Errata to FDA Briefing Document

Meeting of the Pulmonary-Allergy Drugs Advisory Committee

May 11, 2023

This errata contains corrections to FDA's briefing document for the May 11, 2023 meeting of the Pulmonary-Allergy Drugs Advisory Committee. The committee will discuss new drug application (NDA) 214697, for epinephrine nasal spray, submitted by ARS Pharmaceuticals Inc., for the proposed indication of emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kilograms.

For corrections, deleted text is shown with ~~strikethrough~~ and additions are shown with <u>underline</u>.

General comment for EPI 15 PK analyses:

In the FDA Briefing Document, our approach to handling subjects with epinephrine concentrations below the limit of quantification (BLQ) in EPI 15 differed from the Applicant's approach. Our approach excluded data from 3 subjects who had less than 3 quantifiable samples during the first 30 minutes in EPI 15. We have reviewed sensitivity analyses looking at the inclusion or exclusion of these 3 subjects and our interpretation of the results is similar with either dataset. To minimize questions regarding differences in the PK results during the AC meeting, FDA will align with the Applicant's approach and include the data from these 3 subjects in our presentation of results for EPI 15. Thus, our AC presentation for EPI 15 will show slightly different results from what is in the FDA Briefing Document, which will provide transparency as to the results from both datasets.

Page 8 (Table 2) and Page 18 (Table 5):

Replace this table:

PK/PD/Safety Trial	Purpose
Dose ranging (EPI 11, 11b, 12)	Determine an appropriate intranasal epinephrine dose compared to epinephrine injection based on PK similarity.
PK matching (EPI 15)	Bracket the single-dose PK profile of intranasal epinephrine with epinephrine injection products with support of comparable safety and PD profiles.
Second dose (EPI 15)	Assess the PK/PD and safety of two doses of intranasal epinephrine compared to two doses of epinephrine injection.
Nasal allergen challenge (EPI 16)	Assess the effect of nasal congestion on the PK/PD and safety of intranasal epinephrine compared to epinephrine injection.

With this table:

PK/PD/Safety Trial	Purpose
Dose ranging (EPI ~~11~~, 11b~~, 12~~)	Determine an appropriate intranasal epinephrine dose compared to epinephrine injection based on PK similarity.
PK matching (EPI 15)	Bracket the single-dose PK profile of intranasal epinephrine with epinephrine injection products with support of comparable safety and PD profiles.

Second dose (EPI 15)	Assess the PK/PD and safety of two doses of intranasal epinephrine compared to two doses of epinephrine injection.
Nasal allergen challenge (EPI 16)	Assess the effect of nasal congestion on the PK/PD and safety of intranasal epinephrine compared to epinephrine injection.

Page 15, Paragraph 2:

Replace this text:

Beta-2 receptors are located in cardiac muscle, airway smooth muscle, and skeletal muscle arteries; activation of beta-2 receptors increases cardiac chronotropy (i.e., heart rate), bronchodilation, and vasodilation in the skeletal muscles.

With this text:

Beta-2 receptors are located in ~~cardiac muscle,~~ airway smooth muscle, and skeletal muscle arteries; activation of beta-2 receptors leads to ~~increases cardiac chronotropy (i.e., heart rate),~~ bronchodilation, and vasodilation in the skeletal muscles.

Page 19, first paragraph:

Replace this text:

On review of nonclinical studies, it is hypothesized that reversible nasal mucosal damage may take some time (i.e., no immediate carryover effect) to develop following the first IN administration; and the damage peaks in 1 to 2 days, which allows for an increase absorption from the second dose of IN epinephrine.

With this text:

On review of nonclinical studies, it is hypothesized that epinephrine related reversible nasal mucosal ~~damage~~ changes may take some time (i.e., no immediate carryover effect) to develop following the first IN administration; and the ~~damage~~ change peaks in 1 to 2 days, which allows for an increase absorption from the second dose of IN epinephrine.

Page 37, Figure 11, footnote:

Replace this text:

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

With this text:

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 ~~in~~ each in the Adrenalin 0.3 mg, ~~five subjects in the~~ Adrenalin 0.5 mg arm, ~~and two subjects~~ and the ARS-1 with nasal challenge arm did not have pharmacokinetic data.

Page 52, first paragraph:

Replace this text:

6.1.1 Nasal Mucosal Damage

Single-dose IN treatment of ARS-1 in rats induced ARS-1 histopathology changes in the nose, such as minimal ulceration of the exposed mucosa (at ≥2.3-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area), and nasal passages, such as minimal to mild necrosis in the nasal turbinate and parietal wall in the rostral-most level (at ≥1.2-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area).

With this text:

6.1.1 Nasal Mucosal ~~Damage~~ Changes

Single-dose IN treatment of ARS-1 in rats ~~induced ARS-1~~ suggests that epinephrine contributed to histopathology changes in the nose, such as minimal ulceration of the exposed mucosa (at ≥2.3-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area), and nasal passages, such as minimal to mild necrosis in the nasal turbinate and parietal wall in the rostral-most level (at ≥1.2-fold the recommended clinical dose of 2 mg of ARS-1 based on local surface area).