of 20.5 minutes, compared to the other single-dose treatments (Epinephrine 0.3 mg IM = 31.5 minutes and Epinephrine 0.5 mg IM = 31 minutes). The median tEmax values for ARS-1 twice versus Epinephrine 0.3 mg IM twice were similar, 21 minutes versus 21.5 minutes, respectively. Review of the median tEmax values for HR demonstrated that ARS-1 1.0 mg IN had the shortest tEmax value of 15 minutes, compared to the other single-dose treatments (Epinephrine 0.3 mg IM = 30 minutes and Epinephrine 0.5 mg IM = 45 minutes). The median tEmax values for ARS-1 1.0 mg twice was also shorter compared to Epinephrine 0.3 mg IM twice dosing (20 minutes versus 45 minutes, respectively).

Mean/Maximum haemodynamic responses: For both once and twice doses, the mean haemodynamic responses (SBP and HR) following administration of ARS-1 1.0 mg IN were generally more rapid (time to peak response) and more pronounced (mean change) than what was observed following administration of Epinephrine IM.

Least squares analysis: Results of the statistical comparisons of the difference of the least-square mean for change from baseline, and the least square mean for change from baseline, for SBP and HR were compared. ARS-1 1.0 mg IN was compared to Epinephrine 0.3 mg IM, and ARS-1 1.0 mg IN twice was compared to Epinephrine 0.3 mg IM twice. These statistical comparisons were conducted for Emax and the partial AUE values. In most of the comparisons, the change in SBP and HR for ARS-1 1.0 mg IN were statistically greater than what was observed in all Epinephrine IM groups.

Linear Mixed Effect Model Analysis

The relationship between pharmacological effects (mean change from baseline SBP and mean change from baseline HR) and total epinephrine concentrations were examined separately for each of the 5 treatment groups. The analysis performed was a linear mixed-effect model with epinephrine as the fixed effect and subject as the random intercept. For all treatments, a significant correlation was observed for both mean change from baseline SBP and mean change from baseline HR. These analyses demonstrate that for a given epinephrine concentration, while the maximum pharmacological response (mean change from baseline SBP and mean change from baseline HR) is similar across treatment groups, the mean changes are correlated with epinephrine concentration and the mean changes from IN administrations appeared to be greater than that of the IM route.

Table 36 Linear Mixed Effect Model Analysis: Change from Baseline Systolic Blood Pressure vs. Total Epinephrine Concentrations (pg/mL)

Treatment	Effect Level	Estimate	90% Lower CI	90% Upper CI	P Value
ARS-1 1.0 mg IN	Slope	0.0191	0.0160	0.0222	<0.00001
	Intercept	3.04	1.79	4.30	0.000123
ARS-1 1.0 mg IN Twice	Slope	0.0148	0.0131	0.0165	<0.00001
	Intercept	5.76	4.14	7.39	<0.00001
Epinephrine 0.3 mg IM	Slope	0.0262	0.0213	0.0310	<0.00001
	Intercept	-2.32	-3.62	-1.02	0.00387
Epinephrine 0.3 mg IM Twice	Slope	0.0146	0.0114	0.0179	<0.00001
	Intercept	-0.478	-1.92	0.961	0.582
Epinephrine 0.5 mg IM	Slope	0.0170	0.0139	0.0202	<0.00001
	Intercept	-0.213	-1.59	1.17	0.798

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal.

Table 37 Linear Mixed Effect Model Analysis: Change from Baseline Heart Rate vs. Total Epinephrine Concentrations (pg/mL)

Treatment	Effect Level	Estimate	90% Lower CI	90% Upper CI	P Value
ARS-1 1.0 mg IN	Slope	0.0163	0.0140	0.0186	<0.00001
	Intercept	4.45	3.35	5.55	<0.00001
ARS-1 1.0 mg IN Twice	Slope	0.00956	0.00835	0.0108	<0.00001
	Intercept	9.21	7.86	10.6	<0.00001
Epinephrine 0.3 mg IM	Slope	0.0168	0.0132	0.0204	<0.00001
	Intercept	1.13	-0.0459	2.32	0.114
Epinephrine 0.3 mg IM Twice	Slope	0.0164	0.0141	0.0187	<0.00001
	Intercept	3.78	2.80	4.77	<0.00001
Epinephrine 0.5 mg IM	Slope	0.0171	0.0146	0.0195	<0.00001
	Intercept	2.36	1.36	3.36	0.000170

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal.

CHMP comments

Epi 03 was a five-period, five-treatment, randomised crossover study of the pharmacokinetics and pharmacodynamics of epinephrine after I.N. administration of ARS-1 1.0 mg (once and twice) and I.M. epinephrine 0.3 and 0.5 mg (0.3 mg, once and twice) to healthy volunteers. Pharmacodynamic measurements included continuous ECG monitoring for HR and ABPM for BP (systolic and diastolic pressure).

The pharmacodynamic results demonstrated that relative to Epinephrine IM, single- and twice dosed ARS-1 1 mg IN had a greater mean effect on SBP and HR. There were no differences between ARS-1 1 mg IN and EpiPen or Epinephrine IM with regard to the maximum pharmacodynamic effect (maximum increase in HR or SBP). In addition, ARS-1 1 mg IN resulted in a greater change from baseline SBP as compared to the IM route at similar total epinephrine concentrations.

Given the more remarkable mean change in SBP after administration of I.N. from an efficacy perspective, greater efficacy may be expected compared to administration of I.M. However, although the extent of change (Min and Max effect) after administration of I.N. was smaller, the greater mean effect may raise questions about the safety of administration particularly in the elderly population, for example. The applicant is invited to discuss this issue. (OC)

It should also be noted that surrogates of the clinical effect include not only changes in SBP and HR but also DBP. The study results indicate that the impact of ARS-1 on DBP is in a completely different direction

from those of I.M. The applicant is asked to discuss the different DBP responses after I.N. administrations. (OC)

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.

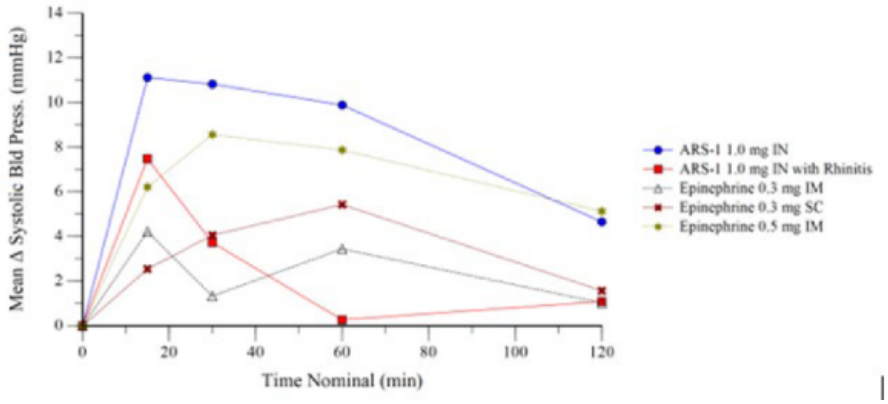
Pharmacodynamic Results

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. After 2 hours, the subjects were allowed to resume normal activity. Given that subjects were permitted to resume normal activity after 2 hours, it was not possible to determine if any changes in vital signs after this timepoint were attributable to a drug effect.

Systolic Blood Pressure

The mean change from baseline by treatment and condition is presented in Figure 21.

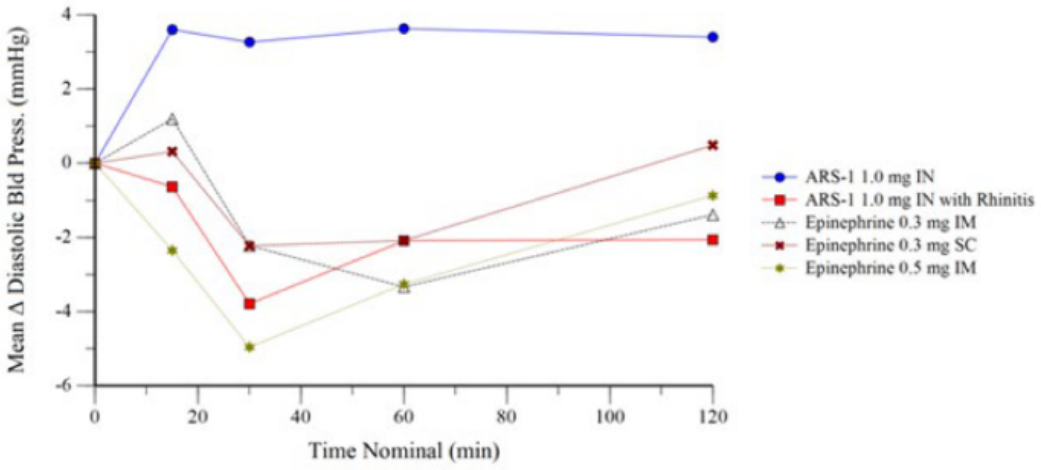
Figure 21 Mean Systolic Blood Pressure Change from Baseline by Treatment



Diastolic Blood Pressure

The mean change from baseline by treatment and condition is presented in Figure 22.

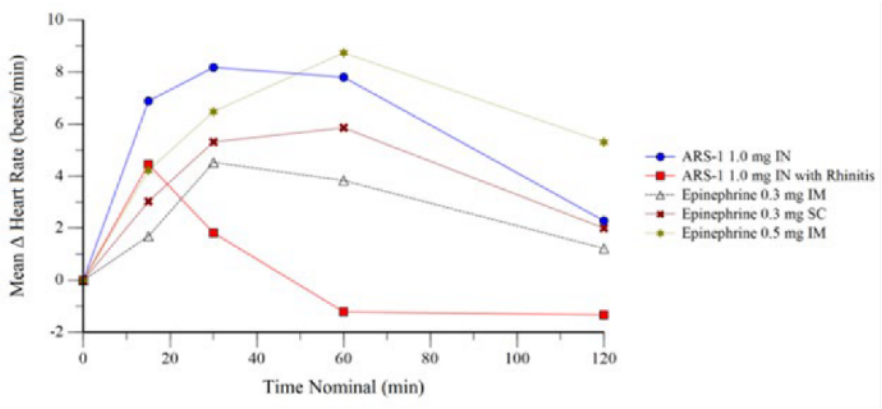
Figure 22 Mean Diastolic Blood Pressure Change from Predose by Treatment



Pulse Rate

The mean change of PR from baseline by treatment and condition is presented in Figure 23.

Figure 23 Mean Pulse Rate Change from Predose by Treatment



CHMP comments:

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 higher than that of Epinephrine 0.3 mg IM.

However, of concern is the significantly more rapid reduction in haemodynamic response (SBP and HR) after ARS-1 administration in patients with induced rhinitis. A significantly more rapid reduction in haemodynamic response (SBP and HR) after ARS-1 administration was observed in patients with induced rhinitis in Study EPI-04. The effect of the drug was significantly reduced 30 minutes after administration and almost disappeared after 60 minutes. Therefore, the applicant should discuss the risk of symptom recurrence in patients, it's management of this and how this can be reflected in the SmPC. (OC).

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 Results

Systolic Blood Pressure

Summary statistics of SBP by time point, sorted by treatment are presented in Table 38.
The mean change from baseline SBP is presented in Figure 24 (once-dosed treatments) and Figure 25 (twice-dosed treatments).

Table 38 Summary Statistics 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	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))
	Min, Max	102.0, 152.0	99.0, 191.0	103.0, 163.0	91.0, 145.0	95.0, 151.0
15 min post dose Change from BL	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

Figure 24 Mean Change in Baseline SBP by Treatment –Once-Dosed Treatments

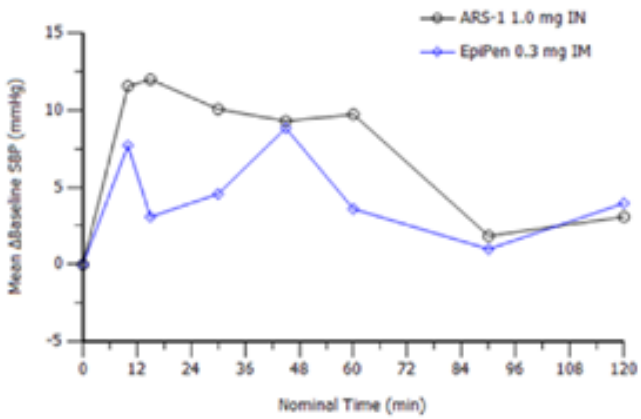
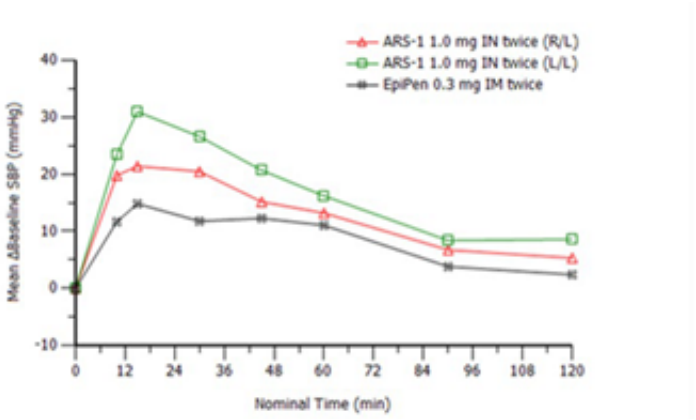


Figure 25 Mean Change in Baseline SBP by Treatment –Twice-Dosed Treatments



Diastolic Blood Pressure

Summary statistics of DBP by time point, sorted by treatment are presented in Table 39. The mean change from baseline DBP is presented in Figure 26 (once-dosed treatments) and Figure 27 (twice-dosed treatments).

Table 39 Summary Statistics 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	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

Figure 26 Mean Change from Baseline DBP by Treatment –Once-Dosed Treatments

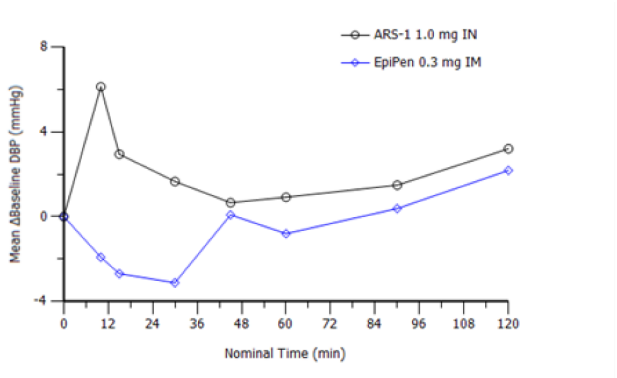
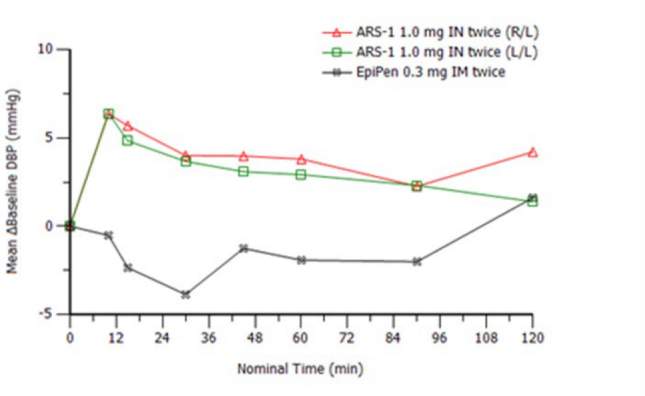


Figure 27 Mean Change in Baseline DBP by Treatment –Twice-Dosed Treatments



Pulse Rate

Summary statistics of PR by time point, sorted by treatment are presented in Table 40. The mean change from baseline PR is presented in Figure 28 (once-dosed treatments) and Figure 29 (twice-dosed treatments).

Table 40 Summary Statistics of Pulse Rate (BPM) 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

Figure 28 Mean Change in Baseline HR by Treatment –Once-Dosed Treatments

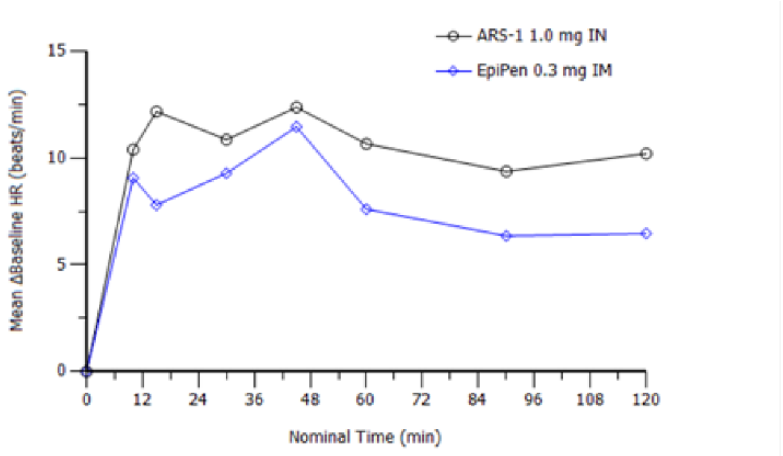
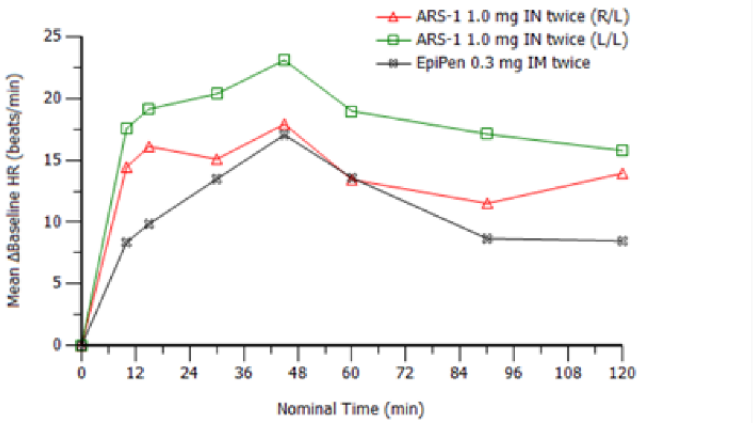


Figure 29 Mean Change in Baseline HR by Treatment –Twice-Dosed Treatments



CHMP comments

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 03 and 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.

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. 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 JP01. A Four-Treatment, Partially Randomized Crossover Study of the Pharmacokinetics of Adrenaline After Administration of ARS -1 or Adrenaline Injection in Subjects with Allergic Rhinitis.

Pharmacodynamic Results

Systolic Blood Pressure

Figure 30 Mean SBP Change from Baseline – 360 minutes

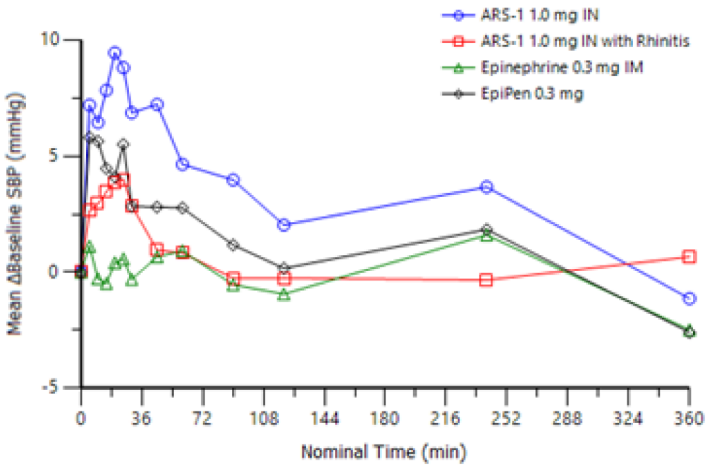
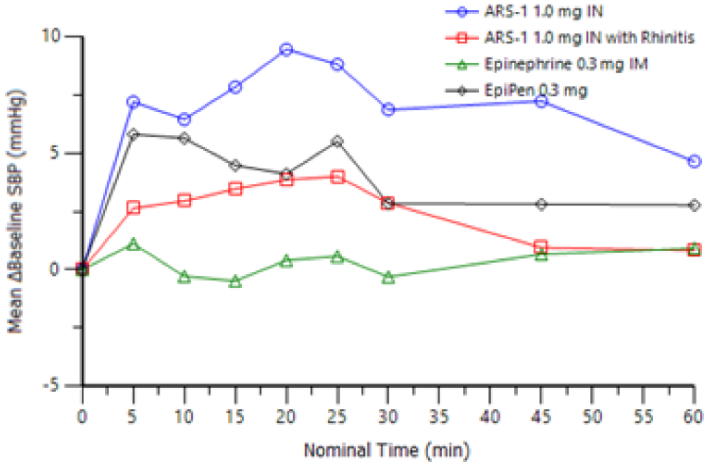


Figure 31 Mean SBP Change from Baseline – First 60 minutes



Diastolic Blood Pressure

Figure 32 Mean DBP Change from Baseline – 360 minutes

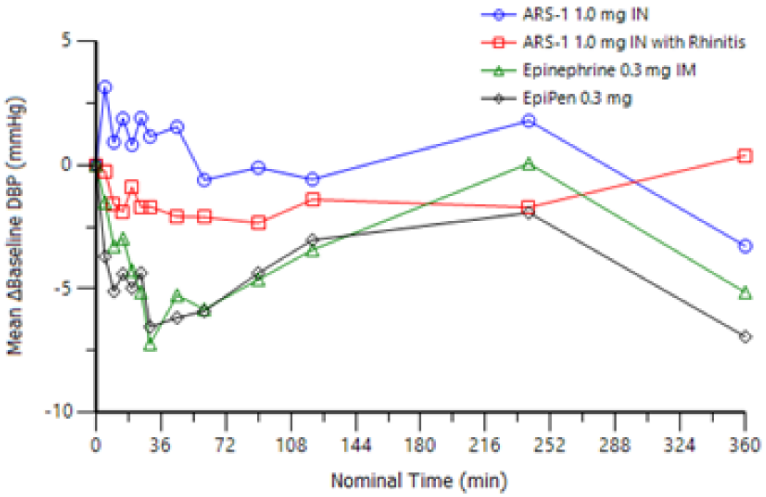
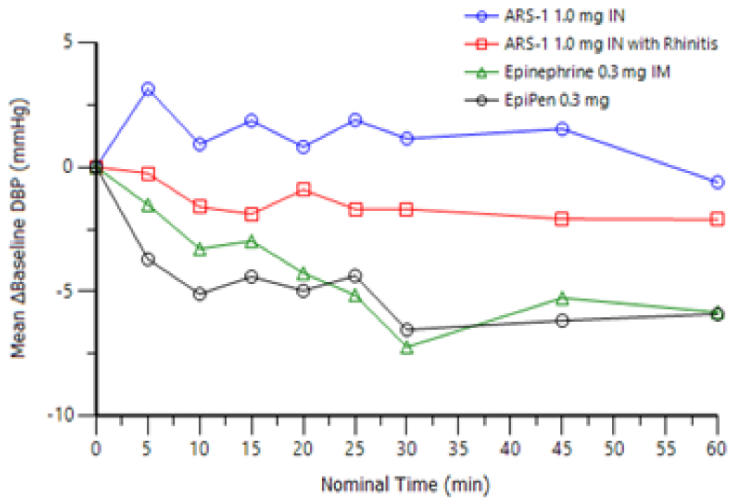


Figure 33 Mean DBP Change from Baseline – First 60 minutes



Pulse Rate

Figure 34 Mean PR Change from Baseline – 360 minutes

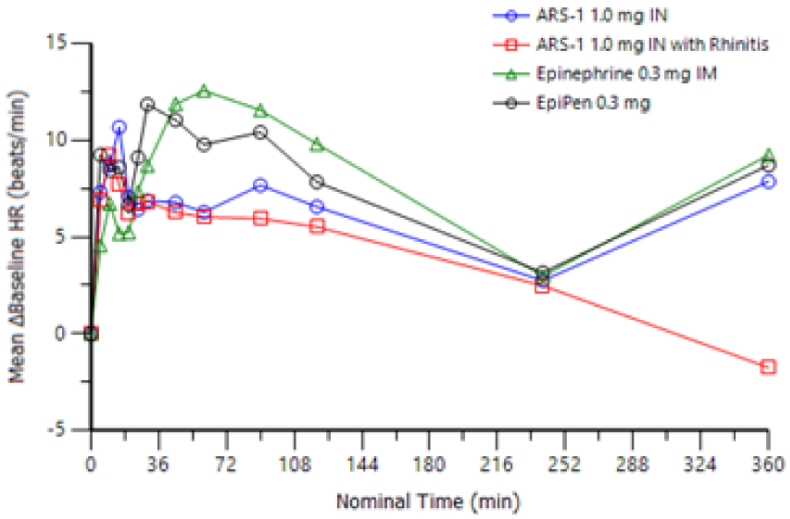
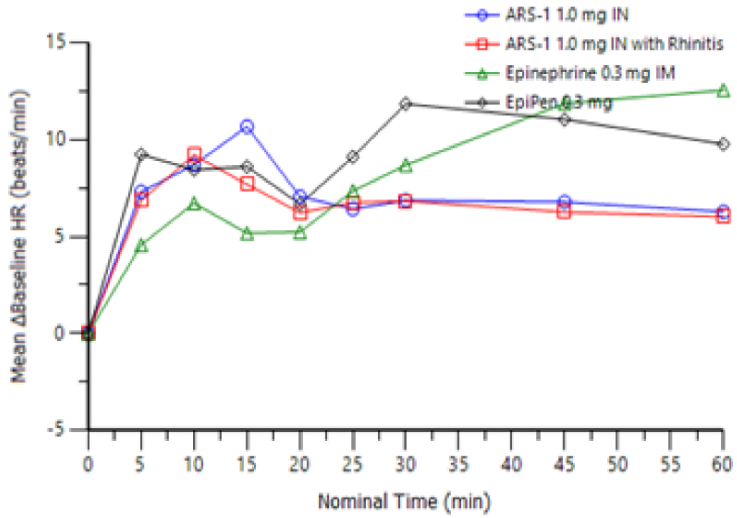


Figure 35 Mean PR Change from Baseline – First 60 minutes



Pharmacodynamic Parameters

Systolic Blood Pressure

Summary statistics for change from baseline SBP by treatment are presented in Table 41.

