EDP-235, a Potent and Once-Daily Oral Antiviral, Demonstrates Excellent Penetration into Macrophages and Monocytes with the Potential for Mitigation of Cytokine Storm in COVID-19 Patients

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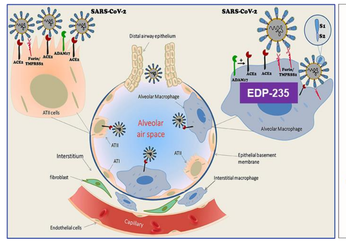
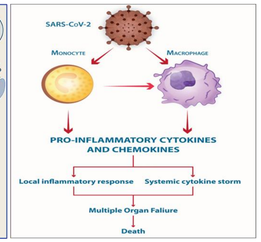
BACKGROUND

Macrophages, including lung alveolar macrophages (AM), and monocytes are the first line of defense against SARS-CoV-2. Several reports have suggested that SARS-CoV-2 can hijack AM and monocytes for replication and viral spread, which may, in turn, drive the cytokine storm associated with severe COVID-19 [1-4].

Herein, we describe one of many advantageous features that EDP-235, a novel and potent SARS-CoV-2 3C-like protease (3CLpro) inhibitor (EC_{50}: 5.1nM) [5] under development as a once-daily oral antiviral therapy for COVID-19, displays - excellent penetration into macrophages and monocytes.





Modified from Front. Immunol., 05 June 2020 | https://doi.org/10.3389/fimmu.2020.01312 & Nature 606, 585–593 (2022). https://doi.org/10.1038/s41586-022-04802-1

METHODS

Intracellular uptake of EDP-235 was tested side-by-side with nirmatrelvir in rat lung AM, human monocytes and human macrophages.

To determine the *in vivo* drug distribution into lung AM, rats were dosed orally with 25 mg/kg of EDP-235 or nirmatrelvir and plasma and AM drug levels were analyzed by LC/MS/MS.

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2. Macrophages and Monocytes: “Trojan Horses” in COVID-19. Viruses 2021, 13, 2178.
3. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature 606, 585–593, 2022.
4. FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. Nature 606, 576–584, 2022.
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Financial Disclosure: All authors are Enanta Employees

RESULTS

EDP-235 is projected to have excellent oral absorption in humans

Drug	P_{app} (10^{-6} cm/s)		Efflux Ratio	Absorption Potential
	A-to-B	B-to-A		
EDP-235	**24.8**	**19.4**	**0.8**	**High**
Nirmatrelvir	2.4	12.4	5.2	Medium

P_{app} = permeability coefficient measured in human colon Caco-2 cells

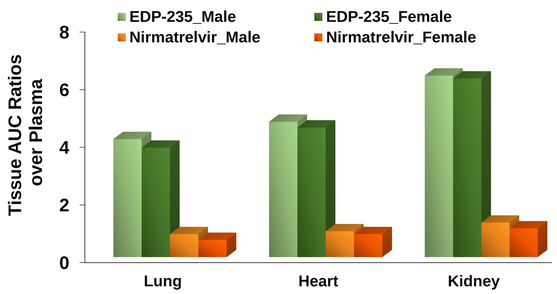
EDP-235 displayed superior plasma exposure and oral bioavailability in preclinical species

Species	Drug 25 mg/kg oral	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg-h/mL)	F (%)
Mouse	**EDP-235**	**2.8**	**10.1**	**100**
	Nirmatrelvir	1.6	2.9	26
Rat	**EDP-235**	**1.9**	**19.0**	**95**
	Nirmatrelvir	2.5	4.9	31*

Single dose PK; oral 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.

EDP-235 exhibited excellent penetration into SARS-CoV-2 target tissues

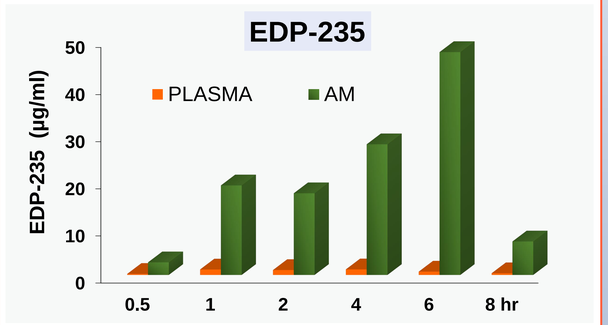
Drug	Sex	AUC Ratios over Plasma		
		Lung	Heart	Kidney
EDP-235	**M**	**4.1**	**4.7**	**6.3**
	F	**3.8**	**4.5**	**6.2**
Nirmatrelvir	M	0.8	0.9	1.2
	F	0.6	0.8	1.0

