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ALG-098340, AN INVESTIGATIONAL, POTENT, PAN-CORONAVIRUS 3CLPRO INHIBITOR FOR PANDEMIC PREPAREDNESS

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INTRODUCTION

The 2019 SARS-CoV-2 outbreak had a devastating effect on worldwide economies and human health, resulting in over seven million deaths worldwide.[1,2] SARS-CoV-2 vaccines are widely available, but maybe limited in efficacy for the elderly and immunocompromised subjects.[3,4] Despite vaccine availability, breakthrough infections still occur.[5] Orally available, safe antiviral treatments are needed for high risk populations and to strengthen preparedness for another potential coronavirus pandemic. Current therapies either lack efficacy, pan-coronaviral coverage, or require co-administration with ritonavir (RTV), that presents drug-drug interaction concerns.[6] The main protease (3CLpro, Mpro) is an ideal target for pan coronavirus inhibition because it has no human homolog, making inhibitors potentially safer; protease inhibition is clinically validated; and 3CLpro is highly conserved across coronaviruses. Inhibition of 3CLpro blocks viral replication by preventing cleavage of the viral polypeptide into essential functional proteins.[7,8,9]

BIOCHEMICAL POTENCY AGAINST CORONAVIRUS 3CLPROS

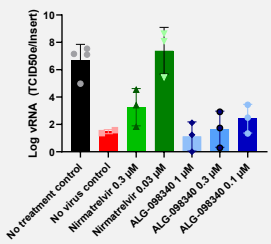
3CLpro	Genus	Enzyme Conc. (nM)	Nirmatrelvir	Ibuzatrelvir	Ensitrelvir	ALG-098340
			IC_{50} (nM) mean ± SD (n≥3)			
SARS-CoV-2	*Beta*	**5**	3.28±0.72	2.34±0.97	3.30±0.70	**2.2±0.4**
SARS-CoV-2 (Omicron)	*Beta*	**5**	5.13±0.31	3.33±0.55	6.1±1.1	**2.60±0.17**
MERS-CoV	*Beta*	**50**	185±119	97.4±69.7	1741±449	**68.0±2.4**
hCoV OC43	*Beta*	**5**	2.18±0.81	2.54±0.94	9.18±1.96	**3.57±0.31**
hCoV HKU1	*Beta*	**5**	5.09±2.53	3.63±3.62	3.24±1.30	**3.67±1.04**
hCoV NL63	*Alpha*	**5**	112±62	332±224	>2000	**4.6±0.2**
hCoV 229E	*Alpha*	**5**	52.9±18.4	178±73	1484±568	**2.83±0.25**
fCoV FIPV	*Alpha*	**5**	25.7±8.5	41.1±1.1	>2000	**1.97±0.38**
Beluga whale CoV	*Gamma*	**5**	6.25±3.40	9.96±5.81	>2000	**1.70±0.36**
IBV	*Gamma*	**5**	50.0±27.2	38.9±10.4	1610±675	**36.5±2.0**

CELLULAR POTENCY

Virus	Variant	EC_{50} (μM)		
		Nirmatrelvir	Ibuzatrelvir	ALG-098340
SARS-CoV-2	GHB-03021/2020 (Wuhan) [1]	0.114	0.167	**0.014**
	B.1.1.7 (2% FBS) [2]	0.101	0.090	**0.246**
	+ 40% HS	0.095	0.192	**0.027**
	JN.1 (10% FBS) [2]	0.157	0.136	**0.044**
	+ 40% HS	0.297	0.332	**0.041**
SARS-CoV-1 [1]		0.150	0.120	**0.026**
MERS-CoV [1]		0.025	0.142	**0.046**
OC43 (β-hCoV) [3]		0.047	0.066	**0.082**
229E (α-hCoV) [4]		0.605	2.00	**0.045**

1.Vero E6-eGFP or Vero 76 in presence of 2 μM of P-glycoprotein inhibitor rCP-100356 or Elacridar; 2.A549-hACE2-hTMPRSS2; 3.HeLa; 4. Huh-7.

PRIMARY HUMAN AIRWAY EPITHELIAL CELL-AIR LIQUID INTERFACE (HAEC-ALI)

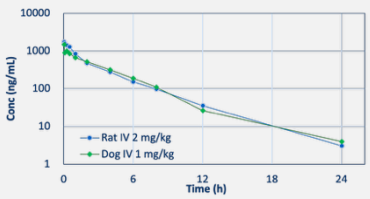


Culture Condition	40% Human Serum	
	ALG-098340	Nirmatrelvir
EC_{90} (nM)	**7**	147
EC_{99} (nM)	**14**	210
$EC_{99.9}$ (nM)	**23**	272

