EDP-323, a First-in-Class, Once-Daily, Oral L-Protein Inhibitor for the Treatment of RSV: Results from a Phase 1 Study in Healthy Subjects and Correlation with In Vitro Antiviral Activity

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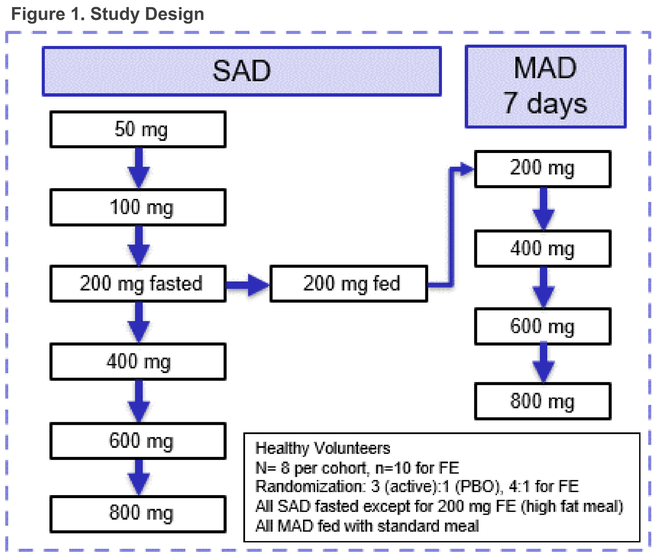
BACKGROUND

- Despite new strategies to prevent RSV, there remains an unmet need for antiviral therapy for the treatment of RSV in vulnerable populations
- EDP-323 is a first-in-class, oral, potent, and selective non-nucleoside inhibitor of the RSV large protein (L-polymerase) designed for the treatment of RSV
- Preclinical studies indicate favorable target tissue distribution of EDP-323 into lungs and alveolar macrophages without off-target brain distribution

METHODS

- EDP 323-001 is a phase 1, randomized, double-blind, placebo (PBO)-controlled study conducted to assess the safety and pharmacokinetic (PK) profile of EDP-323 during single ascending dose (SAD), multiple ascending dose (MAD), and food effect (FE) cohorts in healthy subjects (HS)

Figure 1. Study Design



Key objectives:

- Primary:
  - To evaluate the safety and tolerability of single and multiple doses of EDP-323 administered to healthy participants
- Secondary:
  - To evaluate the PK of single and multiple doses of EDP-323 in plasma and urine in healthy participants
  - To evaluate the effect of food intake on PK of EDP-323 administered as a single dose in healthy participants

- Safety and tolerability assessments:
  - Adverse events, clinical laboratories, physical examination, vital signs, and electrocardiographic evaluations
- Pharmacokinetic assessments:
  - In the SAD phase, intensive plasma PK samples were collected as follows:
    - 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 MAD phase, intensive plasma PK samples were collected as follows:
    - Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 15 hr
    - Predose on Days: 2 (24 hr), 3, 4, 5, and 6
    - 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
- EDP-323 and metabolite concentrations were measured using a validated method
- PK parameters were determined using non-compartmental methods in Phoenix WinNonlin

RESULTS

Subject Disposition and Demographics

- A total of 82 subjects were randomized; n= 50 in SAD, n=32 in MAD
- One subject discontinued dosing during the SAD 200 FE mg cohort
- The majority of subjects in the SAD phase were White or Black/African American, with a mean (range) age of 38 years (21-64) and BMI of 25 kg/m^2 (18.8-29.8)
- Demographics for the MAD phase are summarized in Table 1

