FDA Addendum to Briefing Document

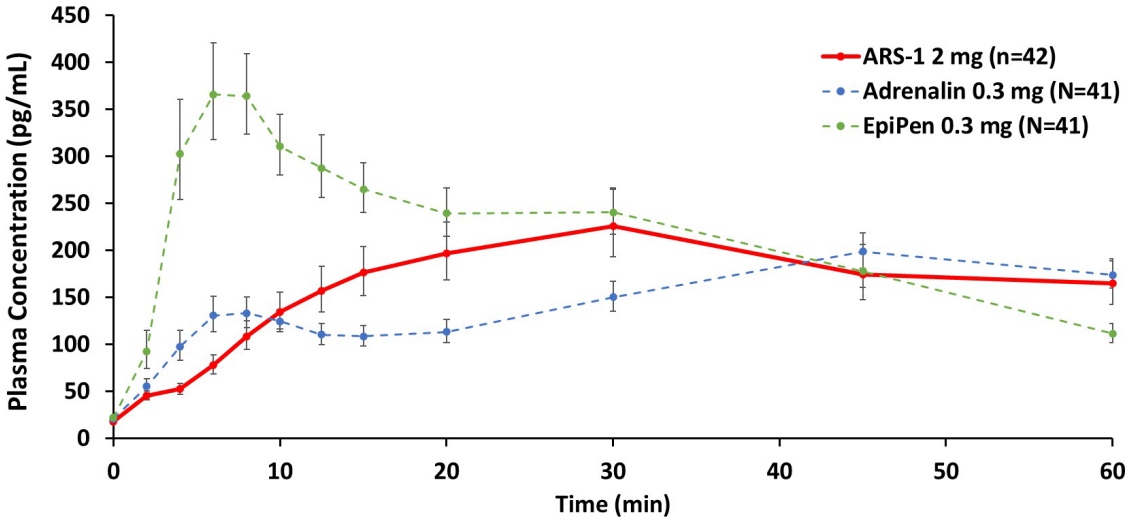
Pulmonary-Allergy Drug Advisory Committee Meeting

May 11, 2023

1. **Clarification regarding the lower ARS-1 pharmacokinetics (PK) in the first 10 minutes seen in EPI 15**

FDA has asked the AC panel to discuss the lower concentration of epinephrine in the first 10 minutes following single-dose ARS-1 compared to epinephrine injection products, including Adrenalin. This trend was identified in the pivotal PK/pharmacodynamic (PD) bioavailability study EPI 15 and is shown in Figure 1 of the Executive Summary, and Figure A below.

Figure A. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profile Following a Single Dose of ARS-1 (2 mg) vs. a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects (EPI 15)

