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Preclinical Evaluation of ALG-097558: A Novel, Orally Bioavailable Pan-Coronavirus 3CLpro Inhibitor for the Treatment of COVID-19

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Overview of SARS-CoV-2 Antivirals

Name	MoA	Approval	Route of Admin.	Pros/cons
Veklury (Remdesivir)	RdRp Inhibitor	FDA full	IV	IV; low risk of resistance
Bebtelovimab	Mab	FDA EUA	IV	IV, susceptible to mutations in spike protein
Evusheld (tixagevimab + cilgavimab)	Mab	FDA EUA	IV	
Paxlovid (nirmaltrelvir + ritonavir)	Protease Inhibitor	FDA EUA	oral	Strong clinical efficacy; low risk of resistance; drug-drug interactions
Lagevrio (molnupiravir)	RdRp inhibitor	FDA EUA	oral	Low risk of resistance

- Activity of tixagevimab + cilgavimab reduced > 600-fold against most Omicron subvariants including BQ1, BQ1.1 [1, 2]
- Paxlovid reduced risk of death or hospitalization due to Covid-19 by 89% compared to placebo [3]
- Protease and polymerase inhibitors provide high variant coverage
  - Very limited clinical resistance observed

Antivirals with 3 different MoAs available

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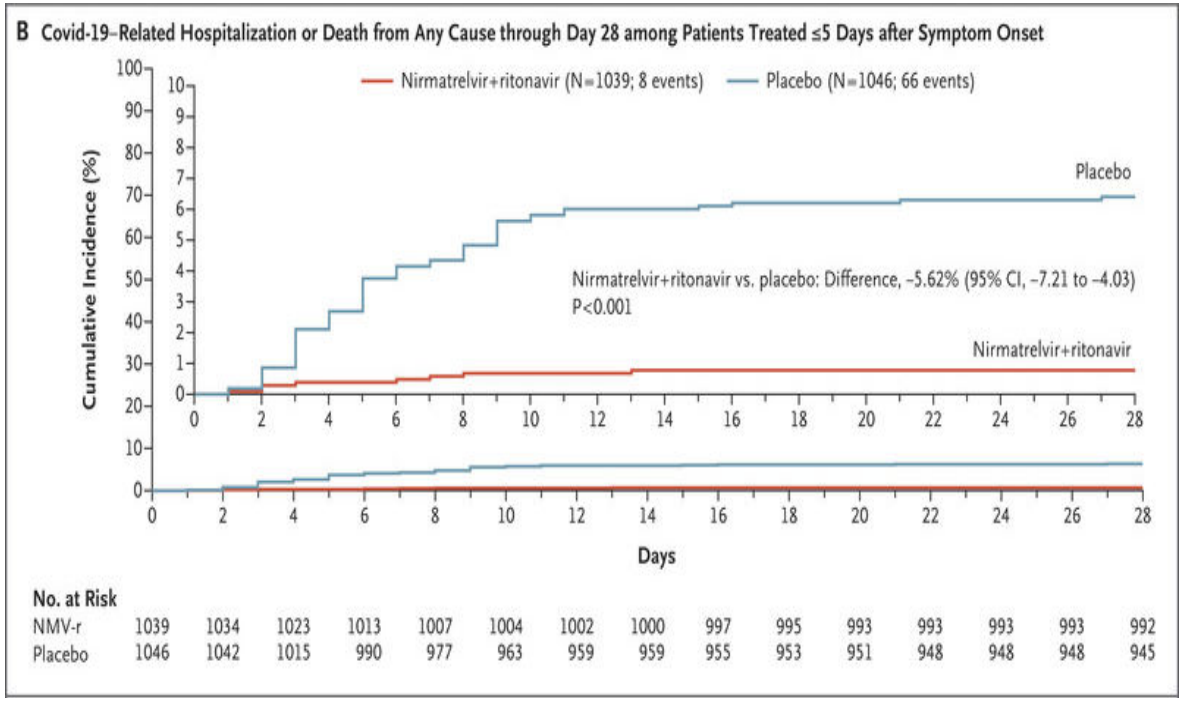
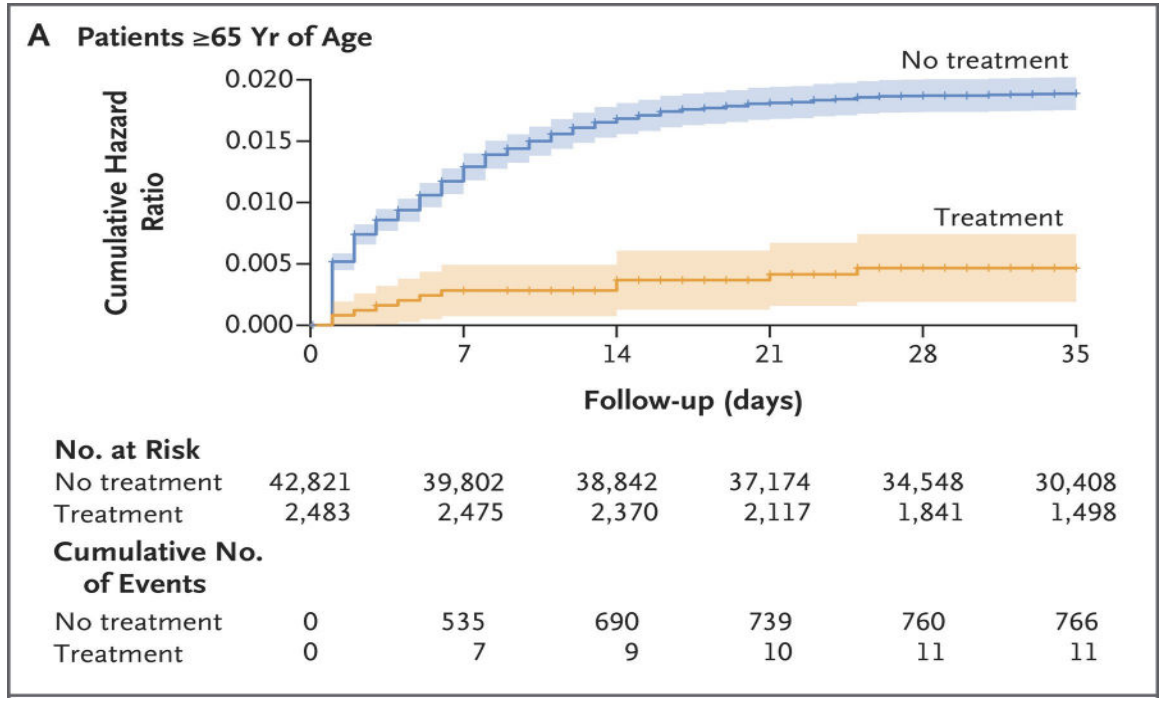
1:Evusheld fact sheet: https://www.fda.gov/media/154701/download
2: Bebtelovimab fact sheet: https://www.fda.gov/media/156152/download
3: Hammond J NEJM 2022; DOI: 10.1056/NEJMoa2118542

