EDP-323, a First-in-Class, Once-Daily, Oral L-Protein Inhibitor for the Treatment of RSV: PK and PKPD Results from a Phase 2 Challenge Study in Healthy Participants Infected with RSV

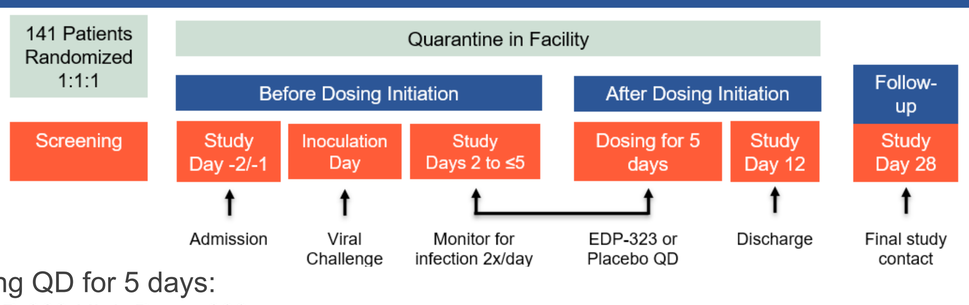
Kimberly Elmore[1], John DeVincenzo[1], Shijie Chen[1], Scott Rottinghaus[1], Alaa Ahmad[1]

[1] Enanta Pharmaceuticals, Inc., Watertown, MA.

BACKGROUND

- Despite new strategies to prevent RSV, there remains an unmet need for antiviral therapy.
- EDP-323 is an oral, potent and selective non-nucleoside inhibitor of the RSV large protein (L-polymerase) designed for the treatment of RSV.
- Safety and pharmacokinetic (PK) outcomes from the first-in-human study, EDP 323-001, supported once-daily (QD) dosing, with strong multiples over the EC_{90} against both A and B strains.
- In the 323-101 challenge study, treatment with QD EDP-323 met primary and secondary endpoints at both the low and high dose, achieving statistically significant reductions in both viral load and clinical symptoms compared to placebo in healthy participants infected with RSV.
- Here, we present PK and PK pharmacodynamic (PK/PD) results of the 323-101 study.

METHODS



- Dosing QD for 5 days:
  - EDP-323 High Dose: 600 mg
  - EDP-323 Low Dose: 200 mg (with 600 mg loading dose [LD] on Day 1)
  - Placebo
- Doses were selected based on the PK results from the EDP 323-001 study, where dosing with 600 and 200 mg EDP-323 for 7 days resulted in concentrations 44-fold and 11-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.
- Intensive plasma PK samples were collected as follows:
  - Dose 1: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15 hours post-dose
  - Dose 2-4: pre-dose
  - Dose 5: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 60, 72 hours post-dose
- EDP-323 concentrations were measured using a validated method
- PK parameters were determined using non-compartmental methods in Phoenix WinNonlin
- To evaluate PK/PD relationships, scatterplots, quartile figures, and Emax curves for plasma EDP-323 area under the curve (AUC) vs viral load AUC and total symptom score (TSS) AUC were generated

RESULTS

Mean EDP-323 Concentration vs Time on Day 1

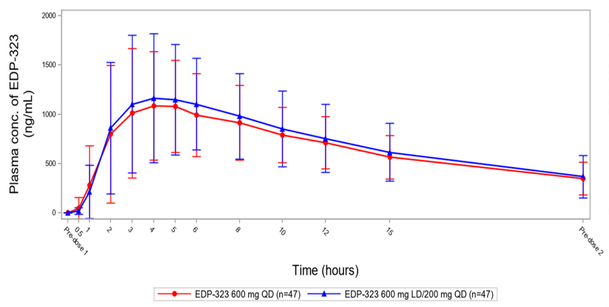


Figure 1. EDP-323 Mean Plasma PK Concentrations vs Time on Day 1 Following Oral Administration of EDP-323 (Linear Scale)

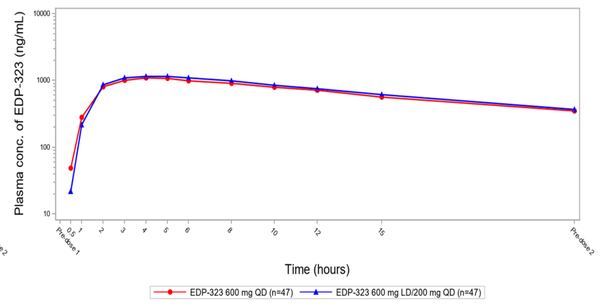


Figure 2. EDP-323 Mean Plasma PK Concentrations vs Time on Day 1 Following Oral Administration of EDP-323 (Logarithmic Scale)

Table 1. EDP-323 Plasma PK Parameters Following Oral Administration of EDP-323 on Day 1 (values presented as mean (SD) except T_{max} is reported as median (min-max)

