neffy, Epinephrine Nasal Spray, Development, from Pharmacokinetics and Pharmacodynamics to Real-World Data in Pediatric Food Allergy Patients

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RATIONALE

- To date, no clinical trials have been conducted to support pediatric doses of epinephrine injection products for the treatment of severe allergic reactions. Instead, FDA/EMA approvals were based on epinephrine's well-established safety and efficacy profiles.
- ***neffy*** (epinephrine nasal spray) was recently approved by the FDA and EMA as the first and only needle-free epinephrine delivery system.
- During the development of ***neffy***, ARS Pharmaceuticals, Inc. conducted two clinical trials in pediatric allergy patients: 1) a Phase 1 pharmacokinetic and pharmacodynamic study in the US; and 2) a Phase 3 oral food challenge (OFC) study in Japan.
- In this analysis, differences in pharmacodynamic responses between those studies were assessed to evaluate a potential link between pharmacodynamic responses and efficacy.

METHODS

STUDY DESIGN AND POPULATION

- Phase 1 study was a single-dose, open label study in 42 pediatric allergy patients aged 4 to 17. Pharmacokinetics and pharmacodynamics were evaluated.
- Phase 3 study was a single-dose, open label study in 15 pediatric food allergy patients aged 6 to 17. Anaphylaxis symptoms were induced, followed by administration of ***neffy*** at onset of moderate anaphylaxis symptoms. Pharmacodynamics were evaluated, however there was no pharmacokinetic analysis.
- In both studies, patients received ***neffy*** 1 mg (15-30 kg) or 2 mg (≥30 kg).

RESULTS

DEMOGRAPHICS

- Patient demographics were comparable across both studies (**Table 1**).

Table 1: Demographic Data

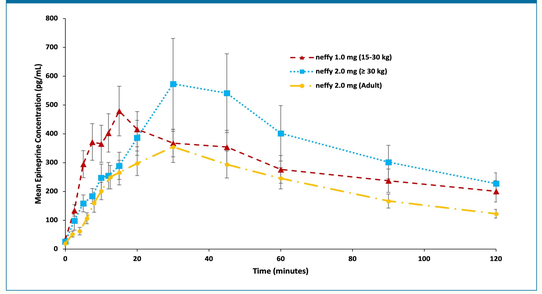
Demographic	Phase 1 Study		Phase 3 Study	
	neffy 1.0 mg (15-<30kg) n (%)	*neffy* 2.0 mg (≥30 kg) n (%)	*neffy* 1.0 mg (15-<30kg) n (%)	*neffy* 2.0 mg (≥30 kg) n (%)
Age (Year)				
n	21	21	6	9
Mean (SD)	7.8 (1.76)	14.1 (2.43)	7.5 (1.97)	12.3 (2.50)
Median	8.0	14.0	7	12
Minimum, Maximum	4,11	8,17	6,11	8,17
Gender				
Male	13 (61.9)	12 (57.1)	1 (16.7)	6 (66.7)
Female	8 (38.1)	9 (42.9)	5 (83.3)	3 (33.3)
Body Weight				
n	21	21	6	9
Mean (SD)	25.3 (3.56)	54.1 (13.5)	20.7 (5.76)	39.4 (7.83)
Median	26.2	53.8	18	40
Minimum, Maximum	18.5, 29.9	30.8, 86	16, 29	30, 54
Body Mass Index				
n	21	21	6	9
Mean (SD)	7.76 (1.76)	14.1 (2.43)	14.3 (1.81)	16.8 (1.53)
Median	8	14	14	17
Minimum, Maximum	4, 11	8, 17	12, 18	15, 19

CLINICAL FINDINGS

Phase 1 Study

- Although the mean maximum plasma concentrations (C_{max}) were comparable between doses (690 pg/mL and 651 pg/mL, for 1 and 2 mg, respectively), the mean epinephrine concentration-time profiles demonstrate that epinephrine levels peak earlier in the 15 - <30 kg) group (1 mg dose).
- Both doses resulted in a noticeable increase in SBP. Both doses of neffy also resulted in an increase in PR.

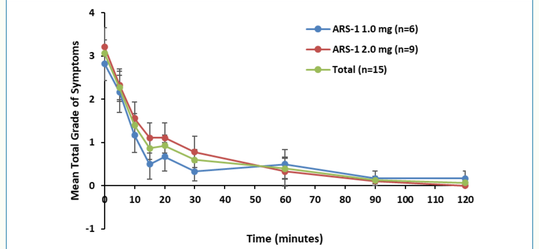
Figure 1: Mean Epinephrine Concentration Versus Time (Phase 1 Study)



Phase 3 Study

- Fifteen patients exhibited at least one Grade 2 CR to the OFC, with a total of 18 Grade 2 events reported and dosed with ***neffy***.
- No patients required a second dose of epinephrine following administration of ***neffy*** except for one patient who developed a biphasic reaction 2 hours and 45 minutes following ***neffy*** administration and received intramuscular epinephrine.
- For both dose groups, the mean total grade started decreasing within five minutes of ***neffy*** administration (the first assessment timepoint).
- The median time to resolve moderate anaphylaxis symptoms was 16 minutes.

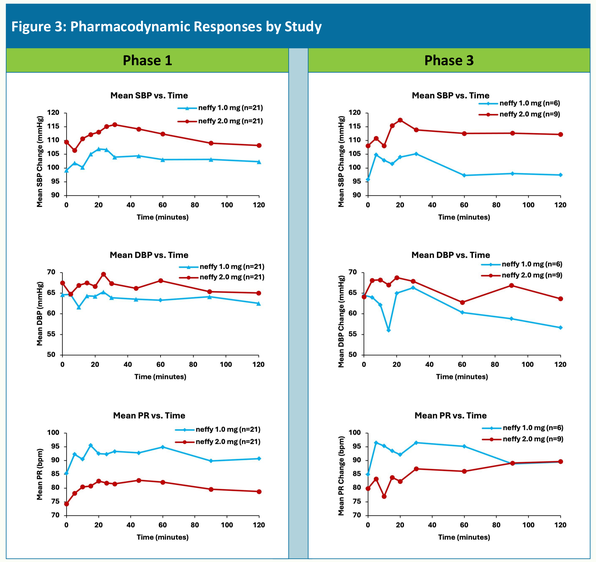
Figure 2: Time Course for Total Grade of Organ System(Phase 3 Study)



PHARMACODYNAMIC COMPARISON BETWEEN STUDIES

- Pharmacodynamic data were generally similar across both studies, with the exception of a more pronounced decrease in DBP at early time points in 15 - <30 kg patients relative to ≥30 kg patients in the OFC study.
- The more pronounced decrease in DBP observed in the younger (15 - <30 kg) patients in the Phase 3 study may be attributable to a greater degree of vascular elasticity in younger children relative to older children. Thus, when exposed to an allergen the younger children would be expected to demonstrate a greater degree of vasodilation and subsequent decrease in DBP relative to the older children.

Figure 3: Pharmacodynamic Responses by Study



CONCLUSIONS

- ***neffy*** is the first epinephrine product studied in pediatric patients.
- Pharmacodynamic data were consistent between studies, with both studies demonstrating increases in SBP and PR and early and transient decreases in DBP.
- This finding is also consistent with the observed efficacy reported in the Phase 3 study, as well as with the well-established pharmacological properties of epinephrine for the treatment of severe allergic reactions/anaphylaxis.
- Taken together, these findings demonstrate that ***neffy*** will be a safe and effective needle-free treatment option for pediatric allergy patients.

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