Table 41 Pharmacodynamic Parameters for SBP Change from Baseline

Treatment	n	t_{Emax} (min)	E_{max} (mmHg)	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	AUEC last
		med (range)	Mean (%CV)	Mean (%CV)									
ARS-1 1.0 mg IN	36	17.5 (5.00–240)	14.7 (46.5)	18.0 (105)	52.1 (94.5)	87.8 (88.5)	131 (82.1)	177 (77.6)	216 (78.5)	321 (79.0)	410 (79.2)	630 (88.1)	1120 (147)
ARS-1 1.0 mg IN with rhinitis	35	20 (0.00–360)	11.2 (73.5)	6.57 (255)	20.5 (236)	36.5 (236)	54.8 (23)4)	74.4 (219)	91.6 (212)	120 (234)	133 (266)	134 (495)	117 (1660)
Epinephrine 0.3 mg IM	35	25 (0.00-240)	7.57 58.7)	2.79 (525)	4.86 (761)	2.93 (1750)	2.71 (2300)	5.14 (1510)	5.79 (1650)	8.36 (1980)	20.1 (1210)	3.43 (16200)	-10.3 (-15100)
EpiPen 0.3 mg	30	22.5 (5.00-360)	11.9 (50.1)	14.5 (121)	43.1 (111)	68.3 (109)	89.8 (115)	114 (118)	135 (121)	177 (132)	219 (138)	298 (185)	372 (403)

Source: PK Report: in-text Table 5

Diastolic Blood Pressure

Summary statistics for change from baseline DPB by treatment are presented in Table 42.

Table 42 *Pharmacodynamic Parameters for DBP Change from Baseline*

Treatment	n	t_{Emax} (min)	E_{max} (mmHg)	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	AUEC last
		Median (range)	Mean (%CV)	Mean (%CV)									
ARS-1 1.0 mg IN	36	25.0 (0.00-240)	7.28 (55.1)	7.85 (155)	18.0 (173)	24.9 (204)	31.6 (225)	38.3 (231)	45.9 (237)	65.9 (256)	72.8 (299)	51.5 (811)	33.2 (2960)
ARS-1 1.0 mg IN with rhinitis	35	20.0 (0.00-360)	5.57 (80.5)	-0.643 (-1870)	-5.29 (-614)	-14.0 (-368)	-21.0 (-342)	-27.5 (-341)	-35.9 (-322)	-64.2 (-279)	-95.7 (-244)	-219 (-188)	-486 (-260)
Epinephrine 0.3 mg IM	35	15.0 (0.00-360)	3.46 (118)	-3.79 (-248)	-15.8 (-162)	-31.4 (-132)	-49.5 (-120)	-73.0 (-102)	-104 (-86.8)	-198 (-73.5)	-281 (-76.3)	-558 (-91.6)	-1070 (-125)
EpiPen 0.3 mg	30	15.0 (0.00-240)	2.83 (117)	-9.25 (-145)	-31.3 (-114)	-55.0 (-101)	-78.4 (-95.6)	-102 (-90.5)	-129 (-84.2)	-224 (-71.3)	-315 (-66.3)	-580 (-66.8)	-1410 (-87.0)

Source: PK Report: in-text Table 4

Pulse Rate

Summary statistics for change from baseline PR by treatment are presented in Table 43.

Table 43 Pharmacodynamic Parameters for PR Change from Baseline

Treatment	n	t_{Emax} (min)	E_{max} (beats/min)	AUEC min*beats/min									
				AUEC 0-5	AUEC 0-10	AUEC 0-15	AUEC 0-20	AUEC 0-25	AUEC 0-30	AUEC 0-45	AUEC 0-60	AUEC 0-120	AUEC last
		Median (range)	Mean (%CV)	Mean (%CV)									
ARS-1 1.0 mg IN	36	15 (5.00-360)	14.5 (34.0)	18.3 (80.8)	58.3 (64.6)	107 (51.4)	151 (45.5)	185 (42.6)	218 (40.8)	320 (41.8)	418 (45.1)	841 (48.5)	2040 (63.0)
ARS-1 1.0 mg IN with rhinitis	35	15.0 (5.00-240)	13.2 (50.8)	17.1 (98.7)	57.3 (85.7)	99.5 (78.3)	134 (78.6)	167 (81.4)	201 (83.3)	299 (86.6)	391 (87.0)	742 (85.5)	1270 (113)
Epinephrine 0.3 mg IM	35	60.0 (5.00-360)	16.7 (31.8)	11.4 (104)	39.6 (85.6)	69.4 (81.8)	95.4 (83.9)	127 (79.9)	167 (71.8)	321 (56.9)	504 (48.2)	1190 (40.3)	2680 (47.6)
EpiPen 0.3 mg	30	30.0 (5.00-360)	16.2 (45.4)	23.1 (51.3)	67.3 (51.0)	110 (55.9)	148 (60.9)	187 (63.1)	240 (61.8)	411 (57.1)	567 (53.2)	1140 (46.0)	2520 (62.7)

Source: PK Report: in-text Table 6

Least Squares Analysis

ARS-1 1.0 mg IN had the greatest impact on SBP Emax but was not statistically significant compared to EpiPen 0.3 mg. Mean SBP Emax ranged from 14.7 mmHg after ARS-1 1.0 mg IN to 7.57 mmHg after Epinephrine 0.3 mg IM. Additionally, Emax occurred earlier for ARS-1 1.0 mg IN (median tEmax 17.5 min) compared to the other treatments.

SBP AUEClast exhibited the following rank order ARS-1 1.0 mg IN > EpiPen 0.3 mg > ARS-1 1.0 mg IN with rhinitis > Epinephrine 0.3 mg IM. ARS-1 1.0 mg with rhinitis resulted in lower SBP Emax than ARS-1 1.0 mg IN (11.9 mmHg vs. 14.7 mmHg). Similar trends were observed for the comparisons of SBP at each scheduled time point.

These results indicate similar pharmacodynamic response between ARS-1 and EpiPen despite higher blood levels from injection in the Japanese population. This outcome may indicate that the higher levels of epinephrine observed in Japanese from EpiPen and Epinephrine 0.3 mg IM as compared to a non-Japanese population of higher total body weight, are not necessary to induce an additional pharmacodynamic response based on increased systolic blood pressure. The slightly lower increase in SBP with ARS-1 in subjects with induced rhinitis may be caused by suppression of expected increase of SBP by histamine, a known vasodilator, and possibly other mediators. ARS-1 in subject with induced rhinitis was still significantly greater than Epinephrine 0.3 mg IM injection, which is well known to be efficacious.

Table 44 Comparison of SBP after Administration of ARS-1 1.0 mg IN, Epinephrine 0.3 mg IM, and EpiPen 0.3 mg (Comparative PD Effect)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1.0 mg IN vs Epinephrine 0.3 mg IM	E_{max}	14.7	7.50	7.17	5.15	9.18	<0.0001
	$AUEC_{0-5}$	18.0	2.71	15.3	9.78	20.77	<0.0001
	$AUEC_{0-10}$	52.1	4.51	47.6	32.04	63.10	<0.0001
	$AUEC_{0-15}$	87.8	2.07	85.7	60.31	111.10	<0.0001
	$AUEC_{0-20}$	131	1.46	130	94.80	164.22	<0.0001
	$AUEC_{0-25}$	177	3.38	173	128.65	217.77	<0.0001
	$AUEC_{0-30}$	216	3.54	212	157.60	266.85	<0.0001
	$AUEC_{0-45}$	321	5.32	316	234.30	397.83	<0.0001
	$AUEC_{0-60}$	410	16.6	394	287.88	499.69	<0.0001
	$AUEC_{0-120}$	630	-0.436	630	438.33	821.57	<0.0001
	$AUEC_{0-last}$	1120	-12.3	1140	588.09	1682.30	0.0010
ARS-1 1.0 mg IN vs EpiPen 0.3 mg	E_{max}	14.7	12.2	2.48	0.36	4.60	0.0551
	$AUEC_{0-5}$	18.0	15.6	2.41	-3.39	8.21	0.4902
	$AUEC_{0-10}$	52.1	45.3	6.76	-9.59	23.12	0.4924
	$AUEC_{0-15}$	87.8	71.0	16.8	-9.85	43.49	0.2964
	$AUEC_{0-20}$	131	93.6	37.3	0.91	73.76	0.0920
	$AUEC_{0-25}$	177	119	58.0	11.26	104.75	0.0425
	$AUEC_{0-30}$	216	141	75.0	17.75	132.33	0.0325
	$AUEC_{0-45}$	321	187	135	48.73	220.37	0.0111
	$AUEC_{0-60}$	410	230	181	69.42	292.09	0.0087
	$AUEC_{0-120}$	630	308	321	119.37	523.50	0.0101
	$AUEC_{0-last}$	1120	441	682	105.59	1258.85	0.0527

Source: PK Report: in-text Table 8

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

Table 45 Comparison of SBP after Administration of ARS-1 1.0 mg IN (Effect of Rhinitis)

Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
E_{max}	11.2	14.7	-3.45	-5.61	-1.28	0.0109
$AUEC_{0-5}$	6.44	18.0	-11.5	-16.30	-6.79	0.0002
$AUEC_{0-10}$	20.2	52.1	-31.9	-44.64	-19.08	0.0002
$AUEC_{0-15}$	36.6	87.8	-51.2	-74.44	-27.91	0.0007
$AUEC_{0-20}$	55.3	131	-75.6	-110.97	-40.28	0.0010
$AUEC_{0-25}$	75.1	177	-101	-147.80	-55.10	0.0008
$AUEC_{0-30}$	92.4	216	-123	-180.07	-66.73	0.0008
$AUEC_{0-45}$	122	321	-200	-283.18	-116.52	0.0003
$AUEC_{0-60}$	135	410	-276	-382.91	-168.24	0.0001
$AUEC_{0-120}$	134	630	-496	-696.14	-295.31	0.0002
$AUEC_{0-last}$	120	1120	-1000	-1533.84	-471.34	0.0030

Source: PK Report: in-text Table 11
[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Diastolic Blood Pressure

Mean DBP Emax ranged from 2.83 to 7.28 mmHg and occurred at a median tmax of 15.0 to 25.0 min. Based on mean AUECs, there was a small positive change in DBP after ARS-1 1.0 mg IN and a negative change in DBP after ARS-1 1.0 mg IN with rhinitis, Epinephrine 0.3 mg IM, and EpiPen 0.3 mg. From the comparison of DBP parameters after ARS-1 1.0 mg IN to those after Epinephrine 0.3 mg IM and EpiPen 0.3 mg, DBP Emax and AUECs were consistently higher after ARS-1 1.0 mg IN. ARS-1 1.0 mg IN with rhinitis resulted in an overall lower mean DBP Emax than ARS-1 1.0 mg IN. Similar trends were observed for the comparisons of DBP at each scheduled time point.

Table 46 Comparison of DBP after Administration of ARS-1 1.0 mg IN, Epinephrine 0.3 mg IM, and EpiPen 0.3 mg (Comparative PD Effect)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1.0 mg IN vs Epinephrine 0.3 mg IM	E_{max}	7.28	3.46	3.81	2.43	5.20	<0.0001
	$AUEC_{0-5}$	7.85	-3.94	11.8	7.60	15.97	<0.0001
	$AUEC_{0-10}$	18.0	-16.3	34.2	23.29	45.19	<0.0001
	$AUEC_{0-15}$	24.9	-32.1	57.0	39.21	74.87	<0.0001
	$AUEC_{0-20}$	31.6	-50.4	82.0	57.31	106.64	<0.0001
	$AUEC_{0-25}$	38.3	-74.3	113	82.55	142.69	<0.0001
	$AUEC_{0-30}$	45.9	-106	151	115.36	187.59	<0.0001
	$AUEC_{0-45}$	65.9	-200	265	210.72	320.13	<0.0001
	$AUEC_{0-60}$	72.8	-283	356	284.79	426.71	<0.0001
	$AUEC_{0-120}$	51.5	-560	612	469.95	753.72	<0.0001
	$AUEC_{0-last}$	33.2	-1070	1100	711.15	1497.68	<0.0001
ARS-1 1.0 mg IN vs EpiPen 0.3 mg	E_{max}	7.28	2.94	4.34	2.88	5.80	<0.0001
	$AUEC_{0-5}$	7.85	-8.96	16.8	12.40	21.21	<0.0001
	$AUEC_{0-10}$	18.0	-30.8	48.7	37.23	60.27	<0.0001
	$AUEC_{0-15}$	24.9	-54.5	79.4	60.69	98.20	<0.0001
	$AUEC_{0-20}$	31.6	-77.4	109	83.01	134.89	<0.0001
	$AUEC_{0-25}$	38.3	-99.9	138	106.57	169.86	<0.0001
	$AUEC_{0-30}$	45.9	-126	172	134.09	210.07	<0.0001
	$AUEC_{0-45}$	65.9	-219	285	227.60	342.80	<0.0001
	$AUEC_{0-60}$	72.8	-309	382	306.66	456.35	<0.0001
	$AUEC_{0-120}$	51.5	-568	619	469.56	769.28	<0.0001
	$AUEC_{0-last}$	33.2	-1350	1390	970.73	1800.50	<0.0001

Source: PK Report: in-text Table 7
[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Table 47 Comparison of DBP after Administration of ARS-1 1.0 mg IN (Effect of Rhinitis)

Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
E_{max}	5.64	7.28	-1.64	-2.84	-0.44	0.0271
$AUEC_{0-5}$	-0.648	7.85	-8.50	-11.76	-5.23	0.0001
$AUEC_{0-10}$	-5.16	18.0	-23.1	-32.52	-13.77	0.0002
$AUEC_{0-15}$	-13.6	24.9	-38.5	-54.17	-22.90	0.0002
$AUEC_{0-20}$	-20.3	31.6	-51.9	-73.01	-30.72	0.0002
$AUEC_{0-25}$	-26.6	38.3	-65.0	-92.36	-37.56	0.0003
$AUEC_{0-30}$	-34.8	45.9	-80.7	-114.39	-47.01	0.0003
$AUEC_{0-45}$	-61.1	65.9	-127	-176.67	-77.33	0.0001
$AUEC_{0-60}$	-91.7	72.8	-164	-228.40	-100.50	0.0001
$AUEC_{0-120}$	-212	51.5	-263	-385.33	-141.12	0.0009
$AUEC_{0-last}$	-474	33.2	-508	-871.17	-144.05	0.0241

Source: PK Report: in-text Table 10

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

Pulse Rate

Mean PR increased for all treatments after dosing with the most prolonged changes observed following Epinephrine 0.3 mg IM and EpiPen 0.3 mg. ARS-1 1.0 mg IN and ARS-1 1.0 mg IN with rhinitis resulted in the earliest PR Emax (median tEmax of 15.0 minutes following ARS-1 1.0 mg IN and ARS-1 1.0 mg IN with rhinitis, 30.0 minutes following EpiPen 0.3 mg, and 60 minutes following Epinephrine 0.3 mg IM). Mean PR Emax ranged from 13.2 beats/min ARS-1 1.0 mg IN with rhinitis to 16.7 beats/min after Epinephrine 0.3 mg IM. Pulse rate AUECs through 30 min were similar for ARS-1 1.0 mg IN, ARS-1 1.0 mg IN with rhinitis, and EpiPen 0.3 mg.

Mean PR AUEClast exhibited the following rank order: Epinephrine 0.3 mg IM > EpiPen 0.3 mg > ARS-1 1.0 mg IN > ARS-1 1.0 mg IN with rhinitis. From the comparison of PR parameters after ARS-1 1.0 mg IN to those after Epinephrine 0.3 mg IM and EpiPen 0.3 mg, differences between treatments were not consistent over the full 360 min measurement period. PR Emax and AUEClast were lower after ARS-1 1.0 mg IN compared to Epinephrine 0.3 mg IM and EpiPen 0.3 mg, but there were no statistical differences between ARS-1 1.0 mg IN and EpiPen 0.3 mg. For the comparisons of PR at each scheduled time point, there were both negative and positive differences.

ARS-1 1.0 mg with rhinitis resulted in an overall decrease in mean PR than ARS-1 1.0 mg IN. But there were no statistical differences in partial AUECs between ARS-1 1.0 mg IN and ARS-1 1.0 mg IN rhinitis except AUEC0-last or HR360.

Table 48 Comparison of PR after Administration of ARS-1 1.0 mg IN, Epinephrine 0.3 mg IM, and EpiPen 0.3 mg (Comparative PD Effect)

Test vs. Ref	Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
ARS-1 1.0 mg IN vs Epinephrine 0.3 mg IM	E_{max}	14.5	16.7	-2.17	-3.97	-0.37	0.0487
	$AUEC_{0-5}$	18.3	11.6	6.64	2.75	10.53	0.0060
	$AUEC_{0-10}$	58.3	40.2	18.1	7.34	28.85	0.0066
	$AUEC_{0-15}$	107	70.1	36.6	18.79	54.41	0.0011
	$AUEC_{0-20}$	151	96.2	54.8	29.92	79.64	0.0005
	$AUEC_{0-25}$	185	128	56.9	25.91	87.86	0.0032
	$AUEC_{0-30}$	218	168	50.2	12.96	87.39	0.0279
	$AUEC_{0-45}$	320	321	-0.782	-59.85	58.29	0.9824
	$AUEC_{0-60}$	418	504	-85.5	-162.55	-8.50	0.0685
	$AUEC_{0-120}$	841	1190	-345	-496.54	-193.65	0.0003
	$AUEC_{0-last}$	2040	2690	-653	-1057.51	-249.23	0.0090
ARS-1 1.0 mg IN vs EpiPen 0.3 mg IM	E_{max}	14.5	16.3	-1.77	-3.68	0.13	0.1250
	$AUEC_{0-5}$	18.3	23.9	-5.68	-9.80	-1.56	0.0247
	$AUEC_{0-10}$	58.3	69.1	-10.8	-22.19	0.56	0.1175
	$AUEC_{0-15}$	107	112	-4.86	-23.69	13.97	0.6678
	$AUEC_{0-20}$	151	149	1.50	-24.78	27.78	0.9245
	$AUEC_{0-25}$	185	189	-4.39	-37.13	28.35	0.8235
	$AUEC_{0-30}$	218	242	-24.3	-63.62	15.06	0.3067
	$AUEC_{0-45}$	320	414	-94.0	-156.41	-31.61	0.0145
	$AUEC_{0-60}$	418	566	-148	-229.45	-66.62	0.0035
	$AUEC_{0-120}$	841	1130	-291	-451.01	-130.90	0.0035
	$AUEC_{0-last}$	2040	2500	-463	-890.51	-35.04	0.0757

Source: PK Report: in-text Table 9
[a] Least Squares Mean; [b] Difference in LSMean (Test – Ref); [c] Ratio(%) = 90% Ratio about the Difference: [d]p-value for the difference in the treatment_id estimates; Significant difference defined *a priori* as $p < 0.05$

Table 49 Comparison of PR after Administration of ARS-1 1.0 mg IN (Effect of Rhinitis)

Dependent Variable	LSMean [a] Test	LSMean [a] Ref	Diff [b]	90% CI [c] Lower	90% CI [c] Upper	p-value[d]
E_{max}	13.2	14.5	-1.27	-2.88	0.33	0.1872
$AUEC_{0-5}$	17.1	18.3	-1.16	-5.82	3.49	0.6749
$AUEC_{0-10}$	57.5	58.3	-0.767	-12.94	11.41	0.9158
$AUEC_{0-15}$	99.9	107	-6.77	-25.20	11.66	0.5386
$AUEC_{0-20}$	135	151	-16.4	-40.97	8.17	0.2669
$AUEC_{0-25}$	167	185	-17.2	-48.63	14.19	0.3605
$AUEC_{0-30}$	202	218	-16.0	-54.56	22.49	0.4864
$AUEC_{0-45}$	300	320	-19.7	-78.55	39.14	0.5750
$AUEC_{0-60}$	393	418	-25.0	-103.44	53.54	0.5944
$AUEC_{0-120}$	750	841	-90.7	-242.16	60.82	0.3187
$AUEC_{0-last}$	1290	2040	-747	-1155.19	-338.42	0.0040

Source: PK Report: in-text Table 12
Test = ARS-1 1.0 mg IN with rhinitis (Period 4); Reference (Ref) = ARS-1 1.0 mg IN a Least Squares Mean; b Difference in LSMean (Test – Ref); c Ratio(%) = 90% Ratio about the Difference: dp-value for the difference in the treatment_id estimates; Significant difference defined a priori as $p < 0.05$

CHMP comment

EPI JP01 was a four-treatment, partially randomised crossover study of the pharmacokinetics of adrenaline after administration of ARS -1 or adrenaline injection in subjects with allergic rhinitis. The following PD parameters for SBP, DBP and PR/HR were calculated using non-compartmental analysis.

The pharmacodynamic results demonstrated that ARS-1 1 mg IN resulted in the greatest increase in SBP, with rhinitis mitigating this effect slightly. Less marked increases were observed following EpiPen 0.3 mg. Mean PRs increased following all treatments, however ARS-1 1 mg IN resulted in the earliest maximum change to PR. The most prolonged change to PR was observed following Epinephrine 0.3 mg

IM. These results indicate similar pharmacodynamic response between ARS-1 and EpiPen despite higher blood levels from injection in the Japanese population. This outcome may indicate that the higher levels of epinephrine observed in Japanese from injection as compared to a non- Japanese population of higher total body weight, are not necessary to induce an adequate pharmacodynamic response based on increased systolic blood pressure.

Secondary pharmacology

Literature has shown that adrenaline also alleviates pruritus, urticaria, and angioedema (Lieberman-2015, Sarkar-2015) through the same mechanism and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder (Sarkar-2015).

In addition, adrenaline uses of adrenaline include, but are not limited to, ventricular fibrillation, pulseless ventricular tachycardia, asystole, pulseless electrical activity, croup, and severe asthma exacerbations unresponsive to standard treatment. In the operating room setting, adrenaline is used as a local anaesthetic block as well (Dalal-2020).

CHMP comment

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

Pharmacodynamic interactions with other medicinal products or substances

Given the clinical history of adrenaline, pharmacodynamic drug interaction data is derived from literature, prior clinical use, as well as clinical data obtained with ARS-1. Therefore, pharmacodynamic drug interaction studies were not conducted with ARS-1.

Based on the mechanism of action, pharmacodynamic drug interactions with adrenaline are already well established. Based on the mechanism of action and the literature, the following consumer labelling of interactions with other medicinal products and other forms of interactions are supported:

Interaction with other medicinal products and other forms of interaction

Caution is indicated in patients receiving drugs that may sensitise the heart to arrhythmias, including digitalis, mercurial diuretics, or quinidine. The effects of adrenaline may be potentiated by tricyclic antidepressants and mono amine oxidase inhibitors (MAO-inhibitors) and catechol-O-methyl transferase inhibitors (COMT-inhibitors), thyroid hormones, theophylline, oxytocin, parasympatholytics, certain antihistamines (diphenhydramine, chlorpheniramine), levodopa, and alcohol.

CHMP comment

Pharmacodynamic drug interaction data come from literature and are the result of clinical history of adrenaline treatment. No study for assessing pharmacodynamic interaction with other medicinal products was performed. While neither studies nor data from literature are presented in the application, PD interactions with other medicinal products are discussed in the PI. It is agreed that no new data should be generated regarding systemic interactions, however, any statements presented in the PI should be supported by data included and discussed in the dossier.(OC)

Genetic differences in PD response

CHMP comment
No clinical studies were performed to reveal if genetic differences could impact PD response of epinephrine.

Relationship between plasma concentration and effect

EPI 06. A five-period, five-treatment, randomized crossover study of the pharmacokinetics of epinephrine after administration of intranasal ARS-1 to healthy volunteers.

