FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Introductory Remarks

New Drug Application (NDA) 214697: epinephrine nasal spray (ARS-1) for emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kg

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May 11, 2023

ARS-1 (Epinephrine Nasal Spray)

- Proposed indication
  - emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kg
- Dose: 2 mg
  - single-use device delivers an intranasal dose containing 2 mg/100 mcL spray
  - If symptoms progress after 10 minutes or an error is made administering, give a second dose with a new device

[1]conditionally accepted proposed tradename; not formally approved

Anaphylaxis

- Severe, potentially fatal, systemic allergic reaction that occurs suddenly (minutes to hours), usually after exposure to allergen to which patient is sensitized to[1]
  - Epinephrine is considered first-line standard of care therapy for anaphylaxis and is the only life-saving treatment. [1]
  - Up to 20% require a second dose of epinephrine[2]

- Fatal anaphylaxis secondary to respiratory and/or cardiac arrest often occurs within 5 to 30 minutes after exposure
  - Estimated prevalence of fatal anaphylaxis of 0.69 per million (approximately 230 deaths/year based on the U.S. population) [3]

- Large population at risk:
  - Food allergy – ~10% of the US population[1]
  - Drug allergy – ~10% of the US population[1]
  - Hymenoptera venom allergy – 3% of the US population[1]
  - Lifetime prevalence ranges between 1.6% to 5.1%.[1]

1. Shaker M.S., et al. Anaphylaxis- a 2020 practice parameter update, systemic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol, 2020; 145: 1082-123.
2. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-S58.
3. Jerschow, E et al. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations, J Allergy Clin Immunol, 134(6):1318-1328 e1317.

Approved Epinephrine Injection Products

Drug Product (Sponsor)	Year of Approval	Dosage Strength	Dosage Form
EpiPen/EpiPen JR (Mylan Specialty LP)	1987	0.15 mg/injection 0.3 mg/injection	Autoinjector
Adrenaclick (Impax Labs, Inc.)	2003	0.15 mg/injection 0.3 mg/injection	Autoinjector
Auvi-Q (Kaleo, Inc.)	2012	0.1 mg/injection 0.15 mg/injection 0.3 mg/injection	Autoinjector
Generic of EpiPen/EpiPen JR (Teva)	2018	0.15 mg/injection 0.3 mg/injection	Autoinjector
Symjepi (Adamis Pharms Corp)	2017	0.3 mg/injection	Prefilled syringe
Adrenalin and epinephrine (Multiple companies); *Medical setting only*	2012	1 mg base/mL	Single and multidose vial

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Community	7.5 kg to 15 kg	15 kg to 30 kg	≥30 kg
	0.1 mg	0.15 mg	0.3 mg

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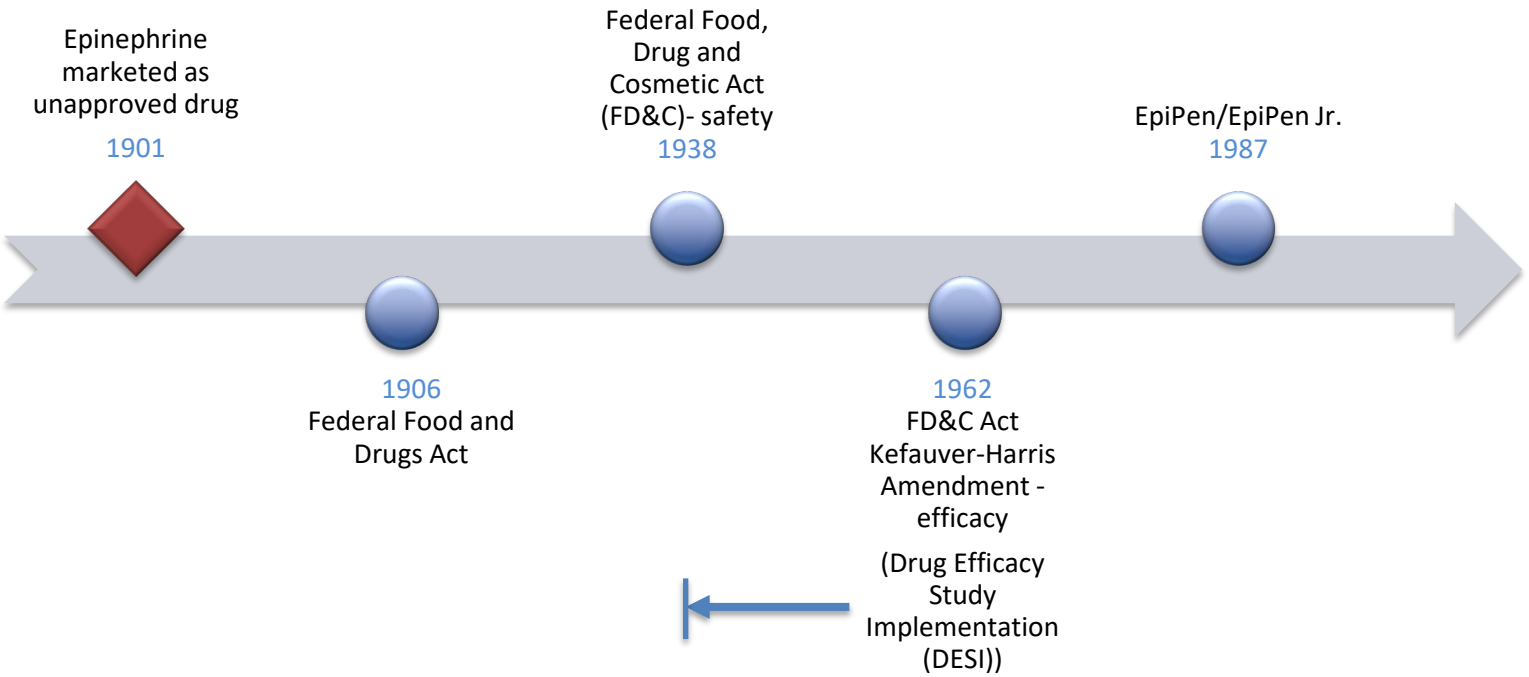
Community	**7.5 kg to 15 kg**	**15 kg to 30 kg**	**≥30 kg**
	0.1 mg	0.15 mg	0.3 mg

Medical setting	**< 30 kg**	**≥ 30 kg**
	0.01 mg/kg up to 0.3 mg	0.3 – 0.5 mg

Epinephrine Regulatory History



Epinephrine Injection Products Approval Process

- EpiPen was approved by FDA based upon literature support for efficacy and safety
  - Clinical trial and pharmacokinetics (PK)/pharmacodynamic (PD) data were not required.

- Recent approvals rely on the established efficacy and safety of an approved epinephrine injection product; 505(b)(2)
  - Chemistry/manufacturing, device, and human factors

- PK/PD data were not required for the approval of more recent epinephrine injection products
  - Similarity of the formulations and route of administration between the new and the approved epinephrine injection product

Development Considerations for Epinephrine Nasal Spray

- ARS proposed a 505(b)(2) application referencing approved epinephrine injection products

- Due to novel route of administration, establish scientific bridge with PK/PD to approved epinephrine injection products

- Uncertainties in translating PK/PD results from healthy subjects to patients with anaphylaxis
  - Would clinical efficacy trial be needed?
  - Clinical efficacy trial feasibility concerns

Challenges With PK/PD Bridging

- Limited PK/PD data for approved epinephrine injection products
  - Critical PK endpoints unknown; dose not evaluated in dedicated clinical efficacy trials
- PK variability and comparator selection
  - ➢ Bracketed approach between approved epinephrine injection products
- Impact of intranasal epinephrine on absorption
  - Blood vessel constriction can impact absorption, especially if second dose is needed
  - ➢ Repeat-dose study
- Impact of anaphylaxis on absorption
  - Rhinitis and nasal congestion may affect local absorption
  - ➢ Nasal allergen challenge study
- Pediatric Considerations
  - Nasal anatomy differences
  - ➢ Dedicated pediatric PK/PD study across ages and body weights

Clinical Pharmacology Program Supporting 2 mg ARS-1

PK/PD/Safety Trial	Purpose
Dose ranging (EPI 11b)	Determine an appropriate ARS-1 dose compared to EpiPen 0.3 mg (autoinjector) and Symjepi 0.3 mg (prefilled syringe) based on PK similarity.
PK matching (EPI 15)	Bracket the single-dose PK profile of ARS-1 with EpiPen 0.3 mg and Adrenalin 0.3 mg (needle-syringe) with support of comparable safety and PD profiles.
Second dose (EPI 15)	Assess the PK/PD and safety of two doses of ARS-1 compared to two doses of EpiPen 0.3 mg.
Nasal allergen challenge (EPI 16)	Assess the effect of nasal congestion on the PK/PD and safety of single-dose ARS-1 compared to Adrenalin 0.3 mg and 0.5 mg.
Self-administration (EPI 17)	Assess if self-administration of a single-dose of ARS-1 changes the PK/PD and safety compared to Adrenalin (staff-administered).
Pediatric PK (EPI 10)	Assess the PK/PD and safety of various single-doses of ARS-1 in pediatric allergy subjects 4 to < 17 years of age and ≥ 15 kg.

PK Summary

- Single-dose of ARS-1 in healthy adults
  - different PK trends across studies in the first 10 minutes compared to Adrenalin 0.3 mg
  - after 10 minutes ARS-1 was reasonably bracketed by Adrenalin 0.3 mg and EpiPen 0.3 mg

- Two doses of ARS-1 in the same or opposite naris in healthy adults
  - lower PK in the first 20 minutes and similar PK 20 min postdose compared to two doses of EpiPen

- Single-dose of ARS-1 in adults with allergen-induced nasal congestion
  - faster absorption rate and faster decline rate at about 10-20 min compared to without nasal congestion and compared to Adrenalin 0.3 mg and 0.5 mg
  - two doses under nasal congestion was not studied

- Single-dose of ARS-1 in pediatric subjects ≥ 30 kg
  - similar PK in the first 10 min and higher PK thereafter compared to ARS-1 in adults

PD Summary

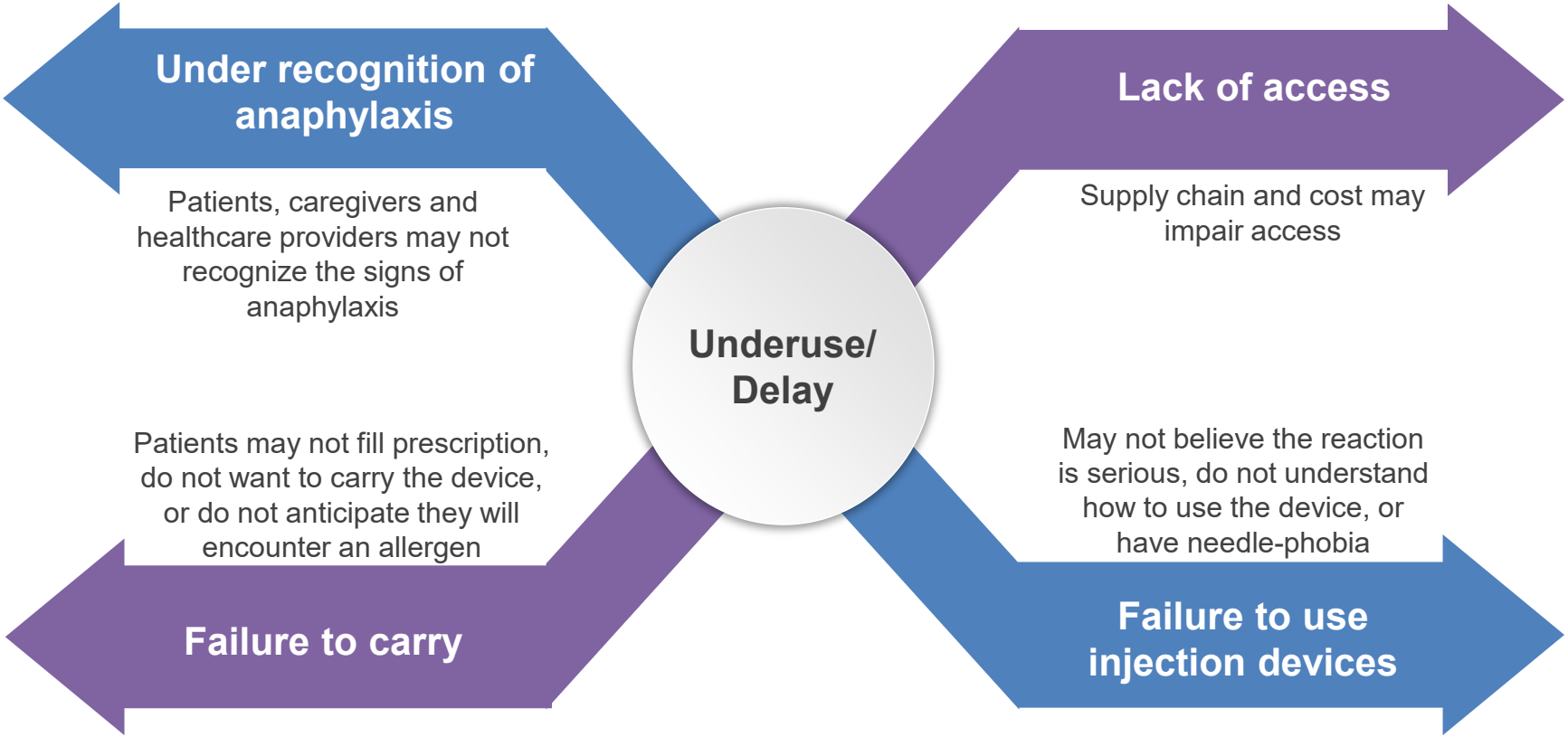
PD: systolic blood pressure, diastolic blood pressure, and pulse rate

- Single and repeat doses of ARS-1 in healthy adults
  - Generally higher and more sustained PD compared to Adrenalin and EpiPen in healthy adults

- Single-dose of ARS-1 in adults with allergen-induced nasal congestion
  - Similar pattern as PK under nasal congestion conditions (faster onset but lack of sustainability) compared to Adrenalin

- Single-dose of ARS-1 in pediatric subjects ≥ 30 kg
  - PD slightly lower compared to adults

Barriers to Epinephrine Use



Benefit / Risk

- Feasibility concerns with clinical efficacy trials
- Rely on PK/PD comparisons to approved epinephrine injection products
- Uncertainties regarding benefit and risk
- Emergency treatment for potentially fatal condition – minimize uncertainties – may require additional data

Topics for Discussion

1. **DISCUSSION**: Discuss the pharmacokinetic/pharmacodynamic (PK/PD) approach for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) including anaphylaxis, specifically:

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   a. The PK-bracketing approach using approved epinephrine injection products.
   b. The relevant PK/PD parameters to support clinical efficacy for the intended indication, including the significance of the following findings:
      - The diminished PK/PD sustainability in subjects with allergen-induced nasal congestion compared to epinephrine injection products and lack of data from repeat dosing under allergen-induced nasal congestion conditions.
      - The different PK comparisons of single-dose ARS-1 and Adrenalin in the first 10 minutes for Study EPI 15, EPI 16 (without allergen-induced nasal congestion), and EPI 17.

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      - The different PK comparisons of single-dose ARS-1 and Adrenalin in the first 10 minutes for Study EPI 15, EPI 16 (without allergen-induced nasal congestion), and EPI 17.
   c. The uncertainty of translation of PK/PD results from healthy subjects and subjects with allergen-induced nasal congestion to patients with anaphylaxis, and whether clinical data are needed.

Voting Questions

2. **VOTE**: Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

    a. If not, what additional data are needed?

Voting Questions

3. **VOTE**: Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children (< 18 years of age) ≥ 30 kg for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

    a. If not, what additional data are needed?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Overview of Clinical Program

New Drug Application (NDA) 214697: epinephrine nasal spray (ARS-1) for emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kg

Jennifer Lan, MD
Medical Officer
Division of Pulmonology, Allergy, and Critical Care
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FDA Presentation Outline

- Overview of Clinical PK/PD Program
  - *Jennifer Lan, MD, Clinical Reviewer*
- Overview of the Clinical Pharmacology Results
  - *Qianni Wu, Pharm D, Clinical Pharmacology Reviewer*
- Clinical Considerations and Risk/Benefit
  - *Jennifer Lan, MD, Clinical Reviewer*

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Development Process Overview

- FDA worked with ARS Pharmaceuticals on a regulatory pathway for the new route of administration of epinephrine
- 505(b)(2) regulatory pathway
- Clinical efficacy trials were considered, but feasibility questionable
  - Emergency department, oral food challenge clinic, allergy immunotherapy clinic
- Clinical pharmacology program may be sufficient

PK/PD Approach to Other Nasal Emergency Products

Naloxone nasal spray

- Emergency treatment of known or suspected opioid overdose for all ages
- Approval based on 1 PK trial in healthy adults comparing nasal to naloxone injection
- Wide safety margin; approved nasal dose surpassed exposure of naloxone injection by ~5x
- No major concerns translating healthy volunteer PK data to patients

Diazepam nasal spray

- Acute treatment of intermittent, stereotypic episodes of frequent seizure activity
- Efficacy based on comparable bioavailability to diazepam gel (efficacy established with adequate and well-controlled trials)
- Approval based on PK studies in healthy subjects and safety/PK studies in patients with epilepsy to address potential PK differences in patients

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  - Effect of nasal mucosal edema on epinephrine absorption?

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  - **EPI 15 Single and Repeat Dose**

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  - – Effect of nasal mucosal edema on epinephrine absorption?
  - ➢ **EPI 16 Nasal Allergen Challenge**

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- PK of self administration vs. investigator administration
  - ➢ **EPI 17 Self-administration Study**

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- PK of self administration vs. investigator administration
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- Pediatric considerations
  - ➢ **EPI 10 Pediatric Trial**

Clinical Pharmacology Program Supporting 2 mg Dose

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FDA Pulmonary-Allergy Drugs Advisory Committee Meeting

Overview of the Clinical Pharmacology Data

Qianni Wu, PharmD
Clinical Pharmacology Reviewer
Division of Inflammation and Immune Pharmacology
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
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Outline

- Background
- Major clinical pharmacology results of ARS-1

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BACKGROUND

Pharmacokinetics of Epinephrine

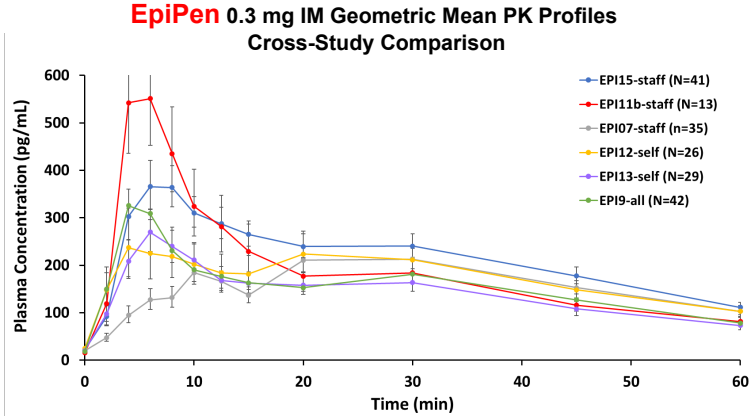
- Literature reported baseline plasma concentration in healthy subjects is ~ 35 pg/mL.

