Pharmacokinetics of EDP-323, a Potent, Once-Daily, Oral Antiviral Treatment for Respiratory Syncytial Virus

P2844

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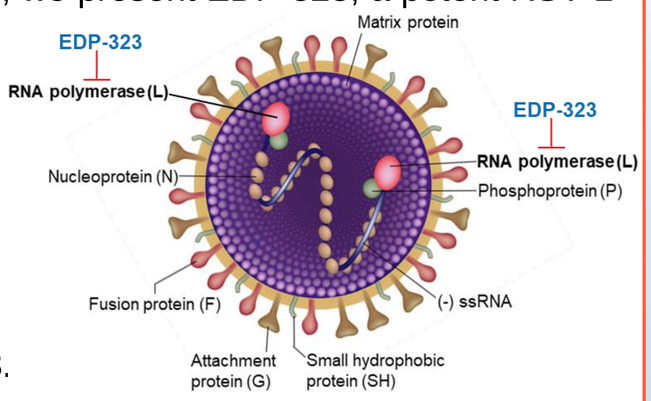
BACKGROUND

- Respiratory syncytial virus (RSV) causes substantial morbidity and mortality in infants, the elderly, and immunocompromised patients. To date, there is no broadly effective antiviral therapy approved for RSV.
- To satisfy this unmet medical need, we present EDP-323, a potent RSV L-protein inhibitor currently in clinical development as a once-daily, oral antiviral therapy for RSV.
- EDP-323 inhibits viral replication *in vitro* with an EC_{50} of 0.16 nM against RSV.[a]
- Here, we describe the preclinical pharmacokinetics (PK) of EDP-323.



Modified from "RSV Structure by Dr. Peter N. Schochet".
https://www.pedilung.com/wp-content/uploads/2016/01/respiratory-syncytial-virus-RSV.jpg

EC_{50}: half-maximal effective concentration
[a] RSV-A Long strain in a three-dimensional primary human airway epithelial cell model

METHODS

Human oral absorption and metabolic stability were tested using Caco-2 cells and human liver microsomes, respectively. The PK profile of EDP-323 was determined in mice, rats, and dogs following a single intravenous (IV) dose of 5 mg/kg or oral (PO) dose of 25 mg/kg. Human PK was predicted based on preclinical *in vivo* data and ADME properties.

RESULTS

A. Predicted high human oral absorption and low plasma clearance

Compound	P_{app} (10^{-6} cm/s)		Efflux Ratio (B-A P_{app} / A-B P_{app})	Plasma clearance CL_p (L/h/kg)
	A-to-B	B-to-A		
EDP-323	16.1	25.8	1.6	0.2

P_{app} = permeability coefficient measured in human colon Caco-2 cells; A = apical side; B = basal side.

B. Excellent oral bioavailability and plasma exposure across multiple species

Compound 25 mg/kg PO	Species	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg•h/mL)	F (%)
EDP-323	Mouse	3.4	7.1	34.8
	Rat	7.2	34.9	70.4
	Dog	4.3	48.0	50.5

Oral dosing formulation: 0.5% Methylcellulose (MC) in water; F(%) = oral bioavailability; $AUC_{0-\infty}$ = area under the curve from zero to infinity time; C_{max} = maximum observed concentration.

C. Good lung tissue distribution with no off-target distribution to brain

Compound	Species	Tissue / Plasma AUC Ratio	
		Lung	Brain
EDP-323	Mouse	1.5	0.03
	Rat	0.8	0.03

Oral dose: 25 mg/kg in mice and 10 mg/kg in rats.

ACKNOWLEDGEMENT

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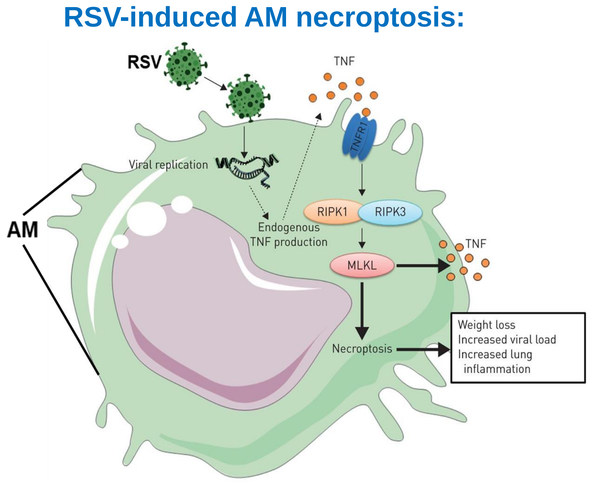
Financial Disclosure: All authors are Enanta employees.

