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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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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
- 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

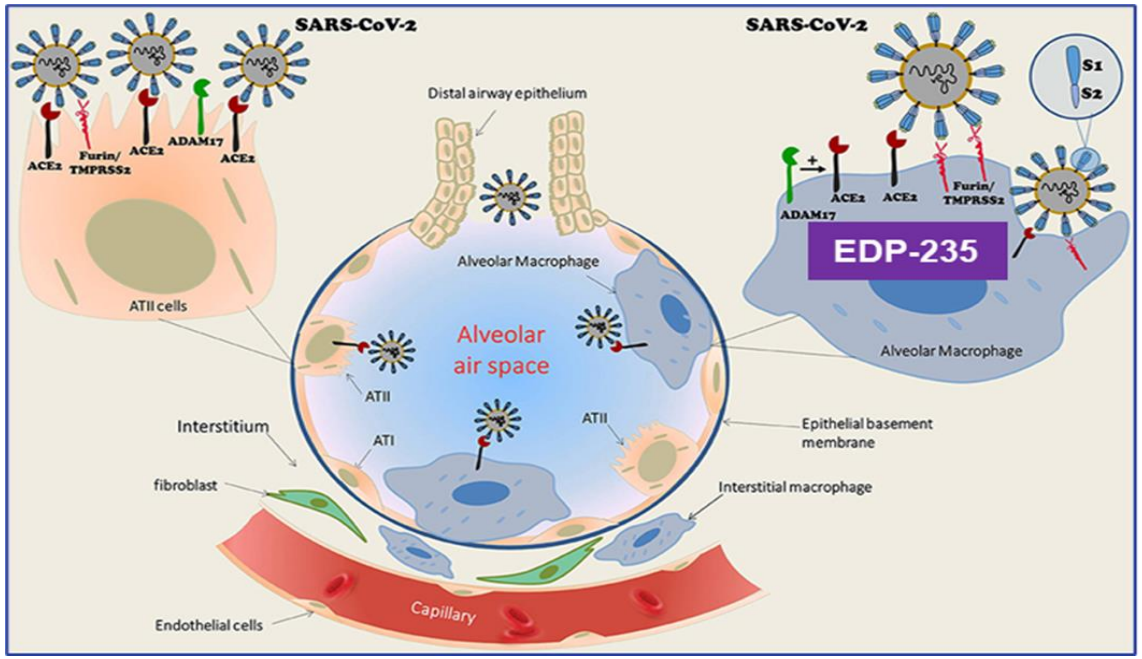
- Good distribution into key target tissues providing the potential to minimize post-treatment viral rebound and/or possible viral replication persistence linked to long COVID

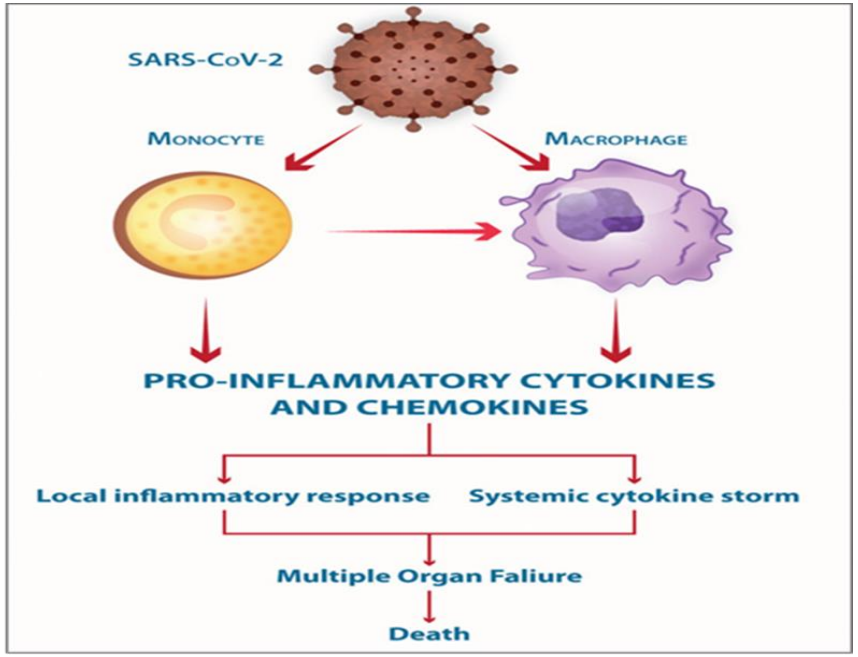
*Multiples by which mean trough drug plasma levels at steady state are higher than protein adjusted EC_{90} as measured in Vero cells

Alveolar Macrophages (AM) Play an Important Role in SARS-CoV-2 Infection

- Macrophages, including lung 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.

