EDP-235, a Potent, Once-Daily, Oral Antiviral, Demonstrates Potential for Treatment and Prevention of Long COVID

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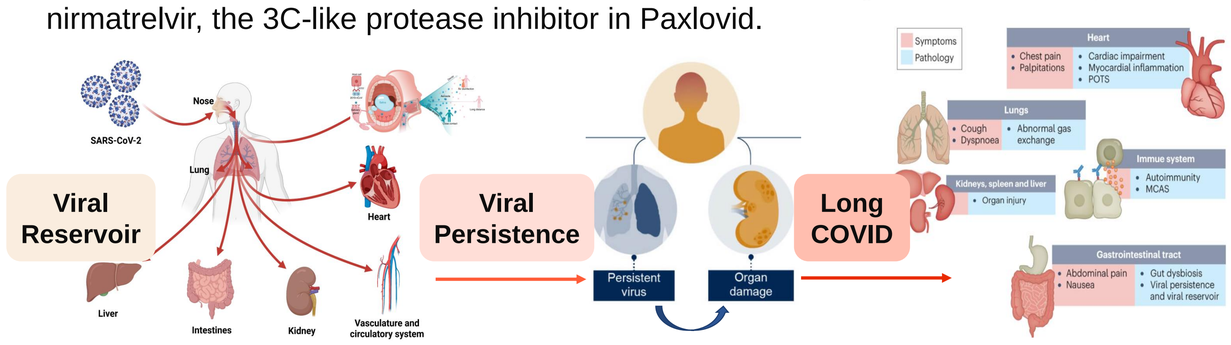
BACKGROUND

- Of COVID-19 survivors, it was estimated that up to 29% have developed symptoms characteristic of long COVID, a health emergency with no approved treatment. While there may be multiple factors causing long COVID symptoms, studies have shown that SARS-CoV-2 is capable of persisting in a wide range of organs for months after the initial infection, which may drive illness in some long COVID patients[1-4].
- Herein, we report that EDP-235, a novel and potent SARS-CoV-2 3C-like protease inhibitor being investigated for treatment of initial SARS-CoV-2 infection in an on-going Phase 2 trial[5], demonstrates superior distribution in target tissues compared to nirmatrelvir, the 3C-like protease inhibitor in Paxlovid.



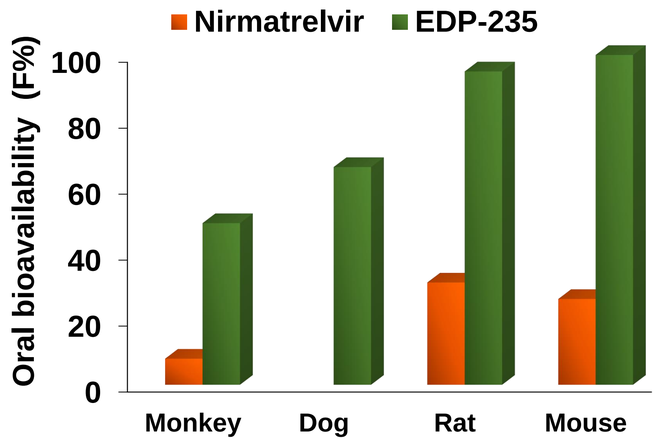
Modified from "Long COVID: major findings, mechanisms and recommendations", Nature Reviews Microbiology; 2023 Mar; 21(3): 133-146.

METHODS

- Intracellular uptake of EDP-235 was tested side-by-side with nirmatrelvir in human and rat cells.
- To determine the *in vivo* drug distribution in SARS-CoV-2 target tissues, rats were dosed orally with 25 mg/kg of EDP-235 or nirmatrelvir. Drug levels in plasma and target tissues—including potential COVID-19 tissue reservoirs: salivary glands, adipose tissues, alveolar macrophages—were measured by LC/MS/MS.

RESULTS

EDP-235 displays superior plasma exposure and oral bioavailability in preclinical species and is projected to have excellent oral absorption in humans



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	**100.0**
	Nirmatrelvir	1.6	2.9	26.0
Rat	**EDP-235**	1.9	19.0	**95.0**
	Nirmatrelvir	2.5	4.9	31.0*
Dog	**EDP-235**	2.1	58.0	**50.3**
	Nirmatrelvir	--	--	--
Monkey	**EDP-235**	0.7	7.0	**49.3**
	Nirmatrelvir	3.6	2.1	8.5**

Single dose PK; oral formulation: 0.5% methylcellulose (MC) in water; F(%) = oral bioavailability; AUC0-∞ = area under the curve from zero to infinity time; Cmax = maximum observed concentration. ; *Reported by Pfizer at 2021 ACS Meeting **Nirmatrelvir p.o. formulation for monkey: 2% Tween 80/ 98% of 0.5% MC in water; Owen et al., Science 374, 1586–1593 (2021).

EDP-235 has favorable pharmacokinetic properties in monkeys

Species	Drug	Route	Sex	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	V_d (L/kg)	CL_p (L/hr/kg)	$AUC_{0-\infty}$ (μg·hr/mL)	F (%)
Monkey	EDP-235	IV	M	0.5	0.1	2.1	5.5	1.8	0.7	-
			F	0.7	0.1	1.8	4.2	1.5	0.9	-
		PO	M	0.7	5.3	4.8	--	--	6.9	49.3
			F	1.0	4.7	2.9	--	--	8.9	49.4

$AUC_{0-\infty}$=Area under the curve from the time of dosing (time zero) to infinity; CL_p=Plasma clearance; C_{max}=Maximum observed concentration; F: bioavailability; $t_{½}$=Terminal half-life; T_{max}=Time of maximum observed concentration; V_d=volume of distribution; **--:** data were not applicable. * Owen et al., Science 374, 1586–1593 (2021).