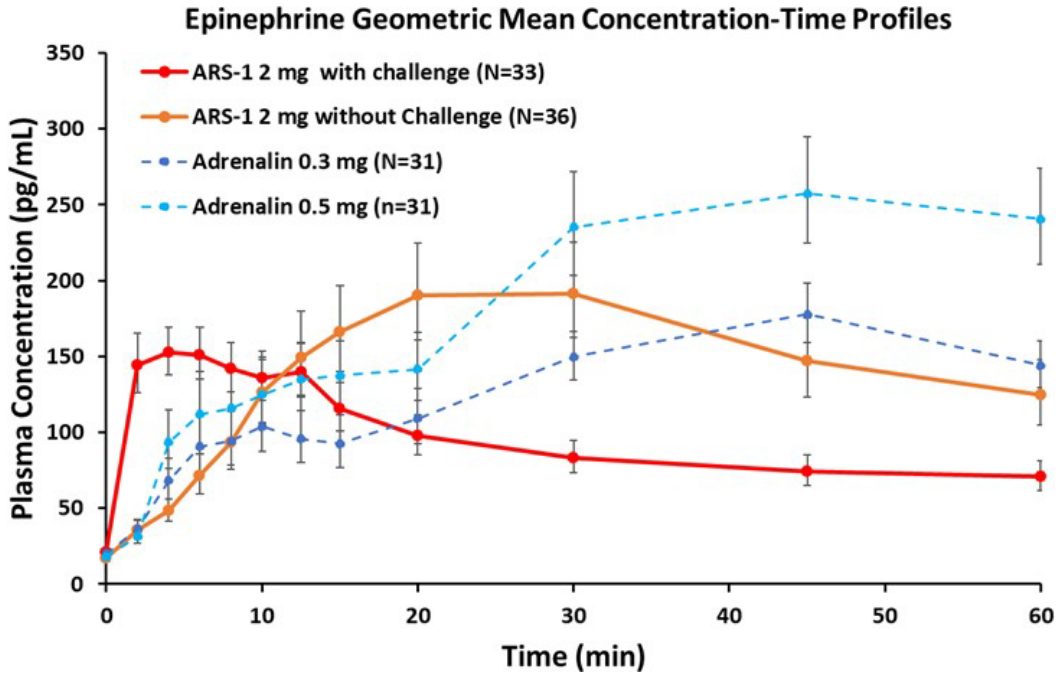


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 15.

One subject each from the Adrenalin and EpiPen arms was excluded due to an insufficient number of postdose samples (N<3) collected within 30 min.

For completeness, ARS-1 under normal nasal conditions was also compared to Adrenalin in EPI 16 and EPI 17. In EPI 16, the trend for the concentration of epinephrine in the first 10 minutes following ARS-1 in subjects without nasal allergen challenge is not distinctly different compared to Adrenalin 0.3 mg as shown in Figure B below and (Figure 11 in the FDA Briefing document).

Figure B. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis (EPI 16)

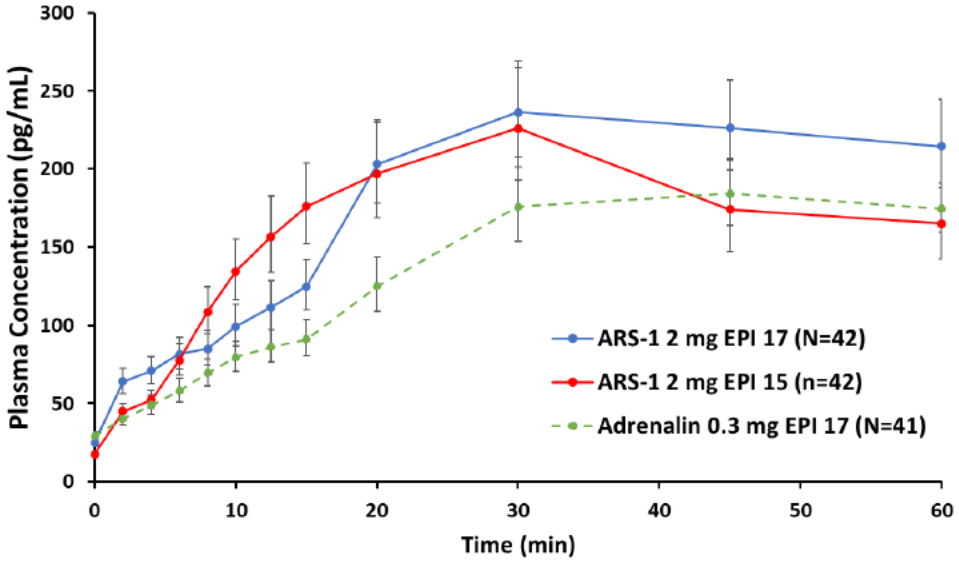


Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 16.

Three subjects each in the Adrenalin 0.3 mg and Adrenalin 0.5 mg arms and one subject in ARS-1 with nasal challenge arm had insufficient number of quantifiable postdose samples (n<3) within 30 min. Two subjects each in the Adrenalin 0.3 mg, Adrenalin 0.5 mg arm, and the ARS-1 with nasal challenge arm did not have pharmacokinetic data.

FDA acknowledges that results from Study EPI 17, the self-administration study, show a different trend - the exposure of ARS-1 is higher than Adrenalin in the first 10 minutes, as shown in Figure 15 to the FDA Briefing Document (and shown below in Figure C). We included the ARS-1 treatment arm from Study EPI 15 for comparison.