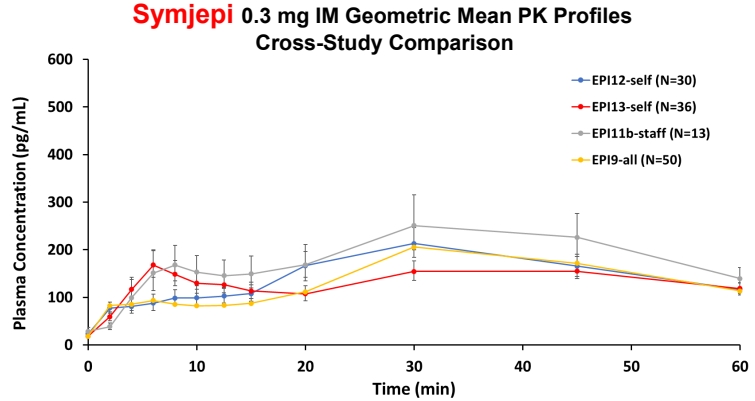
- Elimination
  - The plasma half-life of epinephrine is about 2 to 3 minutes
  - Epinephrine metabolizing enzymes (MAO and COMT) are widely expressed in human body

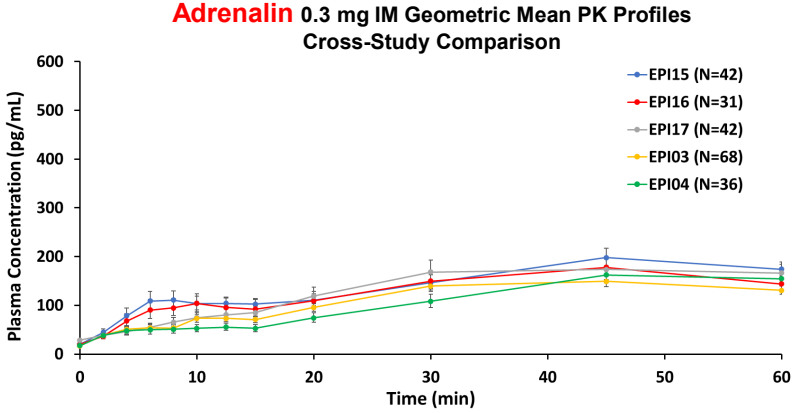
- Epinephrine PK from Auvi-Q and EpiPen autoinjectors shows highly variable nature
  - The mean of maximum plasma concentration (C_{max}) ~ 500 pg/mL (coefficient of variation [CV]% ~ 51% to 80%)
  - The time to maximum plasma concentration (T_{max}) ranged from 5 to 60 minutes

MAO: monoamine oxidases
COMT: catechol-O-methyltransferase

PK Variability of Epinephrine Injection Products in ARS-1 Program







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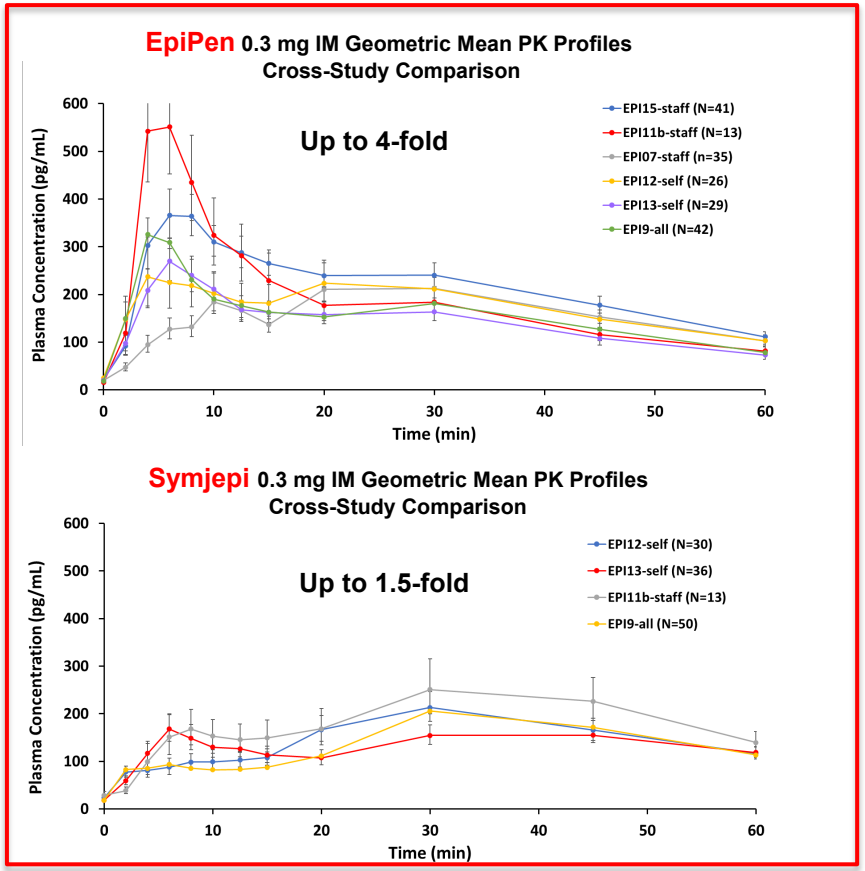

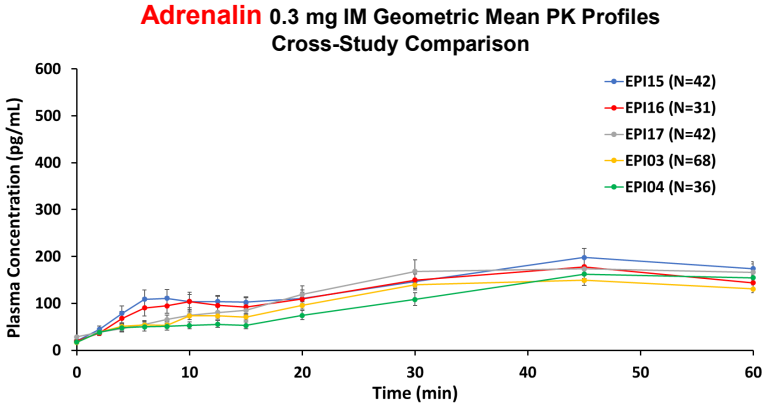

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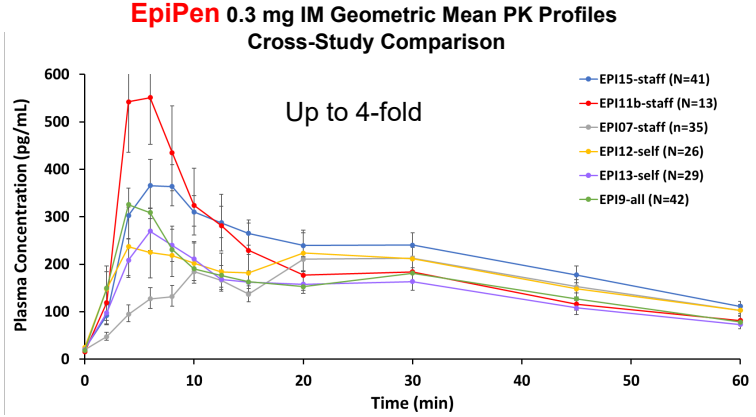

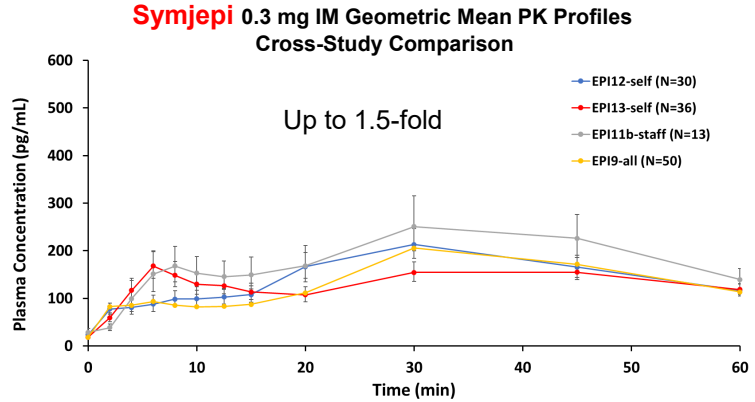

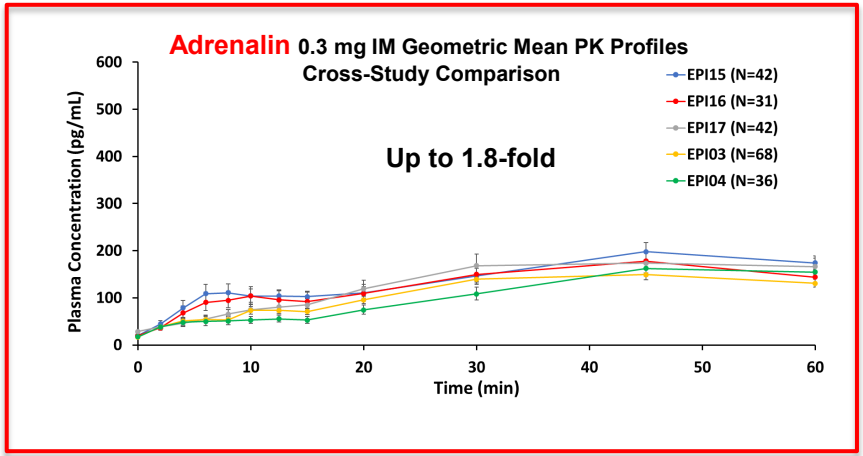

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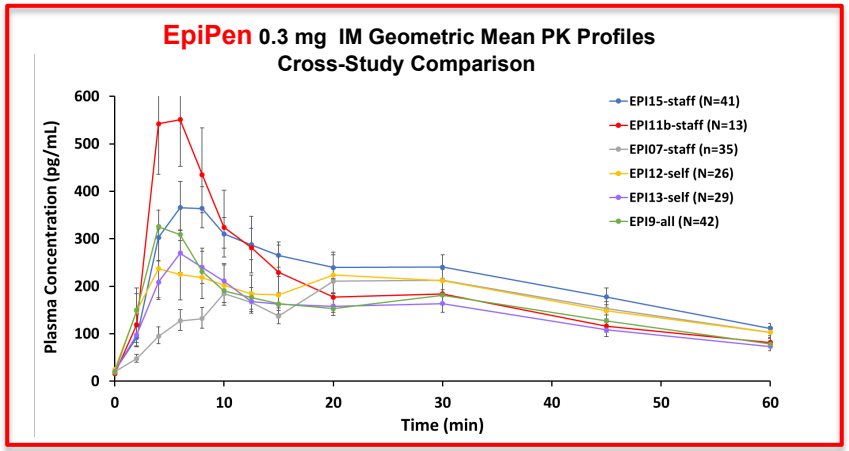

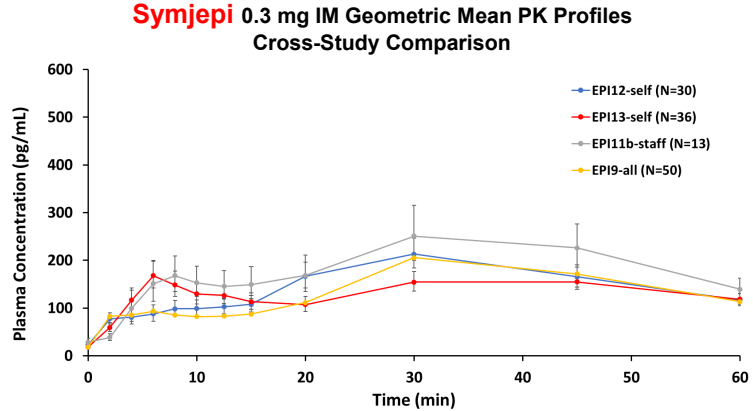

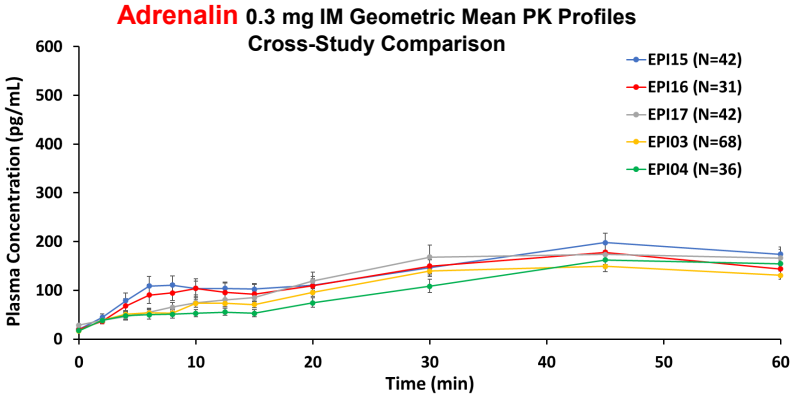

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PK Bracketing Rationale

- Substantial PK variabilities were observed in ARS program
  - across different studies for the same epinephrine injection product
  - across different approved epinephrine injection products
  - across different batches for the same epinephrine injection product

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- A relative bioavailability study with only one approved product/dose increases the uncertainty due to the PK variability of epinephrine

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- A relative bioavailability study with only one approved product/dose increases the uncertainty due to the PK variability of epinephrine

- Introduction of multiple approved injection products/doses in a PK comparison study provides a flexible and reasonable foundation, if the epinephrine PK profile from the proposed product can be reasonably bracketed by the approved products.

PK Bracketing Rationale

- Substantial PK variabilities were observed in ARS program
  - across different studies for the same epinephrine injection product
  - across different approved epinephrine injection products
  - across different batches for the same epinephrine injection product

- A relative bioavailability study with only one approved product/dose increases the uncertainty due to the PK variability of epinephrine

- Introduction of multiple approved injection products/doses in a PK comparison study provides a flexible and reasonable foundation, if the epinephrine PK profile from the proposed product can be reasonably bracketed by the approved products.

- Comparison of epinephrine absorption profiles is critical for epinephrine products with alternative routes of administration

Weighing PD Support

PD comparison plays a limited supportive role to assist in PK matching approach:

- Different trends observed when comparing the PK and PD results between ARS-1 and EpiPen. The definitive mechanism is unknown.

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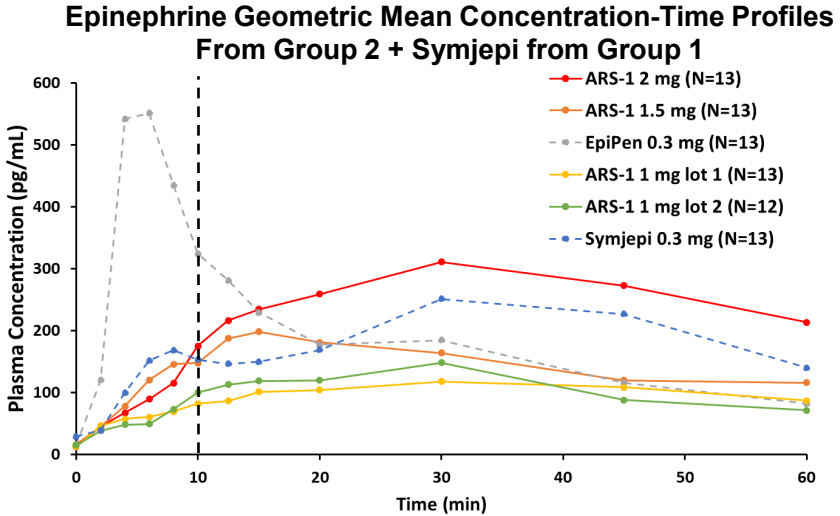
- More uncertainties to translate PD response results from healthy subjects to patients with anaphylaxis.

Dose-Ranging and Formulation-Exploration Study In Healthy Adults

STUDY EPI 11b

Dose Ranging Study – EPI 11b

- EPI 11b: open-label, single-dose, within-group crossover study
  - Group 1 (N=13): ARS-1 vs. Symjepi
  - Group 2 (N=13): ARS-1 up to 2 mg vs. EpiPen



- Washout period between ARS-1 treatments in the same naris: 12 days
- The formulations used in this study is slightly different from the to-be-marketed formulation
- Symjepi results were from Group 1 in the same study

PK Results Presentation for EPI 15, 16, 17 and 10

- Dedicated PK study vs. pooling data
- No baseline adjustment to avoid negative post-dose concentrations
- PK analyses focusing on 60 minutes post-dose
  - For better characterization of early PK profile/area under the concentration-time curve (AUCs), a few subjects with less than 3 PK samples collected within 30 minutes were excluded
- Subject Inclusion/Exclusion for Study EPI 15
- Display of geometric mean in concentration-time profile

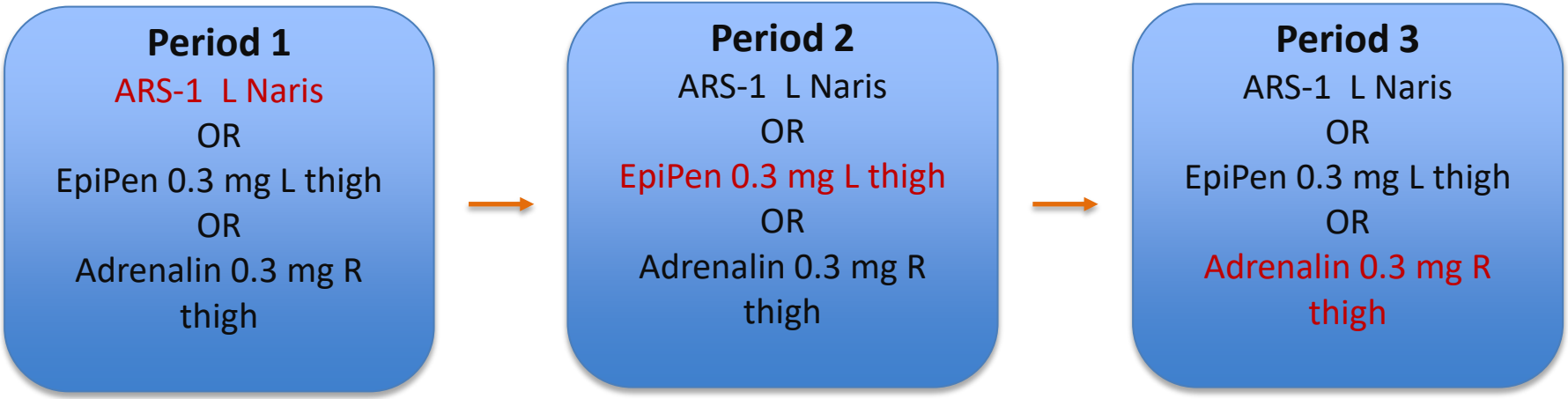
Pivotal PK/PD Study In Healthy Adults

STUDY EPI 15

Study EPI 15 Study Design

- Study Design: two-part, six-treatment, six-period, single and repeat dose, **partial crossover**
  - Part 1: single-dose
  - Part 2: repeat-dose: 2 doses, 10 minutes apart
- Population: healthy adults (N=59)
  - Sample size: 42 subjects for each part
  - Each subject had Nasal Congestion Score (NCS) of zero prior to dosing

