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 deaths[1].
- 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	3CLpro FRET (IC_{50})	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})	A	**4.5** ± 1.7
	Vero E6, CPE (EC_{50})	A (+P-gpi)	**5.1** ± 0.3 [1,3]
	pHAEC, Viral yield + qPCR (EC_{90})	B.1	**33** [2]
	Vero E6, Viral yield (EC_{50})	B.1	**12.1** ± 5.6
	Vero E6, Viral yield (EC_{50})	B.1.1.7	**46**
	Vero E6, Viral yield (EC_{50})	B.1.351	**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

[1] EC_{50} of Pfizer oral 3CLpro inhibitor PF-07321332 (Owen DR, et al. medRxiv, 2021) = 74.5 nM; [2] EC_{50} of PF-07321332 = 181 nM
[3] EC_{50} 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	3CLpro FRET (IC_{50})	HCoV-229E	**5.4** ± 0.9
		SARS-CoV	**1.9** ± 0.3
		MERS-CoV	**70** ± 20
Cellular Activity	HCT-8, qPCR (EC_{50})	HCoV-OC43	**57** ± 24
	LLC-MK2, qPCR (EC_{50})	HCoV-NL63	**6.1** ± 1.8
	MRC-5, CPE (EC_{50})	HCoV-229E	**3.6** ± 1.2 [1]
	Vero 76, Viral yield (EC_{90})	MERS-CoV (EMC/2012)	**130**
	Vero E6, CPE (EC_{50})	SARS-CoV (Toronto-2) +P-gpi	**24** [2]

[1] EC_{50} of Pfizer oral 3CLpro inhibitor PF-07321332 (Owen DR, *et al.* medRxiv, 2021) = 190 nM; [2] EC_{50} 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
	A-to-B	B-to-A	(mL/min/kg)
EDP-235	**24.8**	19.4	**0.2**
PF-07321332 (oral)	2.4	12.4	5.6*

P_{aap} = 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

Intracellular / Extracellular Concentration Ratios in Human Cell Lines					
Compound	**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

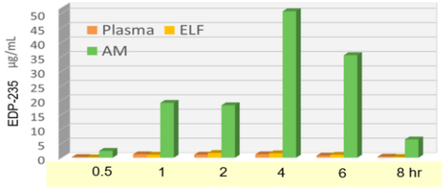
5. EDP-235 displays excellent oral bioavailability and target tissue distribution in rats

Species	Compd.	Plasma PK 25 mg/kg *p.o.*			AUC Ratios over Plasma			
		C_{max} (µg/mL)	$AUC_{0-\infty}$ (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

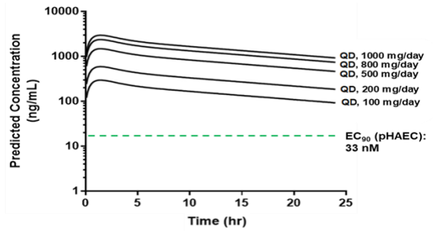


- **Alveolar macrophages are the first line of defense against respiratory infection.**
- **EDP-235 has an excellent distribution into AM with AUC ratio of AM / plasma = 28.4.**

ELF: Epithelial Lining Fluid

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.**