Enanta Pharmaceuticals
Great Chemistry Cures

EDP-235, a Potent, Once-Daily Oral Antiviral Treatment for COVID-19

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on behalf of Enanta COVID-19 Research Team

Discovery on Target: New Antivirals Conference, Boston, MA. October 20th, 2022

Enanta Pipeline

		PRODUCT CANDIDATE	DISCOVERY / PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 3 / MARKET
Virology: Liver	HCV	Protease Inhibitor	Glecaprevir-containing pangenotypic 2-DAA combo (MAVYRET glecaprevir/pibrentasvir)
	HBV	Core Inhibitor	EDP-514
Virology: Respiratory	RSV	N-Protein Inhibitor	EDP-938 *RSVPEDs*
			EDP-938 *RSVTx*
			EDP-938 *RSVHR*
		L-Protein Inhibitor	EDP-323
	hMPV	Non-Fusion Inhibitor	
	COVID-19	Protease Inhibitor	EDP-235 *Phase 2 initiating in 4Q22*
Discovery or Preclinical	RSV, HBV, COVID-19, other		
For Out-license	NASH	FXR Agonists	EDP-305 (Phase 2), EDP-297 (Phase 1)

*Fixed-dose combination contains glecaprevir and AbbVie's NS5A inhibitor, pibrentasvir. Marketed by AbbVie as MAVYRET® (U.S.) and MAVIRET® (ex-U.S.).

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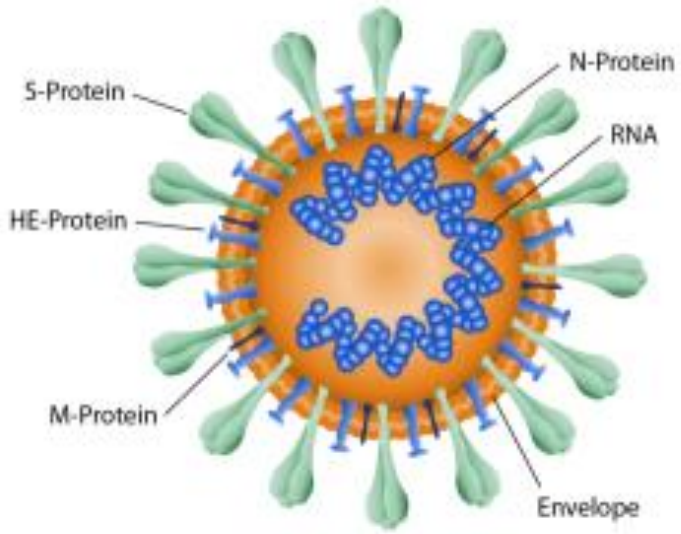
Effective Oral Treatments for COVID-19 with Minimal Drug-drug Interaction & Safety Concerns are Urgently Needed

- Globally, over **620 million cases** of COVID-19 have been reported since its emergence in October 2022 with over **6.2 million deaths**[1]
- Novel vaccines against SARS-CoV-2 were developed and approved with unprecedented speed and helped drive down the number of new cases
- However, novel variants are increasing transmissibility and the ability to evade current vaccines coupled with vaccine hesitancy and the low rate of vaccination in low- and lower-middle-income countries suggest that COVID-19 will persist
- Twice-daily oral antivirals Paxlovid (ritonavir-boosted nirmatrelvir) and Molnupiravir were approved under FDA Emergency Use Authorization (EUA)