Pharmacodynamic Results

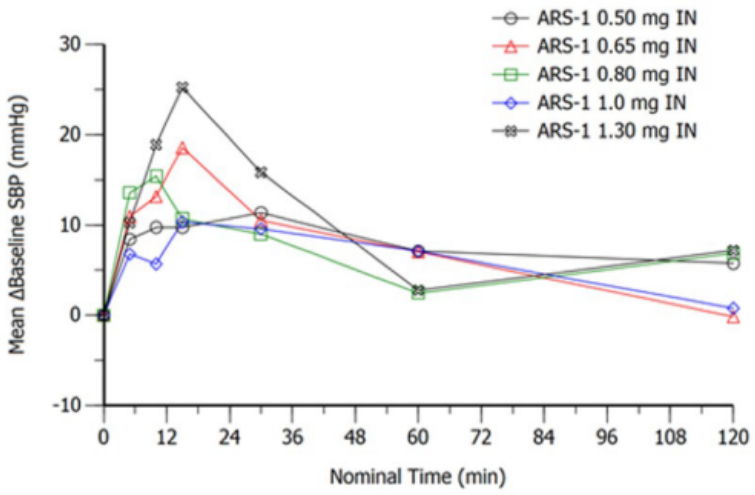
Systolic Blood Pressure

There was an apparent increase in SBP after administration of ARS-1, particularly for the 1.30 mg dose level. Based on mean SBP data, there was an increase of 10 to 25 mmHg above baseline after administration of ARS-1 and, for most dose levels, the maximum SBP was observed at 15 min post dose. In general, mean area under the effect curve (AUEC) for SBP was highest for 1.30 mg, but somewhat variable for lower dose levels. Mean AUEC0-30min ranged from 236 min*mmHg (1.0 mg) to 539 min*mmHg (1.30 mg); mean AUEC0-60min ranged from 495 min*mmHg (1.0 mg) to 869 min*mmHg (1.30 mg). Mean AUEClast was variable across dose levels and ranged from 2140 min*mmHg (1.30 mg) to 2810 min*mmHg (0.50 mg).

Table 50 Noncompartmental Parameters for SBP Change from Baseline after IN Administration of ARS-1

Treatment	N	AUEC 0-2min	AUEC 0-4min	AUEC 0-6min	AUEC 0-8min	AUEC 0-10min	AUEC 0-12.5min	AUEC 0-15min	AUEC 0-20min	AUEC 0-30min	AUEC 0-45min	AUEC 0-60min	AUEC last
		Geometric Mean (% CV)											
ARS-1 0.50 mg	12	3.38 (154%)	13.5 (154%)	29.7 (152%)	47.9 (143%)	67.2 (134%)	91.6 (128%)	116 (123%)	166 (115%)	271 (99.9%)	430 (88.3%)	563 (87.4%)	2810 (89.9%)
ARS-1 0.65 mg	12	4.38 (152%)	17.5 (152%)	38.6 (149%)	62.7 (139%)	89.1 (129%)	126 (121%)	167 (114%)	256 (106%)	402 (105%)	554 (111%)	679 (113%)	2590 (91.8%)
ARS-1 0.80 mg	12	5.46 (67.7%)	21.8 (67.7%)	47.9 (66.8%)	76.9 (63.3%)	107 (60.7%)	142 (58.2%)	174 (56.7%)	228 (60.9%)	327 (67.5%)	448 (70.4%)	523 (76.9%)	2500 (101%)
ARS-1 1.0 mg	12	2.71 (170%)	10.8 (170%)	23.6 (171%)	36.0 (179%)	47.7 (188%)	65.2 (183%)	86.3 (169%)	137 (142%)	236 (127%)	375 (127%)	495 (127%)	2270 (98.5%)
ARS-1 1.30 mg	12	4.12 (112%)	16.5 (112%)	37.1 (109%)	66.3 (96.3%)	103 (85.2%)	155 (74.2%)	212 (65.4%)	334 (56.1%)	539 (56.6%)	750 (62.3%)	869 (66.3%)	2140 (89.8%)

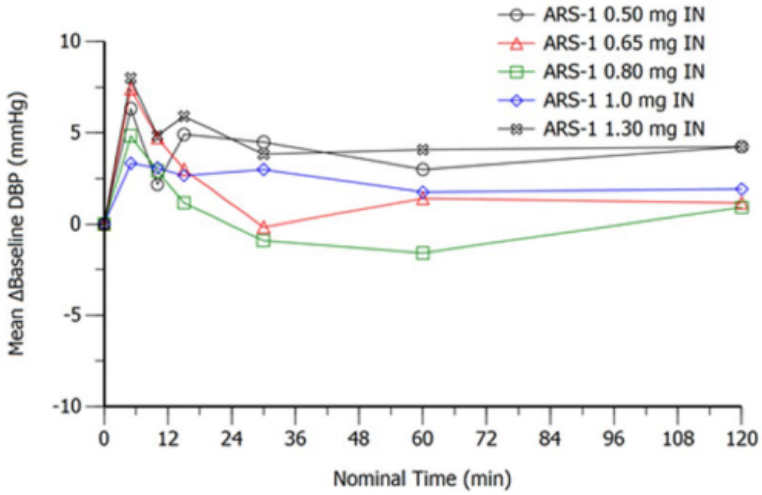
Figure 36 Mean SBP Change from Baseline after IN Administration of ARS-1 (Over 120 Minutes)



Diastolic Blood Pressure

No clear ARS-1 dose-related trends were observed for DBP. A small change in DBP was observed following administration of ARS-1. Based on mean DBP data, there was an increase of 3 to 8 mmHg above baseline at 5 min post dose. Mean AUEC for DBP was variable across dose levels of ARS-1. Mean AUEC0-30min ranged from 48.7 min*mmHg (0.80 mg) to 155 min*mmHg (1.30 mg); mean AUEC0-60min ranged from 14.2 min*mmHg (0.80 mg) to 274 min*mmHg (1.30 mg); mean AUEClast ranged from 578 min*mmHg (0.80 mg) to 1700 min*mmHg (0.65 mg).

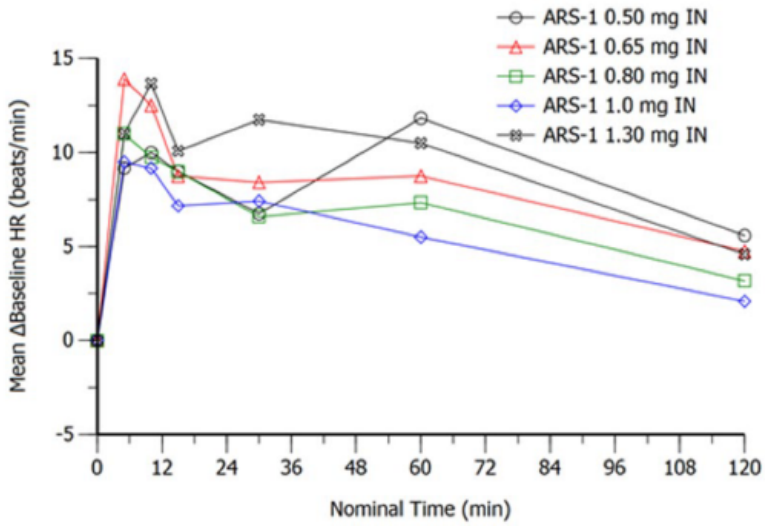
Figure 37 Mean DBP Change from Baseline after IN Administration of ARS-1 (Over 120 Minutes)



Pulse Rate

There was an increase in PR after administration of ARS-1. Based on mean PR data, there was an increase of 10 to 14 beats/min above baseline within 5 to 10 min after administration of ARS-1 and, in general, a decrease toward baseline over 480 min. Mean AUEC for PR increased with ARS-1 dose, but was similar for the 0.65, 0.80, and 1.0 mg treatments. Mean AUEC0-30min ranged from 221 min*beats/min (1.0 mg) to 312 min*beats/min (1.30 mg); mean AUEC0-60min ranged from 421 min*beats/min (1.0 mg) to 650 min*beats/min (1.30 mg). AUEClast was similar for the lowest dose levels; mean AUEClast ranged from 1980 min*beats/min (0.80 mg) to 2680 min*beats/min (0.65 mg).

Figure 38 Mean PR Change from Baseline after IN Administration of ARS-1 (Over 120 Minutes)



Pharmacokinetic Pharmacodynamic Correlations

For SBP, the correlation coefficients ranged from 0.1225 (0.80 mg) to 0.5098 (1.30 mg), suggesting that changes in epinephrine plasma concentration are positively correlated with changes in SBP. For DBP, the correlation coefficients ranged from -0.0481 (0.80 mg) to 0.1736 (1.30 mg). These results suggest that consistent with the lack of ARS-1 dose-related trends in the AUEC values, changes in DBP are not highly correlated to epinephrine plasma concentration. For PR, the correlation coefficients ranged from 0.1894 (0.65 mg) to 0.4915 (1.30 mg), suggesting that changes in epinephrine plasma concentration are positively correlated with changes in PR.

For both SBP and PR, the highest correlation was observed for 1.30 mg ARS-1, likely due to the pronounced change in baseline immediately following administration of ARS-1. The wide range in change from baseline values at low concentrations is due to the inclusion of all data during the entire PK and PD sampling interval; low plasma epinephrine concentrations were observed just after ARS-1 administration during the absorption phase and at the end of the PK sampling interval during the elimination phase.

CHMP comment

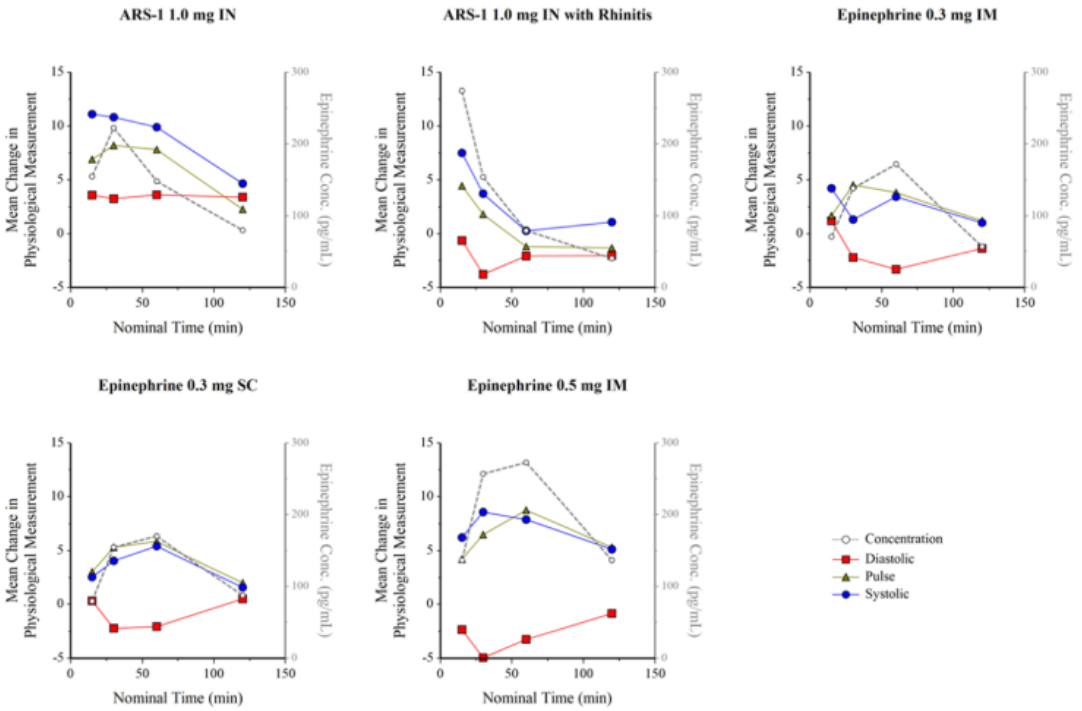
EPI 06 was a five-period, five-treatment, randomised crossover study of the pharmacokinetics of epinephrine after administration of intranasal ARS-1 to healthy volunteers. There was an apparent increase in SBP after administration of ARS-1, particularly for the 1.30 mg dose level). In general, mean area under the effect curve (AUEC) for SBP was highest for 1.30 mg, but somewhat variable for lower dose levels. No clear ARS-1 dose-related trends were observed for DBP. A small change in DBP was observed following administration of ARS-1. Based on mean DBP data, there was an increase of 3 to 8 mmHg above baseline at 5 min post dose. There was an increase in PR after administration of ARS-1. Based on mean PR data, there was an increase of 10 to 14 beats/min above baseline within 5 to 10 min after administration of ARS-1 and, in general, a decrease toward baseline over 480 min. Mean AUEC for PR increased with ARS-1 dose, but was similar for the 0.65, 0.80, and 1.0 mg treatments. When analysing the available data on the PD effect's dose-dependence, no clear correlation between dose and accepted surrogates of efficacy is apparent.

EPI04. 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.

Pharmacokinetic-Pharmacodynamic Analysis

Double y-axis plots of mean plasma epinephrine concentration and the mean change from baseline for SBP, DBP, and PR at initial 120 minutes post dose are presented in Figure 39.

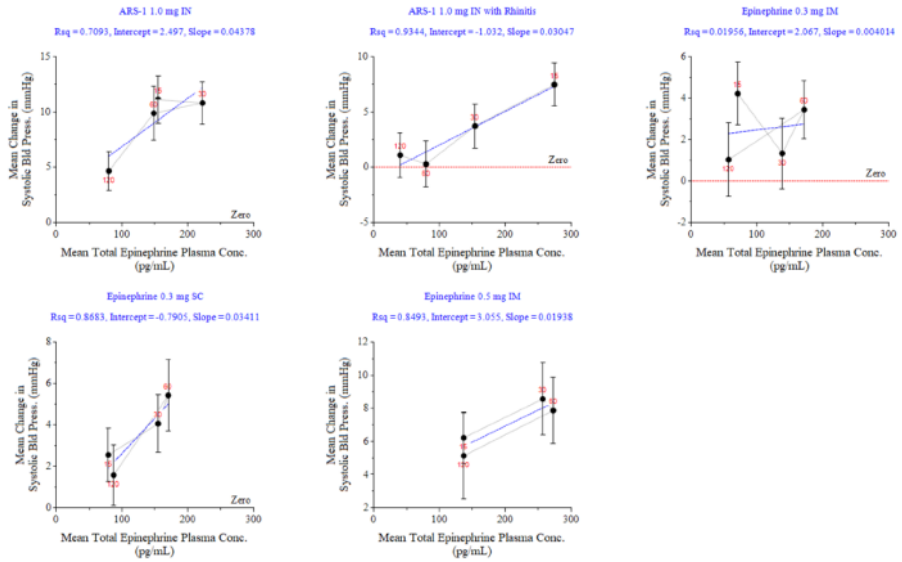
Figure 39 Mean Change in Vital Signs and Epinephrine Plasma Concentration during the Initial 120 Minutes Post dose, Sorted by Allergic Status and Treatment



Systolic Blood Pressure

A plot of the of mean (SD) change in SBP versus mean total epinephrine plasma concentration during the initial 120 minutes post dose is presented in Figure 40.

Figure 40 Hysteresis: Mean Change and (SD) from Baseline SBP vs Mean Epinephrine Concentration, Sorted by Allergic Status and Treatment

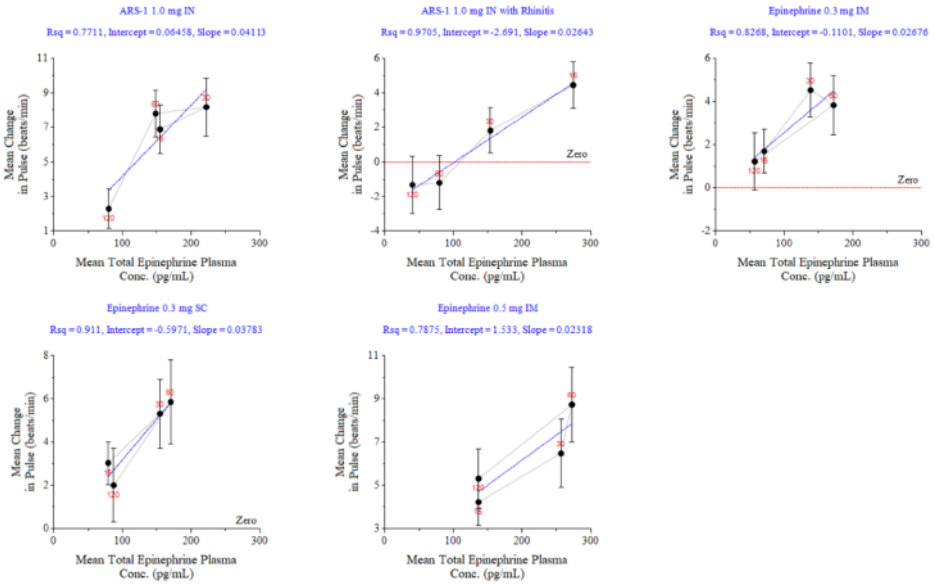


Blue dash line is the regression line, filled circle is the mean value, whiskers are the standard deviation, and the number in red adjacent to circle is the time point the values were averaged over.

Pulse Rate

A plot of the of mean (SD) change in PR versus mean total epinephrine plasma concentration during the initial 120 minutes post dose is presented in Figure 41.

Figure 41 Hysteresis: Mean Change and (SD) from Baseline Pulse Rate vs Mean Epinephrine Concentration, Sorted by Allergic Status and Treatment



Blue dash line is the regression line, filled circle is the mean value, whiskers are the standard deviation (SD), and the number in red adjacent to circle is the time point the values were averaged over.

Linear Mixed Effect Model Analysis

Systolic Blood Pressure

Results of the linear mixed effect analysis of change from baseline SBP versus total epinephrine and baseline corrected plasma concentrations are presented in Table 51.

Table 51 Linear Mixed Effect Analysis: Change from Baseline SBP (mmHg) vs Total Epinephrine and Baseline Corrected Plasma Concentrations

Treatment	Measurement	Slope	P Value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	Total epinephrine	0.0241	0.000628	0.0105	0.0377
	Baseline corrected	0.0244	0.000631	0.0106	0.0381
ARS-1 1.0 mg IN with Rhinitis	Total epinephrine	0.0233	6.12E-07	0.0146	0.0321
	Baseline corrected	0.0233	7.60E-07	0.0145	0.0321
Epinephrine 0.3 mg IM	Total epinephrine	0.00507	0.514	-0.0103	0.0204
	Baseline corrected	0.00488	0.534	-0.0106	0.0204
Epinephrine 0.3 mg SC	Total epinephrine	0.0241	0.000286	0.0113	0.0369
	Baseline corrected	0.0249	0.000196	0.0120	0.0378
Epinephrine 0.5 mg IM	Total epinephrine	0.0165	0.00451	0.00528	0.0278
	Baseline corrected	0.0166	0.00436	0.00536	0.0279

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, SC = subcutaneous.

Diastolic Blood Pressure

Results of the linear mixed effect analysis of change from baseline DBP versus total epinephrine and baseline corrected plasma concentrations are presented in Table 52.

Table 52 Linear Mixed Effect Analysis: Change from Baseline Diastolic Blood Pressure vs Total Epinephrine and Baseline Corrected Plasma Concentrations

Treatment	Measurement	Slope	P Value	Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	Total epinephrine	.00462	0.328	-0.00469	0.0139
	Baseline corrected	0.00475	0.319	-0.00464	0.0141
ARS-1 1.0 mg IN with Rhinitis	Total epinephrine	.00198	0.518	-0.00408	0.00804
	Baseline corrected	0.00195	0.528	-0.00415	0.00805
Epinephrine 0.3 mg IM	Total epinephrine	-0.0145	0.0143	-0.0261	-0.00295
	Baseline corrected	-0.0162	0.00693	-0.0278	-0.00451
Epinephrine 0.3 mg SC	Total epinephrine	-0.00941	0.0406	-0.0184	-0.000409
	Baseline corrected	-0.0103	0.0262	-0.0194	-0.00124
Epinephrine 0.5 mg IM	Total epinephrine	-0.0128	0.000986	-0.0202	-0.00535
	Baseline corrected	-0.0129	0.000923	-0.0203	-0.00544

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, SC = subcutaneous.

Pulse Rate

Results of the linear mixed effect analysis of change from baseline PR versus total epinephrine and baseline corrected plasma concentrations are presented in Table 53.

Table 53 Linear Mixed Effect Analysis: Change from Baseline Pulse Rate vs Total Epinephrine and Baseline Corrected Plasma Concentrations

Treatment	Measurement	Slope		Lower 95% CI	Upper 95% CI
ARS-1 1.0 mg IN	Total epinephrine	0.00648	0.302	-0.00588	0.0188
	Baseline corrected	0.00664	0.297	-0.00591	0.0192
ARS-1 1.0 mg IN with Rhinitis	Total epinephrine	0.0147	0.000259	0.00698	0.0225
	Baseline corrected	0.0147	0.000325	0.00681	0.0225
Epinephrine 0.3 mg IM	Total epinephrine	0.0179	0.00982	0.00439	0.0314
	Baseline corrected	0.0182	0.00944	0.00454	0.0319
Epinephrine 0.3 mg SC	Total epinephrine	0.0367	8.12E-10	0.0258	0.0476
	Baseline corrected	0.0374	4.54E-10	0.0265	0.0483
Epinephrine 0.5 mg IM	Total epinephrine	0.0208	1.58E-09	0.0148	0.0269
	Baseline corrected	0.0209	1.48E-09	0.0149	0.0270

Abbreviations: CI = confidence interval, IM = intramuscular, IN = intranasal, SC = subcutaneous.

CHMP comment

Results of the analysis indicated that epinephrine consistently increased the change in SBP for the various treatments and allergic statuses. The increase in SBP from epinephrine appears to be related to both the rate of absorption (tmax or pAUC0-45) and the maximum concentration (Cmax).

The mean change in DBP versus the mean epinephrine concentrations sorted by treatment and allergic status was also examined. Results of this analysis did not find a consistent positive or negative correlation between epinephrine plasma concentrations and change in DBP for the various treatments and allergic statues. A similar analysis was performed on the mean change in PR versus the mean epinephrine concentrations sorted by treatment and allergic status. Results of this analysis indicated that epinephrine increased the change in PR for the various treatments and allergic statuses. The PR also appears to be related to both the rate of absorption (tmax or pAUC0-45) and the maximum concentration (Cmax).

Linear Mixed Effect Change from Baseline Vital Signs and Mean Epinephrine Concentrations The purpose of this analysis was to quantify the correlations between change from baseline vital signs and epinephrine plasma concentrations. Epinephrine plasma concentrations (both total and baseline-corrected) were found to significantly increase the change from baseline SBP pressure for the various treatment/allergic status with the exception of the Epinephrine 0.3 mg IM. The relationship between epinephrine plasma concentrations and change from baseline DBP showed mixed results, both in terms of whether the correlation was positive or negative, and its statistical significance. With the exception of the ARS-1 1.0 mg IN in the normal condition (not significant), epinephrine plasma concentrations (both total and baseline-corrected, respectively) were found to significantly increase the change from baseline PR for the remainder of the 4 treatments and allergic-status.

EPI JP01. A Four-Treatment, Partially Randomized Crossover Study of the Pharmacokinetics of Adrenaline After Administration of ARS -1 or Adrenaline Injection in Subjects with Allergic Rhinitis.

Pharmacokinetic-Pharmacodynamic Analyses

Double Y Plots

Double y-axis plots of mean PK concentrations and mean SBP and PR change from baseline versus time are presented in Figure 42 (ARS-1 1.0 mg IN), Figure 43 (Epinephrine 0.3 mg IM), Figure 44 (EpiPen 0.3 mg), and Figure 45 (ARS-1 1.0 mg IN with Rhinitis).