Table 1. Demographics of Subjects in MAD Phase

	Placebo (fed, n=8)	200 mg QD (fed, n=6)	400 mg QD (fed, n=6)	600 mg QD (fed, n=6)	800 mg QD (fed, n=6)	Overall (n=32)
Male, n (%)	4 (50.0)	3 (50.0)	4 (66.7)	2 (33.3)	5 (83.3)	18 (56.3)
Race, n (%)						
White	6 (75.0)	4 (66.7)	1 (16.7)	4 (66.7)	3 (50.0)	18 (56.3)
Black or African American	2 (25.0)	2 (33.3)	3 (50.0)	1 (16.7)	3 (50.0)	11 (34.4)
Asian	0	0	2 (33.3)	0	0	2 (6.3)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0	0	0	0
Multiple	0	0	0	1 (16.7)	0	1 (3.1)
Other	0	0	0	0	0	0
Ethnicity, n (%)						
Hispanic or Latino	3 (37.5)	0	0	3 (50.0)	1 (16.7)	7 (21.9)
Age (y)[a]	36.4 (21, 55)	48.7 (41, 62)	39.2 (25, 53)	36.2 (22, 59)	33.5 (21, 41)	38.6 (21, 62)
BMI (kg/m^2)[a]	25.4 (20.4, 29.3)	23.3 (20.7, 25.5)	27.0 (23.8, 29.4)	27.3 (25.7, 28.6)	24.4 (22.3, 27.7)	25.5 (20.4, 29.4)

[a]presented as mean (min, max)
BMI: body mass index; QD: once daily

DISCLOSURES & ACKNOWLEDGEMENTS

- K. Mills, J. DeVincenzo, M. Rhodin, S. Rottinghaus, A. Ahmad are employees of Enanta Pharmaceuticals, Inc. and may be stockholders.
- P Yao is an employee of ICON plc, which was contracted by Enanta Pharmaceuticals, Inc. to conduct the study
- We extend our thanks to those who participated in this study and the ICON site personnel
- Thanks to Christine Marotta (Enanta) for assistance with QC of data and figures

REFERENCES

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- Rhodin, M. 2022. (19 October 2022). *EDP-323, a Small Molecule L-Protein Inhibitor in Development Against Respiratory Syncytial Virus* [Oral Presentation]. Discovery on Target: New Antivirals Conference; Boston, MA.

RESULTS

Safety

- Overall, EDP-323 was well tolerated in healthy subjects up to the highest tested dose of 800 mg once daily for 7 days
- The majority of AEs were mild, with the most frequent being headache (n=3)
- One discontinuation occurred during the SAD 200 FE cohort due to syncope, which was deemed unlikely related to EDP-323. No discontinuations occurred during the MAD phase.
- There were no severe or serious treatment emergent adverse effects (TEAEs)

Table 4: Summary of TEAEs Following Administration of EDP-323 in the MAD Phase

System Organ Class Preferred Term	Placebo (fed, n=8) n (%)	200 mg (fed, n=6) n (%)	400 mg (fed, n=6) n (%)	600 mg (fed, n=6) n (%)	800 mg (fed, n=6) n (%)	Overall (n=32) n (%)
Total Subjects with at Least One TEAE	1 (12.5)	3 (50.0)	2 (33.3)	4 (66.7)	0	10 (31.3)
Eye disorders	0	0	0	1 (16.7)	0	1 (3.1)
Conjunctivitis allergic	0	0	0	1 (16.7)	0	1 (3.1)
Gastrointestinal disorders	0	0	1 (16.7)	2 (33.3)	0	3 (9.4)
Dyspepsia	0	0	1 (16.7)	1 (16.7)	0	2 (6.3)
Frequent bowel movements	0	0	0	1 (16.7)	0	1 (3.1)
Metabolism and nutrition disorders	1 (12.5)	0	0	0	0	1 (3.1)
Hypoglycaemia	1 (12.5)	0	0	0	0	1 (3.1)
Musculoskeletal and connective tissue disorders	0	0	1 (16.7)	1 (16.7)	0	2 (6.3)
Back pain	0	0	1 (16.7)	0	0	1 (3.1)
Pain in extremity	0	0	0	1 (16.7)	0	1 (3.1)
Nervous system disorders	0	3 (50.0)	0	1 (16.7)	0	4 (12.5)
Headache	0	2 (33.3)	0	1 (16.7)	0	3 (9.4)
Syncope	0	1 (16.7)	0	0	0	1 (3.1)
Skin and subcutaneous tissue disorders	0	0	0	2 (33.3)	0	2 (6.3)
Blister	0	0	0	1 (16.7)	0	1 (3.1)
Papule	0	0	0	1 (16.7)	0	1 (3.1)