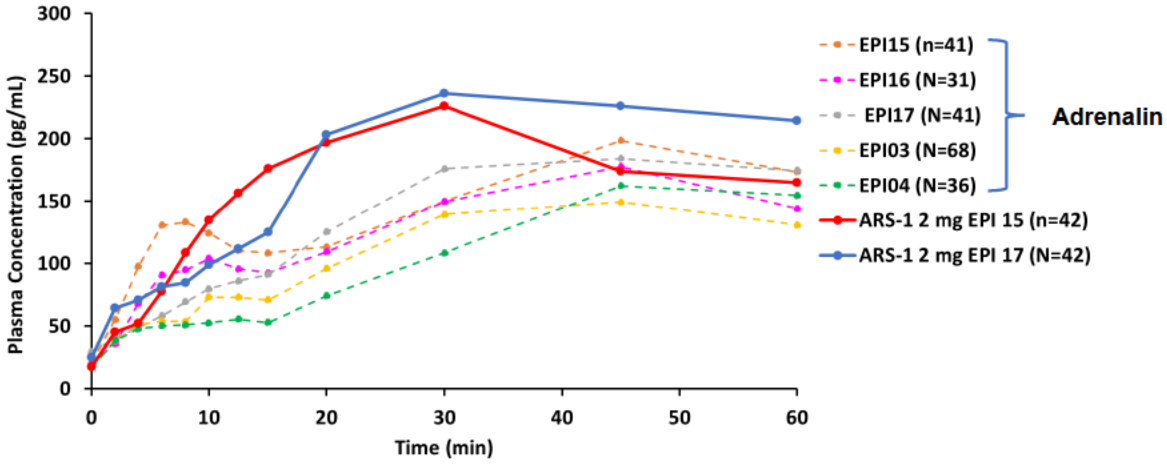
Figure C. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles Following a Single Dose of ARS-1 (Self-Administered), Adrenalin 0.3 mg (Staff-Administered) and Single Dose of ARS-1 (Staff-Administered From EPI 15)



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 17 and EPI 15.

This difference in trends is likely due to the variability that is seen with Adrenalin across trials. Figure D below shows a cross-study comparison of Adrenalin from various studies versus ARS-1 from EPI 15 and EPI 17.

Figure D. Cross-study Comparison of ARS-1 2 mg and Adrenalin Geometric Mean Concentration-Time Profiles



As shown in Figure D, the ARS-1 curves from EPI 15 and EPI 17 are similar, but the PK curve of Adrenalin in EPI 15 is higher than the PK curve of Adrenalin in EPI 17. FDA acknowledges that

the differences seen in the first 10 minutes between EPI 15 and EPI 17 is mostly due to Adrenalin PK variability. Given that EPI 15 was the pivotal PK/PD study that included both EpiPen and Adrenalin for the purposes of bracketing the PK of ARS-1, FDA believes it is important for the AC panel to note the lower exposure of ARS-1 in the first 10 minutes in EPI 15 and consider the available data across the studies to discuss whether there are potential clinical implications.

2. **Clarification regarding FDA perspective on the PK/PD discrepancy**

The Division would like to clarify our perspective on the PK/PD relationship for this application and use of the phrase PK/PD discrepancy. We acknowledge that in literature and in general, epinephrine PK and PD are generally aligned (i.e. when epinephrine PK is higher, the PD response (systemic blood pressure (SBP) and pulse rate (PR)) is higher as well), especially following the intravenous infusion route. We also acknowledge that for ARS-1 this same general alignment was demonstrated, especially under normal nasal condition. When we refer to PK/PD discrepancy in the FDA Briefing Document, we refer to the differences in the PK/PD relationship between epinephrine products. The degree of PK and PD correlation varies. For example, the PK/PD relationship observed for ARS-1 is different from that of epinephrine injection products (i.e. EpiPen and Adrenalin). ARS-1 generally has a lower epinephrine PK profile than EpiPen, but with a generally higher/more sustained PD (SBP/PR) response under normal nasal conditions.