Paxlovid Retains Clinical Efficacy Against Omicron Variants





EPIC-HR Phase 2/3 trial
- July-Dec 2021
- Largely Delta
- No/minimal preexisting immunity

Clalit health system (Israel), retrospective study
- Jan-March 2022
- >90% Omicron
- >78% with preexisting immunity (vaccine or infection)

3CLpro Inhibitors such as Nirmatrelvir Retain Activity Against Omicron Variants

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J Hammond 2022 NEJM DOI: 10.1056/NEJMoa2118542
R Arbel 2022 NEJM; DOI: 10.1056/NEJMoa2204919

Need for 2nd Generation Protease Inhibitors

- Ritonavir Drug-Drug Interactions are a major limitation of Paxlovid

Do not take PAXLOVID if:

- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in PAXLOVID.
- You are taking any of the following medicines:
  - alfuzosin
  - amiodarone
  - apalutamide
  - carbamazepine
  - colchicine
  - dihydroergotamine
  - dronedarone
  - eletriptan
  - eplerenone
  - ergotamine
  - finerenone
  - flecainide
  - flibanserin
  - ivabradine
  - lomitapide
  - lovastatin
  - lumacaftor/ivacaftor
  - lurasidone
  - methylergonovine
  - midazolam (oral)
  - naloxegol
  - phenobarbital
  - phenytoin
  - pimozide
  - primidone
  - propafenone
  - quinidine
  - ranolazine
  - rifampin
  - St. John's Wort (*hypericum perforatum*)
  - sildenafil (Revatio®) for pulmonary arterial hypertension
  - silodosin
  - simvastatin
  - tolvaptan
  - triazolam
  - ubrogepant
  - voclosporin