Pharmacokinetics

Pharmacokinetics: SAD Phase

- In the SAD phase (**Table 2, Figure 2, Figure 3**), EDP-323 exposure increased with ascending single doses up to 600 mg
- Exposures were similar between the 200 mg fasted and fed cohort (high fat meal), indicating no food effect
- Geometric mean $t_{1/2}$ was 12-17 hr across single dose range, supporting once daily dosing
- EDP-323 and metabolite levels in the urine were <5% of the administered dose at all dose levels

Table 2. EDP-323 Plasma PK Parameters Following Oral Administration of Single Doses of EDP-323 (values presented as geometric mean (%GCV) except T_{max} is reported as median (min-max)

PK Parameters	50 mg (fasted, n=6)	100 mg (fasted, n=6)	200 mg (fasted, n=8)	200 mg (fed, n=7)	400 mg (fasted, n=6)	600 mg (fasted, n=6)	800 mg (fasted, n=6)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	3050 (56.0)	4000 (30.2)	8480 (51.9)	8620 (47.2)	16900 (33.3)	22600 (34.2)	17500 (39.6)
C_{max} (ng/mL)	216 (38.3)	390 (23.8)	583 (27.4)	623 (34.4)	964 (27.3)	1100 (31.5)	965 (28.6)
C_{24} (ng/mL)	43 (76.4)	53 (39.0)	127 (56.8)	116 (80.0)	252 (46.3)	388 (27.4)	291 (30.3)
T_{max} (hr)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	3.5 (2.0, 5.0)	5.0 (3.0, 8.0)	3.0 (3.0, 5.0)	3.0 (2.0, 5.1)	3.0 (1.0, 5.0)
$T_{1/2}$ (hr)	14.3 (30.3)	12.4 (31.4)	13.9 (52.0)	15.4 (62.2)	12.9 (27.1)	16.6 (39.0)	13.1 (54.4)
CL/F (L/hr)	16.4 (56.0)	25.0 (30.2)	23.6 (51.9)	23.2 (47.2)	23.7 (33.3)	26.5 (34.2)	45.6 (39.6)
Vd/F (L)	337 (51.8)	448 (37.6)	472 (45.0)	517 (33.6)	441 (24.2)	634 (26.4)	860 (38.6)

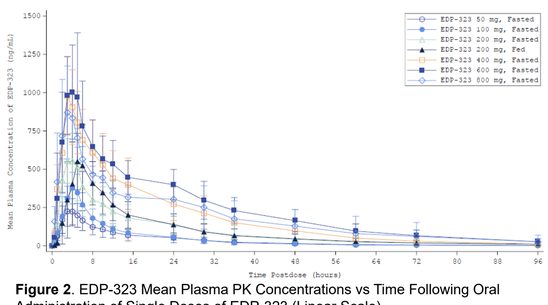

Figure 2. EDP-323 Mean Plasma PK Concentrations vs Time Following Oral Administration of Single Doses of EDP-323 (Linear Scale)

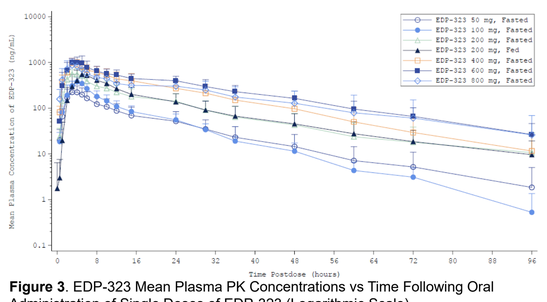

Figure 3. EDP-323 Mean Plasma PK Concentrations vs Time Following Oral Administration of Single Doses of EDP-323 (Logarithmic Scale)