EPI 15 Part I: Single-Dose PK Trial



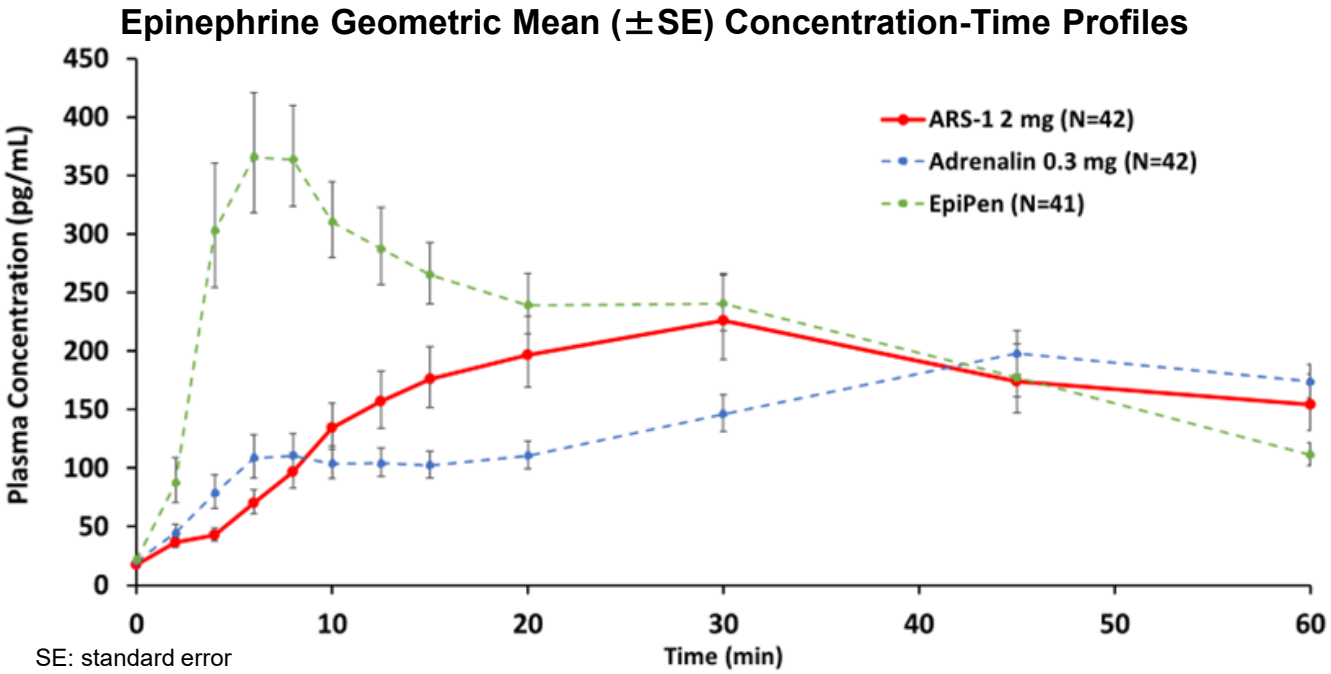
L: left
R: right

Healthy Adults

Fully randomized between the three treatment periods

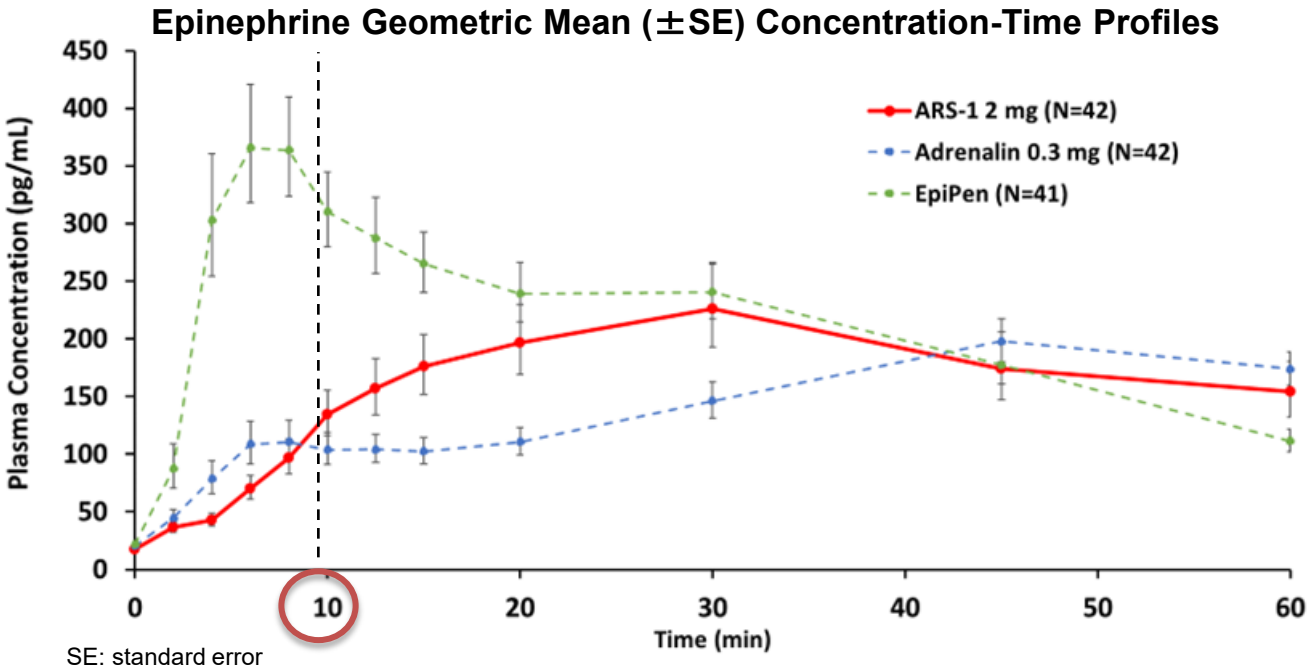
Washout period between treatments: 24 hours

Single-Dose PK Results (EPI 15)



SE: standard error

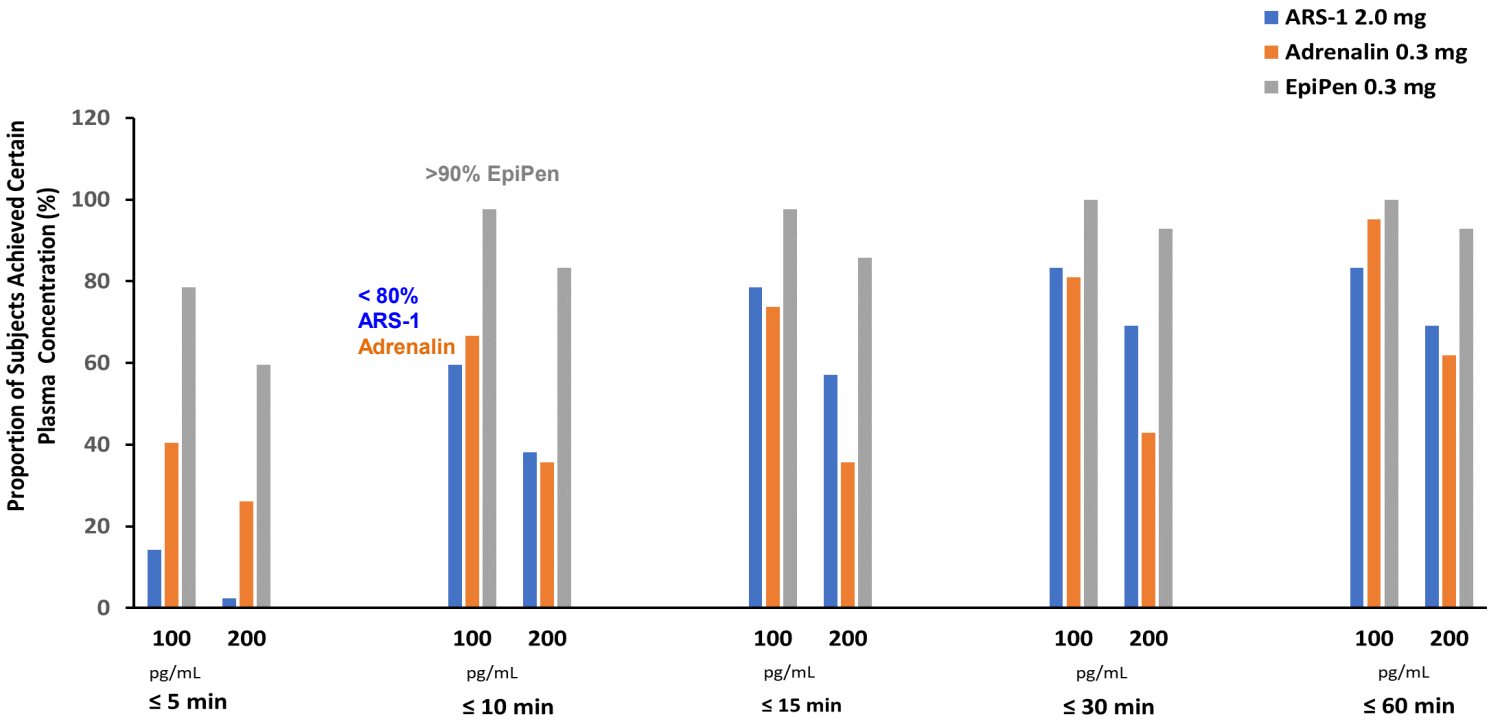
Single-Dose PK Results (EPI 15)



SE: standard error

- A lower epinephrine mean concentration following ARS-1 compared to injection products within 10 minutes post-dose
- The PK profile of ARS-1 is reasonably bracketed by EpiPen and Adrenalin after 10 minutes post-dose

Proportion of Subjects Achieving Certain Plasma Concentrations (100 and 200 pg/mL) After Single-Dose (EPI 15)



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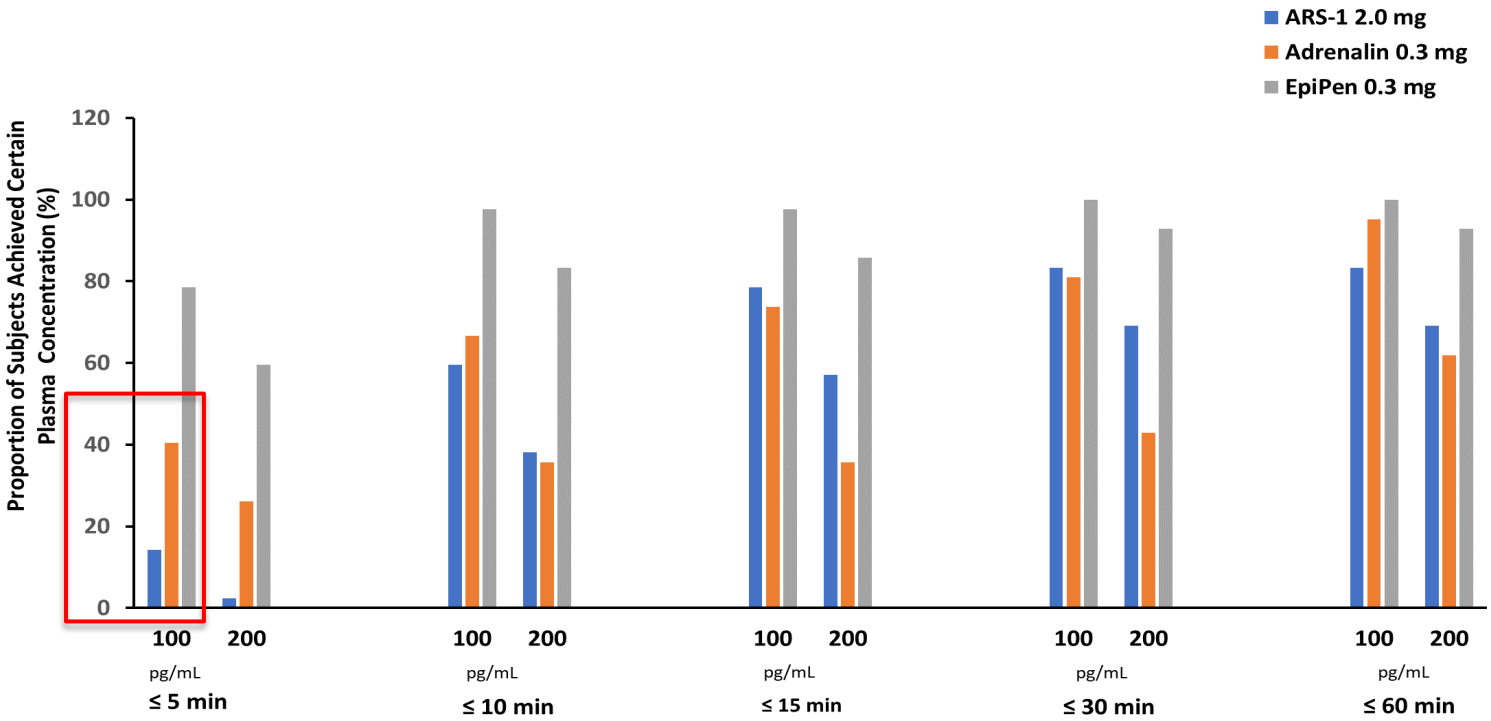
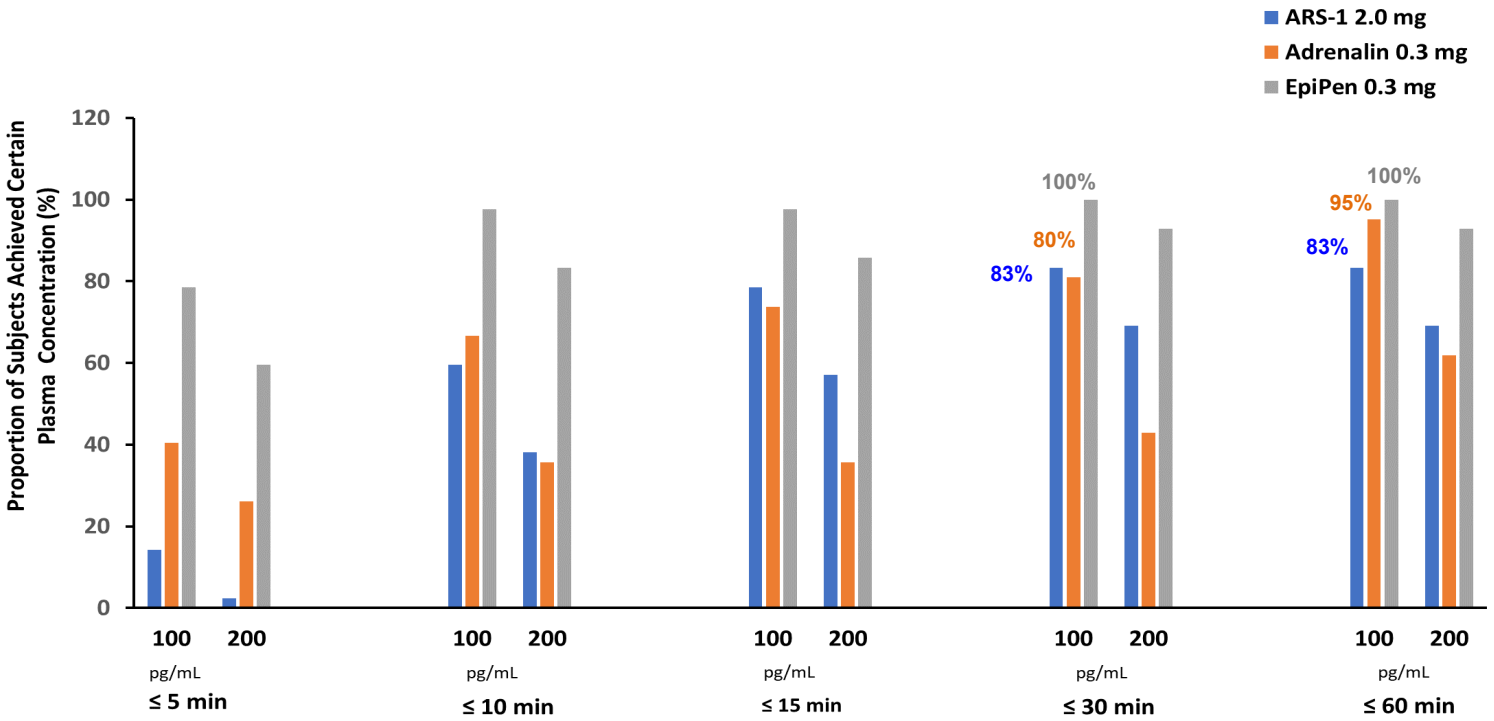


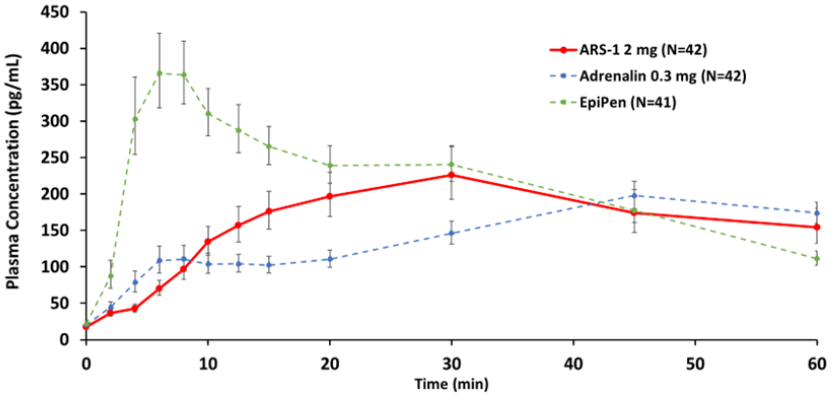
Proportion of Subjects Achieving Certain Plasma Concentrations (100 and 200 pg/mL) After Single-Dose (EPI 15)



Single-Dose PK vs. PD Profiles – Systolic Blood Pressure
EPI 15

PK

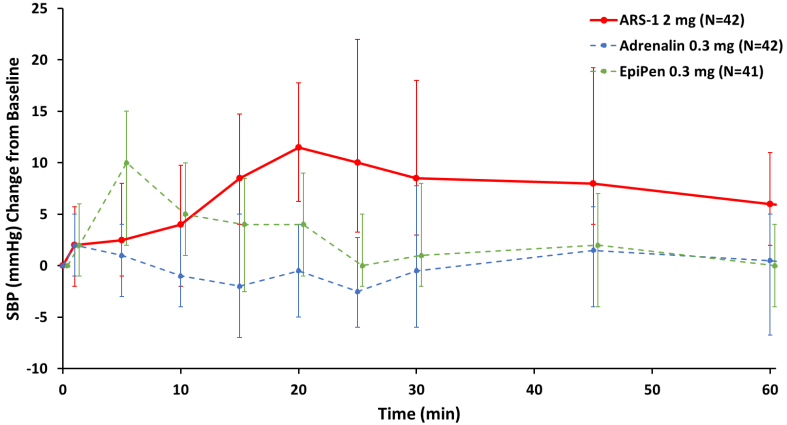
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

PD

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



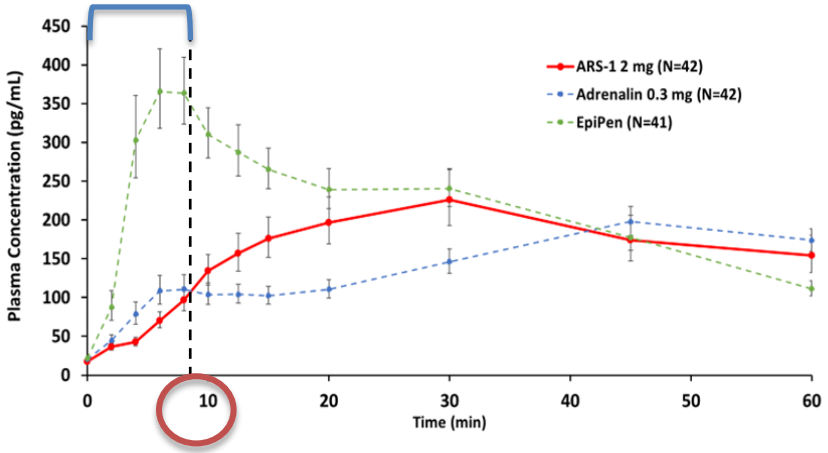
SBP: systolic blood pressure

Error bar: 25th and 75th percentile

Single-Dose PK vs. PD Profiles – Systolic Blood Pressure
EPI 15

PK

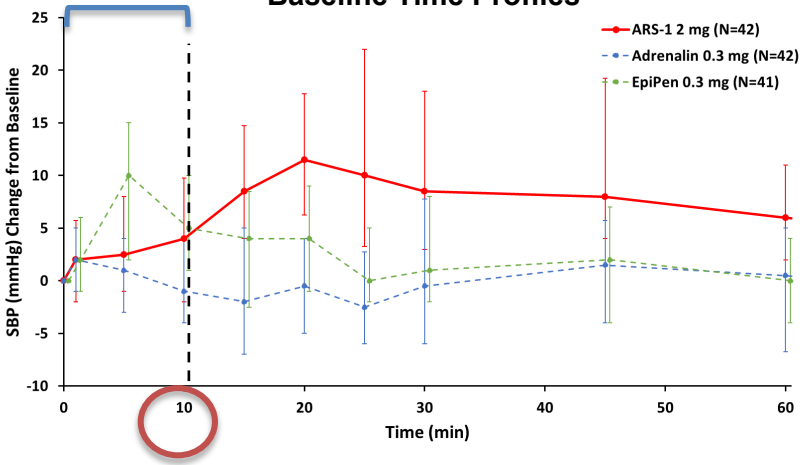
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

PD

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



SBP: systolic blood pressure

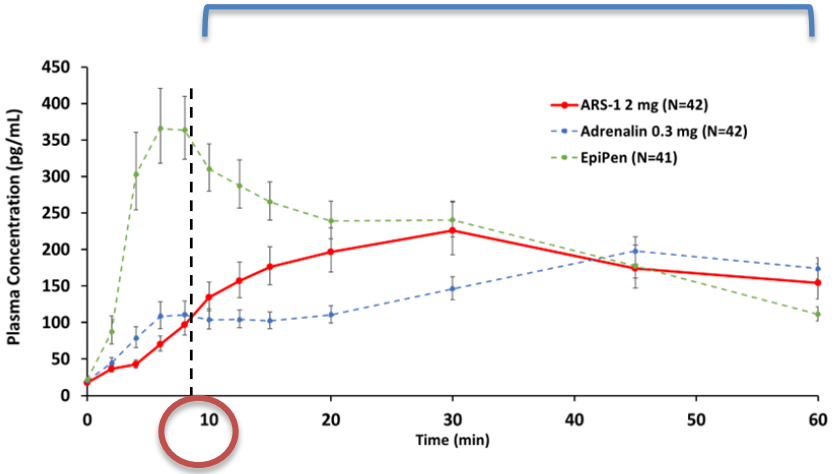
Error bar: 25th and 75th percentile

- The median SBP response is bracketed by EpiPen and Adrenalin within 10 minutes post-dose