SARS-CoV-2 Virus
Causal agent of COVID-19



[1]https://covid19.who.int/ accessed 12 Oct 2022

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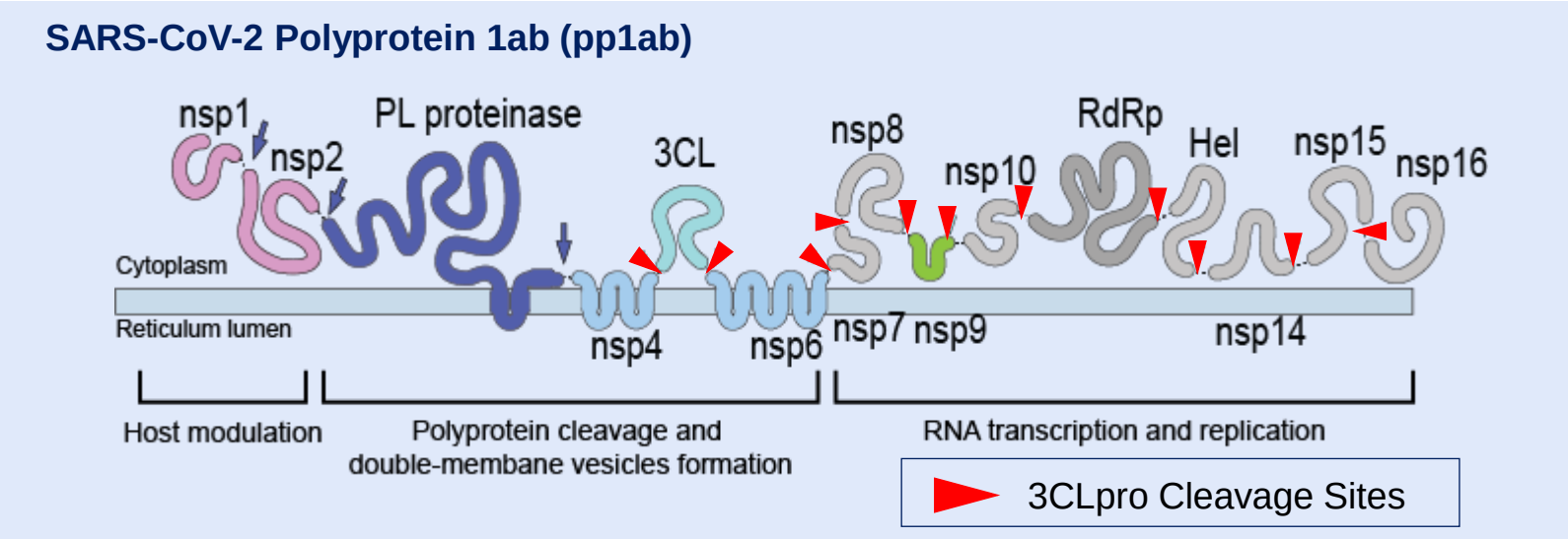
EDP-235: Oral Protease Inhibitor Specially Designed for COVID-19



- SARS-CoV-2 3CLpro (main protease, M^{pro}, nsp5) is the **primary** protease for processing viral polyproteins, which is **critical** for production of the replication-transcription complex (RTC)
- High degree of sequence homology in and around the enzyme active site of 3CLpro
- Catalytic cysteine (Cys145) of 3CLpro is common to all seven human coronaviruses

Modified from; https://viralzone.expasy.org/764?outline=complete_by_protein

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EDP-235: Highly Potent 3CLpro Inhibitor and Retains Activity Against SARS-CoV-2 Variants

Assay		Lineage	Potency (nM)
Biochemical Activity	3CLpro FRET (IC_{50})	B.1.1.529, *BA.2, BA.5,* BA.2.75* (P132H) *[Omicron]*	**4.1** ± 0.8
		A *[Original]* / *B.1.617.2 [Delta]***	**5.8** ± 3.7
		B.1.1.318 (T21I)	**2.0** ± 0.1
		B.1.351 (K90R) *[Beta]*	**2.8** ± 0.9
		B.1.351.2 (K90R/A193V) *[Beta]*	**5.4** ± 1.0
		B.1.617.3 (A194S)	**5.7** ± 0.5
		C.36.3 (G15S)	**4.7** ± 2.5
		P.2 (L205V) *[Zeta]*	**3.4** ± 1.0
Live Virus	Vero E6 +PGPi, CPE readout (EC_{90})	A *[Original]*	**11** ± 8 [1]
		B.1.617.2 *[Delta]*	**9.1** ± 2.9
		B.1.1.529 *[Omicron]*	**5.1** (n=1)

FRET: fluorescence resonance energy transfer, P-gpi: P-glycoprotein inhibitor CP-100356 (2 µM), CPE: cytopathic effect
Values average of replicate experiments except where noted
*Omicron subvariant colloquially known as 'Centaurus'
**3CLpro sequences for the ancestral A lineage and B.1.617.2 (Delta) variant are identical

[1] EC_{90} of nirmatrelvir (Owen *et al*. medRxiv, 2021) = 155 nM

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EDP-235: Highly Selective 3CLpro Inhibitor

Cysteine Proteases
- SARS CoV 2 – PLpro, 3CLpro
- Caspases 1 – 11, 14
- Cathepsins B, C, D, E, G, H, K, L, S, V
- Papain, Calpain 1

