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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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 (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

¹conditionally 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 to¹
  – 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 epinephrine²

• 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 population¹
  – Drug allergy – ~10% of the US population¹
  – Hymenoptera venom allergy – 3% of the US population¹
  – Lifetime prevalence ranges between 1.6% to 5.1%.¹

## Approved Epinephrine Injection Products

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Epinephrine Regulatory History

- Epinephrine marketed as unapproved drug: 1901
- Federal Food, Drug and Cosmetic Act (FD&C) - safety: 1938
- EpiPen/EpiPen Jr.: 1987

- 1906 Federal Food and Drugs Act
- 1962 FD&C Act Kefauver-Harris Amendment - efficacy
  (Drug Efficacy Study Implementation (DESI))
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

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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

Under recognition of anaphylaxis

Patients, caregivers and healthcare providers may not recognize the signs of anaphylaxis

Failure to carry

Patients may not fill prescription, do not want to carry the device, or do not anticipate they will encounter an allergen

Lack of access

Supply chain and cost may impair access

May not believe the reaction is serious, do not understand how to use the device, or have needle-phobia

Failure to use injection devices

Underuse/Delay
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
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:
Topics for Discussion

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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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   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?
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 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

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  – Jennifer Lan, MD, Clinical Reviewer

• Overview of the Clinical Pharmacology Results
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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
Challenges to PK Development

• Unknown critical PK parameters relevant for efficacy
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• High inter-product and intra-product PK variability of epinephrine injection products
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- Unknown if PK in healthy adults can be extrapolated to those with anaphylaxis
  - Effect of nasal mucosal edema on epinephrine absorption?
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  - EPI 16 Nasal Allergen Challenge
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- Pediatric considerations
  - EPI 10 Pediatric Trial
# Clinical Pharmacology Program

## Supporting 2 mg Dose

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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
US Food and Drug Administration
# Outline

- **Background**
- **Major clinical pharmacology results of ARS-1**

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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 ($C_{\text{max}}$) ~ 500 pg/mL (coefficient of variation [CV]% ~ 51% to 80%)
  - The time to maximum plasma concentration ($T_{\text{max}}$) ranged from 5 to 60 minutes

MAO: monoamine oxidases
COMT: catechol-O-methyltransferase

www.fda.gov
PK Variability of Epinephrine Injection Products in ARS-1 Program

**EpiPen 0.3 mg IM Geometric Mean PK Profiles**
Cross-Study Comparison

**Adrenalin 0.3 mg IM Geometric Mean PK Profiles**
Cross-Study Comparison

Symjepi 0.3 mg IM Geometric Mean PK Profiles
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All: self and staff administration
IM: intramuscular
Self: self-administration
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- Up to 4-fold

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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
PK Bracketing Rationale

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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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PK Bracketing Rationale

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- 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.
Weighing PD Support

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

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• There is a substantial PD variability observed in ARS program
  – High inter-subject variability (CV%)
  – PD response following ARS-1 influenced by nasal conditions
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.

- There is a substantial PD variability observed in ARS program
  - High inter-subject variability (CV%)
  - PD response following ARS-1 influenced by nasal conditions

- 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

**Period 1**
- ARS-1 L Naris
- EpiPen 0.3 mg L thigh
- Adrenalin 0.3 mg R thigh

**Period 2**
- ARS-1 L Naris
- EpiPen 0.3 mg L thigh
- Adrenalin 0.3 mg R thigh

**Period 3**
- ARS-1 L Naris
- EpiPen 0.3 mg L thigh
- Adrenalin 0.3 mg R thigh

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)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

- ARS-1 2 mg (N=42)
- Adrenalin 0.3 mg (N=42)
- EpiPen (N=41)

SE: standard error
Single-Dose PK Results (EPI 15)

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

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

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

SE: standard error

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.
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.
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

**Healthy Adults**

Partial randomization to ensure adequate wash out

Washout period between treatments: 6 days, 12 days between intranasal doses
The PK profiles are generally similar between ARS-1 administered ipsilaterally or contralaterally.
Repeat Dose PK Results (EPI 15)

- 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

Exposure is doubled following two doses

EpiPen SD vs. RD

$C_{\text{max}}$ increases by 20% and $\text{AUC}_{0-60\text{min}}$ increases by 50% following two doses
Proportion of Subjects Achieving Certain Plasma Concentrations (100 and 200 pg/mL) After Repeat Doses (EPI 15)

- <80% Adrenalin
- >90% EpiPen

- ARS-1 (L/R)
- ARS-1 (R/R)
- EpiPen (L/R)
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

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

<table>
<thead>
<tr>
<th>1st dose</th>
<th>2nd dose</th>
</tr>
</thead>
</table>

SE: standard error

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Kareol 1 mg (L/R) (N=39)</th>
<th>Kareol 1 mg (R/R) (N=39)</th>
<th>EpiPen 0.3 mg (L/R) (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
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<tr>
<td>20</td>
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</tr>
<tr>
<td>60</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

SE: standard error

• 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

PD

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Kareol 1 mg (L/R) (N=39)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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</tr>
<tr>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Error bar: 25th and 75th percentile

SBP: Systolic blood pressure

www.fda.gov
Repeat Dose PD Results – Pulse Rate & Diastolic Blood Pressure
EPI 15

- 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.

