EDP-938, a Novel, Non-Fusion Replication Inhibitor of Respiratory Syncytial Virus: Final Results of a Phase 1 Study in Healthy Subjects (HS)

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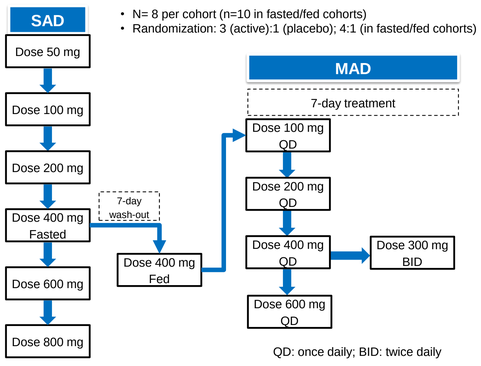
Introduction and Background: EDP-938

- Respiratory Syncytial Virus (RSV) represents an important global health challenge with significant morbidity and mortality in infants, elderly, and immunocompromised populations
- No approved vaccines or therapeutics directly targeting the RSV virus currently exist
- EDP-938 is a novel potent RSV N-protein inhibitor that has been shown to inhibit all RSV lab strains tested *in vitro*
- EDP-938 is also active against RSV-A and -B clinical isolates (*in vitro*)
- EDP-938 demonstrated excellent *in vivo* efficacy, reducing viral load by >4-log in the African Green Monkey model

Methods

- EDP-938-001 is a randomized, double-blind, placebo-controlled, first-in-human (FIH) study of single ascending doses (SAD) and multiple ascending doses (MAD) of orally administered EDP-938 in healthy subjects (HS); (NCT03384823). The study design is shown in Figure 1.
- The key objectives were:
  - To evaluate the safety and tolerability of a single and multiple doses of EDP-938 administered to HS
  - To evaluate the PK of single and multiple doses of EDP-938 in plasma and urine in HS
  - To evaluate the effect of food intake on PK of EDP-938 administered as a single dose in HS

Figure 1.Study Design



- Safety and tolerability assessments evaluated throughout study conduct included:
  - Adverse events, clinical laboratories, physical examination, electrocardiographic evaluations, cardiac markers (troponin T and I), and creatine kinase muscle/brain (MB)
- Pharmacokinetics (PK) assessments
  - Intensive plasma PK samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72, and 96 hr in the SAD phase
  - In the MAD phase, intensive plasma PK samples were collected
    - Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15 hr
    - Days 2 (24 hours), 3 (predose), 4 (predose), 5 (predose), 6 (predose)
    - Day 7: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24 (D8), 30, 36, 48 (D9), 60, 72 (D10), and 96 (D11) hr postdose
  - Urine samples were collected in the SAD phase
  - Concentrations of EDP-938 and its metabolites were measured using a validated method
  - PK parameters were determined using non-compartmental methods in Phoenix WinNonlin (Pharsight Corporation version 6.3)

Disclosures

A. Ahmad, K. Sanderson, N. Adda are employees of Enanta Pharmaceuticals, Inc.
D. Dickerson is an employee of PRA Health Sciences.

Results

Subject Disposition and Demographics

- A total of 90 subjects enrolled: n= 50 in SAD; n=40 in MAD
  - All randomized subjects completed the study (in both SAD and MAD phases)
- In the SAD phase, subjects were mostly male of White or Black/African American race, with a mean (range) age of 32.4 (18-53) year and mean (range) BMI of 24.8 (19.1-30.0) kg/m^2 across all cohorts
- Demographics for the MAD phase are summarized in Table 1

Table 1: Demographics of Subjects in the MAD Phase

	100 mg QD (N=6)	200 mg QD (N=6)	400 mg QD (N=6)	300 mg BID (N=6)	600 mg QD (N=6)	Placebo (N=10)	Overall (N=40)
Male, n (%)	5 (83.3)	4 (66.7)	5 (83.3)	4 (66.7)	4 (66.7)	7 (70.0)	29 (72.5)
Race							
American Indian or Alaska Native	0	1 (16.7)	0	0	0	0	1 (2.5)
Black or African American	2 (33.3)	5 (83.3)	0	4 (66.7)	5 (83.3)	6 (60.0)	22 (55.0)
White	4 (66.7)	0	6 (100)	1 (16.7)	1 (16.7)	4 (40.0)	16 (40.0)
Multiple	0	0	0	1 (16.7)	0	0	1 (2.5)
Ethnicity							
Hispanic or Latino, n (%)	1 (16.7)	1 (16.7)	2 (33.3)	0	0	0	4 (10.0)
Age (yr)[a]	33.3 (25-44)	37.7 (30-55)	34.2 (25-44)	38.2 (27-50)	39.8 (26-47)	37.8 (21-53)	36.9 (21-55)
BMI (kg/m^2)[a]	23.85 (20.5-25.5)	26.5 (22.6-29.7)	23.3 (19.8-26.6)	26.6 (24.4-28.1)	27.5 (24.8-29.7)	25.8 (19.5-29.9)	25.6 (19.5-29.9)