Serine Proteases
- Trypsin
- TMPRSS 2
- Furin

Aspartyl protease
- BACE1

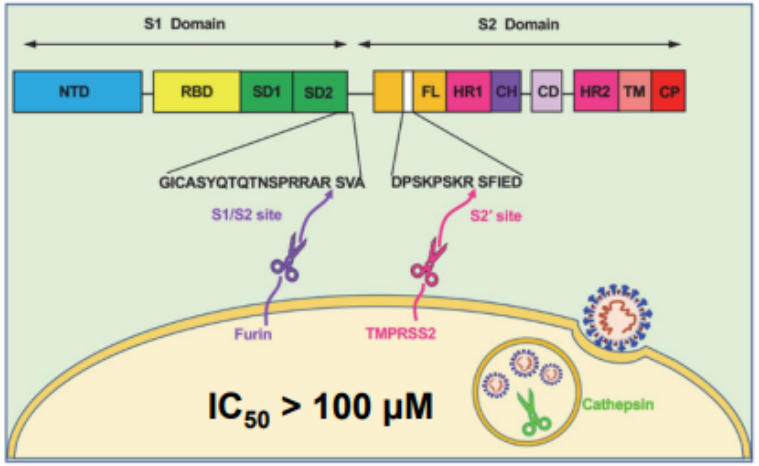
Zn metalloprotease
- ACE 1, 2

- Tested against 31 host proteases of diverse classes
- IC_{50} > 100 µM against 23 out of 31 including host proteases relevant to viral infection

Target	EDP-235 IC_{50} (µM)
Caspase 2	4.6
Caspase 3	4.2
Caspase 6	2
Caspase 7	4.7
Caspase 8	22.5
Caspase 9	4.7
Caspase 14	9
Cathepsin K	18.5
SARS-CoV-2 3CLpro	0.0058
Selectivity Index	**> 340**

Cysteine Proteases

Host proteases in viral entry/fusion



- ACE 2
- Cathepsin B
- Cathepsin L
- Trypsin
- TMPRSS 2
- Furin

1. *Signal Transduction and Targeted Therapy* (2021). 6:233
2. *Int. J. Mol. Sci.* (2020), 21(24), 9523

Balakrishnan, *et al*., Experimental Biology (2022)

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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]

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

[1] EC_{50} of nirmatrelvir (Owen, *et al.* medRxiv, 2021) = 190 nM; [2] EC_{50} of nirmatrelvir = 151 nM

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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**
nirmatrelvir	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

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EDP-235 Displays Superior Plasma Exposure and Oral Bioavailability in Preclinical Species

Species	Compound 25 mg/kg *p.o.*	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*
Monkey	**EDP-235**	0.7	7.0	**49**
	nirmatrelvir	3.6	2.1	8.5**

p.o. formulation: 0.5% methyl cellulose (MC) in water

*Reported by Pfizer at 2021 ACS Meeting

**nirmatrelvir *p.o.* formulation for monkey: 2% Tween 80/ 98% of 0.5% MC in water; https://www.medrxiv.org/content/10.1101/2021.07.28.21261232v1