Figure 42 Mean PK Concentration and Mean SBP and PR Change from Baseline vs. Time Following Administration of ARS-1 1.0 mg IN

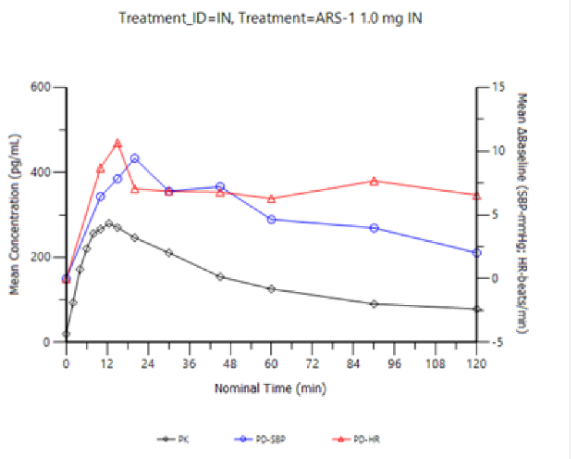


Figure 43 Mean PK Concentration and Mean SBP and PR Change from Baseline vs. Time Following Administration of Epinephrine 0.3 mg IM

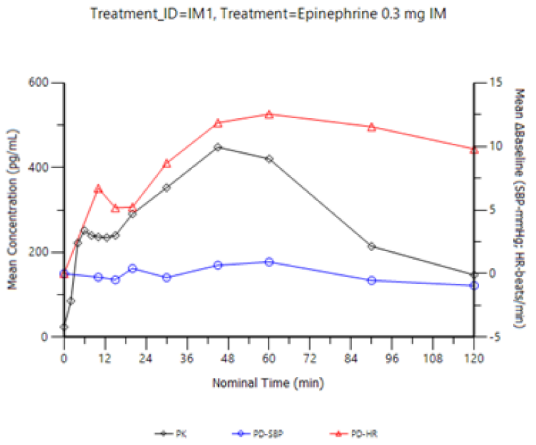


Figure 44 Mean PK Concentration and Mean SBP and PR Change from Baseline vs. Time Following Administration of EpiPen 0.3 mg

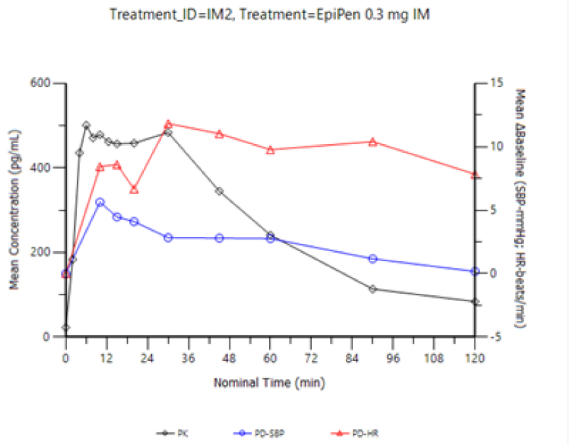
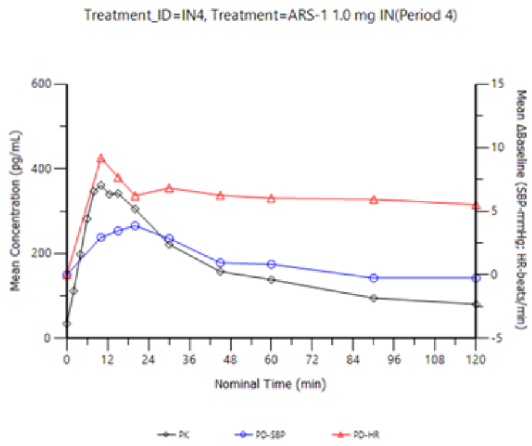


Figure 45 Mean PK Concentration and Mean SBP and PR Change from Baseline vs. Time Following Administration of ARS-1 1.0 mg IN with Rhinitis



CHMP comment

The mean changes from baseline SBP and PR follows a similar time course as that of the PK epinephrine concentration-time curves for all four treatments.

The SBP hysteresis for ARS-1 and EpiPen appear to be counter-clockwise. A clear hysteresis pattern was not consistently observed. DBP hysteresis appear to be clockwise, which indicates that the peak of mean epinephrine concentration occurred after peak of mean DBP. The mean PR showed a possible counter clockwise hysteresis for four treatments, suggesting that the peak of mean epinephrine concentration occurs followed by the peak of mean PR.

There was a significant relationship between change from baseline SBP, DBP, PR and epinephrine concentration for all treatments except Epinephrine 0.3 mg IM for SBP. The relationship between the early partial AUCs and partial AUECs up to 30 minutes for SBP change and up to 120 min for PR change were significant for all treatments.

3.3.3. Discussion on clinical pharmacology

The clinical development programme for Neffy (ARS-1) consists of clinical pharmacology studies which were conducted in healthy subjects and in allergic patients with chronic rhinitis. The clinical studies in the development programme for Neffy for this submission are: biopharmaceutic studies (considered as supportive: EPI 01, EPI 02, and EPI 06) and individual clinical pharmacology studies (considered as pivotal: EPI 03, EPI 04, EPI 07, and EPI JP01). Four studies were conducted with the commercial formulation of Neffy: EPI 03, EPI 04, EPI 07, and EPI JP01. The data to support this MAA is efficacy and safety data from ARS clinical trials based on surrogate pharmacodynamic endpoints. Randomised, controlled clinical studies in the treatment of patients at risk of anaphylaxis are considered unethical. This approach was established and confirmed with the EMA in Scientific Advice (EMEA/H/SA/4077/1/2019/SME/III). Pharmacodynamic scores that were used as a surrogate for adrenaline efficacy included measurements of blood pressure (systolic and diastolic) as well as heart rate. A comparison of PD responses following ARS-1 administrations (once or twice) was also performed as part of the PD analysis, taking into account dose dependence. A comparison was also made with adrenaline administered by the intramuscular route using EpiPen at doses of 0.3 - 0.5 mg. In accordance with the recommendations in the Scientific Advice, 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.

During all clinical studies for PK data assessment, the determination of epinephrine in human plasma was performed. All parameters recommended for assessment according to guideline for bioanalytical methods (EMA/CHMP/ICH/172948/2019) were addressed during validation and all of them were acceptable. However, bioanalysis reports from studies EPI 01, EPI 03 and EPI 04 could not be found in the dossier and should be provided by the applicant. (OC).

The applicant has conducted Population Pharmacokinetic assessments (POP PK) and Physiologically Based Absorption Model (PBAM) to evaluate the data and extrapolate the pharmacokinetics and pharmacodynamics to other populations including children down to age 4 years. In the modelling, the applicant mainly considered body weight as the main factor influencing the pharmacokinetic parameters of ARS-1. No analysis by sex was performed and should be provided. (OC)

For dose escalation, a study EPI 02 was performed. The median tmax was 20 minutes for ARS-1, and 35 minutes for Epinephrine 0.3 mg IM. The geometric mean Cmax and AUC0–t were comparable between the two groups (305 vs. 236 pg/mL and 44,221 vs. 45,294 min•pg/mL, respectively). In most studies, the Tmax for Neffy was 20 minutes. In the part 1 of the study (EPI-02), the time was 28.3, 12.7, 12.3 depending on the dose. The applicant is invited to comment on these changes in the Tmax

in relation to the used dose. (OC). Furthermore, the Cmax obtained for subsequent doses (0.5, 1.0 and 2.0 of ARS) is not proportionally related to the dose used. The applicant is invited to comment this significant increase in Cmax after administration of higher doses. (OC). In both studies, Epi 01 and EPI 02, determination of distribution and elimination PK parameters was to be conducted but results were not submitted. The applicant is asked to attach missing results (OC).

In the study EPI 06 the bioavailability of the following five adrenaline concentrations of Neffy was assessed: 0.50 mg, 0.65 mg, 0.80 mg, 1 mg, and 1.3 mg. Following ARS-1, mean adrenaline plasma concentrations generally increased with dose, although mean adrenaline concentrations after 0.65 mg and 0.80 mg doses were not markedly different from each other. In general, exposure to adrenaline increased with the increasing doses of ARS-1. No clear ARS-1 dose-related trends were observed for DBP. When analyzing the available data on the PD effect's dose-dependence, no clear correlation between dose and accepted surrogates of efficacy is apparent.

Four clinical pharmacology studies were conducted with Neffy (EPI 03, EPI 04, EPI 07, and EPI JP01) to demonstrate the efficacy and safety of adrenaline by the nasal route of administration.

The study EPI 03 assessed the bioavailability of both a single dose and repeat dose of ARS-1 1 mg IN as compared to a single and repeat dose of IM epinephrine injection. Intranasal administration of ARS-1 1 mg reached the epinephrine plasma concentration level of 100 pg/mL as fast, as the IM route of administration. The cumulative time the epinephrine plasma concentrations were above 100 pg/mL were similar for ARS-1 1 mg IN and Epinephrine 0.3 mg IM injection single or twice dosing. However, for the second intranasal administration, the maximum levels obtained were significantly higher. Assuming that the effective level is 100 pg/mL, the observed 600 pg/mL after repeated intranasal administration of I.M. compared to 300 pg/mL after I.M. administration, appears to be an excessive level which raises safety concerns. The applicant is asked to comment on this issue. (OC). The pharmacodynamic results demonstrated that relative to Epinephrine IM, single- and twice dosed ARS-1 1 mg IN had a greater mean effect on SBP and HR. Given the more remarkable mean change in SBP after administration of I.N. from an efficacy perspective, greater efficacy may be expected compared to administration of I.M. However, although the extent of change (Min and Max effect) after administration of I.N. was smaller, the greater mean effect may raise questions about the safety of administration particularly in the elderly population, for example. The applicant is invited to discuss this issue. (OC) It should also be noted that surrogates of the clinical effect include not only changes in SBP and HR but also DBP. The study results indicate that the impact of ARS-1 on DBP is in a completely different direction from those of I.M. The applicant is asked to discuss the different DBP responses after I.N. administrations. (OC)

In the study EPI 04 the comparative bioavailability of epinephrine after IN administration of ARS-1 in subjects with induced allergic rhinitis was assessed and the impact of nasal oedema and congestion on the absorption of epinephrine was evaluated. The study demonstrates that allergic rhinitis results in a more rapid rate of epinephrine absorption following ARS-1 1 mg IN, a slightly higher Cmax values (geometric mean 243 pg/mL versus 320 pg/mL under normal and rhinitis conditions, respectively). While drug exposure during the first 30-minutes following ARS-1 administration (the crucial time period for efficacy) is higher under rhinitis conditions, the overall AUC0-t is lower relative to normal conditions. The effect of the drug is significantly reduced 30 minutes after administration and almost disappears after 60 minutes. This is a worrying phenomenon that raises the issue of the persistence of the post-dose response in patients with anaphylaxis who simultaneously develop symptoms such as rhinitis. The applicant is invited to discuss whether faster elimination of the drug does not carry a risk of recurrence of symptoms resulting from a rapid reduction of adrenaline concentrations. (OC)

The study Epi 07 assessed the comparative bioavailability of epinephrine after IN administration of ARS-1 (1.0 milligram (mg) with EpiPen (0.3 mg IM injection of epinephrine) after both one and two doses in healthy volunteers under fasted conditions.

The pharmacokinetic results of the EPI07 study show that ARS-1 results in similar pharmacokinetic results as EpiPen and that both products have comparable pharmacokinetic parameters with both single and repeat dosing. 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 03 and 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.

The EPI JP01 study the pharmacokinetics (PK) of adrenaline after administration of ARS-1 1 mg IN in Japanese subjects with normal nasal conditions and with induced allergic rhinitis and the impact of nasal oedema and congestion on the absorption of adrenaline was evaluated.

The study JP-01 observed approximately twice as high Cmax values after EpiPen 0.3 mg I.M. compared to ARS-1. Similarly, higher parameters were observed for AUC0-t, indicating a significantly higher exposure than in the Epi03 or Epi07 study other studies. In the EPI JP01 study, the effect on PD parameters after ARS-1 administration was slightly different from previous studies. Administration of ARS-1 in healthy subjects did not result in a similar increase in DBP as in other studies conducted. Furthermore, the change in DBP after administering ARS-1 in patients with rhinitis was different from previous studies, where it resembled that observed after administration of epinephrine I.M.

In general, the PK and statistical methods (descriptive analysis) are considered acceptable. PK endpoints selected (i. e. AUC0-t, AUCpartial, Cmax and tmax) are considered appropriate. The inclusion of early partial AUCs, that should be calculated on each early blood samples until 20 minutes, i.e. starting at 2 minutes and every 2 minutes until 10 minutes was agreed in SA (EMEA/H/SA/4077/1/2019/SME/III).

The intra-subject coefficient of variation (CV) (%) of ARS-1 from the bioequivalence studies EPI 03, EPI 04, EPI 07 and EPI JP01 for Cmax, AUC 0-45 and AUC 0-T usually exceeded 50%. The high variability demonstrated across the studies is considered to be of concern. The applicant has not presented adequate discussion on inter-individual factors that could attribute to it (nasal anatomy of different individuals, condition of nasal mucosa etc). Additional information is required from the applicant. (OC)

All studies were conducted in adult healthy volunteers with maximal age of 55 years and body mass index (BMI) till 30 kg/m2, so data about ARS-1 pharmacokinetics in paediatric and special population (example, elderly and/or patients with BMI ≥30 kg/m2) is not available yet.

However, for this specific type of product to be used in life-threatening emergency situations, where sufficient early systemic exposure (within minutes) is necessary to prevent fatal consequences and randomised clinical trial with patients are not possible, absorption is of paramount importance to inform on anticipated therapeutic effect in target population. Thus, every aspect which might affect absorption of intranasally administered adrenaline should have been studied and discussed, which is not the case with the dossier provided by the applicant. In clinical studies conducted with ARS-1,

absorption is mainly characterised in healthy adult volunteers. Specific patient populations studied are limited to patients with induced allergic rhinitis. Thus, the population studied does not reflect the one expected in real-world clinical practice. No data nor sufficient discussion is provided regarding absorption in patients with damaged nasal mucosa and septal defects, in overweight/ obese patients, in patients using concomitant medicinal products, e.g., nasal decongestants, intranasally administered/ inhaled corticosteroids etc. It should also be noted that even healthy study subjects show significant interindividual variability in absorption parameters, which is far higher than that observed in the same study subjects following IM administration of epinephrine. These findings raise concerns that some patients could fail to reach sufficient plasma concentrations for a therapeutic effect. Moreover, these concerns are exacerbated by proposed shelf-lime assay limits for the active substance and permeability enhancer DDM as well as by non-clinical data on the effect of different DDM concentrations on absorption parameters of the active substance (OC).

In addition, data show that, even with repeated administration of ARS-1 1 mg IN, there were subjects who failed to reach the threshold epinephrine plasma concentration of 100 pg/mL at which Pharmacological responses are anticipated to be elicited. In contrast, 100% of subjects reached this threshold with repeated administration of Epinephrine 0.3 mg IM and EpiPen 0.3 mg.

No clinical study researching the metabolism of adrenaline was performed by the applicant as the metabolism of adrenaline is well established and reviewed in the literature. Furthermore, no inter-conversion, PK of metabolites or consequences of possible genetic polymorphism were researched. The intra and inter variability summary observation revealed that the variability of PK parameters in subjects receiving ARS-1 I.N. is significantly higher than in those receiving I.M. with EpiPen administration. The applicant is asked to discuss the reasons for this increased variability as the application of intranasal form was supposed to reduce the consequences of inappropriate administration of adrenaline injections (OC).

Some issues need to be cleared according to the special populations studies. The applicant has not conducted studies on ARS-1 in the EU population. The applicant is asked to discuss whether the results obtained in other studies on the US population, can be extrapolated to the European population.(OC) No PK interaction study was performed during clinical development of the product, as the adrenaline PK interaction comes from prior clinical use of adrenaline and additional studies would not broad current scientific knowledge.

The PK/PD programme is considered sufficient to support the marketing authorisation, but some concerns need to be addressed (LoQ).

3.3.4. Conclusions on clinical pharmacology

In summary, the available PD data indicate that epinephrine administered intranasally may offer an alternative to treatment with intramuscular injections. The surrogates of efficacy adopted appear adequate, in particular SBP and HR. The relevance of DBP for the assessment of PD effects of ARS-1 appear inconclusive and require further justification. The different response of PD in subjects with allergic rhinitis also needs clarification, particularly in terms of the persistence of the desired clinical effect. Several other issues also need to be clarified.

3.3.5. Clinical efficacy

No efficacy studies have been conducted by the applicant. The Summary of Clinical Efficacy was submitted to summarise the results of pharmacodynamic and pharmacokinetic studies described in Section PK/PD as well as available literature data.

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. Moreover, 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). There are several factors driving the lack of such studies. First, it is often impossible to predict when and whether an allergic episode will progress to anaphylaxis, and the clinical course of allergic reactions can be unpredictable. 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). Second, given the high degree of variability in severe allergic reactions (type of allergen, treatments provided, etc.) a large study population would be required in order to achieve sufficient statistical validity (Fisher-1987, Hu-2004), something that is a particularly large practical barrier given the relative infrequency of anaphylaxis. Third, adrenaline has been accepted as a treatment for anaphylaxis over 100 years with various routes of administration and it is doubtful whether there is sufficient equipoise to support such a trial (Hu-2004, Fisher-1987). Taken together, these issues illustrate why conducting such trials is fraught with ethical and methodological difficulties (Sheikh-2008, Simons-2001). It is worth noting that the approval of EpiPen by the FDA was based entirely on literature without any clinical trials including pharmacokinetic or pharmacodynamic data, and the same is true for subsequent MAA applications for other adrenaline auto-injector products conducted without studies in anaphylaxis or severe allergy patients.

Table 54 Summary of Efficacy for Trial EPI03

<table>
<tr><td colspan="3">Title: A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of ARS-1 and IM Epinephrine to Healthy Volunteers</td></tr>
<tr><td>Study Identifier</td><td colspan="2">EPI 03</td></tr>
<tr><td>Design</td><td colspan="2">Phase 1, randomised, single-dose, five treatment, five-period, crossover study that consisted of a screening period, a baseline period, and an Open-Label randomised treatment period. The bioavailability of both a single dose and repeat dose of ARS-1 1 mg IN was assessed as compared to a single and repeat dose of IM epinephrine injection.
Each subject was randomised to receive one of the following:
• A single 1 mg/100 µL IN dose of ARS-1 1 mg IN in the left nostril,
• Two (2) 1 mg/100 µL IN doses of ARS-1 1 mg IN in the left and right nostril spaced 5 minutes apart,
• A single 0.3 mg in 0.3 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh,
• Two (2) 0.3 mg in 0.3 mL (1 mg/mL) doses of IM epinephrine injection in the left and right anterolateral thigh, spaced 5 minutes apart,
• A single 0.5 mg in 0.5 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:

Duration of Extension phase:</td><td>21-day screening period and 7-day, 6-night, confinement period for dosing.
not applicable>

not applicable></td></tr>
</table>

Hypothesis	The PD responses of adrenaline after IN administration via ARS-1 was comparable to the PD responses following IM injection after both one and two doses in healthy volunteers under fasted conditions.		
Treatments Groups	ARS-1 1 mg IN		A single 1 mg/100 µL IN dose of ARS-1 1 mg IN in the left nostril N = 68
	ARS-1 1 mg IN Twice		Two (2) 1 mg/100 µL IN doses of ARS-1 1 mg IN in the left and right nostril spaced 5 minutes apart N = 70
	Epinephrine 0.3 mg IM		A single 0.3 mg in 0.3 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh N = 68
	Epinephrine 0.3 mg IM Twice		Two (2) 0.3 mg in 0.3 mL (1 mg/mL) doses of IM epinephrine injection in the left and right anterolateral thigh, spaced 5 minutes apart N = 70
	Epinephrine 0.5 mg IM		A single 0.5 mg in 0.5 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh N = 69
Endpoints and Definitions	Systolic Blood Pressure – Maximum Effect	SBP E_{max}	Maximum change from baseline SBP (mmHg)
	Heart Rate – Maximum Effect	HR E_{max}	Maximum change from baseline PR (bpm)
	Time to Maximum SBP Effect	SBP T_{Emax}	Time to maximum SBP effect (minutes)
	Time to Maximum HR Effect	HR T_{Emax}	Time to maximum HR effect (minutes)
Database lock	07 June 2019		

<u>Results and Analysis</u>

As discussed in Section 2.7.3, pharmacodynamic (PD) endpoints are considered surrogates for efficacy.

Analysis description	Primary Analysis					
Analysis population and time point description	The PD analysis set included all subjects who completed least one treatment during this study and had evaluable concentration-time profiles. A total of 70 subjects were enrolled in this study and received at least one dose of study drug					
Descriptive statistics and estimate variability	Treatment group	ARS-1 1 mg IN	ARS-1 1 mg IN Twice	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg IM Twice	Epinephrine 0.5 mg IM
	Number of subjects	68	70	68	70	69
	SBP E_{max} (mean)	17.0	25.6	11.1	13.4	13.1

	SBP E_{max} (CV%)	48.6	50.6	66.3	71.1	78.2
	HR E_{max} (mean)	16.0	23.2	12.8	17.0	15.1
	HR E_{max} (CV%)	56.1	43.4	59.5	45.2	60.5
	SBP T_{Emax} (median)	20.5	21.0	31.5	21.5	31.0
	HR T_{Emax} (median)	15.0	20.0	30.0	45.0	45.0
Effect estimate per comparison	SBP Emax	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.3 mg IM		
		Least Squares Mean Difference		5.96		
		Lower 90% CI, Upper 90% CI		3.87 8.05		
		P-value		$1.03E^{-05}$		
	SBP Emax	Comparison groups		ARS-1 1 mg IN twice vs Epinephrine 0.3 mg IM twice		
		Least Squares Mean Difference		12.2		
		Lower 90% CI, Upper 90% CI		9.41 15.0		
		P-value		$4.92E^{-10}$		
	SBP Emax	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.5 mg IM		
		Least Squares Mean Difference		3.88		
		Lower 90% CI, Upper 90% CI		1.40 6.36		
		P-value		0.0111		
	HR Emax	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.3 mg IM		
		Least Squares Mean Difference		3.25		
		Lower 90% CI, Upper 90% CI		1.11 5.39		
		P-value		0.0135		
	HR Emax	Comparison groups		ARS-1 1 mg IN twice vs Epinephrine 0.3 mg IM twice		

		Least Squares Mean Difference	6.18
		Lower 90% CI, Upper 90% CI	3.85 8.50
		P-value	$3.42E^{-05}$
	HR Emax	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.5 mg
		Least Squares Mean Difference	0.915
		Lower 90% CI, Upper 90% CI	-1.54 3.37
		P-value	0.537
Notes	Overall, ARS-1 1 mg elicited increases in SBP and HR that were both more rapid and more pronounced than the increases observed following IM injection. The more rapid and greater mean increased in SBP and HR that were observed following IN administration may lead to benefits on time-to-effect and potentially overall efficacy in patients with a severe systemic allergic reaction. The haemodynamic responses to ARS-1 1 mg IN dosed once were comparable to the responses observed following Epinephrine 0.5 mg IM, a clinically established safe and effective dose. Additionally, given that it is well published that Epinephrine 0.5 mg IM is more effective than Epinephrine 0.3 mg IM on a single dose, the findings of the present study may indicate a reduced need for a second dose of IN epinephrine		
Analysis description	<Secondary analysis> <Co-primary Analysis> <Other, specify: >		
	No secondary efficacy endpoints		

Table 55 Summary of Efficacy for Trial EPI04

Title: 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	
Study Identifier	EPI 04
Design	Phase 1, single-dose, five-period study that consisted of a screening period, a baseline period, and an open-label treatment period. Healthy volunteer subjects with no apparent rhinitis symptoms were randomised to receive: • ARS-1 1 mg IN • Epinephrine 0.3mg IM injection, and • Epinephrine 0.3mg SC injection The fourth period was a sequential treatment wherein subjects received ARS-1 1 mg IN following an allergy challenge where apparent rhinitis symptoms were confirmed (TNSS score of $\geqslant$ 5 out of 12 and a congestion score of $\geqslant$ 2 out of 3). The fifth period included subjects who previously participated and completed the Treatment period 1-4. These subjects received 0.5 mg IM epinephrine injection. Treatments were separated by a 24-hour wash out period.