- University of Liverpool Drug Interaction website https://www.covid19-druginteractions.org/

Can NOT be co-administered with many immuno-suppressants, heart-failure/hypertension medications, anti-convulsants, lipid-lowering agents and others

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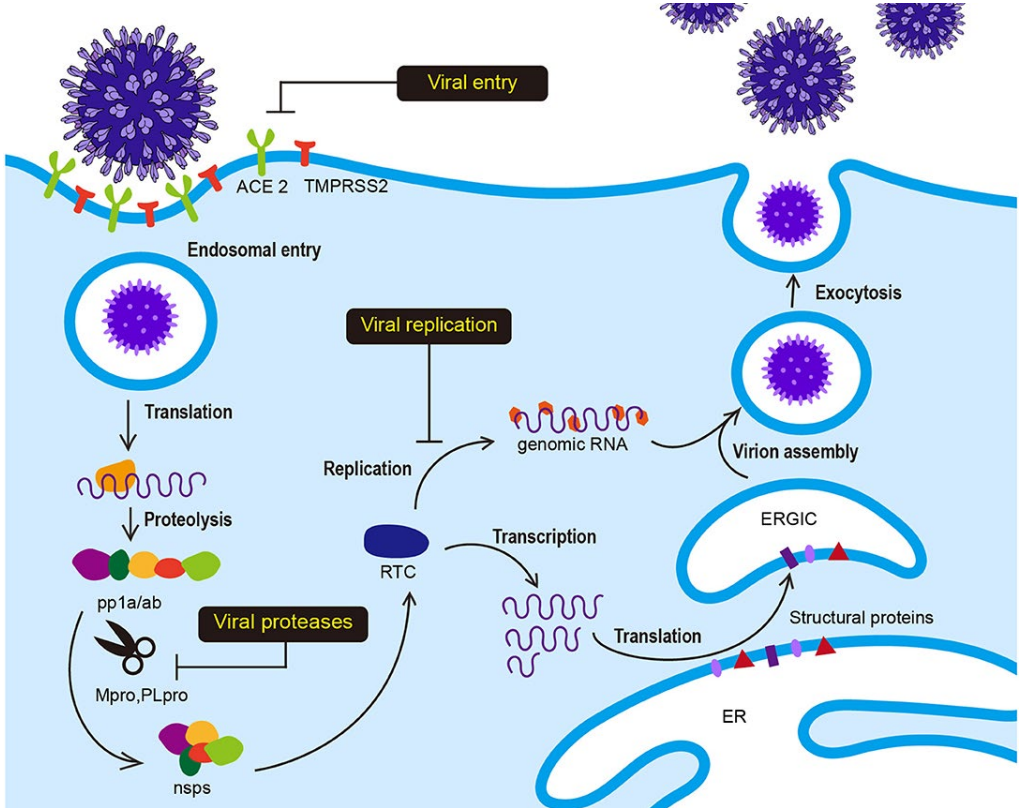
EUA Fact Sheet Paxlovid; https://labeling.pfizer.com/ShowLabeling.aspx?id=16473&format=pdf

Program Goals

- Collaboration established in 2020 between Aligos Therapeutics, CD3, Cistim and the Rega Institute at the KU Leuven
- Protease inhibitors clinically validated
  - HIV, HCV
- Key criteria
  - Orally bioavailable
  - Pan-coronavirus antiviral activity
  - Favorable resistance profile
  - No need for a pharmaco-enhancer such as ritonavir



https://www.frontiersin.org/articles/10.3389/fmicb.2020.01723/full.