Single-Dose PK vs. PD Profiles – Systolic Blood Pressure
EPI 15

PK

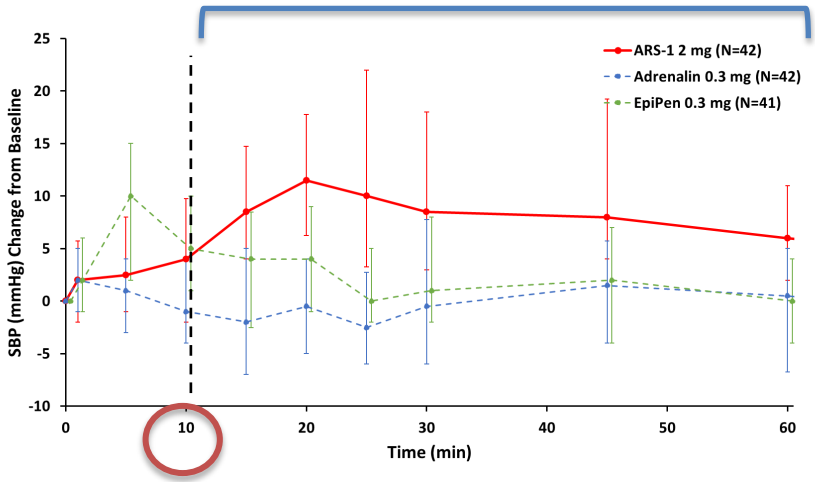
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

PD

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



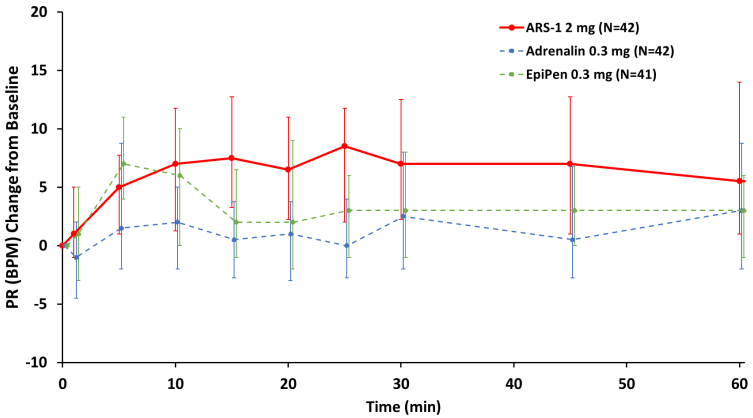
SBP: systolic blood pressure

Error bar: 25th and 75th percentile

- The SBP response is higher and more sustained for ARS-1 compared to EpiPen despite lower epinephrine concentration than EpiPen after 10 minutes post-dose

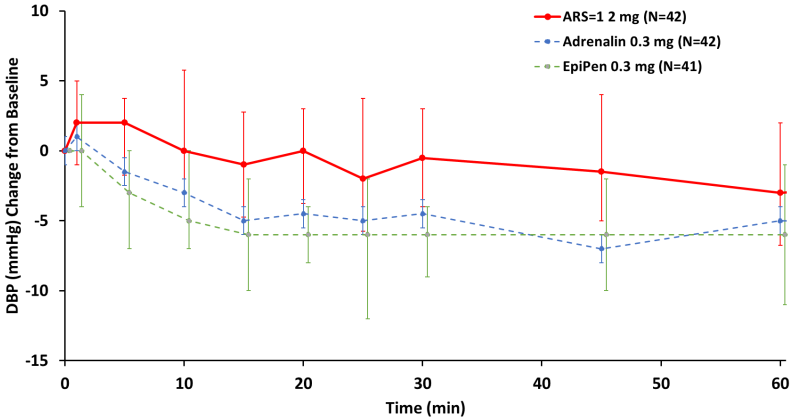
Single-Dose PD Profiles – Pulse Rate & Diastolic Blood Pressure
EPI 15

Median Pulse Rate (BPM) Change From Baseline Time Profiles



PR: pulse rate
BPM: beats per minute

Median Diastolic Blood Pressure (mmHg) Change From Baseline Time Profiles

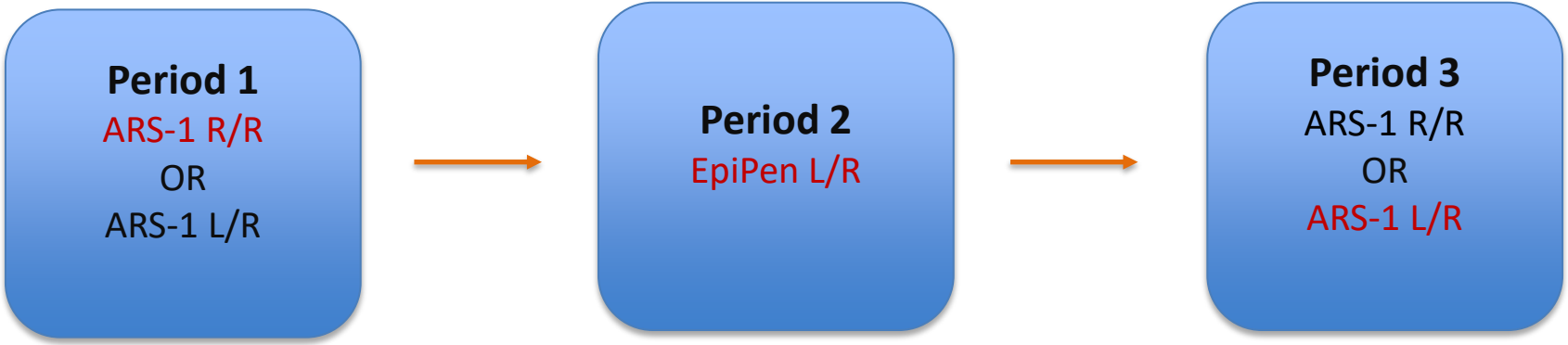


DBP: diastolic blood pressure

Error bar: 25th and 75th percentile

- ARS-1 has a greater and more sustained median PR increase from baseline than injection products.
- ARS-1 maintains a more stable DBP profile than injection products.

EPI 15 Part 2: Repeat Dose PK Trial



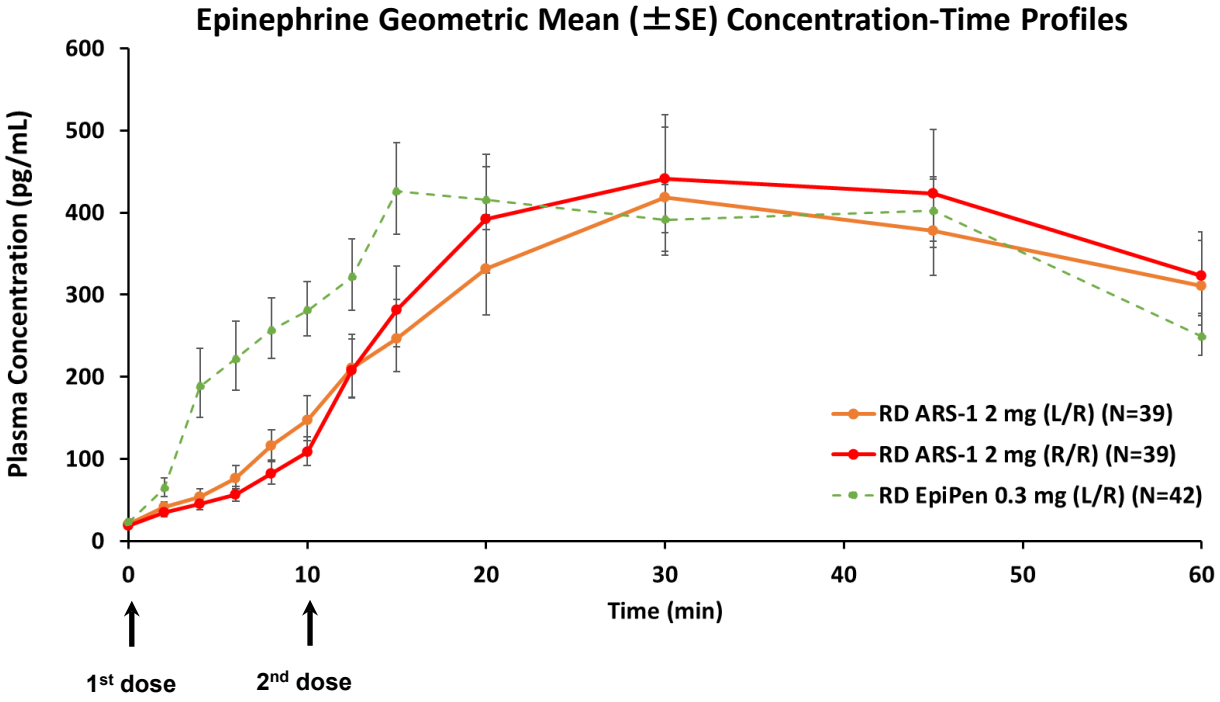
L: left
R: right

Healthy Adults

Partial randomization to ensure adequate wash out

Washout period between treatments: 6 days, 12 days between intranasal doses

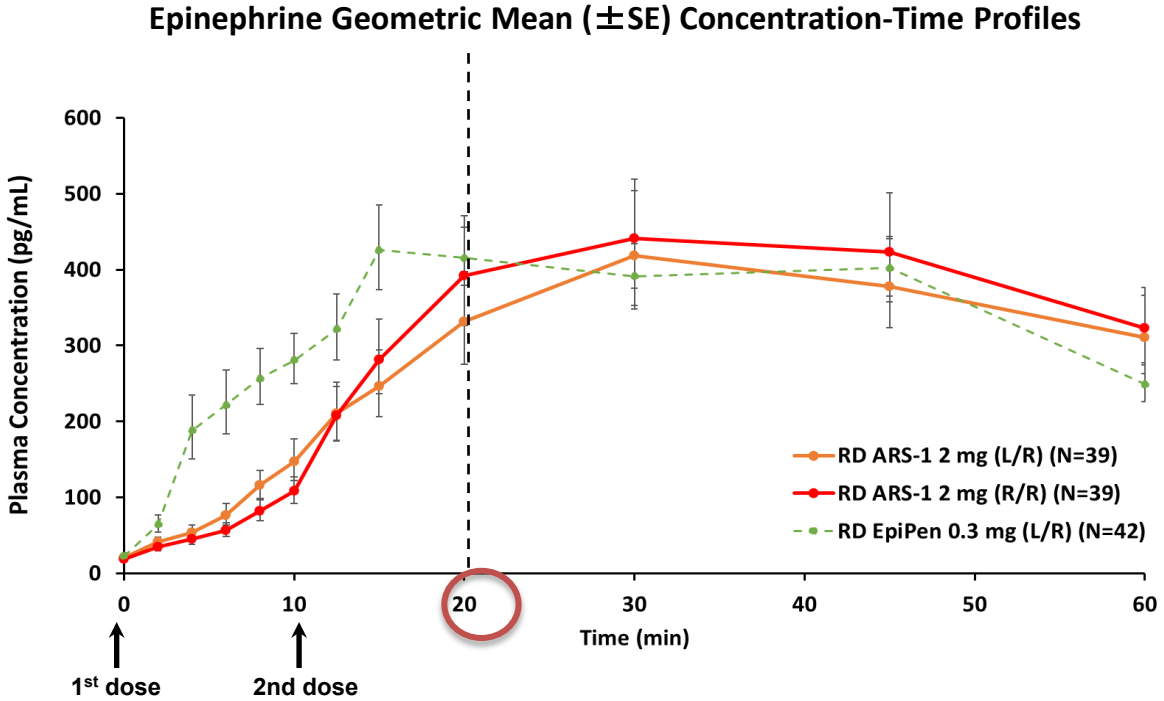
Repeat Dose PK Results (EPI 15)



SE: standard error
RD: repeat dose
L: left
R: right

- The PK profiles are generally similar between ARS-1 administered ipsilaterally or contralaterally

Repeat Dose PK Results (EPI 15)

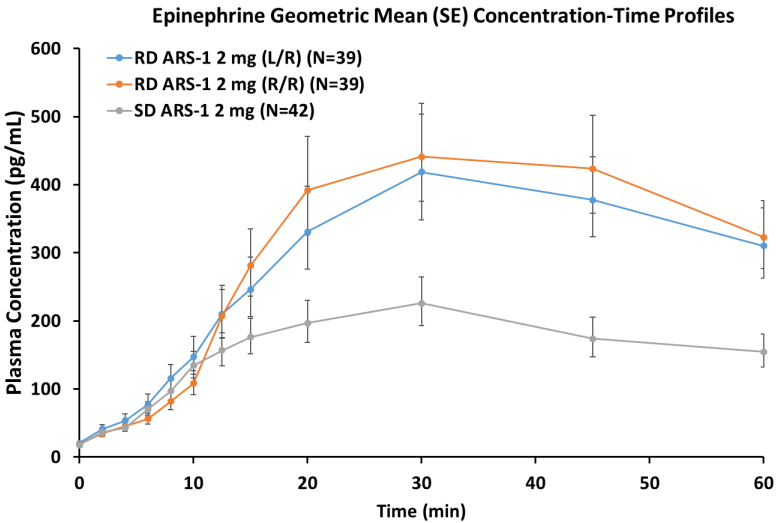


SE: standard error
RD: repeat dose
L: left
R: right

- An overall lower epinephrine concentration following ARS-1 compared to EpiPen within 20 minutes post-first dose.
- The PK profile of two-dose ARS-1 is similar to that of two-dose EpiPen 20 minutes post-first dose.

Single-Dose (SD) vs. Repeat Doses (RD) PK Comparison
EPI 15

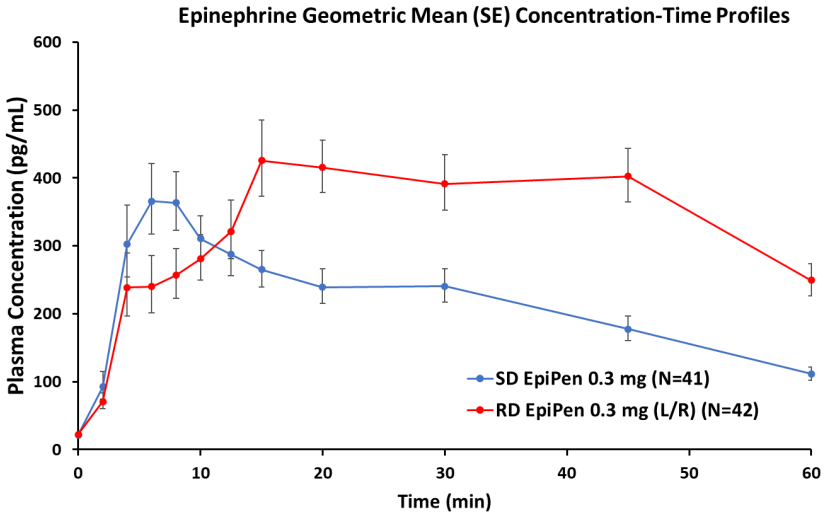
ARS-1 SD vs. RD



SD: single dose
RD: repeat dose

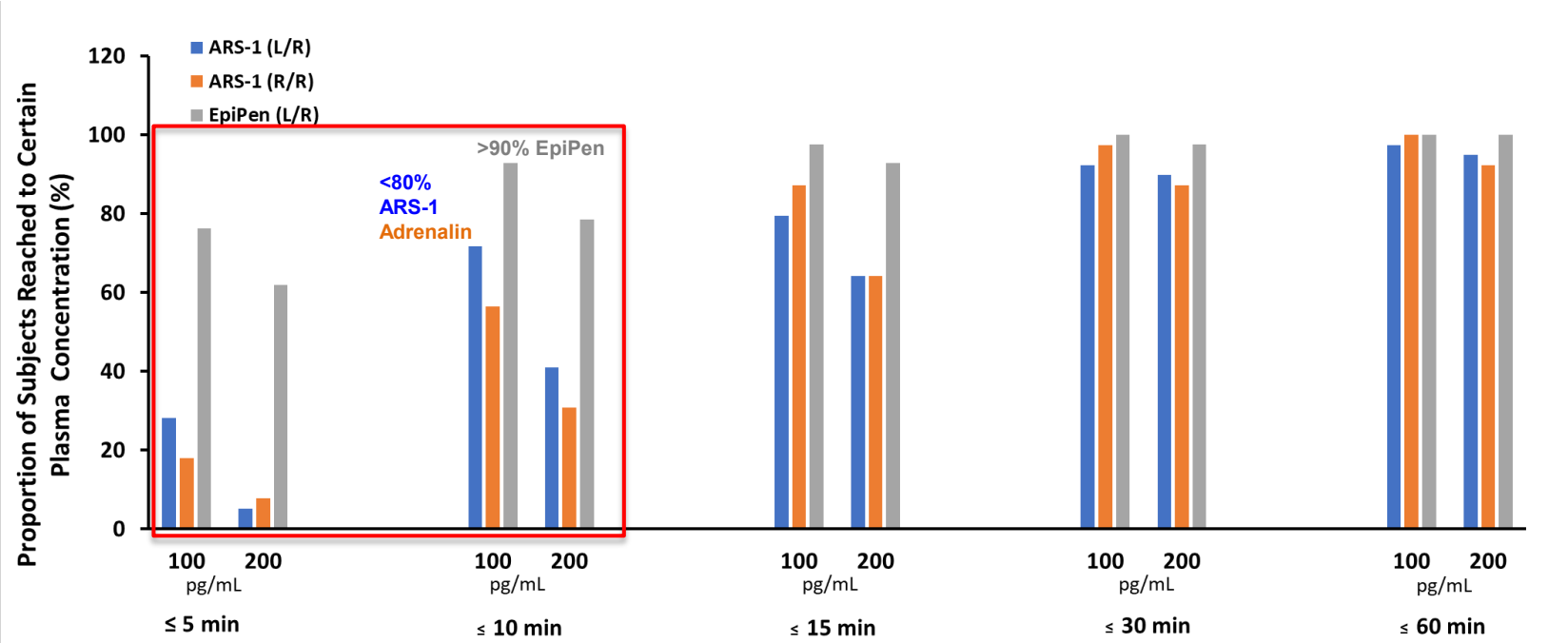
Exposure is doubled following two doses

EpiPen SD vs. RD

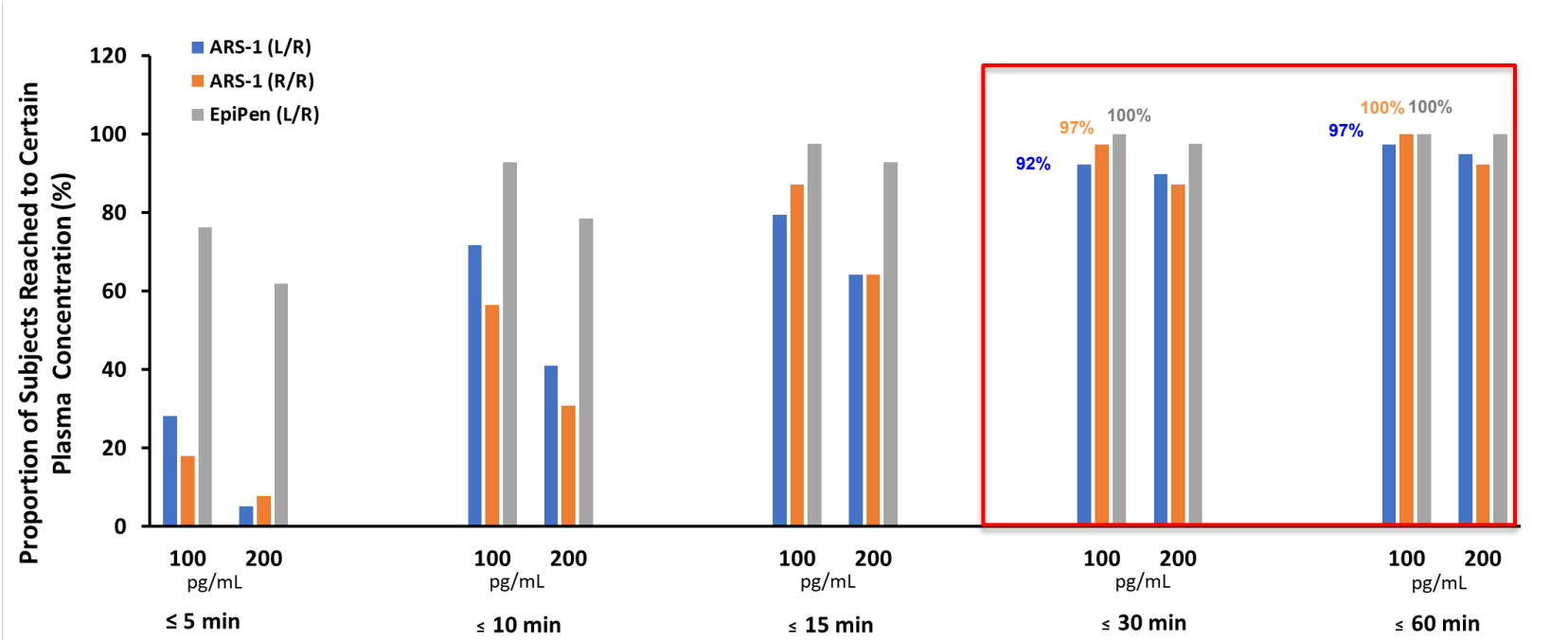


C_{max} increases by 20% and $AUC_{0\text{-}60min}$ increases by 50% following two doses