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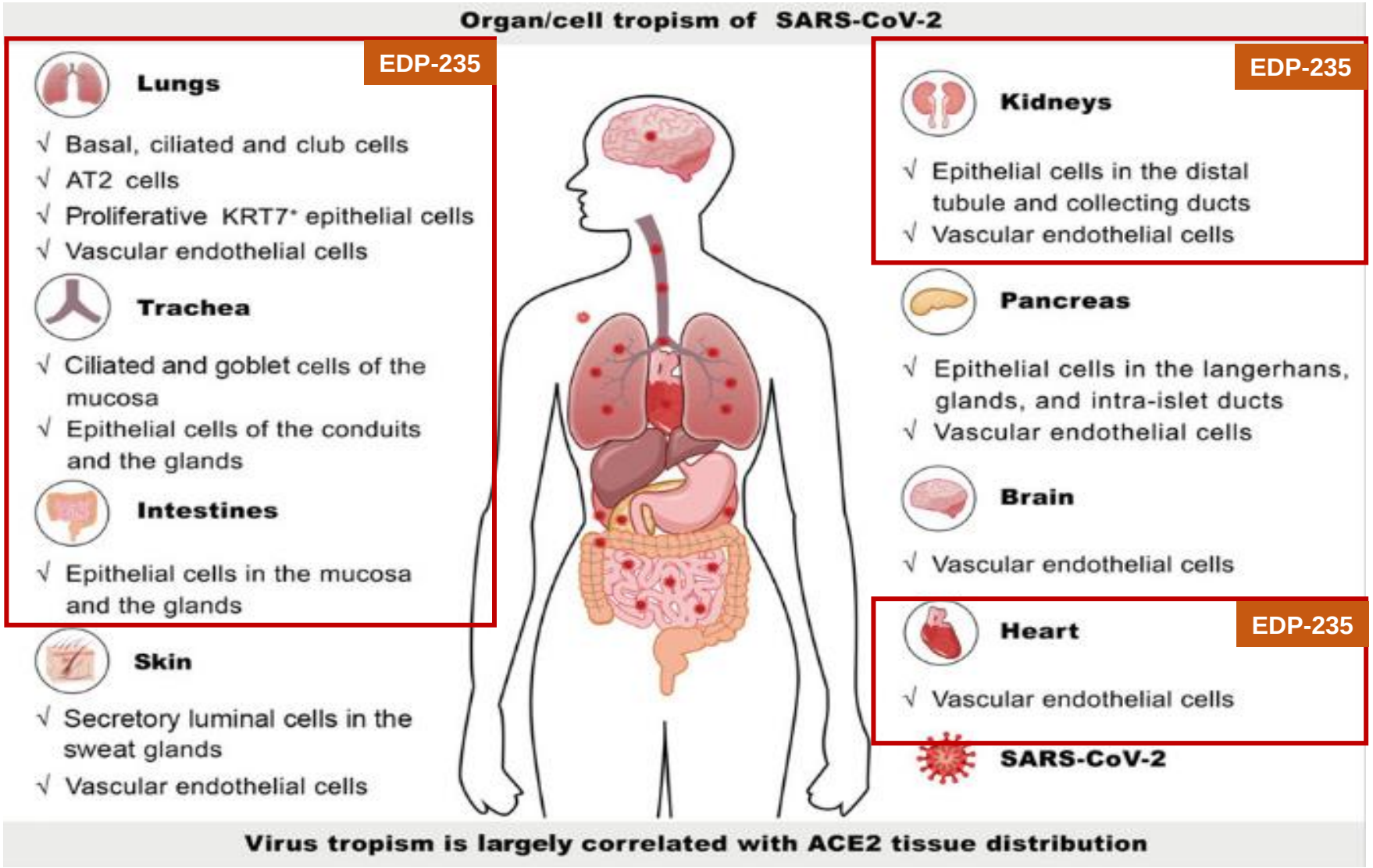
SARS-CoV-2 Tropism and EDP-235 Target Distribution



Liu, J., *et al.* Cell Discovery, 2021. 7(1): p. 17

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EDP-235: Excellent Target Tissue Distribution in Rats