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ALG-097558
Antiviral Activity and Selectivity in Biochemical Assays

Compound	SARS-CoV-2 3CLpro [1]			HRV 3C Protease IC_{50} (nM)	Cathepsin L IC_{50} (nM)
	IC_{50} (nM)	Hill Slope	K_i (nM)		
ALG-097558	**0.26**	**1.99**	**0.074**	**> 10000**	**> 10000**
Nirmatrelvir	2.92	0.91	2.03	> 10000	> 10000
PBI-0451	3.6	1.74	3.4	> 10000	1493

[1] Low 3CLpro enzyme concentration (0.3 nM) was used to accurately determine the Ki of highly active 3CLpro inhibitors in a mass spectrometry-based assay

- ALG-097558 is a selective SARS-CoV-2 3CLpro inhibitor without off-target activity against human Cathepsin L and the Human Rhinovirus protease
- ALG-097558 exhibits reversible 3CLpro binding based on guanidine denaturation experiments (not shown)

ALG-097558 is a highly potent and selective inhibitor of the SARS-CoV-2 3CLpro

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ALG-097558
Pan-Coronavirus Activity in Cellular Assays

Virus	Variant	EC_{50} (μM)		
		ALG-097558	Nirmatrelvir	PBI-0451
SARS-CoV-2	03021/2020 [1]	**0.010**	0.116	n.d.
	B.1.1.7 (alpha) [2]	**0.012**	0.099	0.038
	B.1.617.2 (delta) [2]	**0.013**	0.217	0.126
	B.1.1.529 (omicron) [1]	**0.008**	0.059	0.136
	BA.2 [1]	**0.003**	0.027	0.087
	BA.5 [1]	**0.012**	0.075	0.215
SARS-CoV-1	Isolate Vietnam [1]	**0.022**	0.173	0.323
β-hCoV	OC43 [3]	**0.009**	0.047	0.168
α-hCoV	229E [4]	**0.017**	0.476	0.281

Cell lines used: (1) VeroE6 (in presence of 2 μM of P-glycoprotein inhibitor CP-100356), (2) A549-ACE2-TMPRSS2, (3) HeLa, (4) Huh-7;
No cytotoxicity was detected for ALG-097558 at concentrations up to 100 μM.

- MERS testing pending; bioinformatics predicts retained activity BA.2.12.1, BA.3, BA.4, BQ.1, BQ1.1, BF.1
- Pan-coronavirus activity confirmed in FRET assay using 3CLpro derived from SARS-CoV-2, MERS, human α-CoV 229E and NL63, and human β-CoV HKU-1 (not shown)

ALG-097558 demonstrates pan-coronavirus activity in cell-based assays

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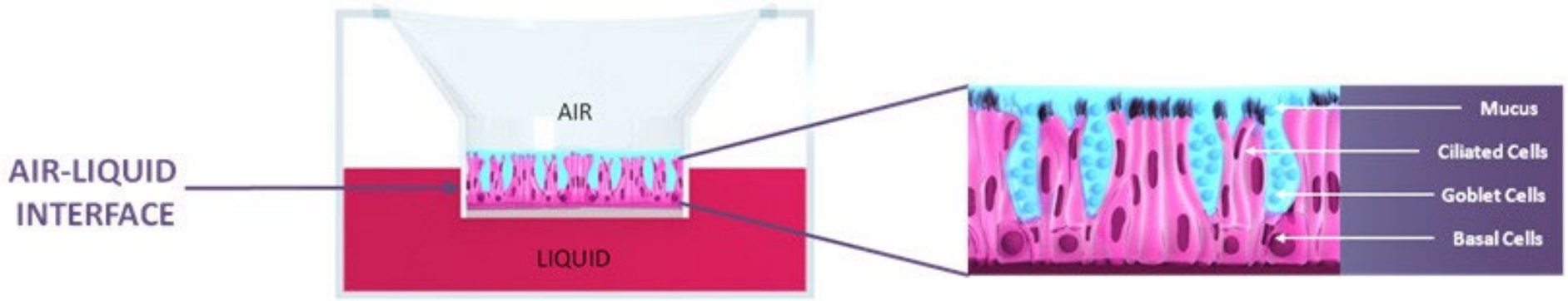
Inhibition of SARS-CoV-2 Replication in 3D Human Airway Epithelium (HAE) Air-Liquid-Interphase (ALI) Cultures



- Human airway epithelial cells are cultured in a 3-dimensional cell culture model at the air-liquid interphase
- Infection with SARS-CoV-2 B.1.1.7 on apical side
- Test compounds are added on basolateral side
- Viral replication is assessed on day 4 post-infection via RT-qPCR
  - Allows determination of EC_{90}, EC_{99} and $EC_{99.9}$, in presence/absence of 40% human serum