Proportion of Subjects Achieving Certain Plasma Concentrations (100 and 200 pg/mL) After Repeat Doses (EPI 15)



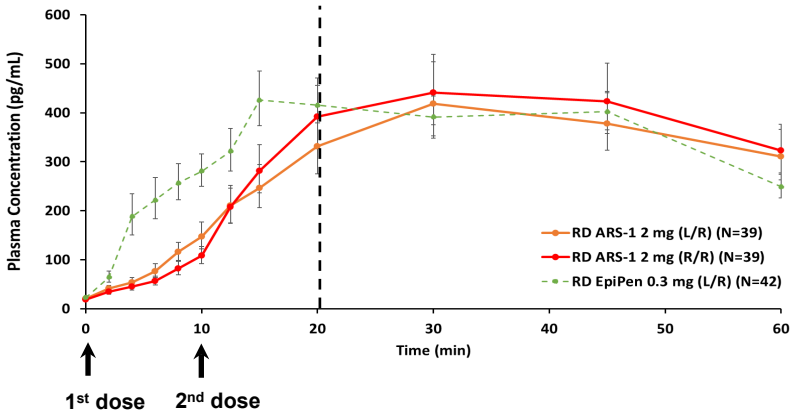
Proportion of Subjects Achieving Certain Plasma Concentrations (100 and 200 pg/mL) After Repeat Doses (EPI 15)



Repeat Dose PK vs. PD Profiles – Systolic Blood Pressure
EPI 15

PK

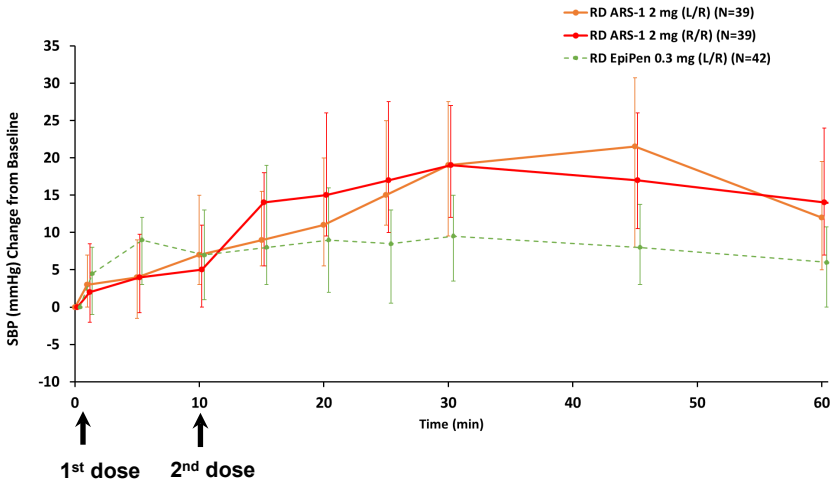
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

PD

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



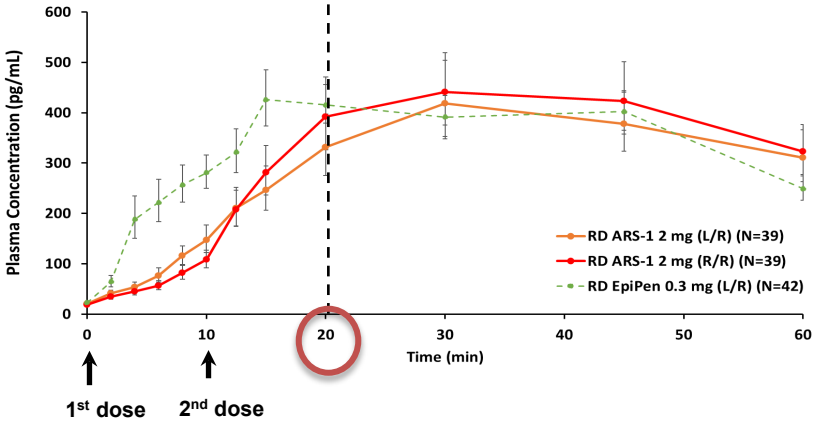
SBP: Systolic blood pressure
RD: repeat dose

Error bar: 25th and 75th percentile

Repeat Dose PK vs. PD Profiles – Systolic Blood Pressure EPI 15

PK

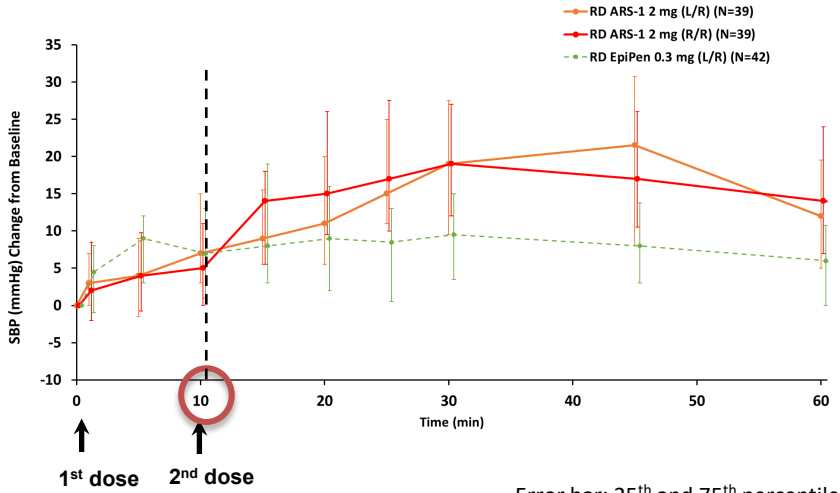
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

PD

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles

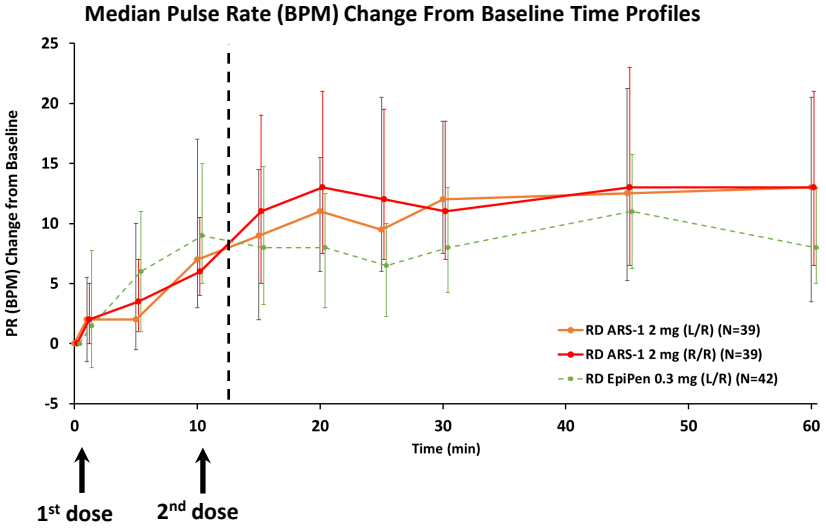


SBP: Systolic blood pressure

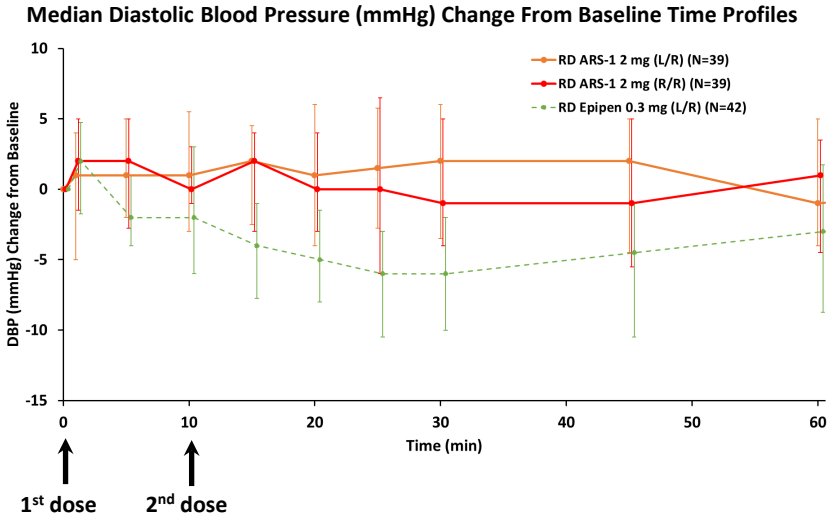
Error bar: 25th and 75th percentile

- The median SBP response for two doses ARS-1 is initially lower than two doses of EpiPen within 10 minutes and becomes higher afterwards
- The PK of two doses of ARS-1 is lower than two doses of EpiPen within 20 minutes and becomes similar afterwards

Repeat Dose PD Results – Pulse Rate & Diastolic Blood Pressure
EPI 15



BPM: beats per minutes
PR: pulse rate



DBP: diastolic blood pressure

Error bar: 25th and 75th percentile

- Repeat dose of ARS-1 has a higher and more sustained PR increase from baseline than EpiPen.
- Repeat dose of ARS-1 maintains a more stable DBP profile than EpiPen.

Self-Administration Study

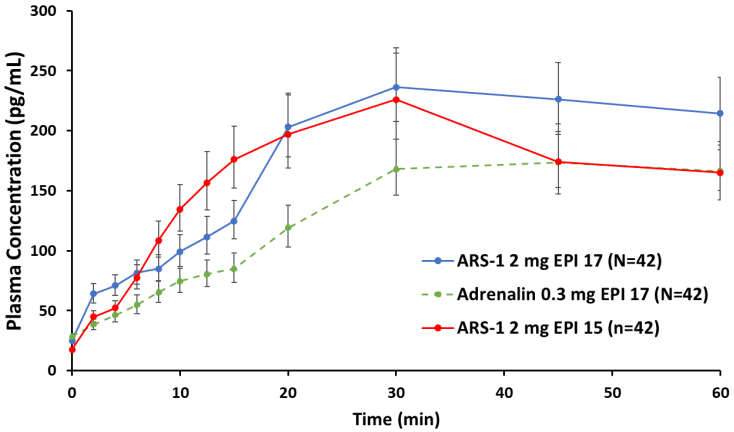
STUDY EPI 17

EPI 17 Study Design

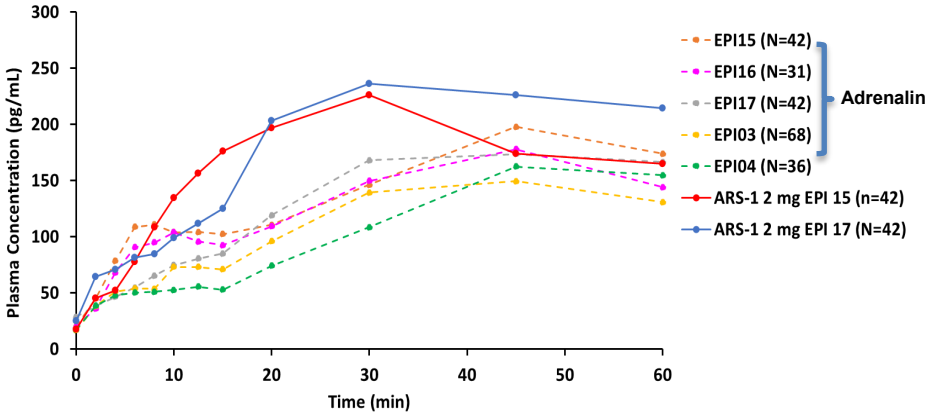
- Study Design: single-dose, two-period, cross-over study
- Population: adult Type I allergy patients (N=42)
- Treatment:
  - ARS-1 self-administered into one naris (right or left)
  - Adrenalin 0.3 mg staff-administered into right thigh

EPI 17: PK Results And Cross-Study Comparisons

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles
EPI 17 + ARS-1 From EPI 15

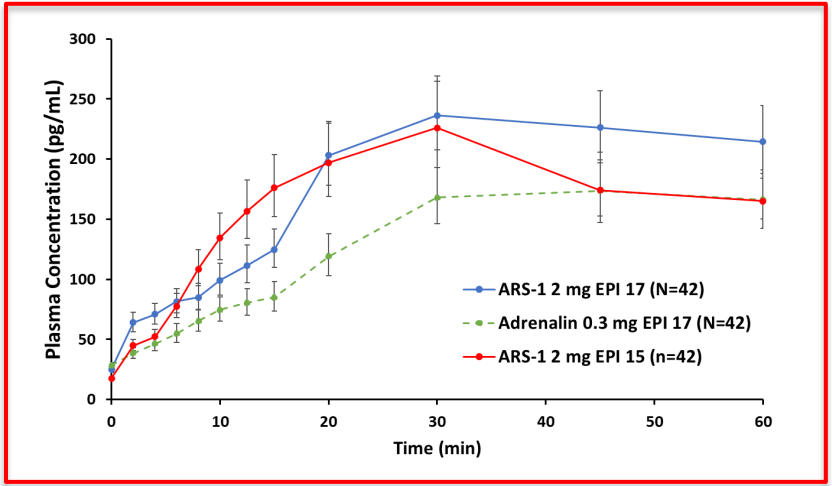


Cross-Study Comparison of Geometric Mean Concentrations

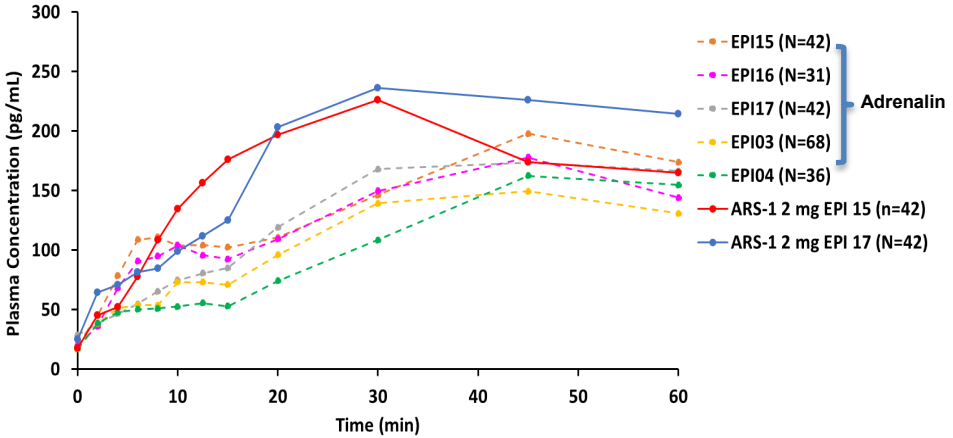


EPI 17: PK Results And Cross-Study Comparisons

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles
EPI 17 + ARS-1 From EPI 15

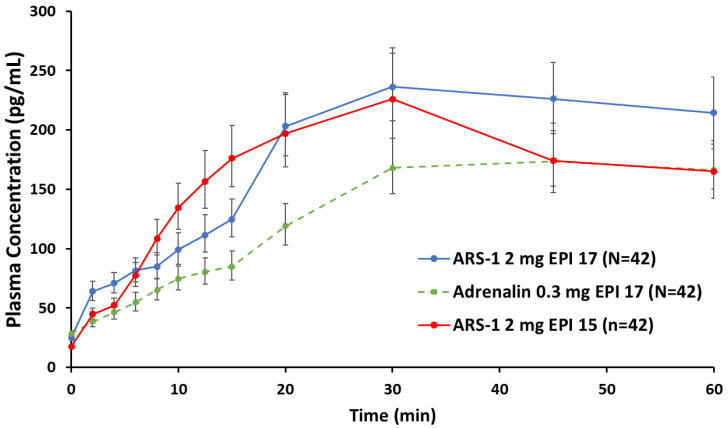


Cross-Study Comparison of Geometric Mean Concentrations

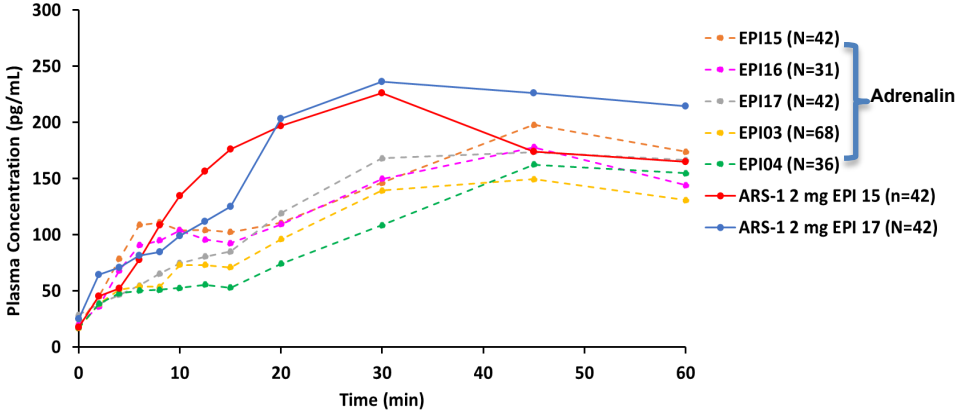


EPI 17: PK Results And Cross-Study Comparisons

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles
EPI 17 + ARS-1 From EPI 15



Cross-Study Comparison of Geometric Mean Concentrations



Nasal Allergen Challenge Study in Allergic Rhinitis Patients

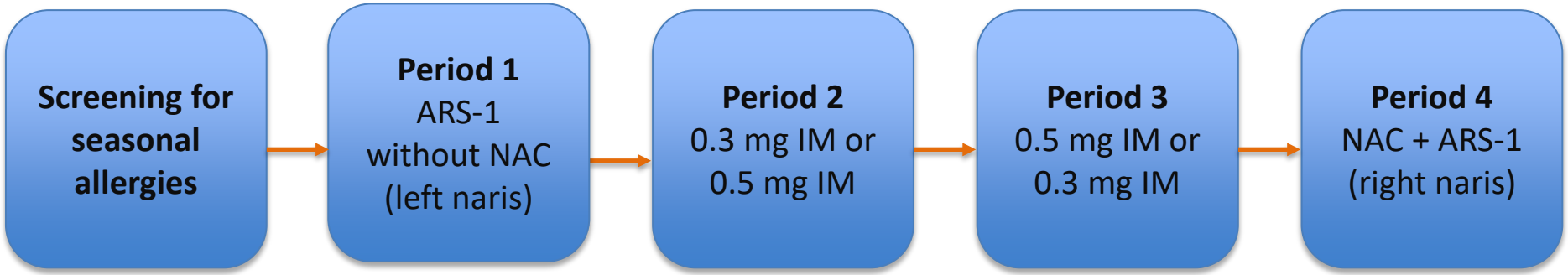
STUDY EPI 16

EPI 16 Nasal Allergen Challenge

Study Design: single-dose, partially randomized, crossover study

Population: adults with confirmed seasonal rhinitis (N=36)

A few subjects were excluded in Period 2 to 4 due to no PK data or insufficient number of PK samples (< 3) collected within 30 minutes post-dose