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

Rat *p.o.* 10 mg/kg
p.o. Formulation: 0.5% Methyl Cellulose (MC) in water

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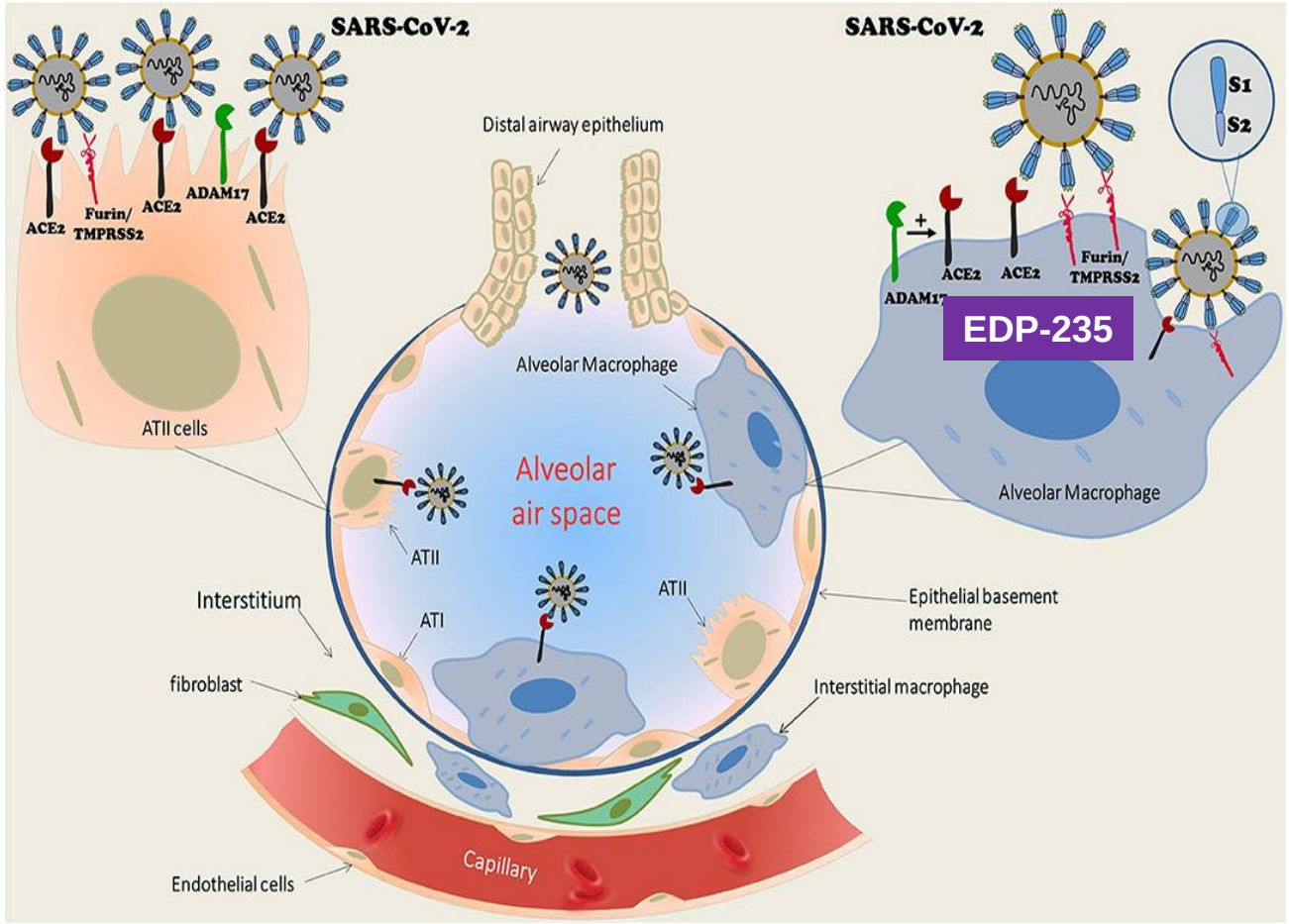
Alveolar Macrophage (AM) Plays an Important Role in SARS-CoV-2 Infection



- Alveolar macrophages (AMs) are the first line of defense against infections, including SARS-CoV-2 infection
- AM and macrophages are infected by SARS-CoV-2 via ACE2 in patients with COVID-19
- Infected macrophages could accelerate spread of SARS-CoV-2 to multiple organs, which may drive the cytokine storm, and lead to failure of multiple organs