[a]presented as mean (range); BID: twice daily; BMI: body mass index; QD: once daily; yr: year

Safety – SAD and MAD Phases

- Overall, no safety concerns have been reported in 68 HS dosed orally with EDP-938 in the SAD and MAD parts of the study
  - During the SAD phase:
    - EDP-938 was generally well-tolerated at single doses up to 800 mg with a total of 8 subjects reporting at least one AE
    - Headache was the most frequently reported AE; all AEs were of mild intensity, and were reported as not related or unlikely related to EDP-938; none occurred in the placebo group
  - During the MAD Phase:
    - EDP-938 was also generally well-tolerated at multiple doses up to 600 mg once daily or 300 mg twice daily for 7 days with a total of 9 subjects (n=6/30 on active, n=3/10 on placebo) reporting at least one AE
    - Headache was the most frequently reported AE; all AEs were of mild intensity, and the majority were reported as possibly related to EDP-938 or placebo, with no relationship to dose (n=3/30 on active, n=2/10 on placebo)
  - No SAEs or AEs that led to study drug discontinuation were reported
- No clinically significant abnormal safety laboratory or abnormal ECG findings nor echocardiogram changes from baseline were reported with single and multiple doses of EDP-938

Pharmacokinetics – SAD Phase

The PK parameters of EDP-938 are presented in Table 2 and the mean plasma concentration time profiles are shown in Figure 2

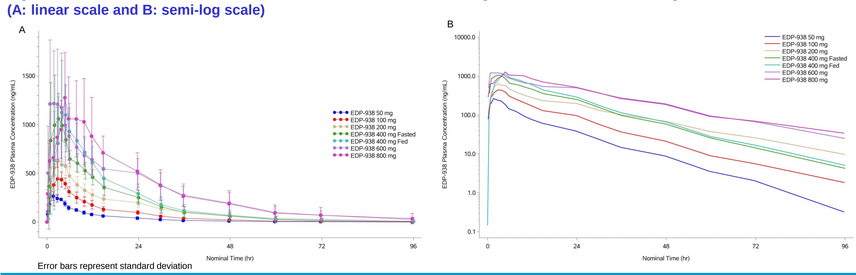
- EDP-938 exposure increased with increasing single doses
- Mean C_{24} ranged from 39-521 ng/mL
- Median T_{max} ranged from 2.0-5.0 hr
- Mean single dose half-life ranged from 10.8-16.8 hr (fed and fasted)
- EDP-938 and metabolites levels in the urine were <5% of administered dose
- The PK exposures were generally similar between the fed and fasted 400 mg cohorts, indicating that food did not impact the PK of EDP-938

Table 2. EDP-938 Plasma PK Parameters Following Oral Administration of Single Doses of EDP-938 (values presented as mean (%CV) except as noted)

PK Parameters	50 mg (N=6)	100 mg (N=6)	200 mg (N=6)	400 mg fasted (N=8)	400 mg fed (N=8)	600 mg (N=6)	800 mg (N=6)
C_{max} (ng/mL)	267 (16.8)	510 (23.2)	671 (20.7)	1250 (30.4)	1250 (37.8)	1450 (38.3)	1320 (33.0)
T_{max} (hr)[a]	2.0 (2-4)	3.5 (2-5)	3.0 (2-5)	2.5 (1-4)	4.5 (3-8)	2.5 (1-6)	5.0 (3-8)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	3060 (20.5)	6380 (18.2)	12200 (23.3)	16200 (26.9)	18300 (32.5)	28800 (33.4)	31300 (32.4)
C_{24} (ng/mL)	39.2 (34.0)	97.2 (20.5)	200 (24.3)	250 (28.7)	291 (34.6)	502 (29.7)	521 (36.8)
$T_{1/2}$ (hr)	10.9 (20.8)	12.7 (25.8)	16.8 (20.1)	10.8 (32.6)	10.9 (32.8)	16.7 (30.7)	16.8 (56.4)
CL/F (L/hr)	16.9 (21.3)	16.1 (19.1)	17.3 (27.7)	26.1 (23.3)	23.8 (30.3)	23.3 (39.6)	27.8 (31.1)
Vd/F (L)	259 (12.7)	300 (40.2)	410 (25.3)	388 (15.2)	357 (27.9)	521 (23.6)	608 (29.3)