At baseline:
TNSS ≤2 out of 12
NCS ≤1 out of 3

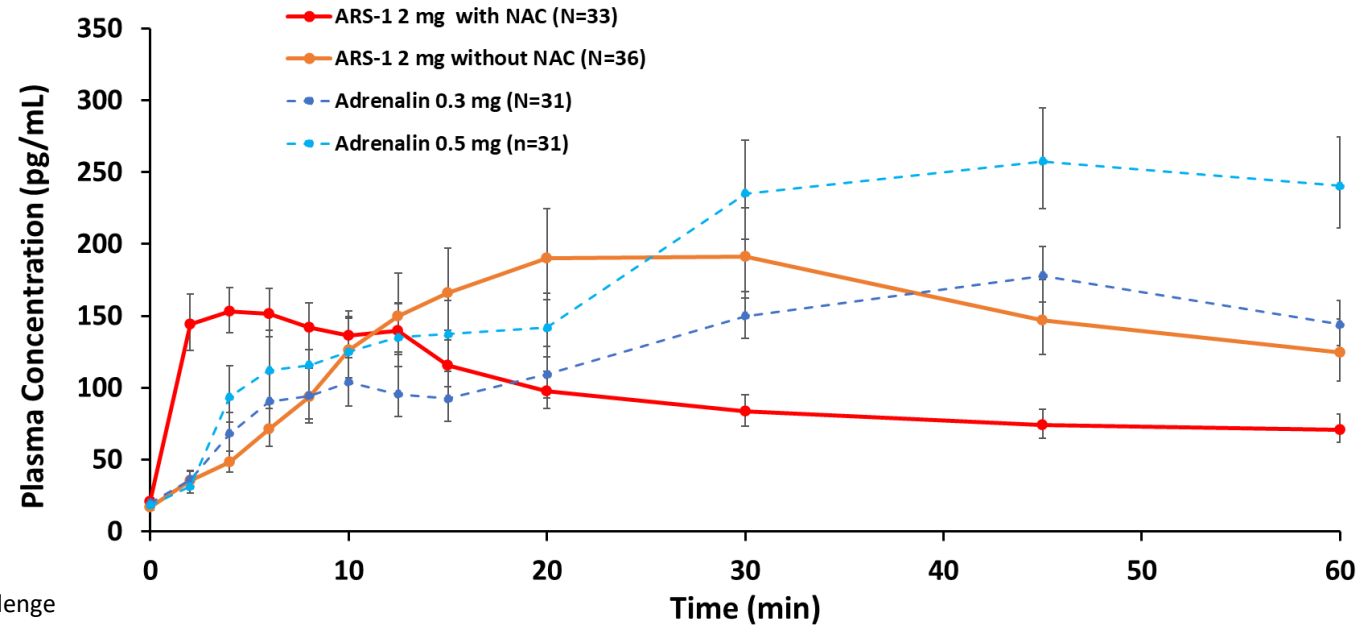
Washout period between Period 1 and 4: **3 days**

Post Challenge:
TNSS ≥5 out of 12
NCS ≥2 out of 3

NAC: nasal allergen challenge
TNSS: total nasal symptoms score
NCS: nasal congestion score

PK Results (EPI 16)

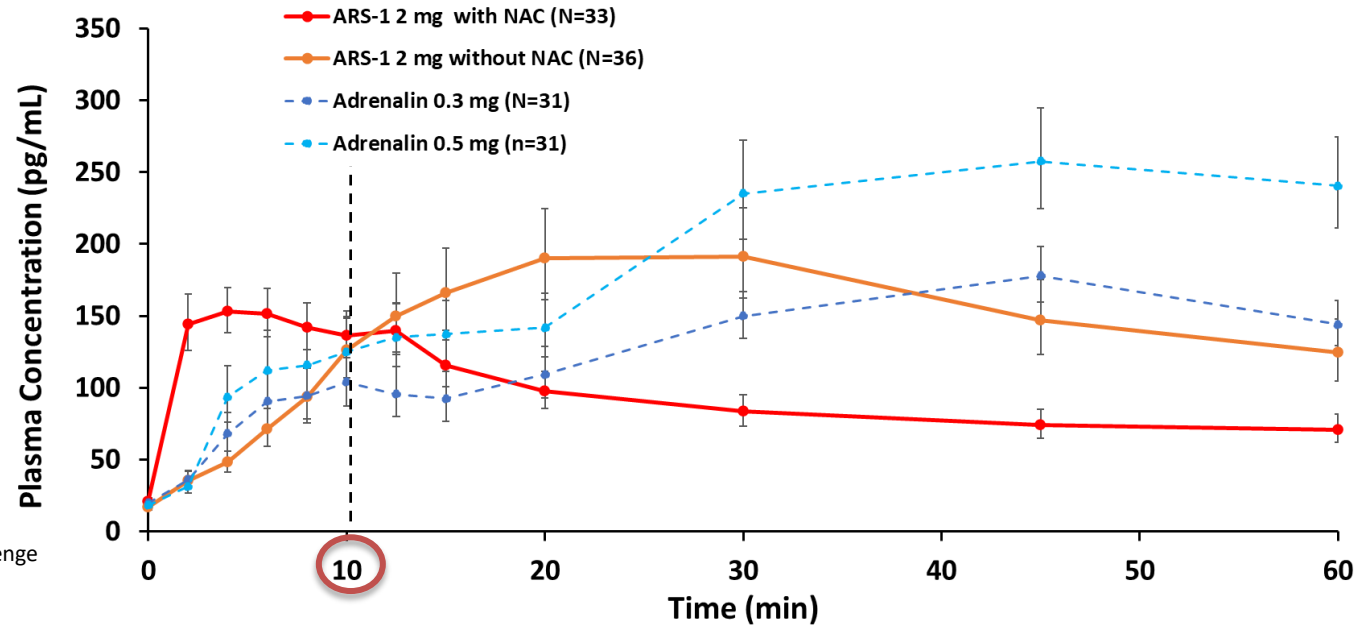
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



NAC: nasal allergen challenge
SE: standard error

PK Results (EPI 16)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

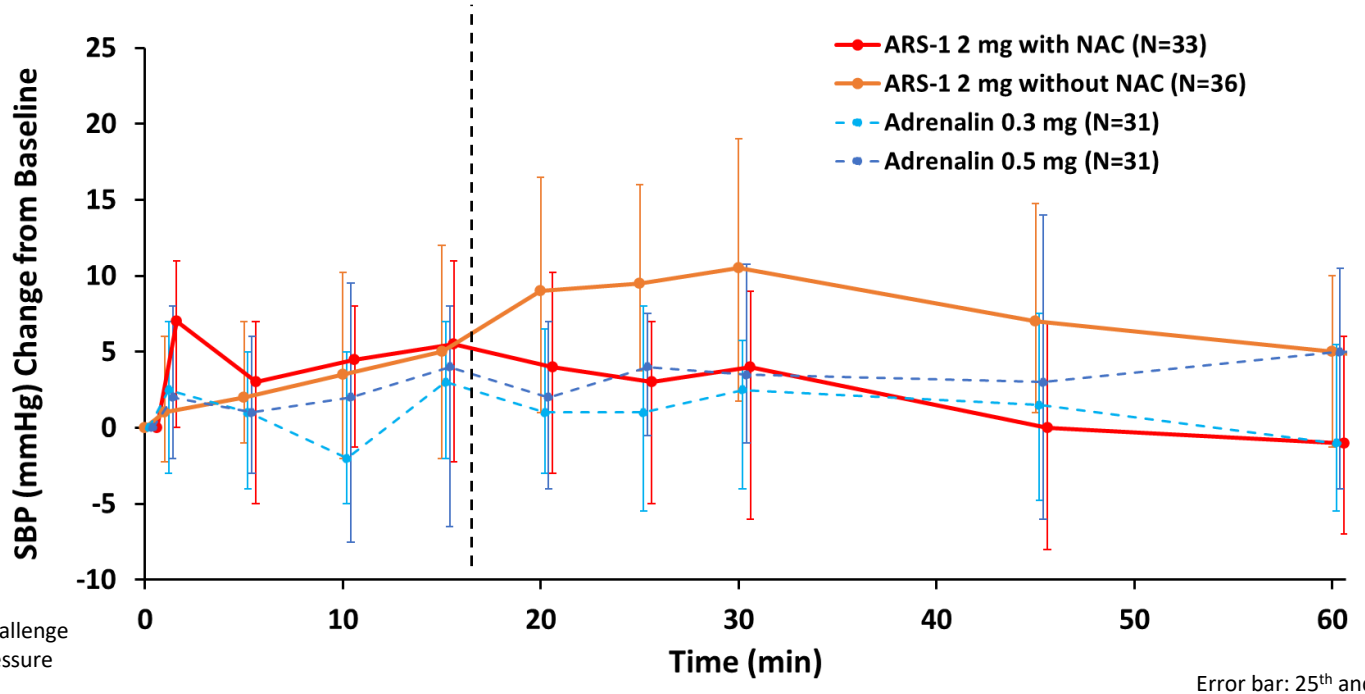


NAC: nasal allergen challenge
SE: standard error

- Faster epinephrine absorption rate following ARS-1 with NAC compared to without NAC.
- Lack of PK sustainability after ~10 min post-dose following NAC compared to without NAC.

PD Results – Systolic Blood Pressure (EPI 16)

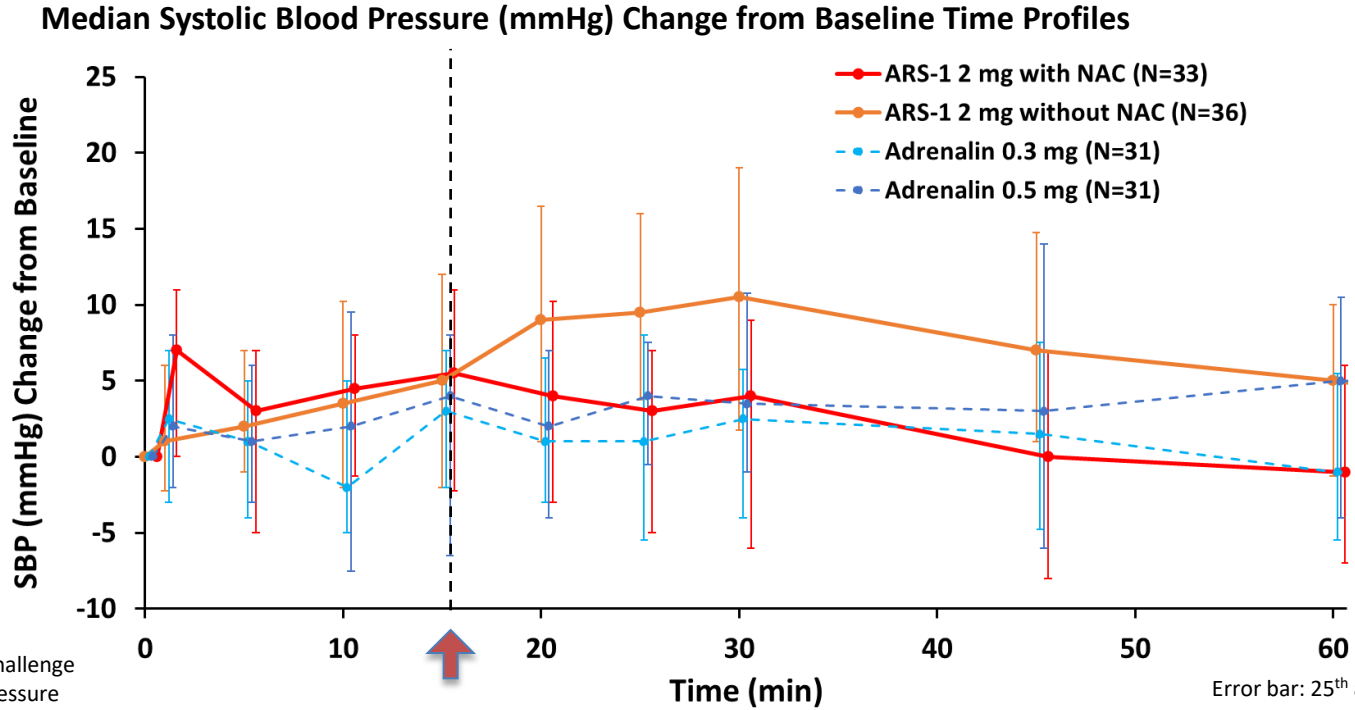
Median Systolic Blood Pressure (mmHg) Change from Baseline Time Profiles



NAC: nasal allergen challenge
SBP: systolic blood pressure

Error bar: 25th and 75th percentile

PD Results – Systolic Blood Pressure (EPI 16)



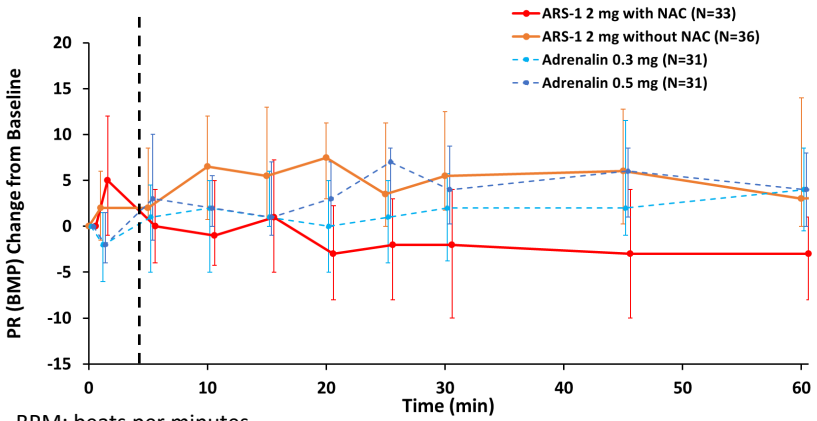
NAC: nasal allergen challenge
SBP: systolic blood pressure

Error bar: 25th and 75th percentile

- A higher median SBP response is observed following ARS-1 administration within 15 minutes under NAC compared to without NAC.
- The median SBP response is reduced after 15 minutes post-dose with NAC compared to without NAC.

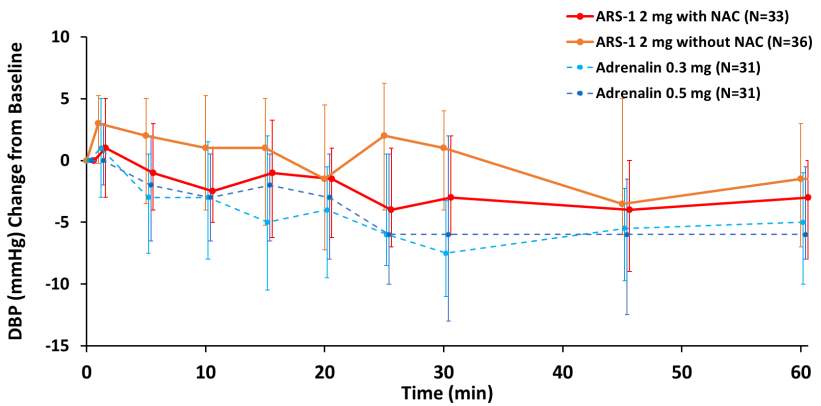
PD Results – Pulse Rate & Diastolic Blood Pressure
EPI 16

Median Pulse Rate (BPM) Change from Baseline Time Profiles



BPM: beats per minutes
PR: pulse rate

Median Diastolic Blood Pressure (mmHg) Change from Baseline Time Profiles



DBP: diastolic blood pressure

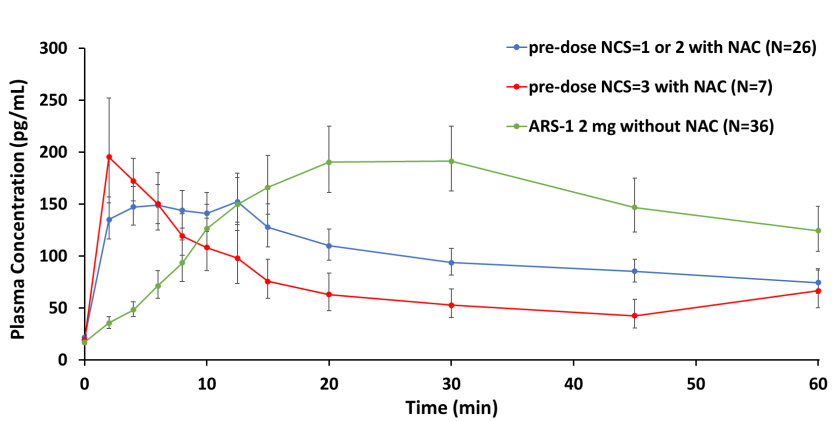
Error bar: 25th and 75th percentile

- An initial higher median PR response is observed following ARS-1 administration under NAC compared to without NAC.
- The median PR response is reduced after ~5 minutes post-dose with NAC compared to without NAC.
- Less stable DBP profile with NAC compared to without NAC.

Impact of Nasal Congestion Score on PK/PD (EPI 16)

Impact on PK

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



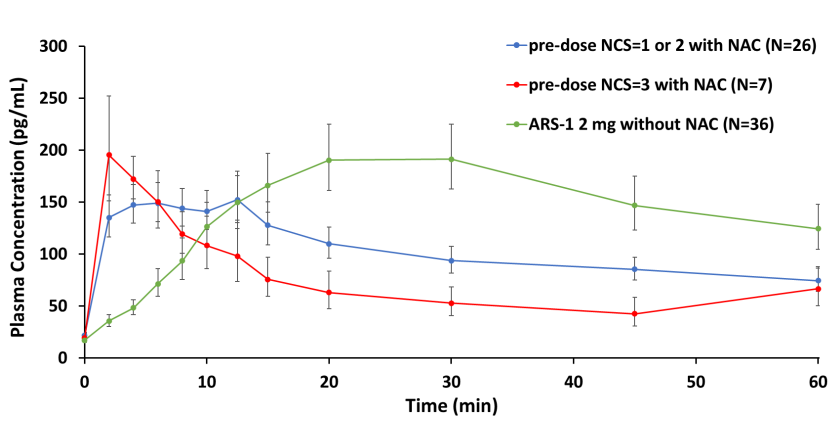
NAC: nasal allergen challenge
Pre-dose: after NAC but prior to ARS-1
SE: standard error

Faster decline of epinephrine concentration in subjects with higher pre-dose nasal congestion score.

Impact of Nasal Congestion Score on PK/PD (EPI 16)

Impact on PK

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

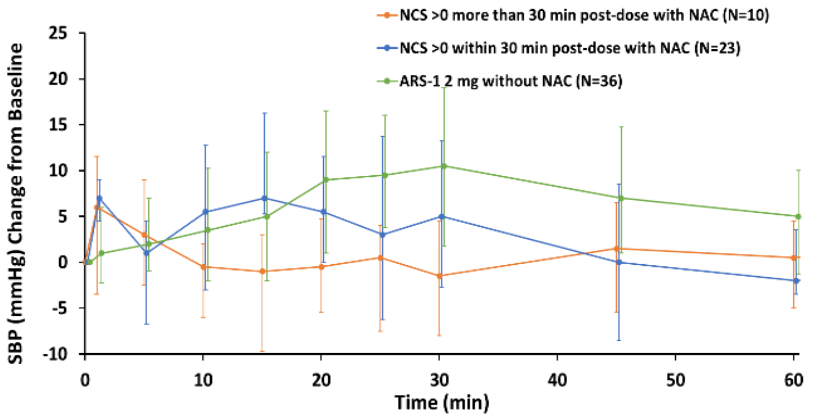


NAC: nasal allergen challenge
Pre-dose: after NAC but prior to ARS-1
SE: standard error

Faster decline of epinephrine concentration in subjects with higher pre-dose nasal congestion score.

Impact on PD

Median SBP (mmHg) Change From Baseline Time Profiles



SBP: systolic blood pressure
Post-dose: after ARS-1

Error bar: 25th and 75th percentile

Less sustainable SBP response in subjects with more persistent post-dose nasal congestion.