Front. Immunol., 05 June 2020 |
https://doi.org/10.3389/fimmu.2020.01312

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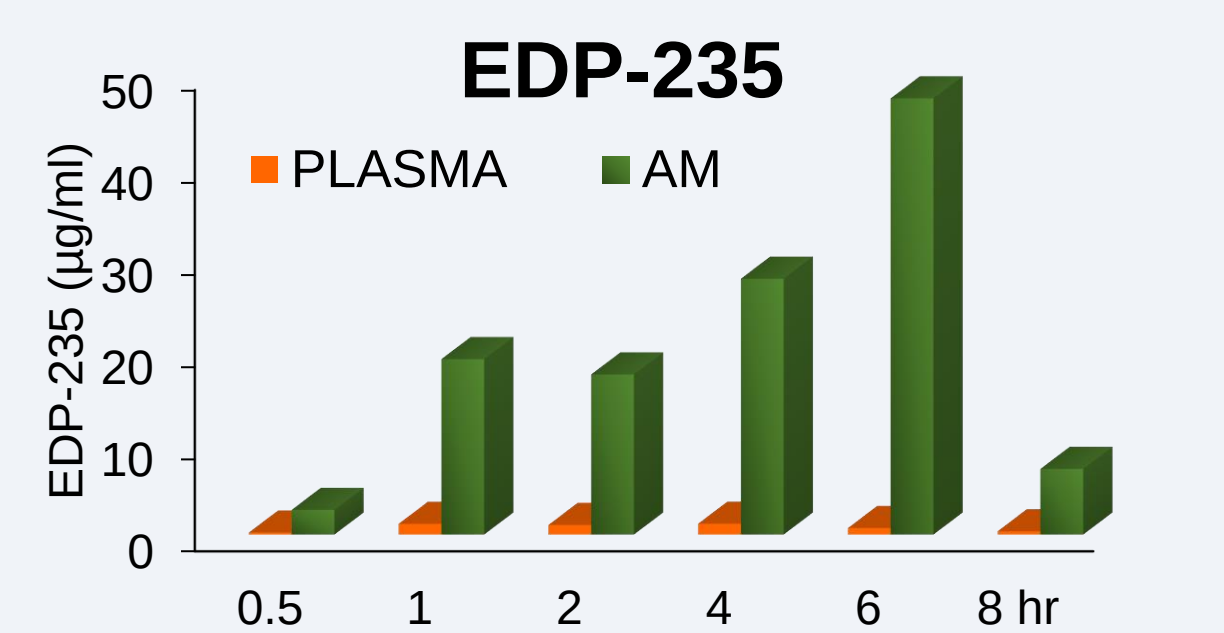
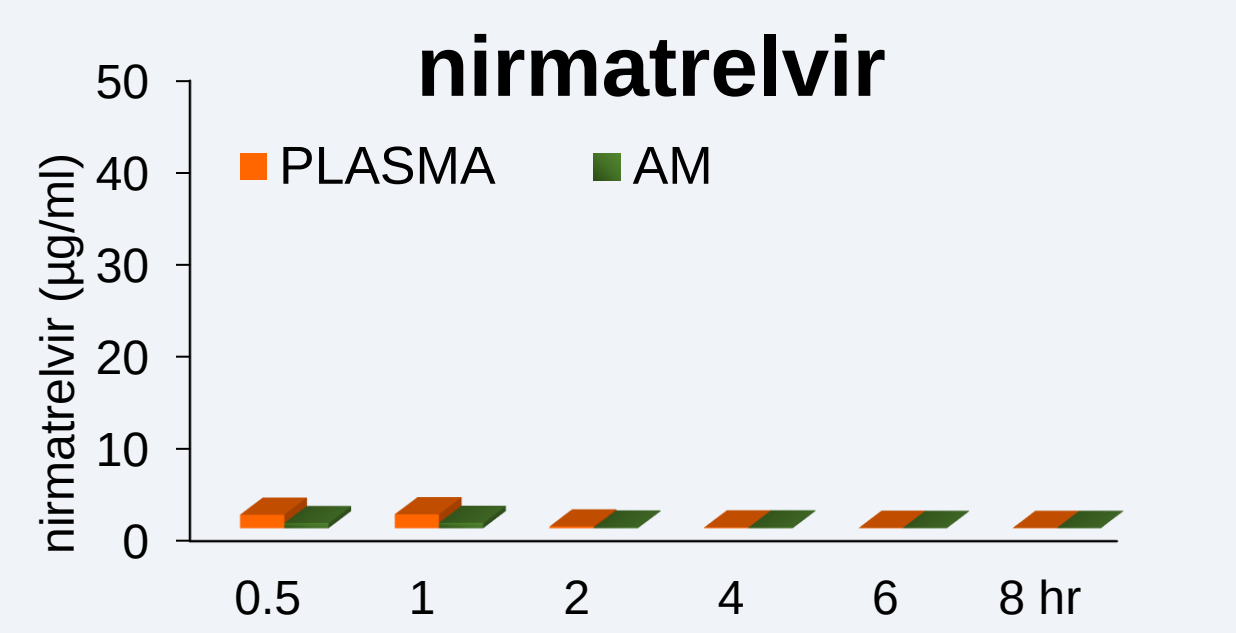
EDP-235: Excellent Penetration into Alveolar Macrophages(AM) in Rats