PK Parameters	High Dose: 600 mg QD x 5 Days (Fasted, n=47)	Low Dose: 600 mg LD, 200 mg QD x 4 Days (Fasted, n=47)
$AUC_{0\text{-last}}$ (hr*ng/mL)	15626 (5983)	16704 (7269)
C_{max} (ng/mL)	1358 (590)	1454 (628)
C_{24} (ng/mL)	351 (166)	368 (216)
T_{max} (hr)	4.0 (1.0, 10.2)	3.9 (1.9, 9.9)

* For C_{24} n=46 for both dose groups

Mean EDP-323 Concentration vs Time on Day 5

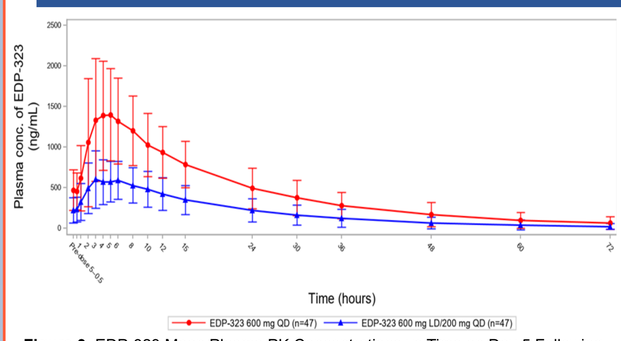


Figure 3. EDP-323 Mean Plasma PK Concentrations vs Time on Day 5 Following Oral Administration of Multiple Doses of EDP-323 (Linear Scale)

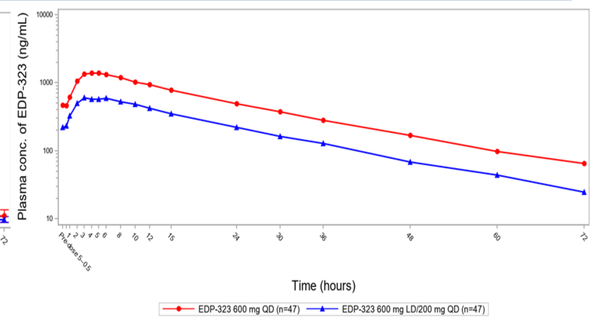


Figure 4. EDP-323 Mean Plasma PK Concentrations vs Time on Day 5 Following Oral Administration of Multiple Doses of EDP-323 (Logarithmic Scale)

Table 2. EDP-323 Plasma PK Parameters Following Oral Administration of Five Daily Doses of EDP-323 (values presented as mean (SD) except T_{max} is reported as median (min-max) *For CL/F, Vd/F, and t1/2 n=46

PK Parameters	High Dose: 600 mg QD x 5 Days (Fasted, n=47)	Low Dose: 600 mg LD, 200 mg QD x 4 Days (Fasted, n=47)
$AUC_{0\text{-tau}}$ (hr*ng/mL)	21585 (7915)	9654 (4246)
C_{max} (ng/mL)	1703 (747)	759 (323)
C_{24} (ng/mL)	493 (250)	221 (142)
T_{max} (hr)	4.8 (2.0, 9.9)	4.1 (1.0, 10.3)
$T_{1/2}$ (hr)	13.1 (4.8)	12.6 (4.6)
CL/F (L/hr)	32.4 (13.6)	24.5 (11.4)
Vd/F (L)	569 (208)	403 (143)
Accumulation Index (AI)	1.5 (0.6)	-

*For CL/F, Vd/F, and $t_{1/2}$ n=46 for both dose groups; AI was not calculated for the low dose group as the first dose is not equivalent to the last dose

RESULTS

Pharmacokinetics:

- Mean $t_{1/2}$ was 13 hours in the high and low dose groups
- The mean AI was 1.49
- EDP-323 administered once daily for 5 days resulted in steady state C_{24} concentrations 16- to 35-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
- CL/F and Vd/F at steady state were similar between dose groups, with a slightly higher CL/F and Vd/F in the high dose group.

PK/PD Analysis:

- No linear or non-linear correlations were observed between dose level and viral AUC in any of the models
- No linear or non-linear correlations were observed between dose level and TSS AUC in any of the models

Viral and Total Symptom Score AUC Scatterplots

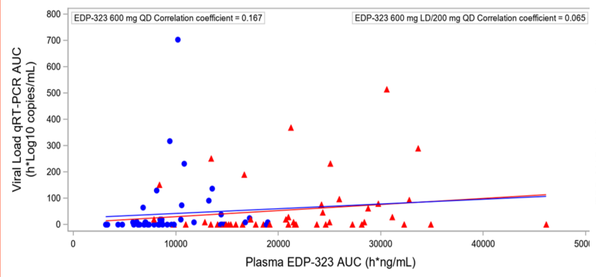


Figure 5. Viral Load qRT-PCR AUC vs Day 5 Plasma EDP-323 AUC Scatterplot Following Oral Administration of Multiple Doses of EDP-323