Pharmacokinetics: MAD Phase

- In the MAD phase (**Table 3, Figure 4, Figure 5**), EDP-323 exposure increased with ascending multiple doses in an approximately dose-proportional manner up to 600 mg
- Geometric mean accumulation index ranged from 1.3 to 1.5 for MAD cohorts
- Geometric mean $t_{1/2}$ was 11-15 hr across the multiple dose range
- EDP-323 administered once daily for 7 days resulted in steady state C_{24} concentrations 11- to 44-fold over the protein adjusted EC_{90} (0.3 nM) determined using primary human airway epithelial cells (pHAEC) grown in a 3-dimensional cell culture system against both RSV A and B strains

Table 3. EDP-323 Day 7 Plasma PK Parameters Following Oral Administration of Multiple Doses of EDP-323 (values presented as geometric mean (%GCV) except T_{max} is reported as median (min-max)

PK Parameters	200 mg (fed, n=6)	400 mg (fed, n=6)	600 mg (fed, n=6)	800 mg (fed, n=6)
$AUC_{0\text{-}tau}$ (hr*ng/mL)	8970 (33.2)	20700 (33.6)	28300 (36.8)	27600 (35.1)
C_{max} (ng/mL)	983 (28.6)	1900 (39.4)	3000 (26.0)	3040 (20.4)
C_{24} (ng/mL)	160 (52.1)	507 (44.3)	628 (58.8)	548 (43.6)
T_{max} (hr)	5.0 (3.0, 5.0)	5.0 (3.0, 6.1)	4.0 (3.0, 5.0)	4.5 (4.0, 5.0)
$T_{1/2}$ (hr)	10.8 (16.3)	14.3 (13.2)	15.4 (26.2)	11.7 (21.4)

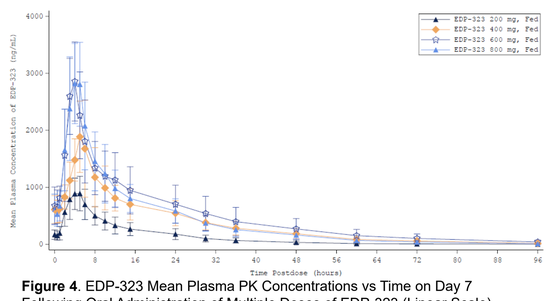

Figure 4. EDP-323 Mean Plasma PK Concentrations vs Time on Day 7 Following Oral Administration of Multiple Doses of EDP-323 (Linear Scale)

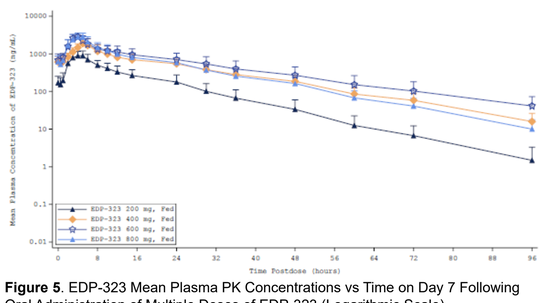

Figure 5. EDP-323 Mean Plasma PK Concentrations vs Time on Day 7 Following Oral Administration of Multiple Doses of EDP-323 (Logarithmic Scale)

CONCLUSIONS

- EDP-323 was well tolerated over a broad range of single and multiple doses up to 800 mg once daily for 7 days
- EDP-323 was rapidly absorbed, and exposures increased with ascending single and multiple doses
- EDP-323 exhibited PK characteristics supporting once daily dosing and can be administered with or without food
- EDP-323 doses ranging from 200 to 800 mg (QD) resulted in strong protein adjusted EC_{90} multiples (up to 44x), against both RSV A and B strains
- A phase 2 human challenge study is planned for 4Q 2023

ESWI Influenza Conference, 17-20 September 2023; Valencia, Spain