RESULTS (continued)

D. Favorable penetration into lung alveolar macrophages (AMs) in rats

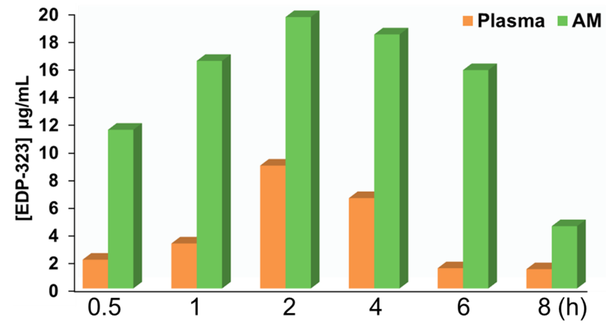
RSV-induced AM necroptosis:



TNF: tumor necrosis factor; RIPK: receptor-interacting protein kinase; MLKL: mixed-lineage kinase domain-like protein.

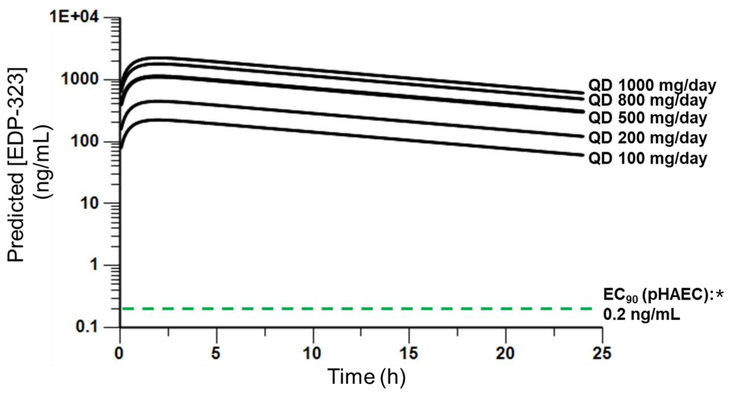
Modified figure from "Leonardo Duarte Santos et al. Eur Respir J 2021;57:2003764".

AMs: the first line of defense against respiratory infection



Compound 25 mg/kg, PO	Plasma		AM		AUC Ratio: AM / Plasma
	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	
EDP-323	9.1	46.2	29.1	173.1	3.7

E. Projected once-daily (QD) oral efficacious dose in humans



EDP-323 is projected to have a long half-life of 11 hours with an efficacious dose of 100 mg once-daily (QD) in humans.

QD Dose (mg/day)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (µg•h/mL)	C_{24} Fold over EC_{90} (Plasma)*	C_{24} Fold over EC_{90} (Lung AM)
100	11	223	4	368	1362
200	11	446	8	731	2705
500	11	1115	21	1824	6749
800	11	1783	33	2923	10815
1000	11	2229	42	3654	13520

*EC_{50} (0.16 nM) and EC_{90} (0.27 nM) against RSV-A long strain in pHAEC from the presentation: "EDP-323, a Small Molecule L-Protein Inhibitor in Development Against Respiratory Syncytial Virus", Discovery on Target: New Antivirals Conference, Boston, MA, Oct 19th, 2022.

CONCLUSIONS

- EDP-323 displayed excellent bioavailablity in preclinical species with low plasma clearance.
- Our data showed favorable target tissue distribution in the lungs and AM without off-target distribution to the brain.
- Human PK projection predicted with a once-daily 100mg oral dose with desired antiviral efficacy.
- Favorable preclinical PK properties support further clinical development of EDP-323 as a novel treatment for RSV infection.
- A Phase 1 clinical trial of EDP-323 in healthy volunteers is ongoing (ClinicalTrials.gov Identifier NCT05587478).