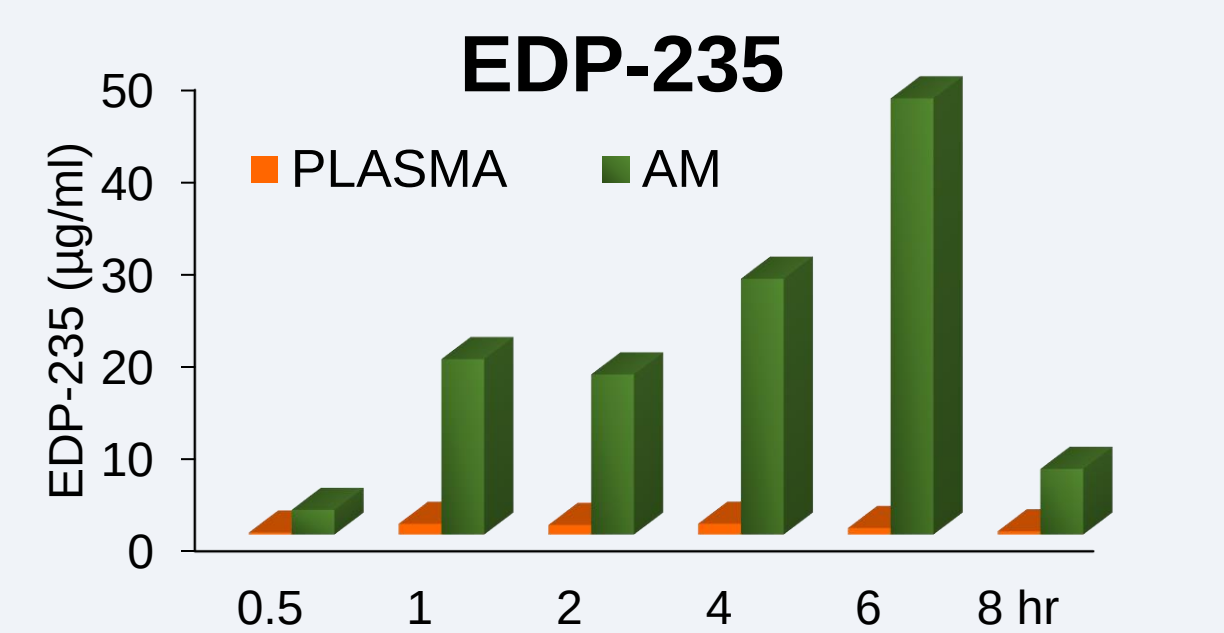


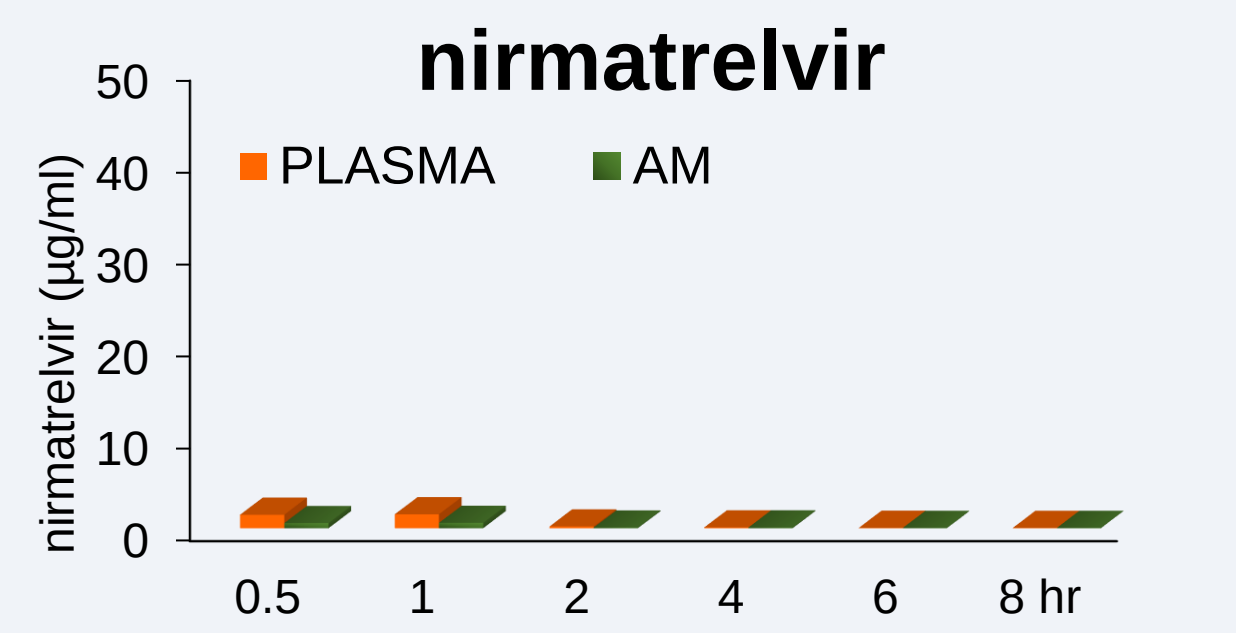


Modified from Front. Immunol., 05 June 2020 | https://doi.org/10.3389/fimmu.2020.01312 & Nature 606, 585–593 (2022). https://doi.org/10.1038/s41586-022-04802-1

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

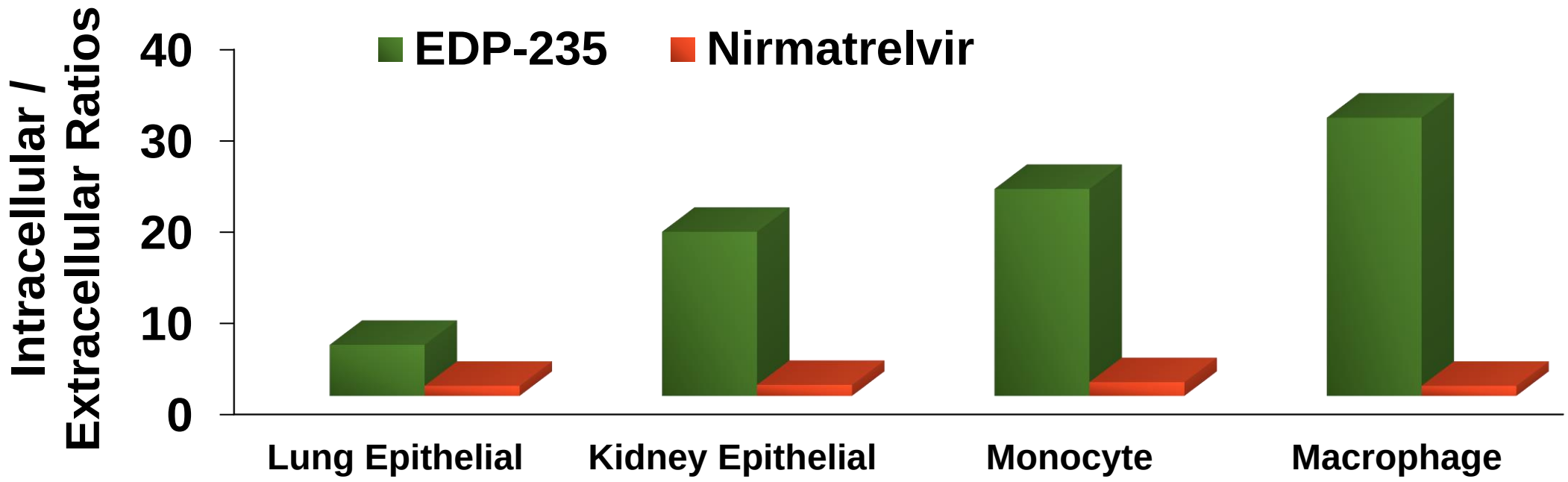
Compd.	Plasma		AM		AUC Ratio over Plasma
	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg-h/mL)	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg-h/mL)	
EDP-235	1.2	9.6	50.7	272.0	28.4
nirmatrelvir	1.5	2.7	0.5	1.3	0.5





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

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$_{\pm 0.2}$

Conclusions

- EDP-235, a novel and potent SARS-CoV-2 3CL protease inhibitor, demonstrated excellent penetration into monocytes and macrophages, including lung alveolar macrophages.
- EDP-235 has the potential to eliminate SARS-CoV-2 replication in sentinel immune cells, thus potentially mitigating macrophage-mediated cytokine storm in COVID-19 patients.
- 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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Please go to Poster 1123 for more information about EDP-235