	Duration of main phase:		60-day screening period; 4-day study period. Treatment 5 consisted of an additional 2 days (1-day baseline period and 1-day study period)			
	Duration of Run-in phase:		not applicable			
	Duration of Extension phase:		not applicable			
Hypothesis	The PD responses of adrenaline after IN administration via ARS-1 was comparable to the PD responses following IM or SC injection, and was not affected by rhinitis.					
Treatments Groups	ARS-1 1 mg IN		A single 1 mg/100 µL IN dose of ARS-1 1 mg IN in the left nostril N = 35			
	ARS-1 1 mg IN with rhinitis		A single 1 mg/100 µL IN doses of ARS-1 1 mg IN in the left nostril following induction of rhinitis N = 33			
	Epinephrine 0.3 mg IM		A single 0.3 mg in 0.3 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh N = 36			
	Epinephrine 0.3 mg SC		A single 0.3 mg in 0.3 mL (1 mg/mL) doses of SC epinephrine injection in the left anterolateral thigh, N = 35			
	Epinephrine 0.5 mg IM		A single 0.5 mg in 0.5 mL (1 mg/mL) dose of IM epinephrine injection in the left anterolateral thigh N = 23			
Endpoints and Definitions	Systolic Blood Pressure – Maximum Effect	SBP Max change from baseline	Maximum change from baseline SBP (mmHg)			
	Heart Rate – Maximum Effect	HR Max change from baseline	Maximum change from baseline HR (bpm)			
Database lock	26 April 2019					
Results and Analysis As discussed in Section 2.7.3, pharmacodynamic (PD) endpoints are considered surrogates for efficacy.						
Analysis description	Primary Analysis					
Analysis population and time point description	The PD analysis set included all subjects who completed least one treatment during this study and had evaluable concentration-time profiles. A total of 36 subjects were enrolled in this study and received at least one dose of study drug					
Descriptive statistics and estimate variability	Treatment group	ARS-1 1 mg IN	ARS-1 1 mg IN with Rhinitis	Epinephrine 0.3 mg IM	Epinephrine 0.3 mg SC	Epinephrine 0.5 mg IM
	Number of subjects	35	33	36	35	23

	SBP Max change from baseline (mean)	13.2	5.4	4.2	7.7	13.6
	SBP Max change from baseline (SD)	18.90	17.18	15.58	15.05	13.36
	HR Max change from baseline (mean)	11.5	6.3	8.6	8.5	10.3
	HR Max change from baseline (SD)	12.94	14.80	13.24	16.16	11.89
Effect estimate per comparison	SBP Max change from baseline	Comparison groups		ARS-1 1 mg IN vs ARS-1 1 mg IN with Rhinitis		
		Least Squares Mean Difference		7.8		
		Lower 95% CI, Upper 95% CI		-0.98 16.54		
		P-value		0.081		
	SBP Max change from baseline	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.3 mg IM		
		Least Squares Mean Difference		-9.0		
		Lower 95% CI, Upper 95% CI		-17.19 -0.81		
		P-value		0.032		
	SBP Max change from baseline	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.3 mg SC		
		Least Squares Mean Difference		-5.4		
		Lower 95% CI, Upper 95% CI		-13.58 2.72		
		P-value		0.188		
	SBP Max change from baseline	Comparison groups		ARS-1 1 mg IN vs Epinephrine 0.5 mg IM		
		Least Squares Mean Difference		0.4		
		Lower 95% CI, Upper 95% CI		-8.72 9.50		

		P-value	0.931
	HR Max change from baseline	Comparison groups	ARS-1 1 mg IN vs ARS-1 1 mg IN with Rhinitis
		Least Squares Mean Difference	5.2
		Lower 95% CI, Upper 95% CI	-1.57 11.88
		P-value	0.131
	HR Max change from baseline	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.3 mg IM
		Least Squares Mean Difference	-2.9
		Lower 95% CI, Upper 95% CI	-9.07 3.33
		P-value	0.358
	HR Max change from baseline	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.3 mg SC
		Least Squares Mean Difference	-2.9
		Lower 90% CI, Upper 90% CI	-9.93 4.04
		P-value	0.403
	HR Max change from baseline	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.5 mg IM
		Least Squares Mean Difference	-1.2
		Lower 90% CI, Upper 90% CI	-7.94 5.55
		P-value	0.724

Notes	The results indicated that all epinephrine formulations increased SBP and PR. ARS-1 1 mg IN administration resulted in a more rapid and pronounced increase in these vital signs compared to Epinephrine 0.3 mg IM. The EPI 04 study was not designed to gather robust haemodynamic data, and the first time point for blood pressure and pulse rate monitoring was at 15 minutes, which was 5 minutes later than the tmax observed following administration of ARS-1 1 mg IN under normal conditions. Given this, it is possible that the peak haemodynamic effect could have occurred prior to the first PD time point. Additionally, even if the haemodynamic response during the Type 1 allergic response (Allergic Rhinitis) was suppressed by the histamine and/or the peak effect was missed, thus underestimating the increase in systolic blood pressure, the effect of ARS-1 1 mg IN on systolic blood pressure was still greater than the response observed following Epinephrine 0.3 mg IM under normal (non-rhinitis) conditions. Given that Epinephrine 0.3 mg IM is well known to be safe and efficacious, the effect of rhinitis in suppressing the blood pressure is not considered a concerned for efficacy.
Analysis description	<Secondary analysis> <Co-primary Analysis> <Other, specify: >
	No secondary efficacy endpoints

Table 56 Summary of Efficacy for Trial EPI07

Title: A Five-Period, Five-Treatment, Randomized Crossover Study of the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 or EpiPen to Healthy Volunteers		
Study Identifier	EPI 07	
Design	Phase 1, randomised, single-dose, five-treatment, five-period, crossover study that consisted of a screening period, a baseline period, and an open-label randomised treatment period. The bioavailability of both a single dose and repeat dose of ARS-1 1 mg IN was assessed as compared to a single and repeat dose of EpiPen (0.3 mg IM epinephrine auto-injector). Each subject was randomised to receive one of the following: • a single 1 mg/100 µL IN dose of ARS-1 in the left nare, • two 1 mg/100 µL IN doses of ARS-1 one in the left and one in the right nare, spaced 10 minutes apart, • two 1 mg/100 µL IN doses of ARS-1 both in the left nare, spaced 10 minutes apart, • a single EpiPen (0.3 mg in 0.3 mL) dose of IM epinephrine injection in the left anterolateral thigh, • two EpiPen (0.3 mg in 0.3 mL) doses of IM epinephrine injection one in the left and one in the right anterolateral thigh, spaced 10 minutes apart.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	28-day screening period and 6-day, 5-night, confinement period for dosing. not applicable> not applicable>
Hypothesis	The PD responses of adrenaline after IN administration via ARS-1 was comparable to the PD responses following IM injection or EpiPen after both one and two doses in healthy volunteers under fasted conditions.	
Treatments Groups	ARS-1 1 mg IN	A single 1 mg/100 µL IN dose of ARS-1 1 mg IN in the left nostril N = 35

	ARS-1 1 mg IN Twice (L/R)		Two (2) 1 mg/100 µL IN doses of ARS-1 1 mg IN in the left and right nostril spaced 10 minutes apart N = 35
	ARS-1 1 mg IN Twice (L/L)		Two (2) 1 mg/100 µL IN doses of ARS-1 1 mg IN both in the left nostril spaced 10 minutes apart N = 36
	EpiPen 0.3 mg		a single EpiPen (0.3 mg in 0.3 mL) dose of IM epinephrine injection in the left anterolateral thigh N = 35
	EpiPen 0.3 mg Twice (L/R)		Two EpiPen (0.3 mg in 0.3 mL) doses of IM epinephrine injection one in the left and one in the right anterolateral thigh, spaced 10 minutes apart N = 36
Endpoints and Definitions	Systolic Blood Pressure – Maximum Effect	SBP E_{max}	Maximum change from baseline SBP (mmHg)
	Heart Rate – Maximum Effect	HR E_{max}	Maximum change from baseline PR (bpm)
	Time to Maximum SBP Effect	SBP T_{Emax}	Time to maximum SBP effect (minutes)
	Time to Maximum PR Effect	PR T_{Emax}	Time to maximum PR effect (minutes)
Database lock	23 August 2019		
Results and Analysis As discussed in Section 2.7.3, pharmacodynamic (PD) endpoints are considered surrogates for efficacy.			
Analysis description	Primary Analysis		
Analysis population and time point description	The PD analysis set included all subjects who completed least one treatment during this study and had evaluable concentration-time profiles. A total of 36 subjects were enrolled in this study and received at least one dose of study drug		

Descriptive Statistics and Estimate Variability	Treatment group	ARS-1 1 mg IN	ARS-1 1 mg IN Twice (L/R)	ARS-1 1 mg IN Twice (L/L)	EpiPen 0.3 mg	EpiPen 0.3 mg Twice (L/R)
	Number of subjects	35	35	36	35	36
	SBP E_{max} (mean)	22.8	30.8	41.6	18.7	27.0
	SBP E_{max} (CV%)	43.7	47.9	41.8	46.9	47.7
	PR E_{max} (mean)	20.7	25.7	29.8	18.9	23.6

	PR E_{max} (CV%)	46.8	39.4	38.3	49.3	41.9
	SBP T_{Emax} (median)	21.0	25.0	21.0	25.0	21.0
	PR T_{Emax} (median)	25.0	25.0	21.0	45.0	38.0

Effect Estimate per Comparison	SBP Emax	Comparison groups	ARS-1 1 mg IN vs EpiPen 0.3 mg
		Least Squares Mean Difference	4.36
		Lower 90% CI, Upper 90% CI	-0.39 9.10
		P-value	0.1308
	SBP Emax	Comparison groups	ARS-1 1 mg IN twice (L/R) vs EpiPen 0.3 mg twice (L/R)
		Least Squares Mean Difference	3.74
		Lower 90% CI, Upper 90% CI	0.98 8.45
		P-value	0.1919
	SBP Emax	Comparison groups	ARS-1 1 mg IN twice (L/L)vs EpiPen 0.3 mg twice (L/R)
		Least Squares Mean Difference	14.6
		Lower 90% CI, Upper 90% CI	9.90 19.25
		P-value	<0.0001
	PR Emax	Comparison groups	ARS-1 1 mg IN vs EpiPen 0.3 mg
		Least Squares Mean Difference	1.84
		Lower 90% CI, Upper 90% CI	-1.32 5.00
		P-value	0.3361
	PR Emax	Comparison groups	ARS-1 1 mg IN twice (L/R)vs EpiPen 0.3 mg twice (L/R)
		Least Squares Mean Difference	1.90
		Lower 90% CI, Upper 90% CI	-1.24 5.05

		P-value	0.3174
	PR Emax	Comparison groups	ARS-1 1 mg IN twice (L/L) vs EpiPen 0.3 mg twice (L/R)
		Least Squares Mean Difference	6.19
		Lower 90% CI, Upper 90% CI	3.07 9.30
		P-value	0.0013
Notes	ARS-1 1.0 mg IN once and twice (L/R) showed higher SBP E_{max} but was not statistically significant compared to EpiPen 0.3 mg and twice (L/R). ARS-1 1.0 mg IN twice (L/L) had the greatest impact on SBP E_{max}. Additionally, E_{max} occurred around the same time in all treatments (median T_{Emax} 21.0 to 25 minutes). There was no statistical difference in PR E_{max} between ARS-1 1.0 mg IN once and twice (L/R) and EpiPen 0.3 mg once and twice (L/R). ARS-1 1.0 mg IN twice (L/L) had the greatest impact on SBP E_{max}. Additionally, E_{max} occurred earlier in ARS-1 than EpiPen. In general, the maximum change in any one individual in SBP and PR was similar across single dose and repeat dose groups with both ARS-1 and EpiPen.		
Analysis description	<Secondary analysis> <Co-primary Analysis> <Other, specify: >		
	No secondary efficacy endpoints		

Table 57 Summary of Efficacy for Trial EPI JP01

Title: A Four-Treatment, Partially Randomized Crossover Study of the Pharmacokinetics of Adrenaline After Administration of ARS -1 or Adrenaline Injection in Subjects with Allergic Rhinitis	
Study Identifier	EPI JP01
Design	Phase 1, single-dose, four-period study that consisted of a screening period, baseline period, and an open-label treatment period. Subjects were randomised to the three following treatment routes during the Treatment periods 1-3. • 1 mg ARS-1 adrenaline intranasal in the left nostril, • 0.3 mg adrenaline IM injection in the left anterolateral thigh via needle/syringe • 0.3 mg adrenaline IM injection in the left anterolateral thigh via EpiPen A fourth treatment period was defined as dosing of ARS-1 after allergy challenge to induce allergic rhinitis symptoms.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		60-day screening period; 4-day study period.) not applicable> not applicable		
Hypothesis	The PD responses of adrenaline after IN administration via ARS-1 was comparable to the PD responses following IM injection or EpiPen and was not affected by rhinitis.				
Treatments Groups	ARS-1 1 mg IN		A single 1 mg/100 µL IN dose of ARS-1 1 mg IN in the left nostril N = 36		
	ARS-1 1 mg IN with rhinitis		A single 1 mg/100 µL IN doses of ARS-1 1 mg IN in the left nostril following induction of rhinitis N = 36		
	Epinephrine 0.3 mg IM		0.3 mg adrenaline IM injection in the left anterolateral thigh via needle/syringe N = 36		
	EpiPen 0.3 mg		0.3 mg adrenaline IM injection in the left anterolateral thigh via EpiPen N = 36		
Endpoints and Definitions	Systolic Blood Pressure – Maximum Effect	SBP Emax	Maximum change from baseline SBP (mmHg)		
	Pulse Rate – Maximum Effect	PR Emax	Maximum change from baseline HR (bpm)		
	Time to Maximum SBP Effect	SBP T_{Emax}	Time to maximum SBP effect (minutes)		
	Time to Maximum PR Effect	PR T_{Emax}	Time to maximum HR effect (minutes)		
Database lock	17 February 2020				
<u>Results and Analysis</u> As discussed in Section 2.7.3, pharmacodynamic (PD) endpoints are considered surrogates for efficacy.					
Analysis description	Primary Analysis				
Analysis population and time point description	The PD analysis set included all subjects who completed least one treatment during this study and had evaluable concentration-time profiles. A total of 36 subjects were enrolled in this study and received at least one dose of study drug				
Descriptive Statistics and Estimate Variability	Treatment Group	ARS-1 1 mg IN	ARS-1 1 mg IN with Rhinitis	Epinephrine 0.3 mg IM	EpiPen 0.3 mg
	Number of subjects	36	35	35	30

	SBP Emax (mean)	14.7	11.2	7.57	11.9
	SBP Max change from baseline (%CV)	46.5	73.5	58.7	50.1
	PR Emax (mean)	14.5	13.2	16.7	16.2
	PR Max change from baseline (%CV)	34.0	50.8	31.8	45.4
	SBP T_{Emax} (median)	17.5	20.0	25.0	22.5
	PR T_{Emax} (median)	15.0	15.0	60.0	30.0

Effect Estimate per Comparison	SBP Emax	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.3 mg IM
		Least Squares Mean Difference	7.17
		Lower 95% CI, Upper 95% CI	5.15 9.18
		P-value	<0.0001
	SBP Emax	Comparison groups	ARS-1 1 mg IN vs EpiPen 0.3 mg
		Least Squares Mean Difference	2.48
		Lower 95% CI, Upper 95% CI	0.36 4.60
		P-value	0.0551
	SBP Emax	Comparison groups	ARS-1 1 mg IN vs ARS-1 1 mg IN with Rhinitis
		Least Squares Mean Difference	-3.45
		Lower 95% CI, Upper 95% CI	-5.61 -1.28
		P-value	0.0109
	PR Emax	Comparison groups	ARS-1 1 mg IN vs Epinephrine 0.3 mg IM

		Least Squares Mean Difference	-2.17
		Lower 95% CI, Upper 95% CI	-3.97 -0.37
		P-value	0.0487
	PR Emax	Comparison groups	ARS-1 1 mg IN vs EpiPen 0.3 mg
		Least Squares Mean Difference	-1.77
		Lower 95% CI, Upper 95% CI	-3.68 0.13
		P-value	0.1250
	PR Emax	Comparison groups	ARS-1 1 mg IN vs ARS-1 1 mg IN with Rhinitis
		Least Squares Mean Difference	-1.27
		Lower 90% CI, Upper 90% CI	-2.88 0.33
		P-value	0.1872
Notes	ARS-1 1.0 mg IN had the greatest impact on SBP Emax but was not statistically significant compared to EpiPen 0.3 mg. Mean SBP Emax ranged from 14.7 mmHg after ARS-1 1.0 mg IN to 7.57 mmHg after Epinephrine 0.3 mg IM. Additionally, Emax occurred earlier for ARS-1 1.0 mg IN (median TEmax 17.5 min) compared to the other treatments. ARS-1 1.0 mg with rhinitis resulted in lower SBP Emax than ARS-1 1.0 mg IN (11.9 mmHg vs. 14.7 mmHg) but was greater than that of Epinephrine 0.3 mg IM. Mean PR increased for all treatments after dosing with the most prolonged changes observed following Epinephrine 0.3 mg IM and EpiPen 0.3 mg. ARS-1 1.0 mg IN and ARS-1 1.0 mg IN with rhinitis resulted in the earliest PR Emax. Mean PR Emax ranged from 13.2 beats/min ARS-1 1.0 mg IN with rhinitis to 16.7 beats/min after Epinephrine 0.3 mg IM.		
Analysis Description	<Secondary analysis> <Co-primary Analysis> <Other, specify: >		
	No secondary efficacy endpoints		

Supportive study

The applicant performed Human Factors Formative Study for ARS-1 Intranasal Epinephrine Spray.

A total of 22 participants, representing the Product's 3 user groups: patients, caregivers and healthcare professionals (HCPs), completed the study between August 12 and August 14, 2019 in a usability testing facility. The study included 8 patient participants, 8 caregiver participants and 6 HCP participants. Participants represented a range of ages, health literacy levels, and experience with nasal spray and epinephrine delivery devices.

All participants simulated untrained, first-time use of the Product in an emergency scenario, performing all tasks required to use the Product. During the testing session, participants were asked to imagine they needed to administer a dose of epinephrine to themselves (patient participants) or to a simulated patient (caregiver and HCP participants) experiencing an allergy emergency. Simulated-use of the Product was followed by knowledge task questions, subjective feedback and probing for root causes on use events observed or reported during the session.

A summary of performance task results is provided below:

•All participants were able to successfully open the box, remove clam-shell packaging from the box and remove a device from clam-shell packaging.

•Ten participants struggled to open the clam-shell packaging because the tabs on the case were difficult to grip or an unexpected amount of force was required to pull apart the two halves of the clam-shell.

•Three participants did not hold the device in a position that allowed for actuation; 1 of these participants eventually self-corrected. These participants reported they assumed the Product was an injection device (and held it accordingly), the space beside the plunger implied the need to place fingers there rather than on the finger flanges, or that the expectation to pull down on the finger flanges rather than push up on the plunger led them to hold the device in unintended ways.

•One participant prematurely actuated the device and released the dose into the air. This participant was exploring the device and accidentally pressed the plunger. Notably, the participant recognised the dose had been wasted and resolved by administering the backup dose.

•Two participants did not insert the device into the patient's nostril; 1 of these participants eventually self-corrected. These participants both assumed the Product was an injection device and attempted to administer the dose to the patient's thigh. Note: 1 of these participants experienced a related use event on Task HDN : Holds the device.

•Three participants did not press the plunger. Participants reported that they did not recognise the plunger was a component that needed to be pushed because they assumed the device was an injection device or because they expected the device to actuate automatically once it had been inserted into the nostril. One participant pressed the plunger lightly but decided that component did not require interaction when it did not move with the expected amount of force. This participant reported the amount of force required to push the plunger in completely was higher than expected.

•One participant did not contact a medical professional after administering a dose because they assumed the purpose of the Product was to alleviate the need for any medical intervention.

CHMP comment

The applicant conducted Human Factors Study for ARS-1. In total 22 subjects participated in the study. However, only 17 of 22 participants were able to deliver a dose of epinephrine. The applicant is invited to comment how the described, potential issues with ARS-1 use will be addressed to mitigate the risk of medication error of ARS-1 (OC).

3.3.6. Discussion on clinical efficacy

Studies in target population (subjects with anaphylaxis) are unethical, so surrogate PD endpoints were selected for evaluation of efficacy of ARS-1. Heart rate and blood pressure are being used as easily measurable indicators of α1 - and β1 adrenergic receptor agonism and, as such, serve as the pharmacodynamic surrogates of efficacy. However, it is critical to note that both heart rate and blood

pressure effects are mediated via α1 and β1 adrenergic receptors, which are less sensitive than the β2 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 β2 receptors, however they cannot be directly measured, particularly in subjects who are experiencing severe allergic reactions but speculated. Given the differential sensitivities of the receptor subtypes, these β2 mediated pharmacodynamic responses can be inferred whenever α1 and β1 effects are observed.

The efficacy of Neffy/ ARS-1 1 mg nasal spray was not assessed in randomised clinical trials in patients. Instead, the MAA is supported by data from four cross-over Phase I PK/PD trials with healthy volunteers and rhinitis patients which were aimed to evaluate comparative PK and PD parameters between Neffy 1 mg intranasal spray and several marketed epinephrine injections, i. e., Epinephrine 0.3 mg and 0.5 mg IM, Epinephrine 0.3 mg SC and EpiPen 0.3 mg (IM). Treatments were dosed once or twice. The approach selected by the applicant is considered acceptable. It is agreed that organising randomised controlled clinical trials to assess the efficacy of adrenaline in treatment of severe allergic reactions and anaphylaxis would not be appropriate due to ethical and practical limitations. While no controlled efficacy study has been conducted with adrenaline to date, it is globally accepted as the first-line treatment for severe allergic reactions that may lead to anaphylaxis. The mechanism of action and efficacy of adrenaline is not questioned. Therefore, during the clinical development of the intranasal dosage form of adrenaline which would provide several benefits for patients in terms of ease of application and time necessary for application, the applicant focused on demonstrating PK similarity supported by PD. A thorough analysis of haemodynamic parameters such as SBP and HR, is presented by the applicant. Data from the studies EPI 03 and EPI 07 show that, for both once and twice doses, the mean haemodynamic responses (SBP and HR) following administration of ARS-1 1 mg IN were generally more rapid (time to peak response) and more pronounced (mean change) or comparable to that observed with Epinephrine 0.3 mg IM and EpiPen 0,3 mg IM, respectively. The maximum increases in SBP or HR were not meaningfully different between treatments. Based on these haemodynamic findings, the applicant concluded that ARS-1 is anticipated to work similarly as EpiPen 0.3 mg in emergency use outside hospital. This statement, however, is not fully supported, as efficacy assessment cannot be based solely on haemodynamic changes. In line with the CHMP Scientific advice, the most important parameters for efficacy are early partial AUCs, which are presented in Clinical Pharmacology section. These data show that exposure to epinephrine is considerably lower after ARS-1 1 mg IN through approximately 30 min post dose compared to EpiPen 0.3 mg IM. While the differences tend to become less pronounced at later time points analysed, this finding is considered critical, when, according to the data from literature presented by the applicant, the median time to respiratory or cardiac arrest is 30 minutes for food allergies, 15 minutes for venom and 5 minutes for iatrogenic reactions (OC).

It is acknowledged that robust data on efficacy in the target population may not be possible to generate. Pharmacokinetic and pharmacodynamic effects of nasal compared to intramuscular administration mainly in healthy volunteers may be an acceptable alternative approach. The applicant has, however, not provided sufficient support for the key assumption that absorption from the nasal mucosa is comparable in healthy volunteers and in patients with acute anaphylaxis. The latter group is expected to have a profound circulatory compromise, which could potentially reduce perfusion in the nasal mucosa and consequently reduce absorption of adrenaline. This could adversely affect clinical efficacy, particularly in the patients that are in most critical need of the product. The applicant is requested to provide any available support, such as data on regulation of perfusion in the nasal mucosa, or non-clinical data from animal models of anaphylaxis, that justifies the extrapolation of results from healthy volunteers to patients with severe circulatory compromise from anaphylaxis. The applicant should also from that perspective justify the proposed wording of the indication, and how the available data supports extrapolation to the specified target population, also adding age-groups in the

indication in line with EMA Guidance on wording of a therapeutic indication (EMA/CHMP/483022/2019). (MO). Moreover, the applicant is invited to justify use of Neffy in persons ⩾30 kg body weight and aged 12 and above. To support the paediatric indication, the formulation and the delivery device need to be suitable for the intended paediatric population. Paediatric acceptability should be part of the QTTP of the product. Acceptability of formulation (choice of excipients, the palatability and sensation of the drug product on administration) and pharmaceutical form for paediatric population should be discussed (included, but not limited to the suitability of the selected device, intended delivered volume, ensuring that the dose will reach the deposition site for the target age group, nostril and nasal cavity size should be taken into consideration. Deposition using suitable models should be discussed). The applicant should discuss the precautions taken to minimise the accidental use by children younger than 12. (Multidisciplinary Quality and Clinical MO).

The applicant conducted Human Factors Study for ARS-1. In total 22 subjects participated in the study. However, only 17 of 22 participants were able to deliver a dose of epinephrine. The applicant is invited to comment how the described, potential issues with ARS-1 use will be addressed to mitigate the risk of medication error with the use of ARS-1(OC).

3.3.7. Conclusion on clinical efficacy

The marketing authorisation application is currently not approvable from the clinical efficacy aspect. The applicant should address the major objections.

3.3.8. Clinical safety

Patient exposure

The applicant's summary of safety incudes safety data from all completed clinical trials (Studies EPI 01, EPI 02, EPI 03, EPI 04, EPI 06, EPI 07, and EPI JP01) in which a total of 229 subjects/patients were included in the Safety population for the studies. An additional 53 ARS-1 1 mg patients are included from the ongoing EPI 09 study.

Table 58 Studies Providing Safety Data (Pivotal studies)

Study ID	Total enrollment (planned/actual)	Design	Dose, Route and Regimen	No of patients by treatment (entered)
EPI 03	70/70	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	One 1 mg 100 µL IN dose of ARS-1 in the left nostril Two 1 mg/100 µL IN doses of ARS-1 in the left and right nostril spaced 5 minutes apart One 0.3 mg in 0.3 mL (1 mg/mL) dose of IM epinephrine in the left anterolateral thigh Two 0.3 mg in 0.3 mL (1 mg/mL) doses of IM epinephrine in the left and right anterolateral thigh	ARS-1 1 mg IN: once; 68 twice 70 Epinephrine IM: 0.3 mg, once; 68 0.3 mg, twice; 70 0.5 mg, once 69
EPI 04	36/36	Phase 1, randomised, single-dose, 5-period, partial cross-over study	ARS-1 1 mg IN in the left nostril Epinephrine 0.3mg IM injection in the left anterolateral thigh Epinephrine 0.3mg SC injection in the left anterolateral thigh ARS-1 1 mg IN in the left nostril with rhinitis Epinephrine 0.5mg IM injection in the left anterolateral thigh	ARS-1 1 mg IN: once; 35 once (rhinitis) 34 Epinephrine IM: 0.3 mg, once; 36 0.5 mg, once 23 35

				Epinephrine SC: 0.3 mg once
EPI 07	36/36	Phase 1, randomised, single-dose, 5-treatment, 5-period, crossover study	A single dose of ARS-1 (1 mg) administered to the left nare Two (2) doses of ARS-1 (1 mg) spaced 10 minutes apart, administered first to the left nare followed by the second dose in the right nare Two (2) doses of ARS-1 (1 mg) spaced 10 minutes apart both administered in the left nare A single dose of EpiPen (0.3 mg) administered to the left anterolateral thigh Two (2) doses of EpiPen (0.3 mg) spaced 10 minutes apart, administered first to the left anterolateral thigh, followed by a second dose to the right anterolateral thigh	ARS-1 1 mg IN once 35 twice (L/L) 36 twice (L/R) 35 EpiPen 0.3 mg once 36 0.3 mg twice 36
EPI JP01	36/36	Phase 1, partially randomised, four-treatment study	ARS-1 1 mg IN in the left nare, Epinephrine 0.3 mg IM the left anterolateral thigh EpiPen 0.3 mg in the left anterolateral thigh ARS-1 1 mg IN in the left nare following rhinitis	ARS-1 1 mg IN 36 Epinephrine 0.3 mg IM 36 EpiPen 0.3 mg 36

Patient exposure

To date, the safety, pharmacokinetics, and pharmacodynamics of Neffy (adrenaline nasal spray) have been evaluated in seven completed clinical trials (Studies EPI 01, EPI 02, EPI 03, EPI 04, EPI 06, EPI 07, and EPI JP01) in which a total of 229 subjects/patients were included in the Safety population for the studies. An additional 53 ARS-1 1 mg patients are included from the ongoing EPI 09 study.