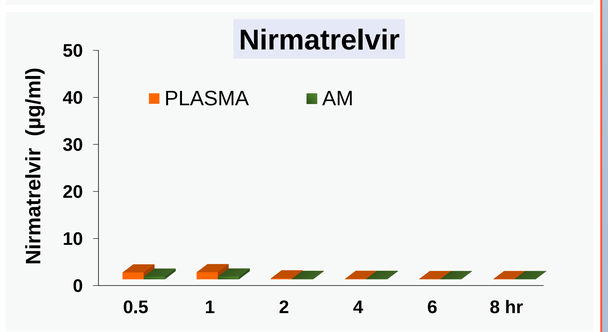


RESULTS

EDP-235 exhibited excellent penetration into lung alveolar macrophages (AM) in rats

Drug	Plasma		AM		AUC Ratio over Plasma
	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg-h/mL)	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg-h/mL)	
EDP-235	**1.2**	**9.6**	**50.7**	**272.0**	**28.4**
Nirmatrelvir	1.5	2.7	0.5	1.3	0.5



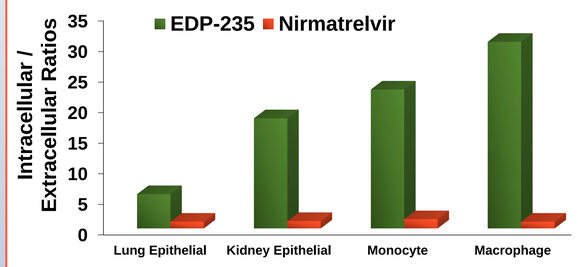


Favorable *ex vivo* and *in vivo* correlation was observed in preclinical species

Drug	Lung		Alveolar Macrophages	
	Ex Vivo	*In Vivo*	*Ex Vivo*	*In Vivo*
EDP-235	**8.7**	**4.1**	**23.6**	**28.4**
Nirmatrelvir	0.8	0.8	0.6	0.5

RESULTS

EDP-235 has superior *ex vivo* intracellular uptake into human cells, including monocytes and macrophages



EDP-235 preclinical profile suggests potential for best-in-class antiviral treatment for SARS-CoV-2 infection

Properties	EDP-235[1]	Nirmatrelvir[2]	PBI-0451[3]	S-217622[4]
Vero Cell EC_{50} (nM) (Potency)*	**5.1**	75	48	69 (Delta)
Oral Bioavailability[5]	**95%**	31 – 50%	n/a	97%
Lung Penetration[6]	**4.1**	0.8[7]	~1	0.7[7]
Projected Efficacious Dose	**200 or 400 mg QD**	300 mg/100 mg ritonavir BID	700 mg BID	375(D1)/125 (D2-5) QD

1. Jiang *et al.*, ISIRV Poster #120, Oct 19, 2021
2. Owen *et al.*, Science November 2021; Owen *et al.* ACS Spring 2021 meeting; EUA fact sheet for healthcare providers
3. Pardes ICAR Presentation March 2022
4. Tachibana, *et al.*, ISIRV oral presentation, Oct 20, 2021; Unoh, *et al.*, bioRxiv 2022; Sasaki, *et al.*, bioRxiv 2022; Yotsuyanagi, *et al.*, ECCMID oral presentation, Apr 24, 2022
5. Oral bioavailability in rats for EDP-235, nirmatrelvir, and S-217622
6. AUC lung to plasma ratio in rats (EDP-235, nirmatrelvir, and S-217622)
7. Data for nirmatrelvir and S-217622 generated by Enanta

* All potency values versus ancestral (A) lineage unless indicated

CONCLUSIONS

- **EDP-235, a novel and potent SARS-CoV-2 3CL protease inhibitor, demonstrated excellent penetration into monocytes and macrophages, including lung AM.**
- **EDP-235 has the potential to eliminate SARS-CoV-2 replication in sentinel immune cells, and thus potentially mitigating the macrophage-mediated cytokine storm in COVID-19 patients.**
- **Phase 2 Clinical trial of EDP-235 for COVID-19 treatment will initiate in Q4 of 2022.**