Pediatric PK/PD Study

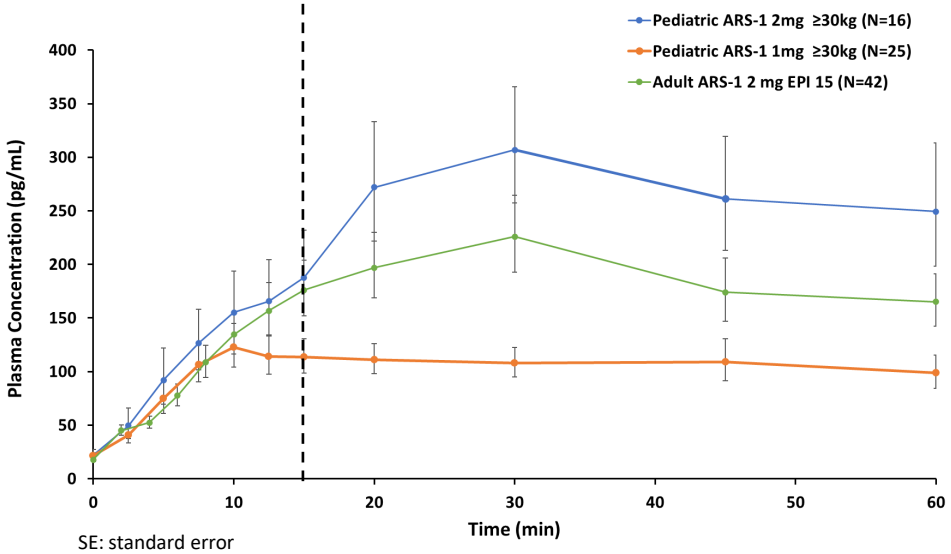
STUDY EPI 10

EPI 10 Study Design

- Study design: single-dose, single-period study
- Treatment for ≥ 30 kg (N=42)
    - ARS-1: 2 mg (N=16)
    - ARS-1: 1 mg (N=26)
- Population: pediatric patients with Type I allergies
    - Baseline body weight: 31 kg to 95 kg (median: 54 kg)
    - Baseline age: 8 years to 17 years (median: 14 years)

Pediatric PK Results (EPI 10)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

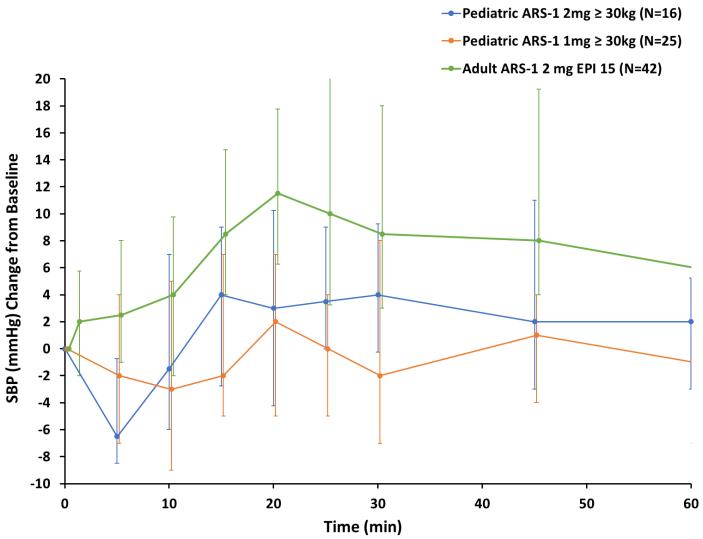


SE: standard error

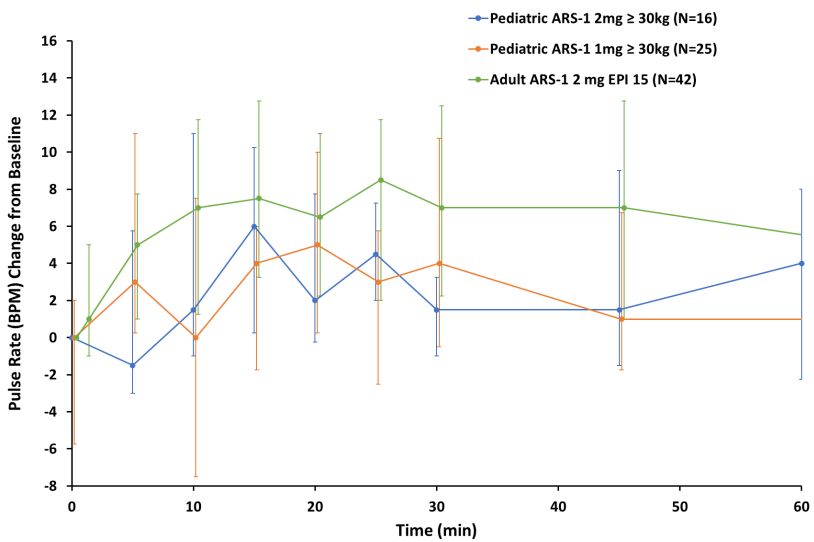
- The PK profile following ARS-1 2 mg in pediatrics subjects ≥ 30 kg is similar to adults within 15 minutes post-dose and higher than adults after 15 minutes.

Pediatric Study PD Results (EPI 10)
Systolic Blood Pressure and Pulse Rate

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



Median Pulse Rate (BPM) Change From Baseline Time Profiles



SBP: systolic blood pressure

BPM: beats per minute

Error bar: 25th and 75th percentile

Drug administration and vital sign measurement positions:

- Adult: sitting
- Pediatric: semi-supine

Clinical Pharmacology Summary (1)

- **PK/PD results from study with healthy adults (EPI 15)**
  - Epinephrine PK profile following a single-dose of ARS-1 is reasonably bracketed by Adrenalin and EpiPen after ~ 10 min postdose in healthy adults. However, epinephrine concentrations for ARS-1 are generally lower than both Adrenalin and EpiPen within the first ~ 10 min postdose.
  - Epinephrine PK profiles following a repeat dose of ARS-1 in the same or opposite naris are similar to repeat doses of EpiPen 0.3 mg after ~ 20 min postdose. However, epinephrine concentrations following repeat dose ARS-1 are generally lower than EpiPen within the first ~ 20 min postdose.
  - A lower proportion of healthy adults achieved 100 pg/mL in ARS-1 and Adrenalin (<80%) within first 10 minutes postdose than EpiPen (>90%) following both single-dose and repeat doses.
  - Generally higher SBP and PR responses following single-dose and repeat-dose ARS-1 than EpiPen after ~ 10 min postdose, despite the ARS-1 PK profile being lower than that of EpiPen.

Clinical Pharmacology Summary (2)

- **PK/PD results from NAC study (EPI 16)**
  - The epinephrine PK profile following single-dose ARS-1 in allergic rhinitis patients without nasal allergen challenge is within the range of single dose Adrenalin following two different approved doses (i.e., 0.3 mg and 0.5 mg).
  - Under nasal allergen challenge conditions, the epinephrine PK following ARS-1 increases more rapidly than Adrenalin, followed by a rapid decline, resulting in the epinephrine concentrations being lower than all comparator arms 10 to 20 min postdose. A similar pattern of SBP and PR responses is observed.
  - Baseline nasal congestion severity and post-dose congestion duration may impact PK/PD of ARS-1.
- **PK/PD results Pediatric study (EPI 10)**
  - Pediatric patients ≥ 30 kg following 2 mg ARS-1 have similar to slightly higher epinephrine PK profiles compared to that of adults. The pediatric SBP and PR responses are slightly lower compared to adults.

FDA Presentation Outline

- Overview of Clinical PK/PD Program
  - *Jennifer Lan, MD, Clinical Reviewer*
- Overview of the Clinical Pharmacology Results
  - *Qianni Wu, Pharm D, Clinical Pharmacology Reviewer*
- Clinical Considerations and Risk/Benefit
  - *Jennifer Lan, MD, Clinical Reviewer*

FDA Pulmonary-Allergy Drugs Advisory Committee Meeting

Clinical Considerations and Risk/Benefit

Jennifer Lan, MD
Medical Officer
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

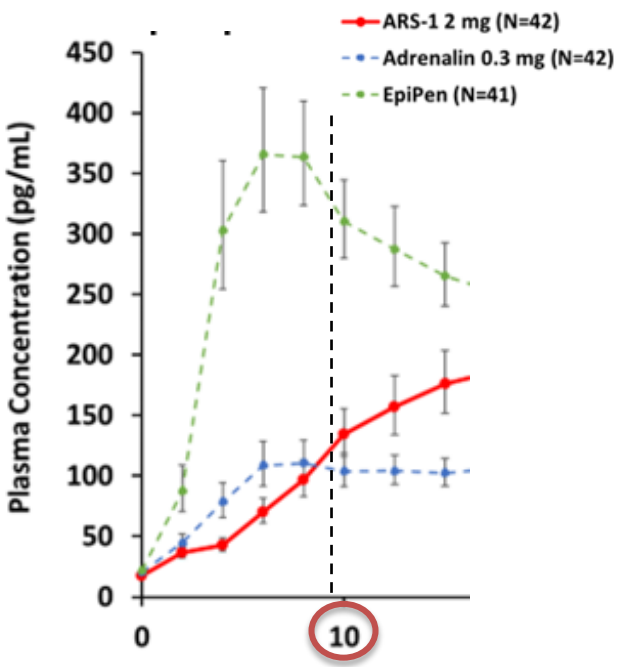
May 11, 2023

Overview

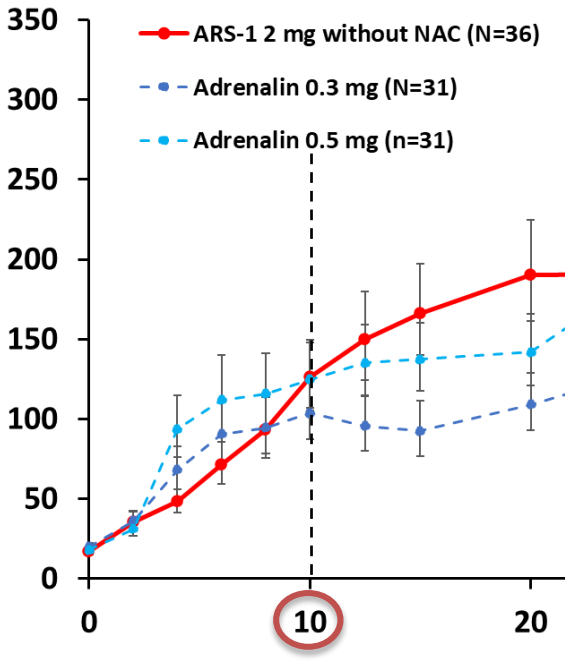
- Clinical interpretation of the PK/PD results
- Overview of the safety profile of ARS-1
- Benefit/Risk Assessment of ARS-1

CLINICAL INTERPRETATION OF PK/PD RESULTS

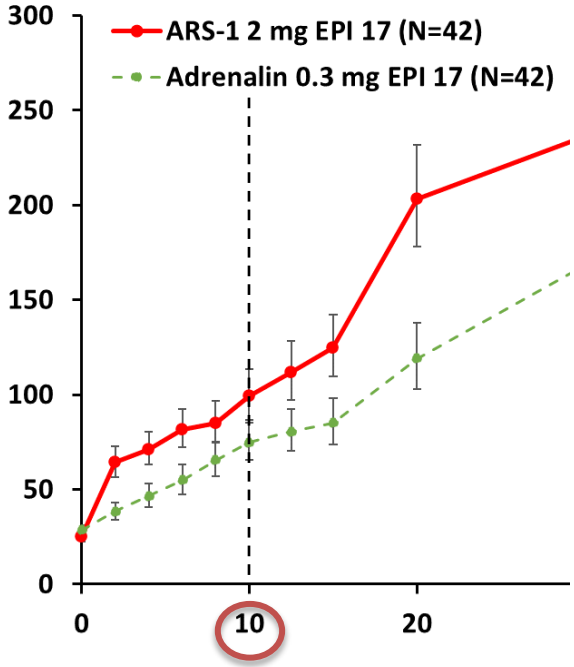
Single-dose PK/PD in Healthy Adults: Different Epinephrine Trends Across Trials In the First 10 Min



EPI 15

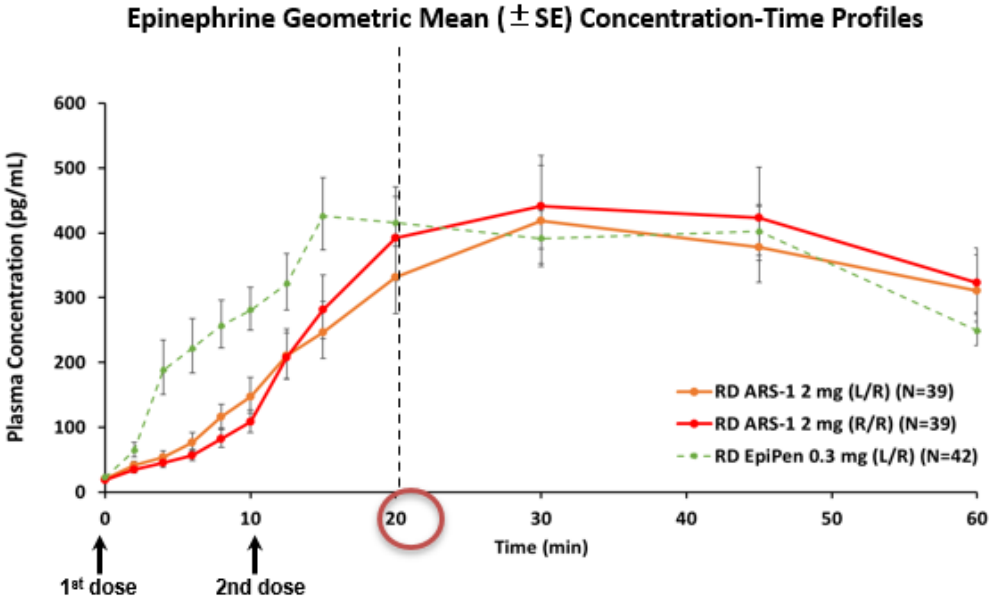


EPI 16



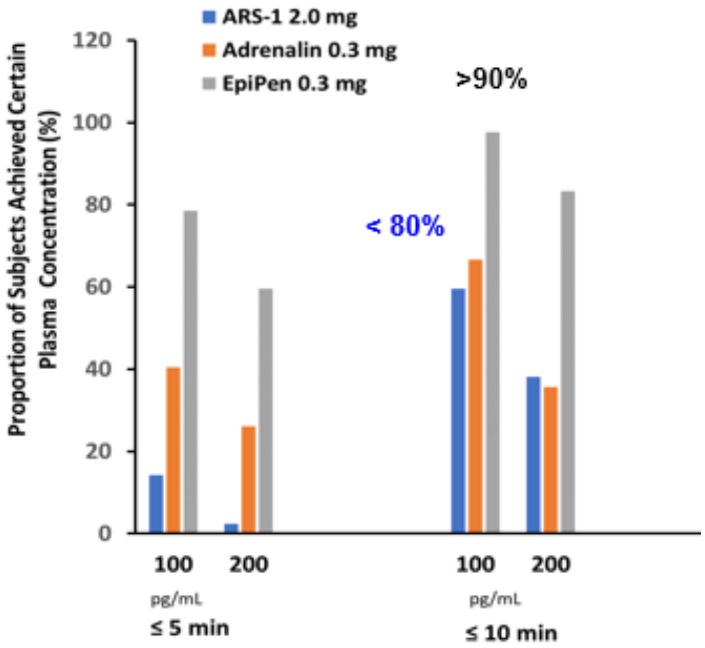
EPI 17

Repeat Dose ARS-1 PK/PD in Healthy Adults (EPI 15)



- Two doses of ARS-1 in the same or opposite naris demonstrated similar PK 20 min postdose compared to two doses of EpiPen
- Generally higher PD for both single and repeat dose ARS-1 compared to Adrenalin and EpiPen

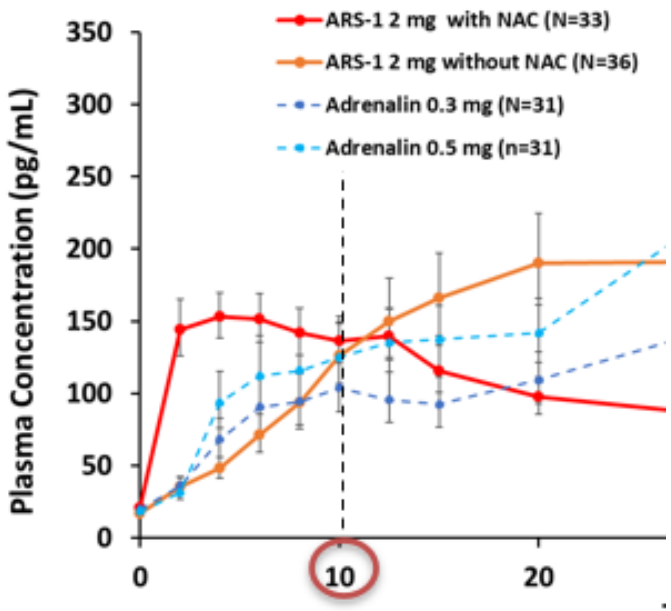
Epi 15: PK/PD in Healthy Adults



- < 80% reached 100 pg/mL with ARS-1 single or repeat doses during first 10 min; similar to Adrenalin, but lower than EpiPen

EPI 16: ARS-1 PK/PD in Nasal Allergen Challenge

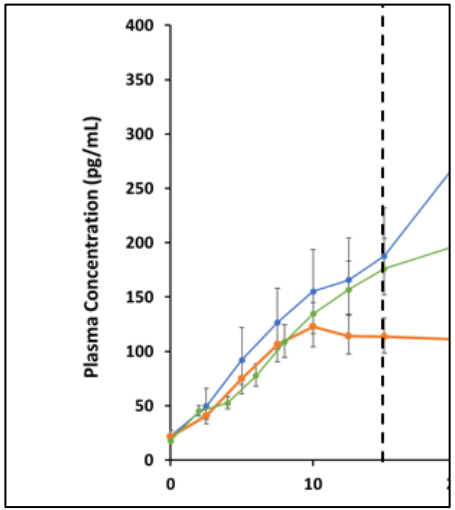
Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



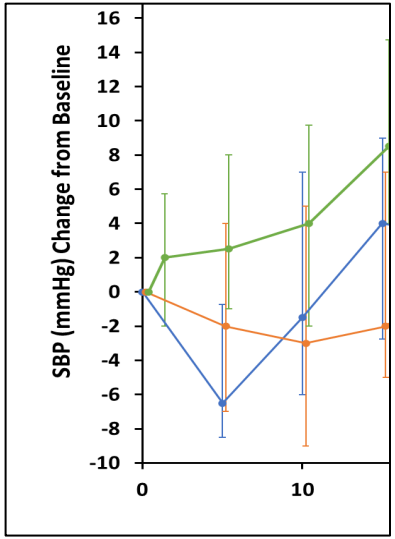
- Under nasal congested state, ARS-1 PK and PD increased more rapidly than Adrenalin followed by a rapid decline 10-20 minutes postdose.
- Since up to 20% of patients with anaphylaxis require a second treatment, repeat doses of ARS-1 may be needed with this rapid decline.
- Nasal congestion reported in 30% of patients post ARS-1
- Do not have data on repeat dose of ARS-1 in nasal congested state

EPI 10: Pediatric PK/PD

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



Median Systolic Blood Pressure (mmHg) Change from Baseline Time Profiles



Pediatric ARS-1 2mg ≥30kg (N=16)
Pediatric ARS-1 1mg ≥30kg (N=25)
Adult ARS-1 2 mg EPI 15 (N=42)

- Pediatric subjects ≥30 kg had similar epinephrine ARS-1 PK profiles compared to adults for first 15 minutes
- Pediatric PD profiles were lower compared to adults for first 10-15 minutes

OVERVIEW OF SAFETY

Safety Profile of Epinephrine Injection

- Systemic safety review relies on determination of the safety of epinephrine injection products.