Compd.	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





Single Dose PK; *p.o.* Formulation: 0.5% Methylcellulose (MC) in water

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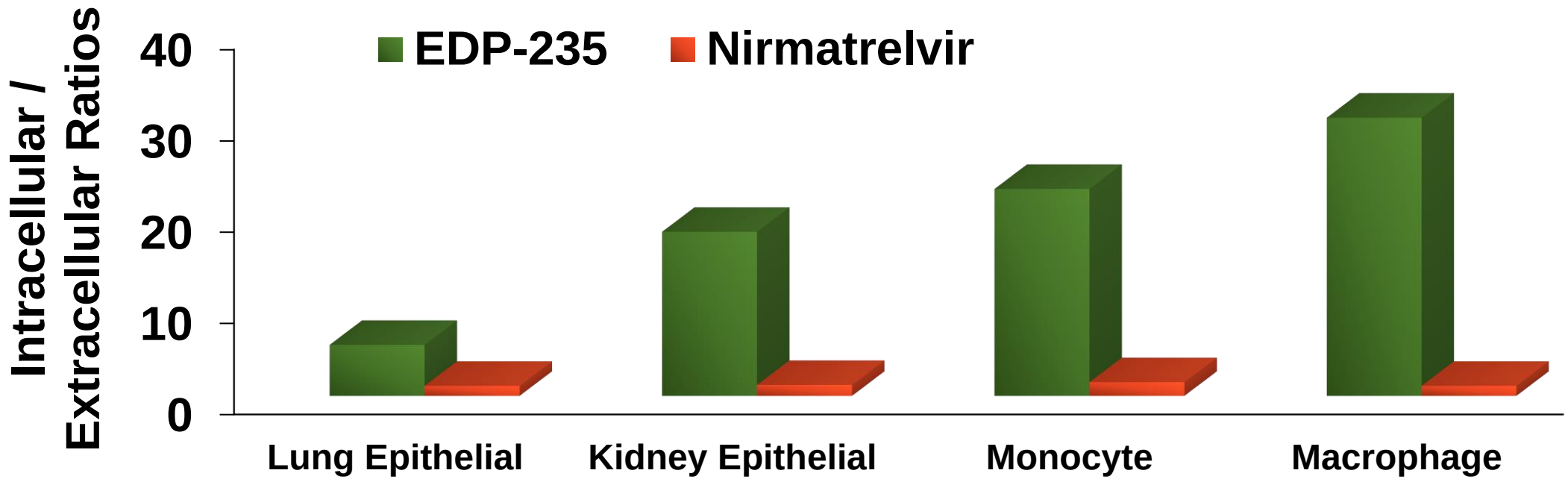
EDP-235: Superior *Ex Vivo* Intracellular Uptake into Target Cells



Intracellular / Extracellular Ratios in Human Cell Lines				
Compound	**Lung Epithelial**	**Kidney Epithelial**	**Monocyte**	**Macrophage**
EDP-235	**8.7$_{\pm 0.6}$**	**18.0$_{\pm 0.8}$**	**22.7$_{\pm 1.4}$**	**30.5$_{\pm 2.9}$**
nirmatrelvir	0.8$_{\pm 0.1}$	1.2$_{\pm 0.2}$	1.5$_{\pm 0.3}$	1.2$_{\pm 0.2}$

