EDP-235, a Potent, Once-daily, Oral Antiviral, Demonstrates Excellent Penetration into SARS-CoV-2 Target Tissues, with the Potential for Mitigation of Viral Rebound in COVID-19 Patients

Y. Li, T. Z. Zang, L. Xu, D. Leonard, K. Hoang, T. Greizer, S. C. Zhang, C. Foster, M. Huang, J. Kibel, J. Klaene, K. Chan, Y. S. Or & L. J. Jiang

Enanta Pharmaceuticals, Inc., Watertown, MA 02472, USA

Enanta Pharmaceuticals

Poster # 523

BACKGROUND

COVID-19 rebound is characterized by a recurrence of symptoms or a new positive viral test after testing negative.

Up to 27% of COVID-19 patients experience viral rebound after Paxlovid (ritonavir-boosted nirmatrelvir) treatment [1-5]. Several reports suggest that viral rebound can occur if SARS-CoV-2 remains in parts of the body to which Paxlovid (specifically nirmatrelvir) has limited access [3,6-9].

Herein, we report that EDP-235, a novel and potent SARS-CoV-2 3C-like protease inhibitor [10], demonstrates superior penetration into SARS-CoV-2 target tissues in preclinical species compared to nirmatrelvir.

METHODS

To determine the *in vivo* drug distribution into SARS-CoV-2 target tissues, rats were dosed orally with 10 mg/kg of EDP-235 or nirmatrelvir, and drug concentrations in plasma and different tissues were analyzed by LC/MS/MS.

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

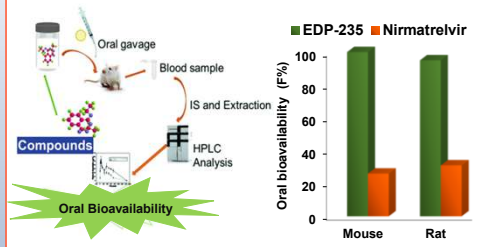
EDP-235 has superior plasma exposure and oral bioavailability in preclinical species

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.

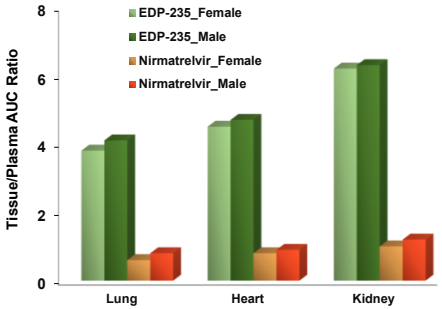
RESULTS

Oral Bioavailability in Preclinical Species



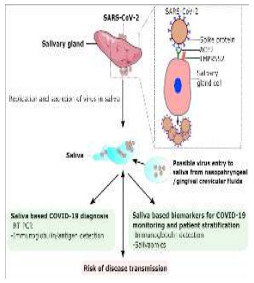
EDP-235 exhibits excellent SARS-CoV-2 target tissue distribution

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

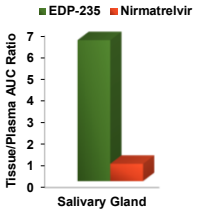


RESULTS

Penetration into Salivary Gland

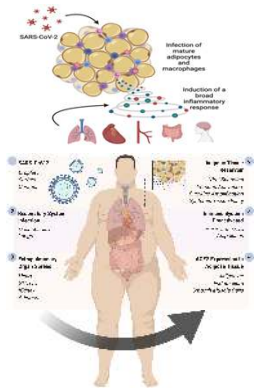


Modified from "COVID-19 salivary signature: diagnostic and research opportunities". J Clin Pathol 2021;74:344–349.

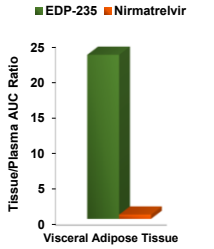


Tissue/Plasma AUC Ratio	
	Salivary Gland
EDP-235	**6.5**
Nirmatrelvir	0.8

Penetration into Adipose Tissue



Modified from "SARS-CoV-2 Infects Fat Tissue, Creates Inflammatory Storm Cloud". Stanford Medicine; Biorender.com.
Adapted from "Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019?" Obesity (Silver Spring). 2020 Jul; 28(7): 1191–1194.



Tissue/Plasma AUC Ratio	
	Visceral Adipose Tissue
EDP-235	**23**
Nirmatrelvir	0.6

RESULTS

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]	Ensitrelvir[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 mg(D1)/125 mg (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 ensitrelvir.
6. AUC lung to plasma ratio in rats (EDP-235, nirmatrelvir, and ensitrelvir).
7. Data for nirmatrelvir and ensitrelvir generated by Enanta.

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

CONCLUSIONS

- **Preferential target tissue distribution and penetration may enable EDP-235 to minimize viral rebound in COVID-19 patients as a first-line treatment.**
- **A Phase 2 clinical trial of EDP-235 for the treatment of COVID-19 is fully enrolled (ClinicalTrials.gov Identifier NCT05616728).**

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