- Common Adverse Events for systemic use of epinephrine: anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.[1]

1: See the epinephrine injection label at https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=db18519b-82a9-435b-85c7-a040d644f057&type=pdf

Safety Profile of ARS-1

- 134 adult subjects received ARS-1 (EPI 15, EPI 16, EPI 17)
- 260 exposures due to crossover design

- No deaths or serious adverse events

- Limited safety profile
  - Small population
  - N= 58 received one dose
  - Frequent use safety unknown and impact on local toxicity

Systemic Safety Profile of ARS-1

Common Adverse Events Occurring at ≥3% Frequency in ARS-1 and Greater Than Epinephrine Injection

Body System or Organ Class	Dictionary-Derived Term	ARS-1 2.0 mg (N=134)		Epinephrine injection 0.3 mg (N=189)	
		Count	%	Count	%
Nervous system disorders	Headache	8	6%	4	2%
	Dizziness	4	3%	2	1%
Gastrointestinal Disorders	Nausea	4	3%	4	2%
Respiratory, thoracic, and mediastinal disorders	Nasal discomfort	13	10%	0	0%
	Rhinorrhea	4	3%	0	0%

Local Safety Profile of ARS-1

Common Adverse Events Occurring at ≥3% Frequency in ARS-1 and Greater Than Epinephrine Injection

Body System or Organ Class	Dictionary-Derived Term	ARS-1 2.0 mg (N=134)		Epinephrine injection 0.3 mg (N=189)	
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Respiratory, thoracic, and mediastinal disorders	Nasal discomfort	13	10%	0	0%
	Rhinorrhea	4	3%	0	0%

Pediatric Safety

- EPI 10: single-arm PK/PD trial in children 4 to 17 years of age with Type I allergy at risk for anaphylaxis
  - ≥ 30 kg, n = 21 subjects (8 to 17 years of age)
    - 8-12 yo: n = 3
    - 13-17 yo: n = 18

- Common Adverse Events:
  - Nasal discomfort (19%)
  - Intranasal paresthesia (19%)
  - Rhinorrhea (14%)
  - Sneezing (14%)
  - Paresthesia (10%)
  - Fatigue (10%)
  - Feeling jittery (10%)

BENEFIT/RISK OF ARS-1

Benefit / Risk Framework

Benefit

Earlier and more frequent epinephrine use

Uncertainties of the Benefit

- No clinical efficacy study; reliance on PK/PD bridge
- High epinephrine PK/PD variability
- Uncertainties in translating PK/PD results from healthy subjects to those in anaphylaxis
- Different epinephrine PK trends in the first 10 minutes across trials
- Lack of epinephrine PK sustainability in nasal allergen induced nasal congestion after one dose
  - No repeat dose data

Risk

- AE profile did not result in unexpected AEs (systemic and local)
- Limited safety data as many received only single dose

Concluding Remarks

- Anaphylaxis is a severe, potentially fatal, reaction
- There are barriers to use of epinephrine injection products
  - An intranasal epinephrine product could address some barriers
- No clinical efficacy trial, reliance on PK/PD data
- Minimizing uncertainty in PK/PD bridge is important

Concluding Remarks

- Adequacy of the PK/PD data to establish efficacy

- Issues raised for discussion
  - Approach to PK/PD bridge, bracketing approach
  - Lack of sustained PK response in nasal allergen induced nasal congestion
  - Different PK trends in first 10 minutes for ARS-1 compared to Adrenalin

- Are additional data needed?
  - PK/PD data
  - Clinical data


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FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
Charge to the Committee

New Drug Application (NDA) 214697: epinephrine nasal spray (ARS-1) for emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kg

Miya Paterniti, MD
Clinical Team Leader
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

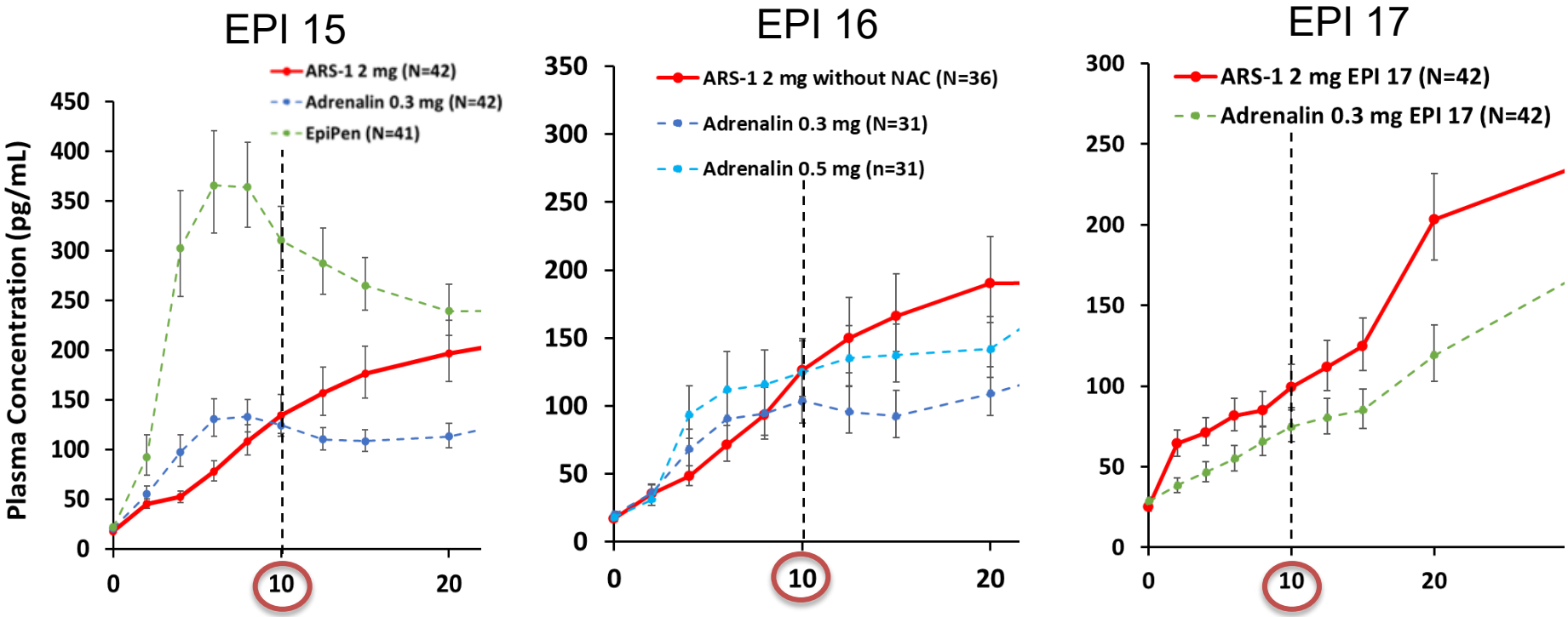
May 11, 2023

ARS-1 (Intranasal Epinephrine): NDA 505(b)(2)

- NDA 505(b)(2)
  - Expressly permits FDA to rely on the Agency's previous finding of safety and effectiveness of an approved drug product
  - Relies on establishing a scientific bridge from ARS-1 to approved epinephrine injection products

- Scientific bridge
  - PK-bracketing of ARS-1 to Adrenalin and EpiPen with PD support
  - Approach
    - Focus on first hour based on anaphylaxis clinical course
    - Assess single and repeat doses in healthy adults
    - Administer ARS-1 in adults with allergen-induced nasal congestion to address potential local absorption differences during anaphylaxis
    - Assess PK/PD in pediatric subjects due to differences in nasal cavity surface area

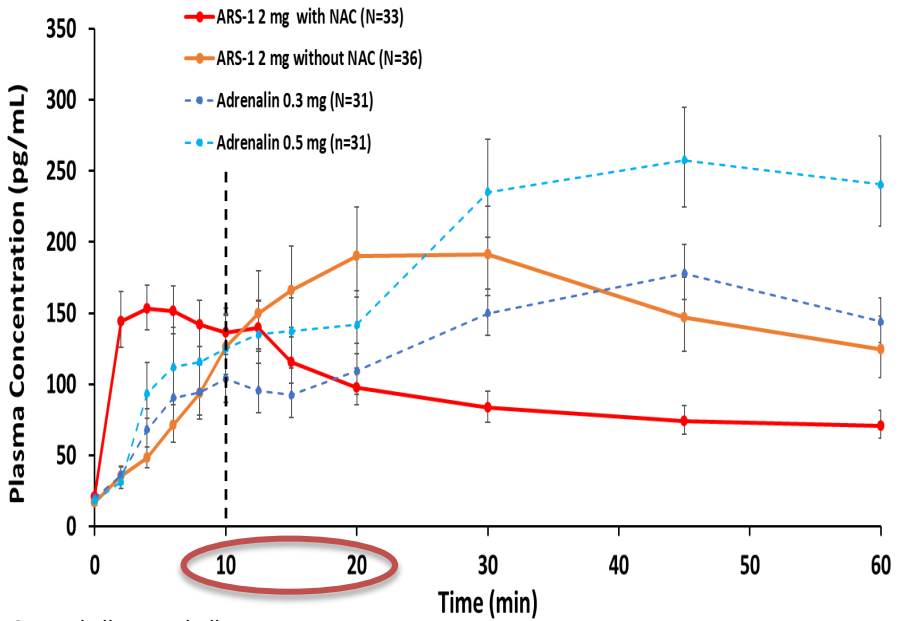
Single-dose PK/PD in Healthy Adults: Different Epinephrine Trends Across Trials In the First 10 Min



PD similar or higher for ARS-1 compared to Adrenalin and EpiPen from baseline

Single-dose PK/PD in Adults with Allergic Rhinitis (EPI 16)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

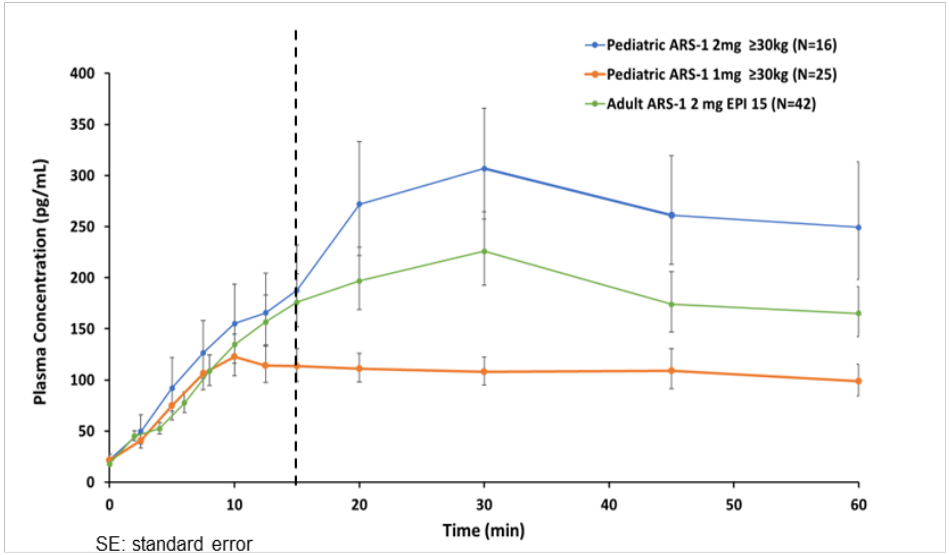


NAC: nasal allergen challenge
SE: standard error

- With nasal allergen challenge
  - High initial PK with rapid decline at 10-20 min compared to Adrenalin 0.3 mg and Adrenalin 0.5 mg
  - PD followed same pattern
  - Nasal congestion reported in 30% of subjects post ARS-1

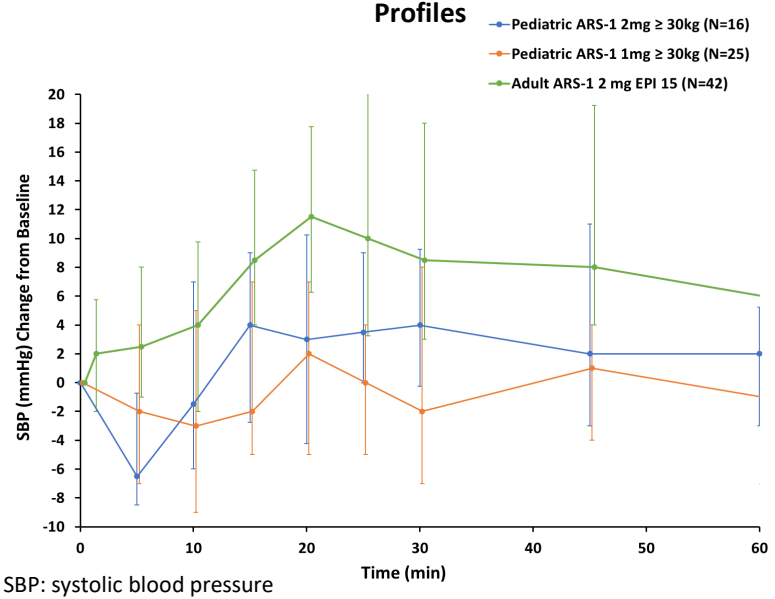
Single-dose PK/PD in Pediatric Subjects ≥ 30 kg (EPI 10)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles



SE: standard error

Median Systolic Blood Pressure (mmHg) Change From Baseline Time Profiles



SBP: systolic blood pressure

- 0-15 minutes: similar PK compared to adults; > 15 minutes: higher PK compared to adults
- PD slightly lower compared to adults

Benefit-Risk Considerations

Benefit

Multiple uncertainties with relying on PK/PD data to support efficacy of ARS-1

- High epinephrine PK/PD variability
- Uncertainties in translating PK/PD results from healthy subjects to those in anaphylaxis
- Different PK trends between ARS-1 and Adrenalin for first 10 minutes
- Lack of epinephrine PK sustainability in allergen induced nasal congestion after a single dose, without a repeat dose study.

Risk

- Systemic safety relies on available data from epinephrine injection products
- Local safety is based only on safety data from ARS-1
- AE profile did not result in unexpected AEs (systemic and local)
- Limited safety profile as many received only single dose

Topics for Discussion

1. **DISCUSSION**: Discuss the pharmacokinetic/pharmacodynamic (PK/PD) approach for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) including anaphylaxis, specifically:

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   a. The PK-bracketing approach using approved epinephrine injection products.

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1. **DISCUSSION**: Discuss the pharmacokinetic/pharmacodynamic (PK/PD) approach for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) including anaphylaxis, specifically:

   a. The PK-bracketing approach using approved epinephrine injection products.
   b. The relevant PK/PD parameters to support clinical efficacy for the intended indication, including the significance of the following findings:
      - The diminished PK/PD sustainability in subjects with allergen-induced nasal congestion compared to epinephrine injection products and lack of data from repeat dosing under allergen-induced nasal congestion conditions.
      - The different PK comparisons of single-dose ARS-1 and Adrenalin in the first 10 minutes for Study EPI 15, EPI 16 (without allergen-induced nasal congestion), and EPI 17.

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1. **DISCUSSION**: Discuss the pharmacokinetic/pharmacodynamic (PK/PD) approach for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) including anaphylaxis, specifically:

   a. The PK-bracketing approach using approved epinephrine injection products.
   b. The relevant PK/PD parameters to support clinical efficacy for the intended indication, including the significance of the following findings:
      - The diminished PK/PD sustainability in subjects with allergen-induced nasal congestion compared to epinephrine injection products and lack of data from repeat dosing under allergen-induced nasal congestion conditions.
      - The different PK comparisons of single-dose ARS-1 and Adrenalin in the first 10 minutes for Study EPI 15, EPI 16 (without allergen-induced nasal congestion), and EPI 17.
   c. The uncertainty of translation of PK/PD results from healthy subjects and subjects with allergen-induced nasal congestion to patients with anaphylaxis, and whether clinical data are needed.

Voting Questions

2. **VOTE**: Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

    a. If not, what additional data are needed?

Voting Questions

3. **VOTE:** Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children (< 18 years of age) ≥ 30 kg for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

   a. If not, what additional data are needed?


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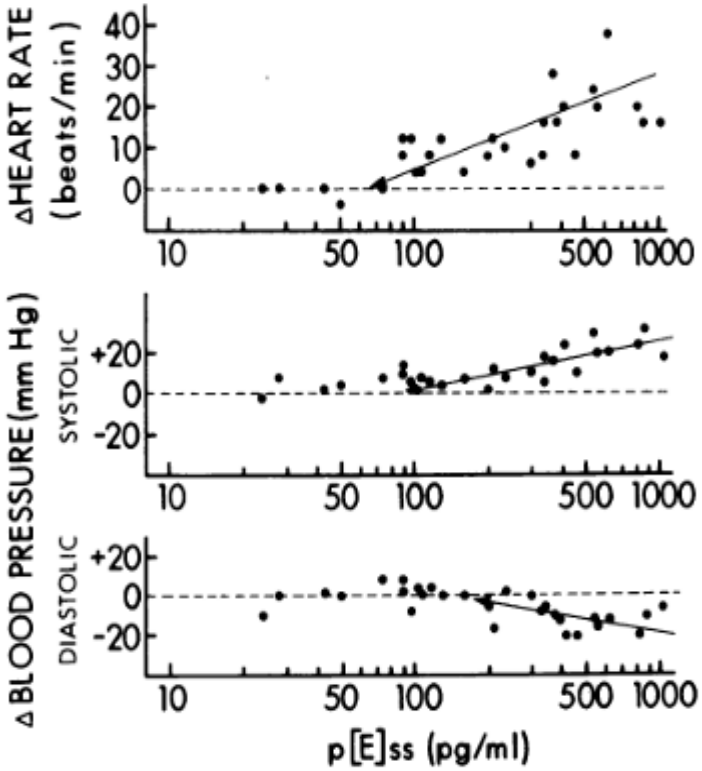
Additional Slides Shown

Bioequivalence Assessment For Single Dose PK EPI 15

	Test: ARS-1 2 mg (N=42) **vs.** **Reference:** Adrenalin 0.3 mg (N=42) **GMR (%) [90% CI]**	**Test:** ARS-1 2 mg (N=42) **vs.** **Reference:** EpiPen 0.3 mg (N=41) **GMR (%) [90% CI]**
C_{max} (pg/mL)	120.2 [94.5, 152.9]	56.2 [44.2, 71.4]
AUC0-10 (pg*min/mL)	**80.1 [61.8, 103.9]**	24.6 [19.0, 31.9]
AUC0-20 (pg*min/mL)	127.3 [101.1, 160.2]	44.0 [34.9, 55.3]
AUC0-30 (pg*min/mL)	142.5 [114.1, 177.9]	56.5 [45.3, 70.6]
AUC0-60 (pg*min/mL)	118.2 [95.8, 145.7]	74.2 [60.2, 91.5]

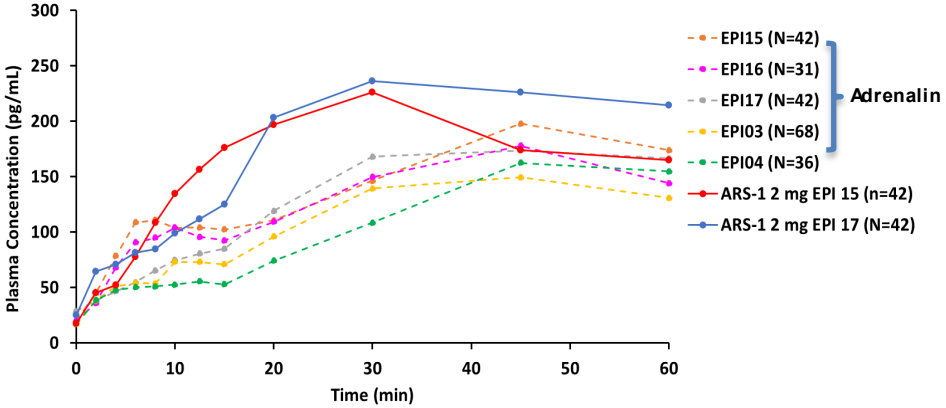
GMR: geometric mean ratio
CI: confidence interval

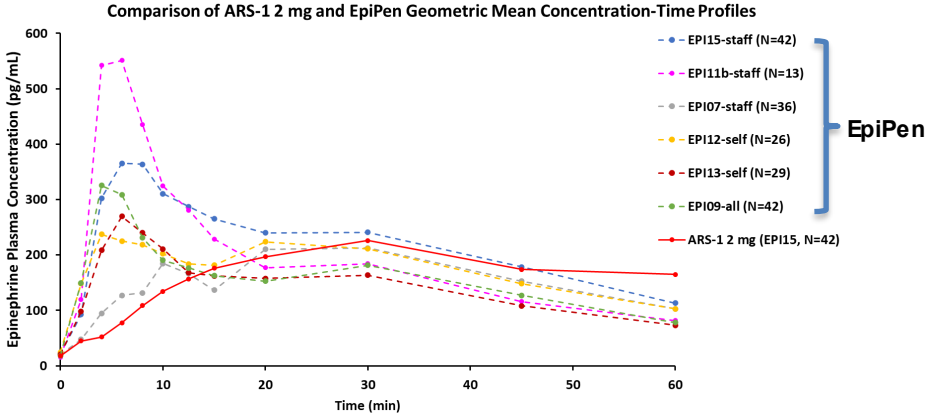
PK-PD Relationship in Healthy Subjects Following Continuous IV Infusion with Fixed Rate

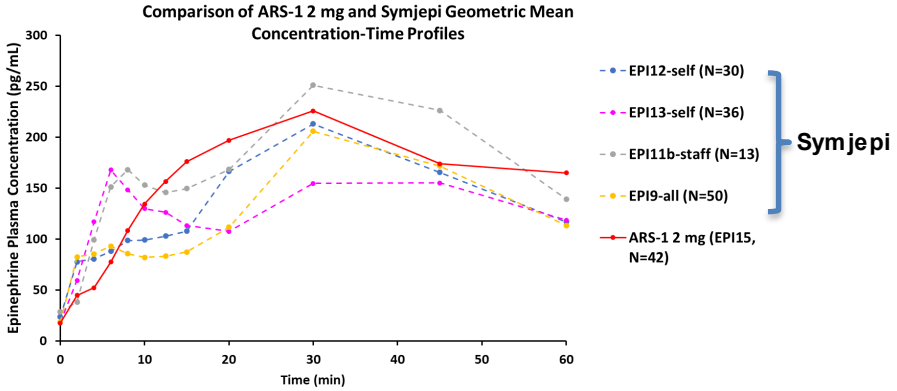


Clutter WE, et. al. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest. 1980 Jul;66(1):94-101

Cross-Study PK Comparisons Between ARS-1 and Epinephrine Injection Products







Impact of Rhinorrhea on Epinephrine PK (EPI16)