3. **Clarification regarding the 2.0 mg ARS-1 dose selected (See Section 3.1.2.1 General PK Considerations: Dose Ranging)**

In Section 3.1.2.1 in the FDA Briefing Document, we discussed results from the pivotal dose ranging study (EPI 11b) and the rationale for the 2 mg dose selection. We stated that the Applicant decided to move forward with the ARS-1 2 mg dose without investigating higher doses. During a pre-NDA meeting in June 2021, ARS provided the results from EPI 11b, which showed PK results from doses of ARS-1 ranging from 1 to 2 mg. Based upon these results, the FDA did caution ARS about safety concerns with higher doses given that the AUC_{0-t} with the 2 mg dose of ARS-1 was higher than EpiPen. We noted this could be due to variability of the PK data or small sample size. Due to uncertainty in dose selection, we recommended conducting EPI 15 before initiating other trials.

Since that pre-NDA interaction in June 2021, ARS has conducted several clinical pharmacology studies that form the basis of the scientific bridge between ARS-1 and approved epinephrine injection products to support this NDA. With review of the data submitted in an NDA, we identified issues that raise questions regarding dose selection. Based upon review of the data

submitted in this NDA, we identified decreased exposure in the first 10 minutes in EPI 15 and lack of sustainability of exposure in the nasal allergen challenge model (EPI 16). These concerns raised the question of whether a higher dose may address these issues. This is a topic we would like the AC to panel to discuss.

4. **Clarification regarding the utility of the epinephrine concentration threshold 100 pg/mL cut off (See Section 3.1.2.2 ARS-1 PK/PD Under Normal Nasal Conditions)**

In the FDA Briefing Document, we presented results for the proportion of subjects whose epinephrine concentration reached 100 pg/mL or 200 pg/mL. We presented the proportional analysis data from EPI 15 as this was the dedicated pivotal PK/PD trial. We noted that these thresholds are arbitrary values used for displaying the proportional results. The clinical relevance of this cut off is unknown. We also acknowledge that these values are based on data from subjects receiving epinephrine continuous intravenous infusions, which could allow time for compensatory mechanisms to adjust for PR and SBP and may limit the relevance to acute administration of epinephrine.

5. **Clarification regarding FDA's use of geometric mean to analyze PK results versus use of arithmetic mean (See Section 3.1.2.1 General PK Considerations: Considerations for Presenting PK results)**

FDA presents the PK data in the FDA Briefing Document using geometric means, while ARS presents the PK data in their briefing document using arithmetic means. The *FDA Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs – General Considerations*[1] recommends both arithmetic and geometric mean values of PK parameters be submitted in an NDA. It is appropriate to consider different analyses of the PK data. Depending on the nature of the data, there may be reasons to place more emphasis on arithmetic vs. geometric means. When we reviewed both methods, we decided to use geometric means for presentation of the PK data from this program. Given the high variability seen with epinephrine PK, the geometric mean is less influenced by extreme outlier values. We note that despite the different approaches in presentation of the PK data (geometric vs. arithmetic means), the results obtained from either geometric means or arithmetic means are similar.

[1] Bioavailability Studies Submitted in NDAs or INDs – General Considerations | FDA

6. **Clarification regarding FDA's comment of pooling PK data (See Section 3.1.2.1 General PK Considerations: PK Data Pooling)**

The *FDA Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs – General Considerations* describes the type of data that can be used to support bioavailability. While pooling of PK data can be utilized for certain purposes (e.g., population pharmacokinetics), we placed more emphasis on the results from the individual dedicated clinical pharmacology studies in this program, rather than PK comparisons pooling PK data from multiple studies. We believe that data from dedicated relative bioavailability studies provides stronger evidence and is the most appropriate approach to establish a scientific bridge between ARS-1 and approved epinephrine injection products. However, we do note that given the different treatment arms in different studies, there may be a role for cross study comparisons (e.g., Study EP 10 does not include an epinephrine injection comparator), and we have performed some of these analyses for this program. However, it is important to note that these types of analyses may have limitations that come with cross study comparisons.