[a] T_{max} presented as median (range)

Figure 2. Mean EDP-938 Plasma Concentration-Time Profiles Following Oral Administration of Single Doses of EDP-938 (A: linear scale and B: semi-log scale)



Error bars represent standard deviation

Pharmacokinetics – MAD Phase

The PK parameters of EDP-938 are presented in Table 3 and the mean plasma concentration time profiles are shown in Figure 3

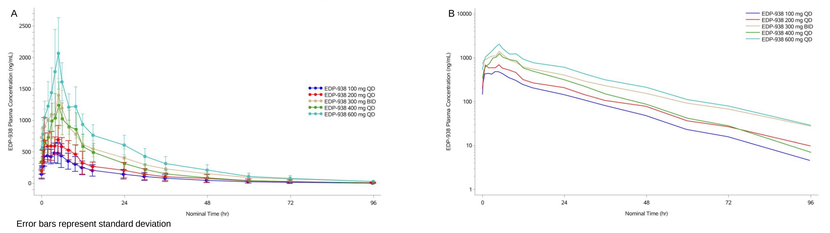
- The PK parameters on Day 1 in the MAD phase were similar to those in the SAD phase at the same doses
- EDP-938 exposure increased with increasing multiple doses
- Mean C_{24} ranged from 146-610 ng/mL following QD dosing (Day 7)
  - Mean C_{12} was approximately 618 ng/mL following 300 mg BID dosing (Day 7)
  - These concentrations are approximately 7-31x higher than the EC_{90} against RSV infected human cells
- Median T_{max} ranged from 2.0 – 5.0 hr across all dosing cohorts
- Mean half-life ranged from 12.9 – 17.6 hr across all dosing cohorts
- Little accumulation was observed from Day 1 to Day 7, with mean accumulation index (AI) ranging from 1.09 to 1.40 following QD dosing, and mean AI of 1.50 following BID dosing

Table 3. EDP-938 Day 7 Plasma PK Parameters Following Oral Administration of Multiple Doses of EDP-938 for 7 days (values presented as mean (%cv) except as noted)

PK Parameters	100 mg QD (N=6)	200 mg QD (N=6)	400 mg QD (N=6)	600 mg QD (N=6)	300 mg BID (N=6)
C_{max} (ng/mL)	595 (20.4)	871 (28.7)	1300 (21.8)	2130 (27.7)	1480 (18.1)
T_{max} (hr)[a]	3.0 (1-8)	2.0 (1-5)	5.0 (3-5)	4.5 (2-6)	5.0 (2-6)
$AUC_{0\text{-}tau}$ (ng*hr/mL)	6790 (31.4)	9360 (30.8)	15600 (24.2)	24700 (19.0)	11600 (12.8)[‡]
C_{24} (ng/mL)	146 (52.1)	209 (58.7)	315 (33.7)	610 (25.6)	618 (19.7)[†]
$T_{1/2}$ (hr)	13.2 (24.9)	15.2 (26.8)	12.9 (15.1)	15.9 (22.7)	17.6 (27.0)
CLss/F (L/hr)	16.1 (33.7)	23.2 (32.0)	27.2 (29.6)	25.0 (18.9)	26.1 (11.8)
Vss/F (L)	288 (16.9)	481 (19.4)	494 (21.3)	562 (17.9)	650 (22.7)
Accumulation Index[◊]	1.12 (22.5)	1.22 (15.9)	1.09 (13.3)	1.40 (13.1)	1.50 (23.0)

[a] T_{max} presented as median (range); [‡] mean total daily AUC = 23200 ng*h/mL; [†] represents C_{12}; [◊] Accumulation index calculated as the ratio of $AUC_{0\text{-}tau}$ of Day 7/Day 1

Figure 3. Mean Day 7 EDP-938 Plasma Concentration-Time Profiles Following Oral Administration of Multiple Doses of EDP-938 for 7 days (A: linear scale and B: semi-log scale)



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Conclusion

- EDP-938 was generally safe and well-tolerated over a broad range of single and multiple doses for up to 7 days
- EDP-938 was rapidly absorbed and EDP-938 exposure increased with increasing single and multiple dosing
- EDP-938 exhibited PK suitable for once or twice daily oral dosing and can be administered regardless of food
- The doses evaluated in this study provide mean EDP-938 exposures that were approximately 7-31x higher than the EC_{90} against RSV-infected human cells
- Data from this study support further development; EDP-938 is being evaluated in a Phase 2 Proof of Concept Challenge Study

Acknowledgments

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