

EDP-235, A Potential Oral, Once-Daily Antiviral Treatment and Preventative for COVID-19

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INTRODUCTION

- Globally, over 230 million cases of COVID-19 have been reported since its emergence in late 2019 with nearly 5 million deaths¹.
- To date, there are no approved oral antiviral therapies that can be administered to a patient early in the course of the disease.
- Here, we describe the preclinical virology and pharmacokinetics (PK) of EDP-235, a novel and potent SARS-CoV-2 3C-like protease (3CLpro) inhibitor under development as a once-daily oral antiviral therapy for COVID-19.

METHODS

- Biochemical activity of EDP-235 against coronavirus proteases was determined in fluorescence resonance energy transfer assays.
- Antiviral activity was evaluated in Vero E6 cells or primary human airway epithelial cells (pHAEC) infected with the SARS-CoV-2 or a SARS-CoV-2 replicon assay in Huh-7 cells.
- Human oral absorption and metabolic stability were tested using Caco-2 cells and human liver microsomes, respectively.
- To determine the PK profile, rats were dosed orally with 10 or 25 mg/kg of EDP-235 and plasma and tissue drug levels were analyzed by LC/MS/MS.
- Human PK was predicted based on allometric scaling.

RESULTS

1. EDP-235 is a highly potent 3CLpro inhibitor and retains antiviral activity against SARS-CoV-2 variants

Assay	Lineage	Potency (nM)
Biochemical Activity	A	5.8 ± 3.7
	B.1.1.318 (T21I)	2.0 ± 0.1
	B.1.351 (K90R)	2.8 ± 0.9
	B.1.617.3 (A194S)	5.7 ± 0.5
	C.36.3 (G15S)	4.7 ± 2.5
	P.2 (L205V)	3.4 ± 1.0
Cellular Activity	SARS-CoV-2 Replicon (EC ₅₀)	4.5 ± 1.7
	Vero E6, CPE (EC ₅₀)	5.1 ± 0.3 ^{1,3}
	pHAEC, Viral yield + qPCR (EC ₉₀)	33 ²
	Vero E6, Viral yield (EC ₅₀)	12.1 ± 5.6
	Vero E6, Viral yield (EC ₅₀)	46
	Vero E6, Viral yield (EC ₅₀)	44

FRET = fluorescence resonance energy transfer; CPE = cytopathic effect; P-gpi = P-glycoprotein inhibitor CP-100356 (2 μM); pHAEC = primary human airway epithelial cells; qPCR = quantitative polymerase chain reaction

¹EC₅₀ of Pfizer oral 3CLpro inhibitor PF-07321332 (Owen DR, et al. medRxiv, 2021) = 74.5 nM; ²EC₅₀ of PF-07321332 = 181 nM
³EC₅₀ of Shionogi oral 3CLpro inhibitor S-217622 (Shionogi R&D Day 2021, 29 Sep-21) = 370 - 500 nM

Reference: ¹<https://covid19.who.int/>
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RESULTS

2. EDP-235 demonstrates potent antiviral activity against other human coronaviruses

Assay	Virus (Isolate)	Potency (nM)
Biochemical Activity	HCoV-229E	5.4 ± 0.9
	SARS-CoV	1.9 ± 0.3
	MERS-CoV	70 ± 20
Cellular Activity	HCoV-OC43	57 ± 24
	HCoV-NL63	6.1 ± 1.8
	HCoV-229E	3.6 ± 1.2 ¹
	MERS-CoV (EMC/2012)	130
	SARS-CoV (Toronto-2) +P-gpi	24 ²

¹EC₅₀ of Pfizer oral 3CLpro inhibitor PF-07321332 (Owen DR, et al. medRxiv, 2021) = 190 nM; ²EC₅₀ of PF-07321332 = 151 nM

3. EDP-235 has high human oral absorption potential and low plasma clearance

Compound	P _{app} (10 ⁻⁶ cm/s)		Plasma Clearance CL _p (mL/min/kg)
	A-to-B	B-to-A	
EDP-235	24.8	19.4	0.2
PF-07321332 (oral)	2.4	12.4	5.6*