RESULTS (continued)

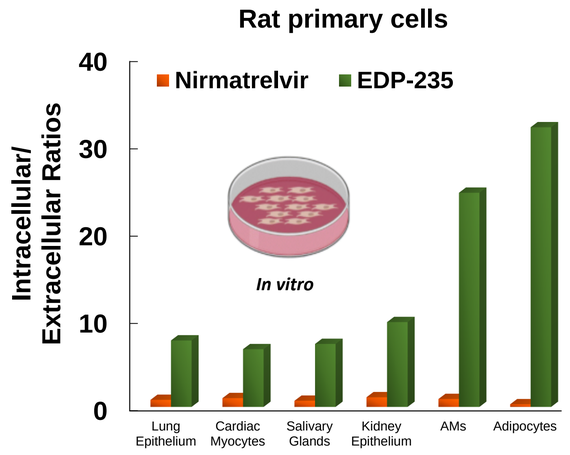
EDP-235 exhibits good plasma exposure and pharmacokinetic profiles in dogs

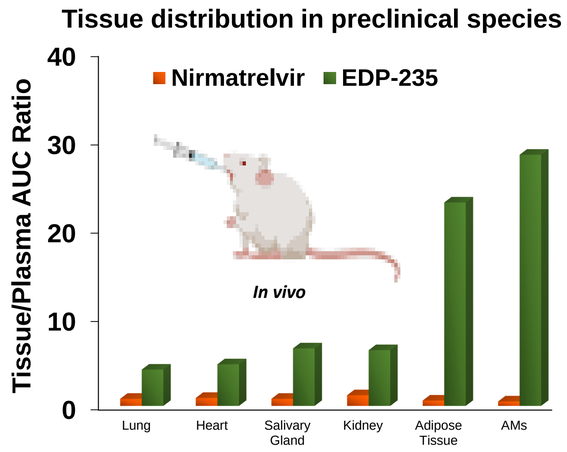
Species	Drug	Route	Sex	C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	V_d (L/kg)	CL_p (L/hr/kg)	$AUC_{0-\infty}$ (μg·hr/mL)	F (%)
Dog	EDP-235	IV	M	1.0	0.1	9.2	2.9	0.2	5.8	--
			F	0.8	0.1	6.6	3.0	0.3	3.9	--
		PO	M	2.1	11.3	13.6	--	--	58.0	50.3
			F	1.7	2.7	15.9	--	--	52.0	66.5

$AUC_{0-\infty}$=Area under the curve from the time of dosing (time zero) to infinity; CLp=Plasma clearance; C_{max}=Maximum observed concentration; F: bioavailability; $t_{½}$=Terminal half-life; T_{max}=Time of maximum observed concentration; V_d=volume of distribution; **--:** data were not applicable.

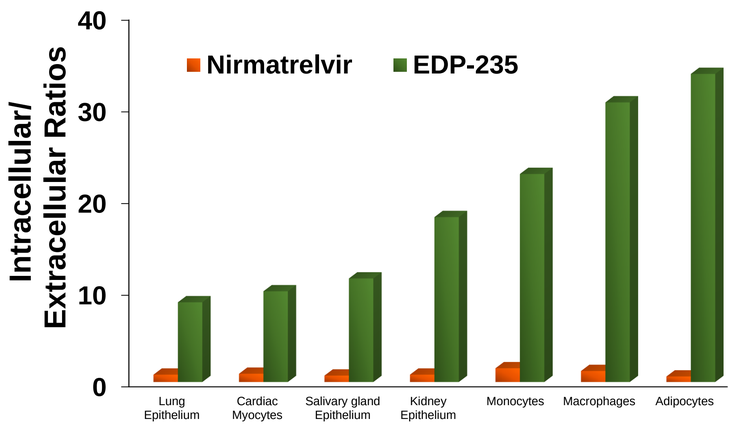
EDP-235 has favorable intracellular uptake and distribution in SARS-CoV-2 target tissues and exhibits a positive *in vitro–in vivo* correlation

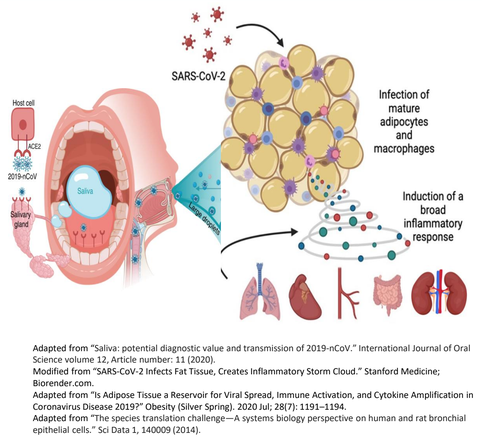
Compound	Sex	Tissue/Plasma AUC Ratio					
		Lung	Heart	Salivary Gland	Kidney	Adipose Tissue	Alveolar Macrophage
EDP-235	**M**	**4.1**	**4.7**	**6.5**	**6.3**	**23.0**	**28.4**
Nirmatrelvir	**M**	0.8	0.9	0.8	1.2	0.6	0.5





EDP-235 has distinguished intracellular uptake into many human cell types, and is projected to have advantageous tissue distribution in humans





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CONCLUSIONS

- Preferential target tissue distribution and cell penetration shown in preclinical studies potentially enable EDP-235 to target viral reservoirs and minimize viral persistence in long COVID patients.
- Administered as a treatment for acute COVID, EDP-235 could potentially prevent progression to long COVID and be a first-line treatment for long COVID.
- 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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