Median Pulse Rate (BPM) Change From Baseline Time Profiles

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

Error bar: 25th and 75th percentile

BPM: beats per minutes
PR: pulse rate

DBP: diastolic blood pressure
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
**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

---

**Screening for seasonal allergies**

**Period 1**
ARS-1 without NAC (left naris)

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

**Period 2**
0.3 mg IM or 0.5 mg IM

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

**Period 3**
0.5 mg IM or 0.3 mg IM

**Period 4**
NAC + ARS-1 (right naris)

**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

www.fda.gov
PK Results (EPI 16)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

NAC: nasal allergen challenge
SE: standard error

Plasma Concentration (pg/mL)

Time (min)

ARS-1 2 mg with NAC (N=33)
ARS-1 2 mg without NAC (N=36)
Adrenalin 0.3 mg (N=31)
Adrenalin 0.5 mg (n=31)
PK Results (EPI 16)

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

- 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
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

- 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

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

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

www.fda.gov
Impact of Nasal Congestion Score on PK/PD (EPI 16)

Impact on PK

Epinephrine Geometric Mean (±SE) Concentration-Time Profiles

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

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

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

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

Error bar: 25th and 75th percentile
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 ($\pm$SE) Concentration-Time Profiles

- The PK profile following ARS-1 2 mg in pediatrics subjects $\geq$ 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

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

 Median Pulse Rate (BPM) 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)

SBP: systolic blood pressure
BPM: beats per minute

Drug administration and vital sign measurement positions:
- Adult: sitting
- Pediatric: semi-supine

Error bar: 25th and 75th percentile
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
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

- 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

- 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

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

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Dictionary-Derived Term</th>
<th>ARS-1 2.0 mg (N=134)</th>
<th>Epinephrine injection 0.3 mg (N=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Count</td>
<td>%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>8</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Nasal discomfort</td>
<td>13</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Rhinorrhea</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>
Local Safety Profile of ARS-1

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

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<td></td>
<td>Rhinorrhea</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>
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
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

- 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

NAC: nasal allergen challenge
SE: standard error
Single-dose PK/PD in Pediatric Subjects ≥ 30 kg (EPI 10)

Epinephrine Geometric Mean (± SE) Concentration-Time Profiles

- 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

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   b. The relevant PK/PD parameters to support clinical efficacy for the intended indication, including the significance of the following findings:
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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.
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   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.
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?
Additional Slides Shown
### Bioequivalence Assessment For Single Dose PK EPI 15

<table>
<thead>
<tr>
<th></th>
<th>Test: ARS-1 2 mg (N=42) vs. Reference: Adrenalin 0.3 mg (N=42) GMR (%) [90% CI]</th>
<th>Test: ARS-1 2 mg (N=42) vs. Reference: EpiPen 0.3 mg (N=41) GMR (%) [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</strong></td>
<td>120.2 [94.5, 152.9]</td>
<td>56.2 [44.2, 71.4]</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-10&lt;/sub&gt; (pg*min/mL)</strong></td>
<td><strong>80.1 [61.8, 103.9]</strong></td>
<td>24.6 [19.0, 31.9]</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-20&lt;/sub&gt; (pg*min/mL)</strong></td>
<td>127.3 [101.1, 160.2]</td>
<td>44.0 [34.9, 55.3]</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-30&lt;/sub&gt; (pg*min/mL)</strong></td>
<td>142.5 [114.1, 177.9]</td>
<td>56.5 [45.3, 70.6]</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-60&lt;/sub&gt; (pg*min/mL)</strong></td>
<td>118.2 [95.8, 145.7]</td>
<td>74.2 [60.2, 91.5]</td>
</tr>
</tbody>
</table>

GMR: geometric mean ratio  
CI: confidence interval
PK-PD Relationship in Healthy Subjects
Following Continuous IV Infusion with Fixed Rate

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

Comparison of ARS-1 2 mg and Symjepi Geometric Mean Concentration-Time Profiles

Comparison of ARS-1 2 mg and EpiPen Geometric Mean Concentration-Time Profiles
Impact of Rhinorrhea on Epinephrine PK (EPI16)