51 subjects at the age between 19 and 54 years of age were enrolled in the supportive studies EPI01,

Adverse events

Common Adverse Events from Pivotal Trials

All the events were mild with the exception of 2 moderate events of nasal oedema, which occurred after induction of rhinitis.

There were no increased in blood pressure or heart rate that required medical intervention and the increase generally is mild and resolves quickly. The reporting of blood pressure and heart rate in studies was inconsistent and given this is an expected therapeutic outcome of adrenaline, these events were not generally considered as adverse.

The most common adverse reactions (⩾ 10%) that occurred in the studies were blood pressure increased, heart rate increased, and palpitation. All of those events were mostly observed in 2 mg (L/L), which is anticipated based on the level of epinephrine increased. The incidences were similar or slightly less in ARS-1 (L/R) than EpiPen (L/R). All of the events were considered as mild and resolved without treatment. The other common adverse reactions include nasal discomfort (1 mg and 2 mg (L/R), rhinitis), nasal congestion (1 mg, rhinitis), and nasal oedema (2 mg (L/R), rhinitis), most of which occurred after induction of rhinitis. All of the events were considered as mild, with the exception of 2 events of nasal oedema after induction of rhinitis, and resolved without treatment. It should be

noted that the preferred term, nasal discomfort, is not to be interpreted to mean nasal pain. Nasal irritation and pain were reported separately as these were actual study evaluations that were conducted. There were no incidences of nasal pain reported in the pivotal studies. Nasal pain reported in supportive studies was all mild in severity.

There is no data provided on patients with pre-existing nasal mucosal disorder and possible impact on PK and adverse events. The applicant is invited to discuss possible differences on PK and adverse events in patients with pre-existing nasal mucosal disorder. (OC)

Among the common adverse reaction (≥ 1% and < 10%) that occurred in all Neffy treatment groups, feeling jittery was the most common in twice dosing, which was comparable to injections. The other common adverse reaction that occurred more than on patient in at least one of the treatment were throat irritation (all treatments), nasal pruritus (1 mg, 2 mg (L/R), rhinitis), rhinalgia and rhinorrhoea (both 1 mg, 2 mg (L/R)), paranasal sinus discomfort (1 mg rhinitis), headache (all treatments), dizziness (1 mg, 2 mg (L/R), rhinitis), nausea (1 mg), and salivary hypersecretion (1 mg, 2 mg (L/R), (L/L).

Nasal symptoms, when observed, were generally mild with the exception of two moderate events after induction of rhinitis. There were no reports of treatment-related nasal pain or application site pain in Neffy treated patients in the pivotal studies. Both pain and nasal irritation were assessed using validated instruments that demonstrated there was no significant adverse outcomes of Neffy. The most common reported nasal adverse event was mild nasal discomfort. Given that subjects did not report significant pain (< 10 mm out of 100 mm VAS) and there was very little nasal irritation, the mild nasal discomfort reported by some subjects may be typical of a nasal spray application.

Table 59 Incidence of Treatment-Related Treatment-Emergent Adverse Events by Pooled Treatment from Studies EPI 03, EPI 04, EPI 07, and EPI JP01

	ARS-1				Epinephrine					
	Nasal				IM			SC	EpiPen	
System Organ Class Preferred Term	1 mg (N=174) n (%)	2 mg (L/R) (N=105) n (%)	2 mg (L/L) (N=36) n (%)	1 mg with rhinitis (N=68) n (%)	0.3 mg (N=140) n (%)	0.5 mg (N=92) n (%)	0.6 mg (L/R) (N=70) n (%)	0.3 mg (N=35) n (%)	0.3 mg (N=72) n (%)	0.6 mg (L/R) (N=36) n (%)
Subjects with at least one treatment-related AE	73 (42.0)	54 (51.4)	29 (80.6)	14 (35.3)	15 (10.7)	16 (17.4)	19 (27.1)	8 (22.9)	12 (16.7)	18 (50.0)
Respiratory, Thoracic and Mediastinal Disorders										
Nasal Discomfort	36 (20.7)	20 (19.0)	0 (0.0)	5 (7.4)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Throat Irritation	7 (4.0)	4 (3.8)	1 (2.8)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Congestion	3 (1.7)	0 (0.0)	0 (0.0)	7 (10.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Nasal Pruritus	3 (1.7)	1 (1.0)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinalgia	3 (1.7)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	3 (1.7)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paranasal Sinus Discomfort	2 (1.1)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Dryness	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Mucosal Disorder	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal Discomfort	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Edema	0 (0.0)	1 (1.0)	0 (0.0)	12 (17.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations										
Blood Pressure Increased	14 (8.0)	20 (19.0)	28 (77.8)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (11.1)	10 (27.8)
Body Temperature Increased	1 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart Rate Increased	1 (0.6)	6 (5.7)	6 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (5.7)	1 (1.4)	4 (11.1)
Nervous System Disorders										
Headache	8 (4.6)	4 (3.8)	2 (5.6)	1 (1.5)	1 (0.7)	2 (2.2)	1 (1.4)	1 (2.9)	1 (1.4)	1 (2.8)
Dizziness	3 (1.7)	1 (1.0)	0 (0.0)	1 (1.5)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysgeusia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	ARS-1				Epinephrine				EpiPen	
	Nasal				IM			SC		
	1 mg (N=174) n (%)	2 mg (L/R) (N=105) n (%)	2 mg (L/L) (N=36) n (%)	1 mg with rhinitis (N=68) n (%)	0.3 mg (N=140) n (%)	0.5 mg (N=92) n (%)	0.6 mg (L/R) (N=70) n (%)	0.3 mg (N=35) n (%)	0.3 mg (N=72) n (%)	0.6 mg (L/R) (N=36) n (%)
Head Discomfort	1 (0.6)	1 (1.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoaesthesia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders										
Palpitations	6 (3.4)	13 (12.4)	9 (25.0)	3 (4.4)	5 (3.6)	5 (5.4)	7 (10.0)	2 (5.7)	3 (4.2)	5 (13.9)
Gastrointestinal Disorders										
Nausea	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gingival Discomfort	1 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Salivary Hypersecretion	1 (0.6)	1 (1.0)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Mouth	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epigastric Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Paraesthesia Oral	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions										
Feeling Jittery	3 (1.7)	10 (9.5)	3 (8.3)	1 (1.5)	3 (2.1)	9 (9.8)	4 (5.7)	0 (0.0)	0 (0.0)	3 (8.3)
Feeling Hot	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Application Site Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Application Site Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
Chest Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection Site Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	3 (3.3)	2 (2.9)	1 (2.9)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders										
Pruritus	1 (0.6)	1 (1.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorders										
Lacrimation Increased	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Photophobia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders										
Muscle Spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)

Subjects with Severe Type 1 Allergies - Adverse Events in Ongoing Study EPI 09

According to the data presented by the applicant, 77.8% of patients from 2mg (L/L) group (pooled analysis of pivotal studies), experienced blood pressure increase. Contrary, only 19% of patients treated with 2mg (L/R) experienced blood pressure increase. Similar trend was observed with respect to the incidence of the increase in heart rate – 5.7% and 16.7% of patients from 2mg (L/R) and 2mg (L/L) groups experienced this TEAE. Moreover, palpitations were observed in 12.4% of patients from 2mg (L/R) group and 25% of patients from 2mg (L/L) group. The applicant is invited to discuss possible reasons for the observed difference (OC).

Overall, 31 out of 55 subjects (56.4%) experienced at least one treatment-emergent adverse event. Thirty subjects (54.5%) experienced TEAEs that were considered treatment related as determined by the Investigator. The presence of severe allergies did not appear to affect the incidence of TEAEs. In the subset of 14 subjects with severe allergies, eight (53.3%) experienced at least one adverse event, with all eight subjects (100%) experiencing events that were considered treatment related as determined by the Investigator. There was one moderate TEAE (presyncope), following administration of ARS-1 1 mg IN to a subject without severe allergies, which resolved without treatment. All other TEAE were considered mild; none were life- threatening or resulted in death. A summary of TEAs by SOC and PT and treatment is presented in the table below.

No AEs were considered serious, resulted in death, or resulted in discontinuation from the study.

Generally, no significant differences in the incidence of TEAE were observed in Study EPI 09 between subjects with severe allergies compared to full safety population, with exception to nasal discomfort, experienced by 21.1% of patients with severe allergies and 13.2% of patients from full safety population.

System Organ Class	Frequency	Adverse drug reaction
Respiratory, thoracic and mediastinal disorders	Very common	Nasal discomfort
	Common	Throat irritation Nasal congestion Nasal pruritus Rhinalgia Rhinorrhoea Paranasal sinus discomfort
	Uncommon	Nasal dryness Nasal mucosal disorder Oropharyngel discomfort
Investigations	Uncommon	Body temperature increased Heart rate increased
Nervous system disorders	Common	Headache Dizziness
	Uncommon	Dysgeusia Head discomfort Paraesthesia Tremor
Cardiac disorders	Common	Palpitations
Gastrointestinal disorders	Common	Nausea
	Uncommon	Gingival discomfort Salivary hypersecretion
General disorders and administration site conditions	Common	Feeling jittery
	Uncommon	Feeling hot
Skin and subcutaneous tissue disorder	Uncommon	Pruritus

Not all treatment related TEAEs that were reported in the studies are reflected in the tabulated list of adverse reactions. The applicant is invited to provide justification for this decision and is invited to perfect the tabulated list with adverse events which frequency cannot be estimated form the available data. (OC)

The safety discussion now mainly focuses on data from the applicant's own studies in healthy volunteers. The characterisation of safety should, however, fully consider the already established safety profile of adrenaline. Fact that previously established adverse reaction has not been reported as a safety issue in the current safety database should not justify its absence in the table in section 4.8 of the proposed SmPC. The applicant is invited to provide information on full adrenaline safety profile and reflect it in product information, including adrenaline effect on haemodynamic as an adverse event and possible differences in populations other than healthy volunteers. (OC)

Serious adverse events and deaths

No cases of serious adverse events or deaths were reported during the overall clinical development programme.

Laboratory findings

There have been no significant clinical laboratory evaluation findings related to the safety of ARS-1 in the overall clinical development programme.

Clinical laboratory testing has been provided as part of screening/baseline period and included standard laboratory tests (e.g. baseline haematology, serum chemistry, coagulation, urinalysis, baseline urine drug, alcohol, and cotinine screen, pregnancy tests; the presence of HIV antibody, HbSAg, and hepatitis C antibody was assessed at screening). These tests obtained at screening and/or baseline only.

A number of patients reported clinical laboratory findings at screening/baseline that were abnormal (marginally above or below the normal range). However, these have been considered not clinically significant by the applicant. Laboratory parameters have not assessed during treatment period in the clinical development programme. Therefore, there were no information available of clinically significant changes in clinical chemistry or haematology in subjects exposed to adrenaline nasal spray (company code ARS-1 or Neffy) even it happened during or shortly after treatment. Thus, there was no evidence of clinical laboratory or haematology safety issues with Neffy treatment. Information have been based on already known literature data of active substance.

However, the mean haemodynamic responses (SBP and HR) were more rapid and greater in ARS-1 and EpiPen 0.3 treated patients compared to IM injections with a needle.

ARS-1 1mg IN and EpiPen 0.3 mg had comparable effects on SBP and HR, with the mean effect vs. time favoring ARS-1 1mg IN. Review of the mean change from baseline data for Emax and partial AUECs for SBP and HR indicated that ARS-1 1mg IN and EpiPen 0.3 mg have comparable responses following both once and twice dosings (L/R). In contrast, Epinephrine 0.3 mg IM showed significantly lower response in SBP and HR compared to ARS-1 1mg IN and EpiPen, in both once and twice dosings.

ARS-1 and EpiPen 0.3 mg have comparable time to maximum effect (tEmax). Review of the tEmax median values for change from baseline for SBP showed that ARS-1 1mg IN and EpiPen 0.3 mg reached Emax at 21 minutes, which were correspondent to their tmax. Median tEmax of Epinephrine 0.3 mg IM was approximately 31.0 minutes, which were slower than other treatments but faster than its tmax of 45 minutes.

While the mean changes vs. time in SBP and HR were greater following ARS-1, the maximal increase in SBP and HR were not meaningfully different between treatments and thus it did not appear that IN administration gave an increase in the maximum response observed as compared to IM injection.

According to the information provided in the Summary of Clinical Safety, data from the preliminary assessment of the continuous ECG finding form the EPI 03 study were provided. The applicant is invited to present the complete data (OC).

Figure 2: Mean Twice Dosed Change from Baseline SBP vs Time by Grouped Treatment and Study, Initial 120 minutes Postdose

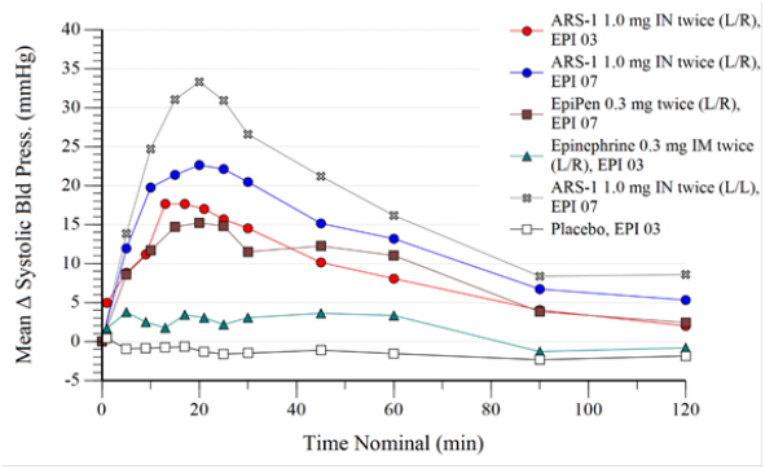


Table 60 Change from Baseline SBP Median, Maximum, and Minimum Change by Treatment

Treatment	Mean (mm Hg)	Median (mm Hg)	Max (mm Hg)	Min (mm Hg)
ARS-1 1mg IN	7	7	44	-20
ARS-1 1mg IN twice (L/R)	12	12	64	-42
Epinephrine 0.3 mg IM	0	1	42	-40
Epinephrine 0.3 mg IM twice (L/R)	2	2	42	-42
Epinephrine 0.5 mg IM	3	3	63	-27
EpiPen 0.3 mg	6	5	40	-21
EpiPen 0.3 mg twice (L/R)	11	10	72	-28
ARS-1 1mg IN twice (L/L)	21	20	69	-25

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

In the Summary of the Clinical Safety sufficient discussion on post exposure baseline SBP changes have not been provided. Considering the significant difference of mean change from baseline SBP in 'ARS-1 1.0 mg IN twice (L/L)' subset, the applicant is invited to discuss the clinical significance of SBP changes in this subset.

Safety in special populations

Additional safety studies in special populations such as *in vitro*/*in vivo* correlation, plasma protein binding, intrinsic and extrinsic factor, as well as certain special population studies were not conducted with adrenaline nasal spray (company code ARS-1). Under Article 8(3) full-mixed legal basis, this application relies, in part, on published literature available in the public domain. The applicant stated that all information of the safety in special population are either supported by clinical studies conducted under GCP or by published literature and when literature is used in lieu of conducting a study, the justification has been provided.

Following the application of strict exclusion criteria to the study population, the majority of study participants were initially healthy adults without significant comorbidities, with a normal weight and up to 55 years of age. Except for two completed studies in which participants had a history of seasonal

allergic rhinitis (5 out of 7 completed clinical trials included only healthy individuals with strict exclusion criteria).

Race, Ethnic, Geographic region and Sex:

There was a higher proportion of male participants (N = 160, n=69.9%). Diversity including different races and ethnicities has been ensured. Currently available pooled data from completed studies on population demographics do not provide sufficient information about the safety in special populations. A complete list of TEAE tables by System Organ Class (SOC), MedDRA preferred term, and sex included in this Module 5 Intagrated Summary of Safety, but not discussed individually. In addition, as noted in the Non-clinical report, absorption studies have been performed only in male animals and female animals were not involved in the study. Incidence and severity of squamous cell metaplasia was slightly increased in female compared to male rats in nonclinical Dodecylmaltoside carcinogenicity study. It is acknowledged that single-dose toxicity study in similar count of male and female animals did not reveal any differences by sex.

No drug discontinuations due to adverse event (AE) reported during the studies and therefore no differences were observed in the incidence of serious adverse events (SAEs) or severe AEs (Grade=3) or any of the events of interest (EOIs) between males and females. The most common AEs reported in both males and females were blood pressure increased, heart rate increased, and palpitation. The other common adverse events include nasal discomfort, nasal congestion, and nasal oedema in IN formulation of adrenaline (Neffy) treatment arm, but calculation of incidence between male and female participants have not been provided by the applicant. In conclusion, clinically significant differences in the profile of AEs by sex are unknown at the current moment. Comparison of treatment related AEs in females when compared to male participants has not been discussed by the applicant in Module 2.

Although race and ethnicity data were generated from various studies, no detailed discussion on possible race/ethnicity related safety aspects is offered by the applicant.

It is noted that regional distribution of subjects was not balanced. The vast 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. The smaller number of subjects from Japan do not provide a relevant comparison with other geographical regions. Based on the submitted literature data, it seems that geographical regions could not play role in AEs profile.

Since adrenalin is a well-known active substance, it is unlikely that race, ethnic, geographic region and sex differences would be an important safety influencing factors.

Weight:

Effect of weight on distribution, metabolism and cardiac effects after exposure of intranasal adrenaline have been discussed in pharmacokinetic and pharmacodynamic part of documentation (see above). The safety aspects effects on cardiac output related PK alterations due to extremely low or high body weight in patients with BMI < 20 kg/m2 and ≥ 30 kg/m^2 after exposure of intranasal adrenalin in comparison to intramuscular route of administration have not been discussed by the applicant.

It is acknowledged that the applicant already discusses (see above) effects of weight on adrenaline concentration following adrenalin injection versus intranasal formulation and concluded that in general, pharmacokinetics for Neffy formulation did not appear to be affected by body weight and BMI, but in contrast, the injectable products were significally affected by body weight, with lower body weight being correlated to a higher adrenalin exposure. The applicant stated that at very low body weights (< 60 kg) it appeared that intra-blood vessel injections from EpiPen 0.3 mg and IM with needle and syringe were more prevalent and gave a significant increase in early exposure. Data were evaluated from pivotal and supportive studies in patients with normal body weight only (see study inclusion

criteria). Based on the pharmacokinetic data submitted by the applicant, Cmax could be reached more rapidly and in some case slightly higher concentration of active substance have been reached after intranasal rout of administration in comparison to intramuscular route of administration; Cardiac output, and, thus, overall organ perfusion increases with increasing body weight, whereas relative adipose tissue blood flow decreases. There are no data available on safety concerns in patients with BMI < 20 kg/m2 and ≥ 30 kg/m^2 after exposure to intranasal adrenaline in comparison to intramuscular route of administration. *The applicant should discuss safety aspects related to possible effects on cardiac output due to PK alterations in extremely low or high body weight* patients with BMI < 20 kg/m2 and ≥ 30 kg/m^2 after exposure to intranasal adrenalin in comparison to intramuscular route of administration (OC)

Age:

Safety studies of the IN formulation of adrenaline (Neffy) have been conducted in adult volunteers only. All included patients from completed studies were in age range 19 – 55.

51 subjects at the age between 19 and 54 years of age were enrolled in the supportive studies EPI01, EPI02 and EPI06.

For the EPI 01 study, a total of 12 subjects enrolled in the study and subjects ranged in age from 19 to 29 years, EPI 02 study 27 subjects enrolled (ranged in age from 20 to 24 years), EPI 06 study 12 subjects enrolled (age from 21 to 54 years); For the EPI 03 study, a total of 70 subjects in age from 21 to 55 years have been enrolled in the study; For the EPI 04 36 subjects enrolled (ranged from 19 to 55); EPI 07 36 subjects enrolled (ranged from 19 to 54 years); For the EPI JP01 36 subjects enrolled (ranged in age from 24 to 55 years) - all of whom experienced at least 1 AE, to make any clinically meaningful comparisons. The incidence of overall AEs was not provided by the applicant in the different age groups. No differences were observed across the age groups for subjects enrolled in the studies for SAEs or severe AEs. The most commonly reported AEs across all age groups included in the studies were seem similar, and this was in line with literature data for the healthy adult population. No discussion has been provided relating clinically significant differences for any of the AEs for any age group included in the study.

Typically, clinical trials conducted in adult population include patients between the ages from 18 to 64 years. The selected age limits for inclusion criteria should be explained by the applicant and safety concerns in elderly should be discussed. Considering limited data available in subjects above 55 years of age, from the safety perspective further justification is needed to support inclusion of this population in the target indication. See section Geriatric below.

It is noted, that no patients above 55 years of age were included in the studies. The applicant is invited to discuss safety of adrenaline in elderly patients based on the literature data (OC). Moreover, the applicant should discuss whether any difficulties can be expected in using the device by elderly people (OC).

It is noted that no safety data available from the age group of 12-18. The applicant should discuss safety of adrenaline in this age group (OC).

Published literature

Due to ethical reason no studies provided with adrenaline nasal spray (company code ARS-1) in patients with impaired renal function, impaired hepatic function, pregnancy, lactation, elderly, clinically significant gastrointestinal, neurologic, haematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, severe seasonal or non-seasonal allergies.

The applicant stated that patients with clinically significant gastrointestinal, renal, hepatic, neurologic, haematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease,

severe seasonal or non-seasonal allergies, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration, traumatic injury or abnormality, any other condition which, in the opinion of the PI, would jeopardise the safety of the subject or impact the validity of the study results were excluded from currently ended clinical trials. Smokers were excluded from clinical trials.

Safety concerns for mentioned special population have been concluded by applicant based on scientific literature data available in public domains. Clinical report refers 139 publications up to 2020. In the light of the above literature, a very brief summary of the safety in special population have been provided by the applicant. A detailed literature review on safety in special population based on the submitted scientific literature has not been submitted by the applicant.

According to the explanation provided by the applicant, the active substance adrenaline is an endogenous compound found in all higher animal species and human exposures from ARS-1 are within the normal physiologic range that occurs from physical exercise and fear. Adrenaline is secreted by the adrenal gland. Endogenous plasma concentrations in resting adults are normally less than 30 pg/mL, but may increase markedly during exercise with plasma adrenaline levels as high as 653 pg/mL and greater than 10,000 pg/mL during stress (Stratton-1982, Wortsman-2002).

The acute exposure of adrenaline encountered with anaphylaxis treatment (mean exposures approximately 250 to 500 pg/mL Cmax per 0.3 mg IM dose), such as with intramuscular administration by autoinjectors, is considerably within the range of that experienced naturally with endogenous levels. Anticipated mean peak plasma levels (Cmax) after administration of intranasal ARS-1 are between 300 pg/mL and 500 pg/mL. Thus, well within the endogenous exposure range.

The justification for not conducting additional clinical safety studies, including special population studies, includes:

- Adrenaline is an endogenous substance and exposures are within normal physiologic range in humans and below peak exposures experienced from exercise and fear
- The acute use of the product for emergency treatment of severe allergic reactions
- Extensive data already exists in the public domain
- New clinical studies are unlikely to further the scientific knowledge of the pharmacologic profile of adrenaline.

The applicant stated that there are no known absolute contraindications to the use of ARS-1 during an allergic emergency.

Drug-disease considerations in the opinion of the applicant include (Cambell-2014):

• Patients with heart disease: Adrenaline is ordinarily administered with extreme caution to patients who have a heart disease. Use of adrenaline with drugs that may sensitise the

heart to arrhythmias, e.g., digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by adrenaline in patients with coronary insufficiency.

•Patients with Parkinson's disease: Adrenaline may be associated with a transient worsening of Parkinson's symptoms such as rigidity and tremor.