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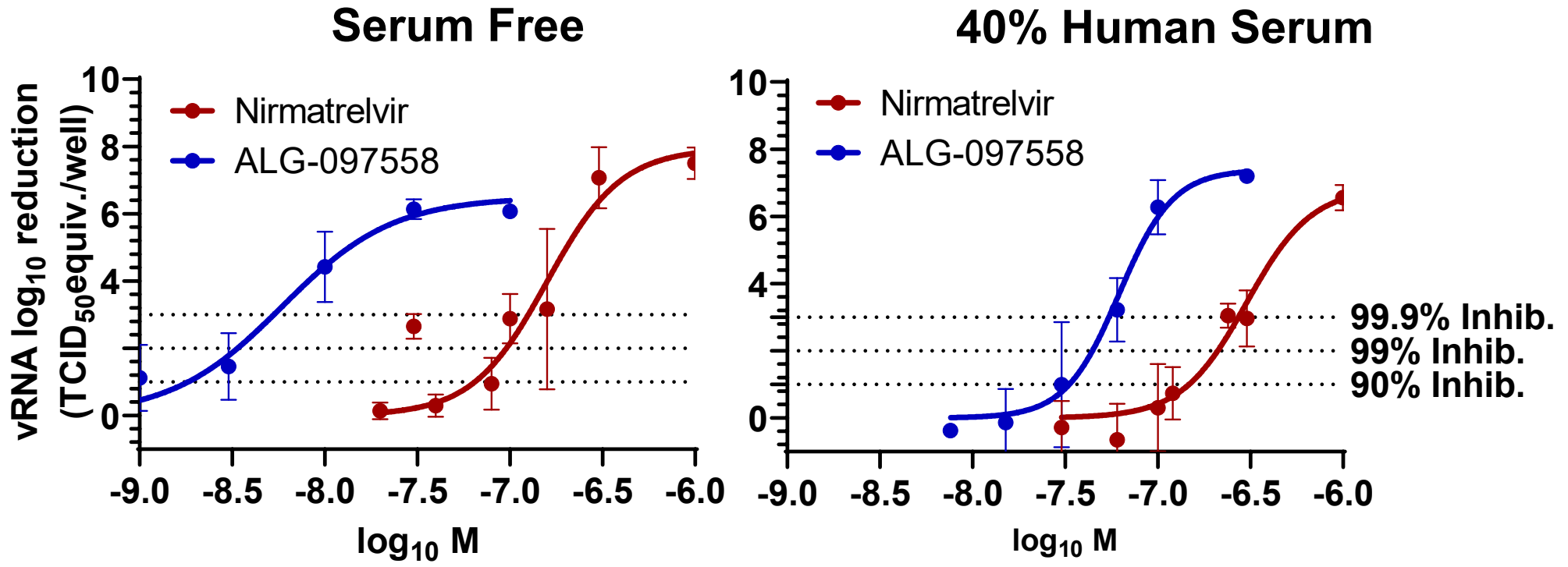
Inhibition of SARS-CoV-2 Replication in 3D Human Airway Epithelium (HAE) Air-Liquid-Interphase (ALI) Cultures



- Viral replication is assessed on day 4 post-infection via RT-qPCR, in the absence or presence of 40% human serum

ALG-097558 $EC_{99.9}$ of 5.3 and 54 nM, in the absence or presence of 40% human serum, respectively

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ALG-097558
Preliminary Resistance Characterization

- Resistance selection using SARS-CoV-2 B.1.1.7 ongoing; preliminary findings, to be confirmed:
  - Only slow increases in drug pressure possible, suggesting high barrier to resistance
  - Increase in drug pressure at slower pace than other 3CLpro inhibitors (e.g., nirmatrelvir)
  - Further increase in ALG-097558 concentration resulted in suppression of viral replication
- ALG-097558 retains antiviral activity against known resistance mutations in enzymatic assay

Compound	Biochemical Potency Fold IC_{50} Compared to Wild-type (Resistance)				
	L50F/E166A/L167F	F140A	S144A	H172Y	Q189K
ALG-097558	**3 (n=3)**	**0.8**	**1**	**2**	**1**
Nirmatrelvir	66 (n=6)	4	3	7	1
PBI-0451	> 65 (n=2)	4	2	20	0.6