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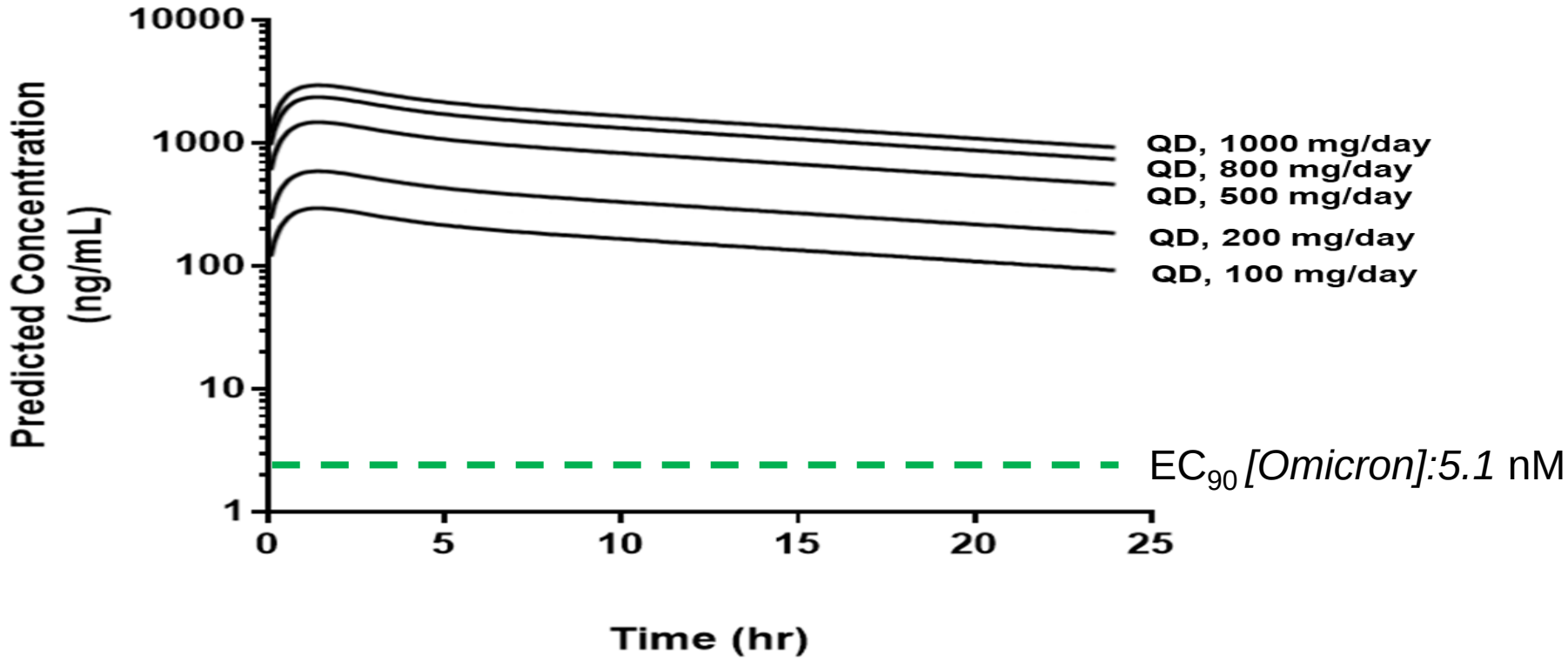
Human Efficacious Dose Prediction: 100 - 500 mg Oral QD

Considering Excellent Target Tissue Penetration



- 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

Jiang, *et al*., ISIRV Poster #120, Oct 19, 2021

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EDP-235: Phase 1 Safety, Tolerability and Pharmacokinetics

- Randomized, double-blind, placebo-controlled Phase 1 study in healthy volunteers (n=72)
  - Single and multiple ascending doses (SAD: 50 – 800 mg and MAD: 200 – 800 mg once-daily)
- Generally safe and well-tolerated up to 400 mg doses for 7 days in humans
- Excellent human plasma pharmacokinetics support efficacious doses of 200 mg or 400 mg once daily (QD) without the need for boosting (*e.g.*, ritonavir)
  - Projected to have 4x higher drug level in lung tissue compared to plasma based on preclinical animal models

Measured Plasma Drug Multiples*

Variant	200mg QD	400mg QD
Alpha	3x	6x
Omicron	7x	13x

Predicted Lung Drug Multiples*

Variant	200mg QD	400mg QD
Alpha	12x	24x
Omicron	28x	52x

  - Consistent half-life ranging from 13 to 22 hours
- EDP-235 demonstrated an excellent correlation between preclinical and clinical pharmacokinetics

*Multiples by which mean trough drug plasma levels at steady state are higher than protein adjusted EC_{90} as measured in Vero cells

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EDP-235 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, S-217622)
7. Data for nirmatrelvir and S-217622 generated by Enanta

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

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EDP-235 is a Potent 3CLpro Inhibitor with Potential as a Best-in-Class Antiviral Treatment for SARS-CoV-2 Infection

- Novel, oral, directing–acting antiviral specifically designed to target the SARS-CoV-2 protease
- Nanomolar potency against emerging SARS-CoV-2 variants (including Delta & Omicron) with high barrier to resistance observed in multiple cellular models
- Generally safe and well-tolerated up to 400 mg doses for 7 days in humans
- Good distribution into key target tissues providing the potential to minimize post-treatment viral rebound and/or possible viral replication persistence linked to long COVID
- Phase 2 clinical trial of EDP-235 for COVID-19 treatment will initiate in 4Q of 2022

Emerging data support a convenient EDP-235 dosing regimen, targeting one pill, once-daily effective against COVID-19 variants of concern

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Acknowledgements

Enanta Pharmaceuticals, Inc.'s SARS-CoV-2 Team:

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Thank you!

Questions?

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