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Preclinical Pharmacokinetic and Pharmacodynamic Characterization of EDP-938, a Novel and Potent Non-Fusion Replication Inhibitor of Respiratory Syncytial Virus (RSV)

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ABSTRACT

Background: Respiratory syncytial virus (RSV) infection presents a significant health challenge in young children, the elderly, and immunocompromised patients. To date, there are no effective treatments available. EDP-938 was designed to meet this unmet medical need and is currently in Phase 2 clinical trials. Herein we report its preclinical pharmacokinetic (PK) and pharmacodynamic (PD) properties**. Method:** The pharmacokinetics of EDP-938 following single intravenous and oral doses were determined in mice, rats, dogs, and monkeys. *In vitro* cellular permeability and metabolic stability were assayed using Caco-2 cells and human liver microsomes, respectively. *In vivo* pharmacodynamic efficacy of EDP-938 was conducted in an African green monkey model, in which animals experimentally challenged with RSV were orally dosed twice daily with 100 mg/kg EDP-938 for 6 days starting 24 hours prior to infection. **Results:** EDP-938 was well absorbed in the preclinical species with oral bioavailability values ranging from 27.1% in dogs to 35.4% in mice, 35.7% in rats, and 39.5% in monkeys, after a single oral dose when formulated in 0.5% methylcellulose. EDP-938 showed a moderate *in vitro* permeability of 3.6 x 10^{-6} cm/sec in Caco-2 cells. Based on the outcome of these absorption studies, EDP-938 was projected to have good oral absorption in humans. EDP-938 had low intrinsic clearance of 5 µL/min/mg in human liver microsomes. Moreover, EDP-938 demonstrated potent antiviral efficacy in an African green monkey model of RSV infection. In untreated monkeys the RSV RNA viral load in the bronchoalveolar lavage fluid peaked at 10^6 copies/mL on day 5 post infection, by comparison in animals treated with EDP-938 the viral load was below the limit of detection by day 3 post infection. The PK/PD modeling suggested that plasma trough concentrations ≥10 x EC_{90} led to >4-log viral load reduction in EDP-938-treated monkeys. **Conclusion:** The favorable preclinical PK and PD properties of EDP-938 support its further clinical development as a novel treatment for RSV infection.

INTRODUCTION

- ❖EDP-938, a novel and potent non-fusion replication inhibitor of RSV, is currently in Phase 2 clinical development for the treatment of RSV infection.
- ❖EDP-938 achieved highly statistically significant ($p<0.001$) reductions in RSV viral load and RSV-associated clinical symptoms compared to placebo in the Phase 2a RSV challenge study in healthy adults[1].

METHOD

***In Vitro* Metabolic Stability**

- EDP-938 or control (1 µM) incubated with liver microsomes (1 mg/mL) in PBS (100 mM, pH 7.4), $MgCl_2$ (2 mM), EDTA (1 mM) and NADPH (2 mM) at 37 °C.
- Samples were collected at 0, 5, 10, 20, 30, 45 and 60 mins for LC-MS/MS and Intrinsic clearance calculation.

***In Vivo* Pharmacokinetics**

- IV dose: 2 - 5 mg/kg; PO dose: 10 - 25 mg/kg
- PO formulation: 0.5% methylcellulose in water

***In Vivo* Efficacy in African Green Monkeys (AGMs)**

- AGMs were inoculated with $2x10^5$ PFU of RSV A2 on Day 0. EDP-938 (100 mg/kg BID, n=4) or vehicle control (n=4) was given orally for 6 days starting 24 hours prior to infection.
- Samples were taken on Days 1, 3, 5, 7, 11 and 15 through bronchoalveolar lavage (BAL) and nasopharyngeal (NP) swab to measure RSV levels.

RESULTS

A. EDP-938 *In Vitro* Metabolic Stability

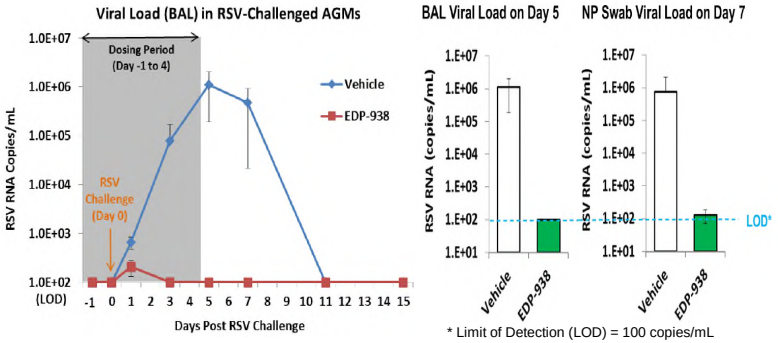
Cl_{int}, *in vitro* (µL/min/mg)				
Human	Monkey	Dog	Rat	Mouse
5.0	18.3	5.0	42.8	11.2

RESULTS (continued)

B. EDP-938 Preclinical Pharmacokinetics Across Different Species

Species	Route	Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	V_z (L/kg)	CL (L/hr/kg)	$AUC_{0-\infty}$ (µg·hr/mL)	F (%)
Mouse	*i.v.*	5	3.79	--	0.81	1.13	0.97	5.17	--
	p.o.	25	3.18	1.0	2.54	--	--	9.14	35.4
Rat	*i.v.*	2	0.98	--	1.06	3.66	2.38	0.84	--
	p.o.	10	0.47	0.5	1.75	--	--	1.50	35.7
Monkey	*i.v.*	5	3.74	--	4.15	4.65	0.77	6.54	--
	p.o.	25	1.05	6.0	5.33	--	--	12.91	39.5
Dog	*i.v.*	5	3.91	--	2.46	2.07	0.20	29.02	--
	p.o.	25	2.82	4.0	5.67	--	--	39.30	27.1

C. EDP-938 *In Vivo* Efficacy in AGMs



* Limit of Detection (LOD) = 100 copies/mL

RESULTS (continued)

D. EDP-938 Steady State Plasma Trough Concentrations in AGMs

AGM #	Plasma C_{12} (ng/mL)	Fold EC_{90}
#1	580	10.5
#2	526	9.5
#3	1150	20.7
#4	994	17.9
Average	812.5 ± 307.1	14.6 ± 5.5

EDP-938 *in vitro* EC_{90} = 55.5 ng/mL against RSV A2 in Vero cells

CONCLUSIONS

- EDP-938 was well absorbed in the preclinical species with low intrinsic clearance in human liver microsomes.
- EDP-938 demonstrated potent antiviral efficacy in an AGM RSV infection model.
- The PK/PD modeling suggested that EDP-938 plasma trough concentrations ≥10x RSV EC_{90} were associated with >4-log RSV viral load reduction in EDP-938-treated AGMs.
- The favorable preclinical PK and PD properties of EDP-938 support its further clinical development as a novel treatment for RSV infection.

[1] Coakley, *et.al.* "EDP-938, a Novel RSV N-Inhibitor, Administered Once or Twice Daily Was Safe and Demonstrated Robust Antiviral and Clinical Efficacy in a Healthy Volunteer Challenge Study", #LB6, IDWeek™ 2019