PHARMACOKINETICS IN RAT AND DOG

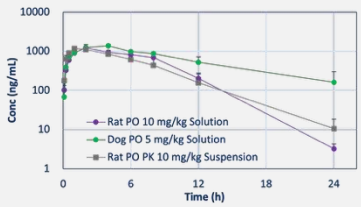
Parameter	ALG-098340
Simulated gastric/intestinal fluid, plasma (R, D, H)	**$t_{1/2}$ > 180 min**
Liver microsomes $t_{1/2}$ (min) Ha/M/R/D/C/H	**<15/ <15/ >60/ >60/ 25/ >60**
Systemic CL (as % liver blood flow)	**16% and 17% (R, D)**
Steady state Vss, fold body water V	**2.5 and 1.7 (R, D)**
%F using solution formulations	**53, 97% (R, D)**
Plasma $t_{1/2}$ (PO)	**2 h in R, 6.5 h in D**
CYP Induction via PXR %CNTRL at 10 μM	**38 (Weak)**
hERG/CaV/NaV (at 0.3-10 μM)	**IC_{50} > 10 μM**
Off Target Receptor Binding Screen 10 μM	**No hits**
Kinase Panel Screen (58 total) at 10 μM	**Negative** <30% inhibition
Ames, in vitro MNT assay	**Negative** <30% inhibition
Substrate for AO metabolism	**Negative**

MEAN PLASMA CONCENTRATION FOLLOWING SINGLE IV DOSE



Rat IV 2 mg/kg (blue, n=3). Dog IV 1 mg/kg (green, n=3). Following IV dose, systemic CL was low, 16% of hepatic blood flow in rat and 17% in dog. Steady state volume of distribution (Vss) in rat = 1.7 L/kg, and dog 0.97 L/kg. Plasma protein binding in rat 98% bound, and 97% dog. Vehicle: 80% aq. PEG 400.

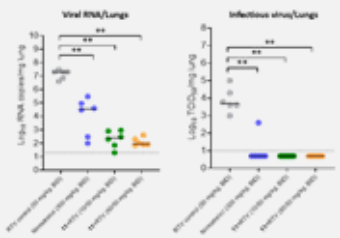
MEAN PLASMA CONCENTRATION FOLLOWING SINGLE PO DOSE



Rat oral dose 10 mg/kg (PEG 400 in water, purple, n=3). Rat PO 10 mg/kg suspension in 0.5% CMC and 0.2% TWEEN 80 in water (gray, n=3). Dog PO 5 mg/kg (PEG 400 in water, green, n=3). Following oral dose, rat bioavailability (%F) was 53% as a solution and 45% in suspension. Dog bioavailability 97%.

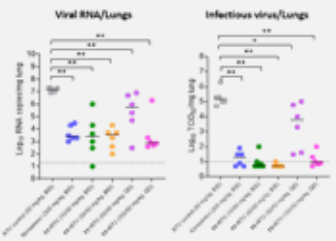
IN VIVO EFFICACY

MOUSE INFECTION STUDY



Efficacy in SARS-CoV-2 infected SCID mice. Left) Viral RNA levels in the lungs of orally treated animals; infected with 1x10⁵ TCID50 SARS-CoV-2 beta variant at day 3 post-infection (pi). Individual data and median values are presented. Right) Infectious viral loads in the lungs of SARS-CoV-2 infected mice at day 3 pi are expressed as log10 TCID50 per mg lung tissue. Vehicle: 43% v/v EtOH and 27% (w/v) propylene glycol in water (n=6).

HAMSTER INFECTION STUDY



Efficacy in SARS-CoV-2 infected Syrian hamsters. Left) Viral RNA levels in the lungs of orally treated hamsters infected with 1x10⁶ $TCID_{50}$ SARS-CoV-2 delta variant at day 3 post-infection (pi). Right) Infectious viral loads in the lungs of infected hamsters at day 3 pi are expressed as log_{10} $TCID_{50}$ per mg lung tissue Individual data and median values are presented. Vehicle: 43% v/v EtOH and 27% (w/v) aq. propylene glycol (n=6).

HIGH SELECTIVITY OVER HOST PROTEASES

Human Protease	% Inhibition*
Calpain 1	13
Caspase 2	39
Cathepsin B	27
Cathepsin D	4
Cathepsin K	10
Cathepsin L	6
Cathepsin S	16
Cathepsin V	8
Chymotrypsin	25
Elastase	13
Thrombin a	5
Trypsin	2

*at 10 μM concentration

CONCLUSIONS

- ✓ALG-098340 is an investigational, novel inhibitor of the 3CLpro enzyme with pan-coronavirus activity.
- ✓Cellular assays demonstrate that ALG-098340 has greater potency than nirmatrelvir, ensitrelvir and ibuzatrelvir against current (Omicron variants), prior SARS-CoV-2 isolates and other hCoVs including MERS-CoV and SARS-CoV-1.
- ✓ALG-098340 demonstrates potent, broad-spectrum inhibition of 3CLpros from various SARS-CoV-2 strains, other human CoVs as well as bird, bat, cat and whale CoVs in biochemical experiments.
- ✓ALG-098340 demonstrated potent in vivo efficacy using RTV in animal models where liver microsomal stability was less.
- ✓ALG-098340 has a favorable in vitro safety screening profile.
- ✓PK properties of ALG-098340 in preclinical species demonstrate the potential for once daily dosing in humans.

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