P_{app} = permeability coefficient measured in human colon Caco-2 cells; CL_p = human plasma clearance calculated from human liver microsomal stability; *CL_p of 6 mL/min/kg was reported by Pfizer at the 2021 ACS Meeting

4. EDP-235 has favorable intracellular uptake into human target tissue cells

Compound	Intracellular / Extracellular Concentration Ratios in Human Cell Lines				
	Lung Epithelial	Kidney Epithelial	Hepatocyte	Monocyte	Macrophage
EDP-235	5.6 ± 0.2	18.0 ± 0.8	23.3 ± 2.0	22.7 ± 1.4	30.5 ± 2.9
PF-07321332	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.5 ± 0.3	1.2 ± 0.2

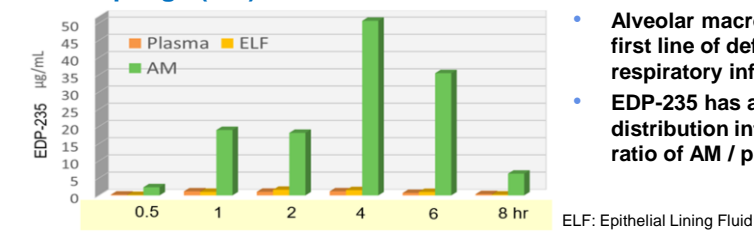
5. EDP-235 displays excellent oral bioavailability and target tissue distribution in rats

Species	Compd.	Plasma PK 25 mg/kg p.o.			AUC Ratios over Plasma			
		C _{max} (μg/mL)	AUC _{0-∞} (μg-h/mL)	F (%)	Lung	Liver	Kidney	Heart
Rats	EDP-235	1.9	19.0	95.0	4.1	18.9	6.3	4.7
	PF-07321332	2.5	4.9	30.6*	0.8	5.4	1.2	0.9

Single dose PK; p.o. formulation: 0.5% Methylcellulose (MC) in water; F(%) = oral bioavailability; AUC = area under the curve; *Oral bioavailability of 31% was reported by Pfizer at the 2021 ACS meeting

RESULTS

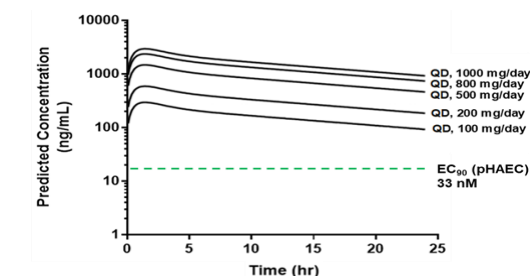
6. EDP-235 demonstrates excellent penetration into lung alveolar macrophage (AM) in rats



- Alveolar macrophages are the first line of defense against respiratory infection.
- EDP-235 has an excellent distribution into AM with AUC ratio of AM / plasma = 28.4.

7. EDP-235 is projected to have an efficacious dose of 100 – 500 mg once-daily in humans

QD Dose (mg)	t _{1/2} (hr)	AUC ₀₋₂₄ (μg-h/mL)	C _{max} (ng/mL)	C ₂₄ Fold over EC ₉₀ (Plasma)	C ₂₄ Fold over EC ₉₀ (Intracellular lung AM)
100	16	4	296	5	140
200	16	8	593	10	280
500	16	20	1482	25	700
800	16	32	2371	41	1,148
1000	16	40	2963	51	1,428



- EDP-235 is projected to have a long half-life of 16 hours with an efficacious dose of 100 - 500 mg once-daily (QD) in humans.

CONCLUSIONS

- EDP-235 is a novel oral SARS-CoV-2 3CL protease inhibitor with nanomolar potency against currently circulating COVID-19 variants as well as other known human coronaviruses.
- EDP-235 has an optimized PK profile with targeted tissue penetration and has the potential for convenient once-daily oral dosing without ritonavir boosting.
- The combination of potent antiviral activity with a favorable PK profile positions EDP-235 as a potentially best-in-class oral therapy for the treatment and prevention for COVID-19.
- Clinical trials with EDP-235 are planned to start in early 2022.