•Sodium metabisulphite allergy: Adrenaline contains a low concentration of sodium metabisulphite, a sulphite that may, in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using adrenaline in a life-threatening situation may not be satisfactory. The presence of a sulphite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

•Other considerations: There is a risk of adverse reactions following adrenaline administration in patients with hyperthyroidism, hypertension, diabetes, high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia, and hypokalaemia.

• Use in Pregnancy and Lactation
Adrenaline should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. While an endogenous substance and within normal physiologic ranges, adrenaline increases blood pressure and heart rate which can impact the foetus.

It is not known whether adrenaline is excreted in human milk. Adrenaline should be used during lactation only if the potential benefit justifies the potential risk.

According to submitted literature data there is no information regarding the presence of epinephrine in human milk or the effects of epinephrine on the breastfed infant or on milk production. However, due to its poor oral bioavailability and short half-life, epinephrine exposure is expected to be very low in the breastfed infant.

Epinephrine is the first-line medication of choice for treatment of anaphylaxis; it should be used in the same manner for anaphylaxis in breastfeeding and non-breastfeeding patients.

Epinephrine should be given to a pregnant woman only if clearly required in critical situations/emergencies. Epinephrine may delay the second stage of labour.

The fact that no pivotal studies have been conducted could be acceptable based on the available literature references and PK/PD profile of the compound; as well as well metabolism and elimination. Very brief summary of the safety in special population have been provided by the applicant. Since this is a full-mix application literature references replacing study reports have been submitted in Module 5 by the applicant. However, justification provided in Module 2.7. and 2.5. seems too brief for this kind of application dossier. The applicant is reminded that literature references, when replacing required study reports, should be summarised in Module 2 as required for any other study report.

The applicant should submit updated Module 2.5 and 2.7 and comprehensive robust summary of all literature references were important safety issues in special populations are available and discussion should be provided by the applicant how these data support contraindications, warnings, and precautions in the proposed product information and affect benefit/risk balance for IN formulation of adrenaline (Neffy) in special population compared to intramuscular use in these patients (including an in-depth discussion of the safety of IN adrenaline in patients who have congenital or acquired nasal abnormalities). The safety characteristics based on literature review should be covered in the product information (OC).

• Paediatric Use: Clinical use data support weight-based dosing for treatment of anaphylaxis in paediatric patients, and other reported clinical experience with the use of adrenaline suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults (Simons-1998, Simons-2002). Applicant stated that there are no known differences in the adverse event profile in paediatrics versus adults (Simons-1998, Simons-2002).

According to the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver (MEA-002749-PIP01-19) no nonclinical studies have been conducted or are planned to be conducted to support the use of IN formulation of adrenaline (Neffy) in paediatric age groups. The safety of epinephrine in children after systemic exposure is well understood and the doses of epinephrine given result in normal physiologic levels of epinephrine as an endogenous compound. Further, there are no well-known models in animals for paediatric nasal absorption and fluctuations of endogenous epinephrine in animals makes studies to characterise absorption in children impractical. Animal studies were conducted to confirm that there is no important local toxicity after administration

by the nasal route and in healthy adult studies there was no clinically meaningful pain or irritation of the nasal mucosa from administration of IN formulation of adrenaline. The device has been approved for use in children from age 6 and above for other products marketed in the EU and US, but is not currently approved for younger age populations.

Extrapolations and models to predict outcomes in children has been provided by the applicant. Based on pharmacology conclusion provided by the applicant predicted exposures in paediatrics are in line with the expected values in adults supporting the 0.65 mg dose in children 15 to <30 kg and the 1 mg dose for children ⩾30 kg and the general adolescents and adult populations. The applicant committed to conduct additional studies in paediatric different age subgroups according to PDCO recommendations.

Therefore, from safety point of view Neffy 1 mg may be used in persons ≥ 30 kg body weight and aged 12 and above. Studies in paediatric patients less than 12 years of age have not yet been completed. The waiver applies to the paediatric population from birth to less than 1 year. Subset(s) of the paediatric population concerned by the PIP from 1 to less than 18 years of age.

The applicant committed to conduct additional studies in paediatric different age subgroups according to PDCO recommendations.

Safety in children have been partly explored within the PK modelling exercise.

Apparently safety in the paediatric population has been mainly addressed by adolescent data, which is the intended target population. For children an appropriate justification is available in the group from 12 years and above, while data for younger children are currently relatively sparse and are awaiting the further evaluation and/or completion of future studies.

According to recent publications, the safety of excipient benzalkonium was questioned: benzalkonium may be involved in maintaining the allergic process in children with asthma. Paradoxical bronchospasm from benzalkonium chloride (BAC) preservative in albuterol nebuliser solution in a patient with acute severe asthma have been reported. A case report and literature review of airway effects of BAC are available. The applicant should provide additional information about the risk of any side effects related to the excipient benzalkonium chloride in the paediatric population. (OC)

• Geriatric Use:

Clinical studies for the treatment of anaphylaxis have not been performed in subjects aged 55 and over to determine whether they respond differently from younger subjects. However, other reported clinical experience with use of adrenaline for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of adrenaline (Wood-2013, Kawano-2017). Therefore, for the treatment of anaphylaxis, consider starting with a lower dose to take into account potential concomitant disease or other drug therapy.

Due to technical reasons it is not possible to reduce the dose of Neffy, therefore the applicant should explain meaning of mentioned recommendation to reduce dose of Neffy in geriatric patients. (OC)

The applicant is asked further discuss safety in special population, populations older than 55.

No robust literature-based comparison of safety findings in elderly patients using nasal formulation versus parenteral formulations has been provided. The applicant is asked to provide tabulated assessment of safety data in elderly population > 55 years available from the submitted literature.

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs				
Serious Aes – Total				
- Fatal				
- Hospitalisation/prolong existing hospitalisation				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

CHMP comment

No patients above 55 years of age were included in the clinical studies conducted by the applicant.

The applicant should provide tabulated summary of safety data according to the template (see above) as part of response to the day 120 LoQ. Any clinically relevant safety findings in elderly population should be properly addressed in the Product information (OC).

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

No studies have been performed by the applicant.

A list of treatment period Concomitant Medications from pivotal studies have been included in Module 5 Integrated Summary of Safety, but not further evaluated in Module 2. No analysis of adverse event data in subjects who received concomitant medication versus subjects without concomitant medication have been provided by the applicant. Most often used concomitant medication for female subjects was hormonal contraceptives. One case of concomitant use of Ketotifen fumarate antiallergic eye drops solution has been detected. In one case food supplements containing proteins have been used by participant. Taking into account available knowledge about pharmacology of adrenaline, no interactions are expected following to concomitant use of adrenaline and above medicinal products. No new safety concerns have been raised.

Pharmacodynamic interaction studies have not been conducted with Neffy. This is generally acceptable given that adrenaline PK/PD profile is well known. Very brief summary of the potential drug-drug interactions and associated risks have been provided by the applicant. Since this is a full-mix application literature references have been submitted in Module 5. However, justification provided in Module 2.7. and 2.5. is too brief for this kind of application dossier. Appropriate summary of all literature references included in Module 5 to support information for drug-drug interactions included in the proposed SmPC should be included in the updated Module 2.5 and 2.7. The discussion whether the topical nasal decongestants may have any effect on absorption of intranasal adrenalin also is missed. See issue raised by the CHMP in the pharmacokinetic part of list of questions.

Rebound Phenomena

There is some risk of an allergic event recurring after treatment with adrenaline and apparent resolution. Patients and caregivers are typically trained to recognise signs of recurrence of symptoms and actions to be taken. Neffy labelling recommends that patients and caregivers always carry two sprayer devices in the event of a second dose needed to treat the allergic reactions or in the event of recurrence of symptoms. While rare, Neffy labelling instructs patients and caregivers that if the second dose is needed or there is recurrence of symptoms after treatment with the first dose, that emergency medical assistance should be contacted.

Potential for Dependence or Abuse

Neffy is not expected to have any potential for dependence or abuse. Adrenaline exposures are acute and within the normal endogenous exposures obtained from strenuous activity or exercise. Endogenous adrenaline is always present and thus there is no significant potential for dependence or abuse.

Discontinuation due to AES

There were no discontinuations due to adverse events in any of the studies, according to the information provided in the SCS.

Several studies reported cases of premature discontinuation, though, no information on reasons has been provided. The applicant is invited to discuss the reasons for premature discontinuation. (OC)

Post marketing experience

Post marketing data is not available. Neffy (ARS-1) is not approved in any country. The applicant is invited to provide and discuss information on post marketing data of similar medical products, if available. (OC)

3.3.9. Discussion on clinical safety

Patients population

In total 229 subjects were exposed to Neffy in the completed clinical studies. Moreover, 59 patients have been exposed in the ongoing study EPI09. All included patients were between 19 and 55 years of age. Generally, patients were well balanced with respect to sex and race. 51 subjects at the age between 19 and 54 years of age were enrolled in the supportive studies EPI01, EPI02 and EPI06. The vast majority were male, only 2 were women included.

It is noted, that no patients above 55 years of age were included in the studies. This information should be added to the SPC (OC). The applicant is invited to discuss safety of adrenaline in elderly patients based on the literature data (OC). Moreover, the applicant should discuss whether any difficulties can be expected in using the device by elderly people (OC). Due to technical reasons it is not possible to reduce the dose of Neffy, therefore the applicant should explain meaning of mentioned recommendation to reduce dose of Neffy in geriatric patients. (OC)

The applicant should provide tabulated summary according to the template as part of response to the day 120 LoQ. Any clinically relevant safety findings in elderly population should be properly addressed in the Product information. (OC)

It is noted that no safety data available from the age group of 12-18. The applicant should discuss safety of adrenaline in this age group (OC). The applicant should provide additional information about the risk of any side effects related to the excipient benzalkonium chloride in the paediatric population. (OC)

There are no data available on safety concerns in patients with BMI < 20 kg/m2 and ≥ 30 kg/m^2 after exposure to intranasal adrenaline in comparison to intramuscular route of administration. The applicant should discuss safety aspects related to possible effects on cardiac output due to PK alterations in extremely low or high body weight patients with BMI < 20 kg/m2 and ≥ 30 kg/m^2 after exposure to intranasal adrenalin in comparison to intramuscular route of administration. (OC)

The applicant should submit updated Module 2.5 and 2.7 and comprehensive robust summary of all literature references were important safety issues in special populations are available and discussion should be provided by the applicant how these data support contraindications, warnings, and precautions in the proposed product information and affect benefit/risk balance for IN formulation of adrenaline (Neffy) in special population compared to intramuscular use in these patients (including an in-depth discussion of the safety of IN adrenaline in patients who have congenital or acquired nasal abnormalities). The safety characteristics based on literature review should be covered in the product information. (OC)

Adverse events

Overall, in all completed studies conducted by the applicant, 44.8%, 52.4% and 80.6% of patients exposed to nasal adrenaline dose of 1 mg, 2mg (L/R) and 2mg (L/L) experienced at least 1 TEAE, respectively. 42.9% patients with severe allergies compared to 28.3% in full safety population experienced at least 1 TEAE during the ongoing study EPI 09.

The most common adverse reactions that were observed in the clinical studies were palpitations and blood pressure and heart rate increase. However, these adverse events were mostly observed in patients who received 2mg of adrenaline, all were mild and resolved without treatment.

Respiratory disorders mainly were nasal discomfort, nasal congestions, nasal pruritus, nasal oedema, rhinalgia, rhinorrhoea, and paranasal sinus discomfort. All cases were classified as mild, with exception of two moderate episodes of nasal oedema. It is important to note that nasal pain was assessed separately from nasal discomfort and was not common.

In the subset of participants with induced rhinitis incidence of adverse events were same or lower than in other groups, with exception of higher reported incidence of nasal congestion and nasal oedema.

There is no data provided on patients with pre-existing nasal mucosal disorder and possible impact on PK and adverse events. The applicant is invited to discuss possible differences on PK and adverse events in patients with pre-existing nasal mucosal disorder. (OC)

In Investigations section main observed adverse event was increased blood pressure. In Summary of Clinical Safety the applicant states that increased blood pressure is expected effect of adrenaline and should not be considered adverse. Considering the facts that severe allergic reactions are not always accompanied by hypotension and that for normotensive or hypertensive patients increased blood pressure can be adverse.

The safety discussion now mainly focuses on data from the applicant's own studies in healthy volunteers. The characterisation of safety should, however, fully consider the already established safety profile of adrenaline. Fact that previously established adverse reaction has not been reported as a safety issue in the current safety database should not justify its absence in the table in section 4.8 of the proposed SmPC. The applicant is invited to provide information on full adrenaline safety profile and reflect it in product information, including adrenaline effect on haemodynamic as an adverse event and possible differences in populations other than healthy volunteers. (OC)

According to the data presented by the applicant, 77.8% of patients from 2mg (L/L) group (pooled analysis of pivotal studies), experienced blood pressure increase. Contrary, only 19% of patients treated with 2mg (L/R) experienced blood pressure increase. Similar trend was observed with respect to the incidence of the increase in heart rate – 5.7% and 16.7% of patients from 2mg (L/R) and 2mg (L/L) groups experienced this TEAE. Moreover, palpitations were observed in 12.4% of patients from 2mg (L/R) group and 25% of patients from 2mg (L/L) group. The applicant is invited to discuss possible reasons for the observed difference (OC). Considering the significant difference of mean change from baseline SBP in 'ARS-1 1.0 mg IN twice (L/L)' subset, the applicant is invited to discuss the clinical significance of SBP changes in this subset. (OC).

Generally, no significant differences in the incidence of TEAE were observed in Study EPI 09 between subjects with severe allergies compared to full safety population, with exception to nasal discomfort, experienced by 21.1% of patients with severe allergies and 13.2% of patients from full safety population.

Not all treatment related TEAEs that were reported in the studies are reflected in the tabulated list of adverse reactions. The applicant is invited to provide justification for this decision and is invited to perfect the tabulated list with adverse events which frequency cannot be estimated form the available data. (OC).

No cases of serious adverse events or deaths were reported during the overall clinical development programme.

There have been no significant clinical laboratory evaluation findings related to the safety of the test article. However, according to the information provided in the Summary of Clinical Safety, data from the preliminary assessment of the continuous ECG finding form the EPI 03 study were provided. The applicant is invited to present the complete data (OC).

Only preliminary data from the ongoing study EPI 09 were presented. The applicant is invited to clarify when the complete results can be expected (OC).

Some patients exposed by adrenaline nasal spray (company code ARS-1 or Neffy) had dose reduction during treatment due to adverse events. Some of these patients had marginally abnormal laboratory tests (e.g. patient EPI-07-127(L/R and L/L)) at screening/baseline period (e.g. at the screening/baseline period marginally elevated urea, glucose levels have been detected) and have dose reduction due to problems with elevated blood pressure. The applicant is asked to discuss all any clinically relevant safety findings in exposed population in light of marginally abnormal laboratory tests at screening/baseline period in some subjects. (OC)

No discontinuations due to adverse events were reported in clinical trials of ARS-1. Several studies reported cases of premature discontinuation, though, no information on reasons has been provided. The applicant is invited to discuss the reasons for premature discontinuation. No discontinuations due to adverse events were reported in clinical trials of ARS-1. (OC)

No post marketing data is available since Neffy is not approved in any country. The applicant is invited to provide and discuss information on post marketing data of similar medical products, if available. (OC)

Additional expert consultation

N/A

Assessment of paediatric data on clinical safety

N/A

Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances

N/A

3.3.10. Conclusions on clinical safety

There were no major safety concerns identified. However, several other concerns remain to be addressed by the applicant.

3.4. Risk management plan

The Safety Specification (Part II, SI-SVIII) from RMP version 1.0, dated 01-06.2020 is assessed below.

The CHMP considers the data presented in the RMP as follows:

- Epidemiology of the indications and target population

There are an estimated 20 million people in the United States with severe allergic reactions and at risk of anaphylaxis. The incidence of actual anaphylaxis in the United States is 49.8 cases per 100,000 person-years (Tang, 2009), translating to approximately 150,000 events a year. Lifetime prevalence of an anaphylaxis event is up to 2%, with a mortality rate of approximately 1% (Kemp, 2007, Tang,

2009, Arnold, 2011). The prevalence of anaphylactic reactions in different parts of Europe and different subpopulations has been extensively described in the literature. The prevalence is typically described as events per 100,000 persons per year with a relatively wide variance observed.

By far the highest prevalence is described by a report from 2012 in Spain, in the subpopulation of children aged 0-4 years. The prevalence reported for this subgroup is 313.58/100,000 persons/year (Tejedor Alonso *et al*., 2012). As this group only represents a fraction of the overall population, this figure should not be regarded as a realistic estimate of the actual number of cases in any country. The highest reported prevalence is 40.4 events/100.000 persons per year for adults in Denmark (Ruiz Oropeza *et al*., 2017).

- Clinical trial exposure

Please refer to section 4.2.

- Populations not studied in clinical trials

No pregnant or breastfeeding women, as well as patients with the following comorbidities:

• Patients with hepatic impairment

• Patients with renal impairment

• Patients with cardiovascular impairment

• Immunocompromised patients

were included.

- Post-authorisation experience

Not applicable.

CHMP comment

Healthy volunteers as well as in subjects with history of allergic conditions (EPI-04 and JP01) were included in the clinical studies conducted by the applicant. Of note, only subjects between 19 and 55 years of age were enrolled.

- Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for abuse of Neffy is reduced by the lack of any observable euphoric effect. Neffy is a prescription-only medication, which limits the potential for abuse. There is no addiction potential with adrenaline.

CHMP comment

The applicant's statement is acknowledged. Based on the substance and mechanism of action, there is no evidence to indicate a potential for misuse for illegal purposes.

- Identification of safety concerns in the RMP submission

Risks considered important for inclusion in the list of safety specification

Important identified risks

Lack of drug effect

Lack of efficacy due to medication error or mishandling

Important potential risks

Serious allergic reaction to sodium metabisulphite content

Serious cardiovascular adverse reactions in predisposed patients

Missing information

Nasal irritation

Increased absorption due to rhinitis or damaged nasal mucosa

Off label paediatric use under the age of 12

Use in elderly patients

Use in pregnancy

CHMP comment

The applicant's proposal is endorsed.

Risks not considered important for inclusion in the list of safety specification

Known risks that require no further characterisation and are followed up via routine pharmacovigilance

namely through signal detection and adverse event reporting, and for which the risk minimisation messages in product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member State where the product is authorised):

• Use in patients with high intraocular pressure

• Use in patients with severe renal impairment

• Use in patients with prostatic adenoma, leading to residual urine, hypercalcaemia, and hypokalaemia

• Use in patients with Parkinson's disease

• Use with drugs that may sensitise the heart to arrhythmias

• Use in patients with hyperthyroidism

• Use in patients with diabetes

These risks are included in the Summary of Product Characteristics for Neffy, within the 'Special warnings and precautions for use' section. Healthcare professionals prescribing Neffy will be aware of these warnings and should be satisfied that the benefit of using Neffy outweighs any potential risks.

CHMP comment

The applicant´s justifications for non-inclusion of risk included in the SPC as important safety concerns are accepted.

- Details of important identified risks, important potential risks, and missing information

Important identified risks

The important identified risks in this section were not observed in the clinical trials involving Neffy, but have been included based on the experience with adrenaline auto-injector products for the same indication.

Neffy nasal spray device not working in a critical situation

Risk-benefit impact:

As the indication of anaphylactic reaction is potentially life-threatening, failure of the device to work as intended represents a risk. If administered promptly following an anaphylactic reaction, adrenaline is effective and can be life-saving.

Intramuscular injections of adrenaline via an auto-injector have been used as a successful treatment for anaphylactic reactions for many years. Neffy is designed to be used by lay people, to allow for easy, rapid self-administration in an allergy emergency in order to treat the symptoms a serious allergic reaction before it can progress to anaphylaxis. It is beneficial that Neffy is delivered as a single dose, as it eliminates the risk of delayed or inaccurate dosing.

The use of autoinjectors is more complex and difficult than Neffy, thus while training is needed, human factor studies with Neffy and other nasal spray products in emergency setting that use the same device, demonstrate that training or dummy devices are not needed beyond the instructions for use.

The inappropriate use of Neffy can be minimised through education of the patient and any caregiver on the proper use of the product. Patient should also be reminded to replace the product when it has past the expiry date, in order to ensure efficacy. Assuming that users are properly trained on how to administer the product, the likelihood of administering the product incorrectly is low.

Products that patients can administer to themselves during an anaphylactic reaction are therefore of benefit, in order to reduce the likelihood of the reaction becoming serious, requiring hospitalisation or being fatal.

The benefit of being able to easily carry and rapidly administer adrenaline using a small nasal sprayer device will outweigh the risk of administering the product incorrectly.

Lack of drug effect

Risk-benefit impact:

Lack of drug effect in the indication of an anaphylactic reaction could be potentially fatal. It is therefore of crucial importance that the product has the intended effect and is efficacious. Use of expired products may result in a sub-therapeutic response. Patients and caregivers should ensure that all devices are within their expiry date and that new nasal spray devices are requested when the expiry date is nearing, to ensure that if the product is required in an emergency situation, that it is has not already expired.

Lack of efficacy due to medication error or mishandling

Risk-benefit impact:

There is a potential risk associated with the inappropriate use of Neffy. If the person administering Neffy is not properly trained in the use of the nasal spray device, there is a risk of the patient receiving an inappropriate dose. It may be difficult for particularly young or elderly patients to administer the product in the correct manner. Disabled patients may also be affected. For this reason, healthcare professionals should ensure that all patients prescribed with Neffy and all caregivers who could potentially be required to administer the product are properly trained in the use of the device. Providing the correct training will mitigate the potential risk of a medication error or mishandling.

Important potential risks

Serious allergic reaction to sodium metabisulphite content

Risk-benefit impact:

Neffy contains a small concentration of sodium metabisulphite as an excipient. Patients with a sensitivity or allergy to sulphites may therefore experience allergic reactions. In patients where the sensitivity is considered mild, the benefit of using Neffy in the indication of an anaphylactic reaction would likely outweigh the potential risk, and treatment should not be delayed.

Serious cardiovascular adverse reactions in predisposed patients

Risk-benefit impact:

Patients with underlying cardiovascular diseases, such as high blood pressure or cardiac valve disease may be at increased risk of experiencing serious cardiovascular adverse reactions following adrenaline reactions.

The benefit of using Neffy in these patients should be carefully evaluated. It is expected that the potential risk of experiencing cardiovascular adverse events is lesser than the risk of delaying treatment with adrenaline in the event of an anaphylactic reaction.

Missing information

Nasal irritation

Risk-benefit impact:

There is the potential for patients to experience localised reactions to one or more of the excipients contained within Neffy, leading to nasal irritation or swelling. This may represent a risk if the patient is required to administer a second dose of the product. Patients who have demonstrated a reaction to one or more of the excipients contained with Neffy should avoid using the product unless a healthcare professional has deemed that the expected benefit outweighs the potential risk.

Increased absorption due to rhinitis or damaged nasal mucosa

Risk-benefit impact:

Patients with allergies, such as allergic rhinitis, and patients who abuse recreational drugs may experience transient changes in the nasal mucosa, which may have some effect on the delivery of Neffy. This may result in more rapid absorption thus leading to a more rapid onset of action. In some rare cases, this may increase the risk of cardiovascular side effects.

Dosing a second time in one nostril increases the local concentration and may result in higher blood levels than with one dose in each nostril. This may result in more rapid and higher blood levels than if dosed as prescribed. In some rare cases, this may increase the risk of cardiovascular side effects.

Neffy is used very infrequently so while there is some small risk of Neffy itself damaging the nasal mucosa, particularly if the patient has sensitivity to one of the ingredients in the product. This would be of a greater risk if Neffy was used regularly, but due to the indication, it should only be used in emergency situations, reducing the risk of damage of the nasal mucosa by the product.

Off label paediatric use under the age of 12

Risk-benefit impact:

Based on clinical studies conducted in adults and modelling studies done to extrapolate pharmacokinetics and pharmacodynamics for Neffy support the use in patients aged 12 years and

over. There is the potential for Neffy to be prescribed to patients under the age of 12 years, especially due to the simple administration method. Healthcare professionals prescribing Neffy to patients aged less than 12 years should be satisfied that the benefit of using Neffy in the patient would outweigh any potential risk, and that caregivers are properly trained in the use of the Neffy device.

Use in elderly patients

Risk-benefit impact:

Elderly patients were not involved in the clinical study for Neffy. As adrenaline has a well-established safety profile, particularly for the indication of anaphylactic reactions, it can be assumed that the benefit of using Neffy for the indication outweighs the potential risks.

Use in pregnancy

Risk-benefit impact:

Pregnant patients were not involved in the clinical study for Neffy. As adrenaline has a well-established

safety profile, particularly for the indication of anaphylactic reactions, it can be assumed that the benefit of using Neffy for the indication outweighs the potential risks. Healthcare professionals prescribing Neffy should consider that the benefit of using Neffy in an anaphylactic reaction outweighs any potential risk in pregnant patients.