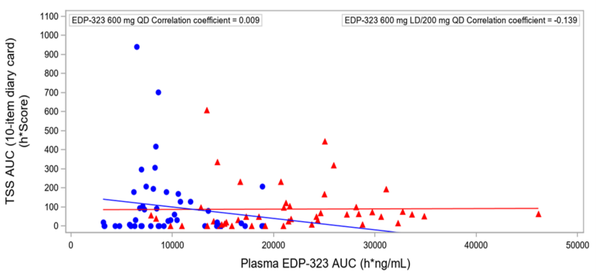


Figure 6. TSS (10-item) AUC vs Day 5 Plasma EDP-323 AUC Scatterplot Following Oral Administration of Multiple Doses of EDP-323

Viral and Total Symptom Score AUC vs Plasma EDP-323 AUC by Quartile

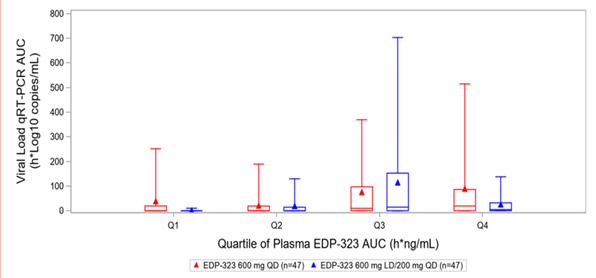


Figure 7. Viral Load qRT-PCR AUC vs Day 5 Plasma EDP-323 AUC Quartiles Following Oral Administration of Multiple Doses of EDP-323

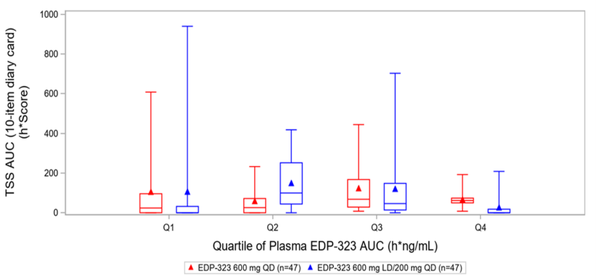


Figure 8. TSS (10-item) AUC vs Day 5 Plasma EDP-323 AUC Quartiles Following Oral Administration of Multiple Doses of EDP-323

Viral and Total Symptom Score Emax Model Plots

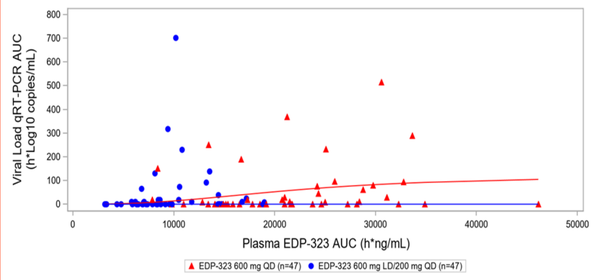
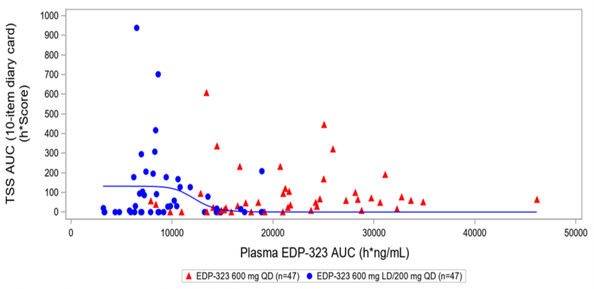


Figure 9. Viral Load qRT-PCR AUC vs Day 5 Plasma EDP-323 AUC Emax Model Plot Following Oral Administration of Multiple Doses of EDP-323



*A stable Emax model was not found for EDP-323 600 mg QD

Figure 10. TSS (10-item) AUC vs Day 5 Plasma EDP-323 AUC Emax Model Plot Following Oral Administration of Multiple Doses of EDP-323

CONCLUSIONS

- EDP-323 demonstrated pharmacokinetics similar to previous studies, with a $t_{1/2}$ of 13 h in the high and low dose arms, supportive of QD dosing.
- Mean trough plasma concentrations were maintained at 16-fold above the protein-adjusted EC_{90} with the low dose, and 35-fold above the protein-adjusted EC_{90} with the high dose.
- No PK/PD relationships were observed, consistent with robust efficacy at both doses.

ACKNOWLEDGEMENTS & DISCLOSURES

- K. Elmore, J. DeVincenzo, S. Chen, S. Rottinghaus, A. Ahmad are employees of Enanta Pharmaceuticals, Inc. and may be stockholders.
- We extend our thanks to those who participated in this study and the hVIVO site personnel
- Thanks to Christine Marotta (Enanta) for assistance with QC of data and figures

REFERENCES

- Mills, K. (2023, 17-20 September). *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* [Poster Presentation]. ESWI Influenza Conference; Valencia, Spain.
- DeVincenzo, J. (2025, 12-15 March). *EDP-323, a First-in-Class, Once-Daily, Oral Non-nucleoside L-Protein, Replication Inhibitor Antiviral for the Treatment of RSV: Results from a Phase 2a Human Viral Challenge Study* [Oral Presentation]. ISIRV 2025; Iguazu Falls, Brazil.