CHMP comment

The presentation of important risks includes the characterisation of the risk, risk factors and risk groups, preventability, impact on the risk-benefit balance of the product and public health impact.

The presentation of missing information includes evidence source, population in need of further characterisation and the anticipated risk/consequence of the missing information.

No amendments are considered necessary at the moment.

3.4.1. Safety Specification

Summary of safety concerns

Table 61 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Neffy nasal spray device not working in a critical situation Lack of drug effect Lack of efficacy due to medication error or mishandling
Important potential risks	Serious allergic reaction to sodium metabisulphite content Serious cardiovascular adverse reactions in predisposed patients
Missing information	Nasal irritation Increased absorption due to rhinitis or damaged nasal mucosa Off label paediatric use under the age of 12 Use in elderly patients Use in pregnancy

CHMP comment:

Having considered the data in the safety specification, the CHMP considers that the safety concerns listed by the applicant are not appropriate.

The following issues should be discussed:

The revision of safety concerns is recommended according to the definitions of important risks and missing information detailed in the GVP Module V. The RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product. These risks usually require further evaluation as part of the pharmacovigilance plan. Scientific rationale is needed for defining of the safety concerns in the RMP.

Such known risks as *Serious allergic reaction to sodium metabisulphite content* and *Serious cardiovascular adverse reactions in predisposed patients* likely do not affect risk-benefit balance for this product used in the emergency indication and thus should not be included in the safety concerns.

Also, the absence of data itself (e.g. population not studied) does not automatically constitute a safety concern. Thus, *Nasal irritation, Increased absorption due to rhinitis or damaged nasal mucosa, Off label paediatric use under the age of 12, Use in elderly patients, Use in pregnancy* should be deleted from the missing information.

All three important identified risks might be merged as they are related to the mishandling of the device. Implementation of additional RMM for the risk of mishandling of the device is recommended.

3.4.2. Discussion on safety specification

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification it is not agreed that the safety concerns listed by the applicant are appropriate. Please see LoQ.

3.4.4. Pharmacovigilance plan

The applicant states that there are no further routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. For details relevant to routine pharmacovigilance activities, the applicant refers to PSMF.

3.3.4.1 Summary of planned additional PhV activities from RMP

Table 62 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
-	-	-	-	-
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
-	-	-	-	-
Category 3 - Required additional pharmacovigilance activities				
-	-	-	-	-

According to the applicant, there are two ongoing studies with Neffy:

- EPI 09: Self-Administration of ARS-1, EpiPen and Symjepi (N=60), Interim safety data reported
- EPI 10: Pediatric Study for ARS-1 in Severe Allergy Patients Age 4 to 11 (N=20) and Age 12 to 17 (N=20)

No further information on the studies is provided in the RMP version 1.0.

CHMP comment: It is unclear, whether the applicant suggests the studies EPI 09 and EPI 10 as additional pharmacovigilance activities. If any studies apply as additional pharmacovigilance activities, they should be presented in table form. (OC)

The applicant should explain, which safety concern does the suggested additional pharmacovigilance study EPI 09 address. (OC)

The paediatric study EPI 10 is included in paediatric investigation plan (PIP) of Neffy. As a consequence, the study should not be listed as an additional pharmacovigilance activity in the RMP. (OC)

3.3.4.2. Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

This section not included in the RMP version 1.0.

CHMP comment: There are additional risk minimisation measures suggested by the PRAC (subject to CHMP decision on the final safety specification). The applicant should discuss, how the effectiveness of the proposed additional risk minimisation measures could be evaluated. (OC)

3.3.4.3. Overall conclusions on the PhV Plan

As the safety specification is still under discussion, the preliminary view is that the pharmacovigilance plan needs updating. Depending on the final list of safety concerns proposed by the CHMP, changes may be needed to pharmacovigilance plan.

3.4.5. Risk minimisation measures

3.3.5.1. Routine Risk Minimisation Measures

Table 63 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Neffy nasal spray device not working in a critical situation	Routine risk communication: *SmPC section 4.2* Section 4.2 of the SmPC outlines the instructions for use for Neffy adrenaline nasal spray. Section 4.2 of the SmPC discusses that patients should ensure that they carry more than one Neffy adrenaline nasal spray device. In the rare case of failure of one device, the second can be administered. *PL section 2* Section 2 of the PL outlines that patients should be prescribed more than one Neffy spray device, and that patients should carry more than one device.

Safety concern	Routine risk minimisation activities
Lack of drug effect	Routine risk communication: *SmPC section 4.2* Section 4.2 of the SmPC discusses that patients should ensure that they carry two Neffy adrenaline nasal spray devices. In the rare case of failure of one device, the second can be administered. *PL section 2*

	Section 2 of the PL outlines that patients should be prescribed more than one Neffy spray device, and that patients should carry more than one device.
Lack of efficacy due to medication error or mishandling	Routine risk communication: *SmPC section 4.2* Section 4.2 of the SmPC outlines the instructions for use for Neffy adrenaline nasal spray. *PL section 3* Section 3 of the PL provides instructions to patients on how to use the Neffy nasal spray device.
Serious allergic reaction to sodium metabisulphite content	Routine risk communication: *SmPC section 4.4* Section 4.4 discusses that the presence of sodium metabisulphite as an excipient in Neffy may cause allergic-type reactions. *PL section 2* Section 2 discusses that Neffy contains sodium metabisulphite, which may rarely cause severe allergic-type reactions.
Serious cardiovascular adverse reactions in predisposed patients	Routine risk communication: *SmPC section 4.4 and 4.8* Section 4.4 provides a warning that adrenaline should be administered with extreme caution in patients with heart disease. Section 4.8 highlights that cardiac arrhythmias may occur following administration of adrenaline. *PL section 2 and 4* Section 2 discusses that patients should talk to their doctor when they are prescribed Neffy if they have a heart disease. Section 4 lists arrhythmia following use of adrenaline.
Nasal irritation	Routine risk communication: *SmPC section 4.8* Section 4.8 of the SmPC lists nasal discomfort and nasal congestion as undesirable effects. *PL section 4* Section 4 of the PL lists nasal discomfort and nasal congestion as possible side effects.
Increased absorption due to rhinitis or damaged nasal mucosa	Routine risk communication: *SmPC section 5.2* Section 5.2 of the SmPC discusses that in patients with rhinitis, adrenaline is absorbed more rapidly with the maximum concentration observed in about 10 minutes. *PL section 2* Section 2 of the PL advises that Neffy can be used even in the case of a cold or a congested nose.

Safety concern	Routine risk minimisation activities
Off label paediatric use under the age of 12	Routine risk communication: *SmPC section 4.2* Section 4.2 of the SmPC discusses that Neffy may be used in patients aged 12 and above. *PL section 3*

	Section 3 of the PL outlines that Neffy should not be used in patients under the age of 12 years.
Use in elderly patients	Routine risk communication: *SmPC section 4.4* Section 4.4 of the SmPC outlines that adrenaline should only be prescribed to elderly patients if the potential benefit justifies the potential risk. It also highlights that elderly patients may be at greater risk of developing adverse reactions following adrenaline administration. *PL section 2* Section 2 of the PL outlines that elderly patients should talk to their doctor when prescribed Neffy, as there is a greater risk of getting side effects in elderly patients.
Use in pregnancy	Routine risk communication: *SmPC section 4.4 and 4.6* Section 4.4 of the SmPC highlights that pregnant patients may be at greater risk of developing adverse reactions following adrenaline administration. Section 4.6 advises that adrenaline should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus, and that adrenaline increases the blood pressure and heart rate, which may impact the foetus. *PL section 2* Section 2 of the PL outlines that pregnant patients should talk to their doctor when prescribed Neffy, as there is a greater risk of getting side effects in pregnant patients.

CHMP comment: The suggested routine risk minimisation measures are acceptable. If changes are made to safety specification and to the SmPC, the description of routine risk minimisation measures should be updated. (OC)

3.3.5.2. Additional risk minimisation measures

The applicant states that routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

3.3.5.3. Overall conclusions on risk minimisation measures

The final safety specification is subject to CHMP decision. However, the PRAC considers that the safe use of this medicinal product requires additional risk minimisation measures.

The applicant should propose and develop appropriate educational material for Neffy. The applicant should suggest key elements to educational material containing eg.:

- a training device, which would allow prescribers, patients and caregivers to familiarise themselves with the Neffy nasal spray device and the administration procedure before its actual use.
- a checklist for prescribers aiming to facilitate the discussion between the prescriber and the patient and to provide sufficient information on the optimal way of use, administration and storage of the product.
- digital educational material, which explains in detail how the product is to be used and the different steps for administration. (OC)

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.0 is not acceptable.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on 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 Neffy is needed, as it cannot follow the already existing entry for epinephrine (5-year PSUR cycle). 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 should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Significance/Non-Conformity of paediatric studies

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

Anaphylaxis is a life-threatening, systemic hypersensitivity reaction (Joint Task Force on Practice

Parameters, 2005). It is the most severe form of allergic reaction and is almost always unexpected (Tang, 2009). Delay in clinical diagnosis and treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters, 2005). There are an estimated 20 million people in the United States with severe allergic reactions and at risk of anaphylaxis. The incidence of actual anaphylaxis in the United States is 49.8 cases per 100,000 person-years (Tang, 2009), translating to approximately 150,000 events a year. Lifetime prevalence of an anaphylaxis event is up to 2%, with a mortality rate of approximately 1% (Kemp, 2007, Tang, 2009, Arnold, 2011). The prevalence of anaphylactic reactions in different parts of Europe and different subpopulations has been extensively described in the literature. The prevalence is typically described as events per 100,000 persons per year with a relatively wide variance observed.

By far the highest prevalence is described by a report from 2012 in Spain, in the subpopulation of children aged 0-4 years. The prevalence reported for this subgroup is 313.58/100,000 persons/year (Tejedor Alonso *et al*., 2012). As this group only represents a fraction of the overall population, this figure should not be regarded as a realistic estimate of the actual number of cases in any country. The highest reported prevalence is 40.4 events/100.000 persons per year for adults in Denmark (Ruiz Oropeza *et al*., 2017).

5.1.2. Available therapies and unmet medical need

Adrenaline is considered as the first-line drug of choice for allergic emergencies. Adrenaline also effectively reverses the symptoms of rhinitis, urticaria, bronchospasm, and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels, and other tissues.

Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of severe allergy events leading to anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in the published literature.

Commercially available adrenaline autoinjectors are the current out-of-hospital practice standard of care and in some situations is prescribed to all patients who have experienced anaphylactic reactions or are 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.

Early injection of adrenaline in anaphylaxis, defined as injection when severe allergic reaction starts, but before leading to anaphylaxis or Emergency Department (ED) arrival, can significantly reduce the likelihood of hospital admission, as compared with initial injection after ED arrival. Delayed injection of adrenaline has been reported in other anaphylaxis-related fatalities in which only 23% of the 92 individuals received adrenaline before anaphylactic shock and cardiac arrest. However, 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 develop into an anaphylaxis event, or at least less severe (Simons, 2001).

Although adrenaline injection has an acceptable post-approval safety profile and is effective in the management of anaphylaxis, auto-injectors are considered inconvenient and cumbersome, particularly for paediatric patients, because use of the product requires administration intramuscularly or subcutaneously by patients themselves or by a caregiver in an emergency setting. The difficulty for patients to even carry the auto-injectors is a documented concern by medical professionals as the devices are not always available when needed in an emergency situation. Furthermore, apprehension to use an auto-injector due to the pain, cost, and reluctance to use the device in a public setting often leads to delays in the treatment of severe allergic reactions in emergency situations. Delayed treatment is known to lead to more severe events and more frequent fatalities. Thus, the use of adrenaline auto-injection is one of the common reasons for the lack of use of adrenaline in emergency situations leading to poor treatment outcomes (Simons, 2010, Campbell, 2014).

Reported rates of patients with anaphylactic reactions receiving adrenaline in medical practice range from 27% to 44%, while only 4 to 10% receive more than one dose (Alvarez-Perea et al., 2017, Grabenhenrich et al., 2018, Grabenhenrich et al., 2019).

5.1.3. Main clinical studies

The clinical development programme for adrenaline (ARS-1, Neffy) consists of clinical pharmacology studies which were conducted in healthy subjects and in allergic patients with chronic rhinitis. The clinical studies in the development programme for Neffy for this submission are: biopharmaceutic studies (considered as supportive: EPI 01, EPI 02, and EPI 06) and individual clinical pharmacology studies (considered as pivotal: EPI 03, EPI 04, EPI 07, and EPI JP01). Four studies were conducted with the commercial formulation of Neffy: EPI 03, EPI 04, EPI 07, and EPI JP01.

The study EPI 03 assessed the bioavailability of both a single dose and repeat dose of ARS-1 1 mg IN as compared to a single and repeat dose of IM epinephrine injection. During the study EPI 04 the comparative bioavailability of epinephrine after IN administration of ARS-1 in subjects with induced allergic rhinitis was assessed and the impact of nasal oedema and congestion on the absorption of epinephrine was evaluated. The study Epi07 assessed the comparative bioavailability of epinephrine after IN administration of ARS-1 (1.0 milligram (mg) with EpiPen (0.3 mg IM injection of epinephrine) after both one and two doses in healthy volunteers under fasted conditions, to evaluate the comparative PD response based on HR and BP. The EPI JP01 study the pharmacokinetics (PK) of

adrenaline after administration of ARS-1 1 mg IN in Japanese subjects with normal nasal conditions and with induced allergic rhinitis and the impact of nasal oedema and congestion on the absorption of adrenaline was evaluated.

5.2. Favourable effects

The data to support this MAA is efficacy and safety data from ARS clinical trials based on surrogate pharmacodynamic endpoints.

Four clinical pharmacology studies were conducted with Neffy (EPI 03, EPI 04, EPI 07, and EPI JP01) to demonstrate the efficacy and safety of adrenaline by the nasal route of administration. The PK data from the clinical pharmacology studies demonstrate that Neffy has an injection-like pharmacokinetic profile compared to intramuscular dosing by an EpiPen.

The comparative bioavailability of Neffy in four pharmacokinetic studies (EPI 03, EPI 04, EPI 07, and EPI JP01) provided similar exposure (Cmax and AUC0–t) of adrenaline and pharmacodynamic response as compared to injection products. The time to Cmax (Tmax) after Neffy administration is faster than EpiPen 0.3 mg. Single dosing of Neffy was additionally tested under simulated conditions of nasal oedema and congestion (EPI 04 and EPI JP01).

The studies showed that subjects who received ARS-1 1.0 mg IN showed higher PB and more significant 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 higher than that of Epinephrine 0.3 mg IM.

In addition, because a patient experiencing a Type I allergic reaction may require a second dose of the drug in the event of symptoms recurrence, the pharmacokinetics of twice dosing of Neffy were compared to twice dosing of IM adrenaline injection and EpiPen 0.3 mg in two clinical studies (EPI 03 and EPI 07). Twice dosing of Neffy was shown to be comparable to twice dosing with IM adrenaline injection or EpiPen 0.3 mg. However, an increase in absorption after misdosing twice in the same nostril was observed.

Haemodynamic data indicate that Neffy 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. On the other hand, the maximum change in HR or SBP was similar between treatments.

5.3. Uncertainties and limitations about favourable effects

It is acknowledged that robust data on efficacy in the target population may not possible to generate. Pharmacokinetic and pharmacodynamic effects of nasal compared to intramuscular administration mainly in healthy volunteers may be an acceptable alternative approach. The applicant has, however, not provided sufficient support for the key assumption that absorption from the nasal mucosa is comparable in healthy volunteers and in patients with acute anaphylaxis. The latter group is expected to have a profound circulatory compromise, which could potentially reduce perfusion in the nasal mucosa and consequently reduce absorption of adrenaline. This could adversely affect clinical efficacy, particularly in the patients that are in most critical need of the product.

In addition, 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.

Epinephrine levels were shown to rise more rapidly after I.N. administration in subjects with rhinitis. However, at the same time, a more rapid decline in blood concentrations was observed.

Thus, while a faster onset of action should not pose a clinical problem, a more rapid decline may raise some doubts regarding the risk of a possible recurrence of symptoms.

The observation of PD parameters supports these doubts. Circulatory effects appear to be shortened (both BP and HR). After 60 minutes, these parameters return to baseline before drug administration. Therefore, it is necessary to analyse the changes in PK and PD after drug administration in a population with rhinitis in terms of the risk of a possible recurrence of symptoms.

No analysis by sex was performed. Because the average absorptive surface of the nasal mucosa is smaller in women, it is requested to provide a sex analysis of PK and PD parameters with simultaneous consideration of body weight. Similarly, there is no data about ARS-1 in the elderly population.

Additionally, twice the administration of ARS-1 results in much higher the epinephrine concentration compared to I.M. administration. It is unclear whether this significantly higher concentration would not entail a worsening of the safety profile compared to intramuscular administration.

The applicant has not conducted studies on ARS-1 in the EU population. It is not clear whether the US population's results can be extrapolated to the EU population.

The clinical significance of one of the PD parameters - diastolic pressure - also needs to be discussed. The observed pattern of changes in this parameter seems to differ depending on the epinephrine administration route - I.M. or I.N.

In addition, the use of antimicrobial preservative is questioned, and the applicant is asked to reformulate the product. Therefore, additional data are requested in order to thoroughly justify that the absorption of the active substance through nasal mucosa is not altered by the reformulation of the product and subsequent discussion of benefit/risk profile is needed.

5.4. Unfavourable effects

In total 229 subjects were exposed to Neffy in the completed clinical studies. Moreover, 59 patients have been exposed in the ongoing study EPI09.

Overall, in all completed studies conducted by the applicant, 44.8%, 52.4% and 80.6% of patients exposed to nasal adrenaline dose of 1 mg, 2mg (L/R) and 2mg (L/L) experienced at least 1 TEAE, respectively. 42.9% patients with severe allergies compared to 28.3% in full safety population experienced at least 1 TEAE during the ongoing study EPI 09.

20.7% of patients treated with ARS-1 (1mg) experienced nasal discomfort, 4.6% headache and 4% throat irritation.

The most common adverse reactions that were observed in the clinical studies were palpitations and blood pressure and heart rate increase. However, these adverse events were mostly observed in patients who received 2mg of adrenaline, all were mild and resolved without treatment.

77.8% of patients from 2mg (L/L) group (pooled analysis of pivotal studies), experienced blood pressure increase. Contrary, only 19% of patients treated with 2mg (L/R) experienced blood pressure increase. Similar trend was observed with respect to the incidence of the increase in heart rate – 5.7% and 16.7% of patients from 2mg (L/R) and 2mg (L/L) groups experienced this TEAE. Moreover, palpitations were observed in 12.4% of patients from 2mg (L/R) group and 25% of patients from 2mg (L/L) group.

Generally, no significant differences in the incidence of TEAE were observed in Study EPI 09 between subjects with severe allergies compared to full safety population, with exception to nasal discomfort, experienced by 21.1% of patients with severe allergies and 13.2% of patients from full safety population. Nasal oedema was observed in 17.6% of patients with rhinitis. There were no reports of treatment-related nasal pain or application site pain in ARS-1 treated patients in the pivotal studies

There have been no significant clinical laboratory evaluation findings related to the safety of the test article.

No cases of serious adverse events or deaths were reported during the overall clinical development programme.

5.5. Uncertainties and limitations about unfavourable effects

It is noted that no patients above 55 years of age were included in the studies. Therefore, safety of adrenaline in elderly patients based on the literature data should be discussed. Moreover it is not clear how risk of misuse of Neffy will be mitigated, especially with regard to elderly people.

Significant differences in prevalence of increase in blood pressure and heart rate between patients from 2mg (L/L) and patients form 2mg (L/R) groups should be further discussed by the applicant.

There are only very limited data regarding safety of Neffy in patients with subjects with confirmed Type 1 allergies, including a subset of subjects with severe Type 1 allergies. Only preliminary data from the ongoing study EPI 09 were presented.

5.6. Effects Table

Table 64 Effects Table for Neffy

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects (PD surrogate results)						
SBP (systolic blood pressure)	SBP Emax (mean)	mmHg	ARS-1 1.0 mg I.N. 18.9	EpiPen 0.3 mg I.M. 18.4	Pooled data ARS-1 (N - 103) EpiPen 0.3 (N – 35)	Epi03 and 07
HR (heart rate)	HR E_{max} (mean)	bpm	ARS-1 1.0 mg I.N. 17.4	EpiPen 0.3 mg I.M. 17.9	Pooled data ARS-1 (N - 103) EpiPen 0.3 (N – 35)	Epi03 and 07
DBP (systolic blood pressure)	DBP Emax (mean)	Mm Hg	ARS-1 1.0 mg I.N. 13.7	EpiPen 0.3 mg I.M. 9.09	Pooled data ARS-1 (N - 103) EpiPen 0.3 (N – 35)	Epi03 and 07
SBP (systolic blood pressure)	SBP Emax (mean)	mmHg	ARS-1 1.0 mg I.N. 14.7	EpiPen 0.3 mg I.M. 11.9	ARS-1 (N - 36) EpiPen 0.3 (N – 30)	Epi JP01
HR (heart rate)	HR E_{max} (mean)	bpm	ARS-1 1.0 mg I.N. 14.5	EpiPen 0.3 mg I.M. 16.2	ARS-1 (N - 36) EpiPen 0.3 (N – 30)	Epi JP01
DBP (systolic blood pressure)	DBP Emax (mean)	Mm Hg	ARS-1 1.0 mg I.N. 7.28	EpiPen 0.3 mg I.M. 2.83	ARS-1 (N - 36) EpiPen 0.3 (N – 30)	Epi JP01
SBP (systolic blood pressure)	SBP Emax (mean)	mmHg	ARS-1 1.0 mg I.N. 17.18	EpiPen 0.3 mg I.M. 15.58	In participants with rhinitis ARS-1 1 mg IN administration resulted in a more rapid and pronounced	Epi04

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
HR (heart rate)	HR E_{max} (mean)	bpm	ARS-1 1.0 mg I.N. 14.80	EpiPen 0.3 mg I.M. 13.24	increase in these vital signs compared to Epinephrine 0.3 mg IM.	Epi04
Unfavourable Effects						
Nasal discomfort		%	20.7% in ARS-1 group	0 % in EpiPen group	Other nasal AE (pruritus, dryness, oedema) were reported with much lower incidence	Pooled analysis (4 pivotal studies)
Headache		%	4.6% in ARS-1 group	2.8% in EpiPen 0,6 group	In patients with rhinitis, headache was reported in 1.5% of patients	Pooled analysis (4 pivotal studies)
Throat irritation		%	4.0% in ARS-1 group	0 % in EpiPen group	In patients with rhinitis, throat irritation was reported in 1.5% of patients	Pooled analysis (4 pivotal studies)

Abbreviations:ARS-1 – Neffy
Notes:

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The data to support this MAA is efficacy and safety data from ARS clinical trials based on surrogate pharmacodynamic endpoints. The applicant utilised haemodynamic endpoints as surrogate markers for the mechanism of action that are predictive of clinical efficacy through activation of α- and β-adrenergic receptors. Pharmacodynamic scores that were used as a surrogate for adrenaline efficacy included measurements of blood pressure (systolic and diastolic) as well as heart rate. A comparison of PD responses following ARS-1 administrations (once or twice) was also performed as part of the PD analysis, taking into account dose dependence. In accordance with the recommendations in the Scientific Advice, 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.

Adrenaline is considered as the first-line drug of choice for allergic emergencies. Early injection of adrenaline in anaphylaxis, defined as injection when severe allergic reaction starts, but before leading to anaphylaxis or Emergency Department (ED) arrival, can significantly reduce the likelihood of hospital admission, as compared with initial injection after ED arrival. Adrenaline injection has an acceptable post-approval safety profile and is effective in the management of anaphylaxis.

The clinical pharmacology studies which were conducted with Neffy demonstrated that its pharmacokinetic and pharmacodynamic profile may be compared to intramuscular dosing by an EpiPen. Most of the data suggest similarity of PK and PD profiles for epinephrine administered to I.M. and Neffy. Nevertheless, some differences in particular for patients with rhinitis need to be clarified.

As Neffy Nasal Spray, solution in a single dose container, is a single use product, the inclusion of antimicrobial preservatives is not considered acceptable for single use preparations. The finished product should be reformulated without preservatives. This issue is considered as major from the quality point of view.

No major safety issues were reported in the clinical studies.

5.7.2. 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 surrogates of efficacy adopted appear adequate, in particular SBP and HR. The different PD epinephrine profile in subjects with allergic rhinitis needs clarification, particularly in terms of the persistence of the desired clinical effect as well as in terms of safety. The importance of DBP for the assessment of ARS-1 effects appear inconclusive, and its clinical relevance requires further justification.

Nevertheless, the applicant has not provided sufficient support for the key assumption that absorption from the nasal mucosa is comparable in healthy volunteers and in patients with acute anaphylaxis. This group is expected to have a profound circulatory compromise, which could potentially reduce perfusion in the nasal mucosa and consequently reduce absorption of adrenaline. This could adversely affect clinical efficacy, particularly in the patients that are in most critical need of the product.

In addition, several other issues also need to be clarified.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable.

5.8. Conclusions

The overall B/R of Neffy is currently negative.