  - L50F/E166A/L167F mutant demonstrates high replication fitness and transmissibility in hamster model [1]
  - Assessment of additional mutants ongoing
  - Confirmed with recombinant mutant viruses in cell-based experiments

ALG-097558 has a favorable activity profile against selected resistance mutants

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[1] Abdelnabi R 2022 **doi:** https://doi.org/10.1101/2022.09.28.509903

ADME Profile of ALG-097558

Parameter	Data	Profile
Stability in simulated gastric and intestinal fluids, and in plasma (R, D, H)	$t_{1/2}$ > 480 min	Stable
Stability in liver microsomes $t_{1/2}$ min Ha/M/R/D/H	<15/ <15/ >60/ >60/ 50	Good stability in R,D and H
Systemic clearance across species	4.33 -50.7 mL/min/kg	Low to moderate in non-rodents; high in rodents
Steady state volume of distribution	0.434-1.23 L/kg	Low to moderate
Bioavailability using solution formulations	5 to > 50% in R, D, and C	Orally bioavailable
Plasma $t_{1/2}$ (PO)	2-3 h in R, D, and C	Short, suggestive of BID regimen

C: Cyno, D: Dog, Ha: Hamster, H: Human, M: Mouse, R: Rat

Favorable ADME Profile Allowing Advancement to Clinical Development

Low Stability in Hamster and Mouse (but NOT Other Species) Requires RTV-Boosting in Efficacy Studies

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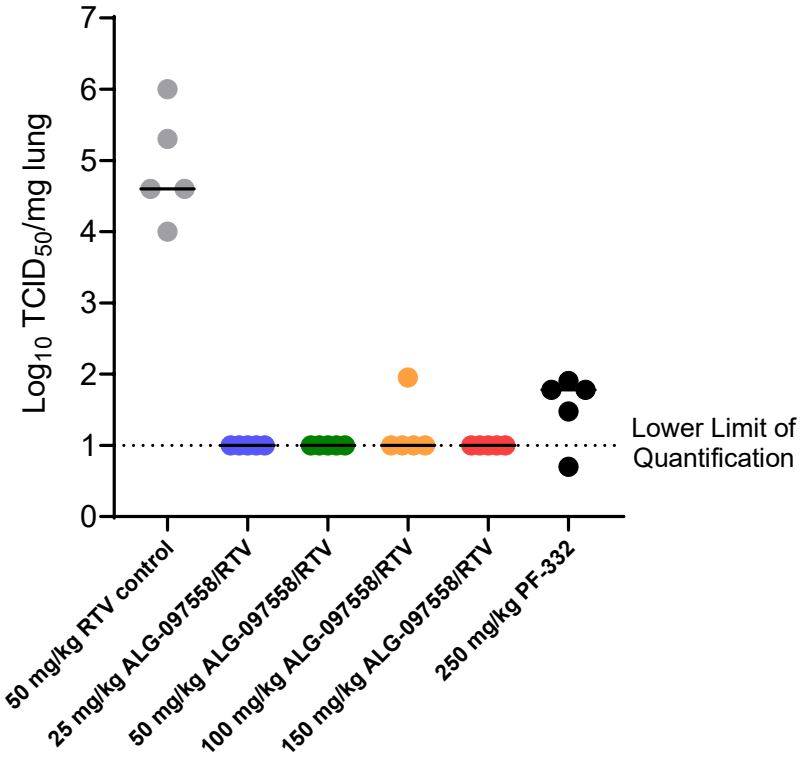
SARS-CoV-2 Hamster Model: Efficacy After Prophylactic Dosing

- Intranasal infection with SARS-CoV-2 B.1.617.2 delta ($1x\ 10^4\ TCID_{50}$)
- Compounds dosed orally, BID for 3 days
  - Treatment start immediately before infection
  - Nirmatrelvir as positive control
- Five animals/group
- Lungs tested on day 4 for viral RNA and infectious virus
- Significant decrease in lung infectious titer
  - At LLOQ in nearly all animals
  - Confirmed with lung viral RNA read-out (not shown)



Significant reduction in lung viral RNA loads and infectious virus titers after oral treatment with ALG-097558

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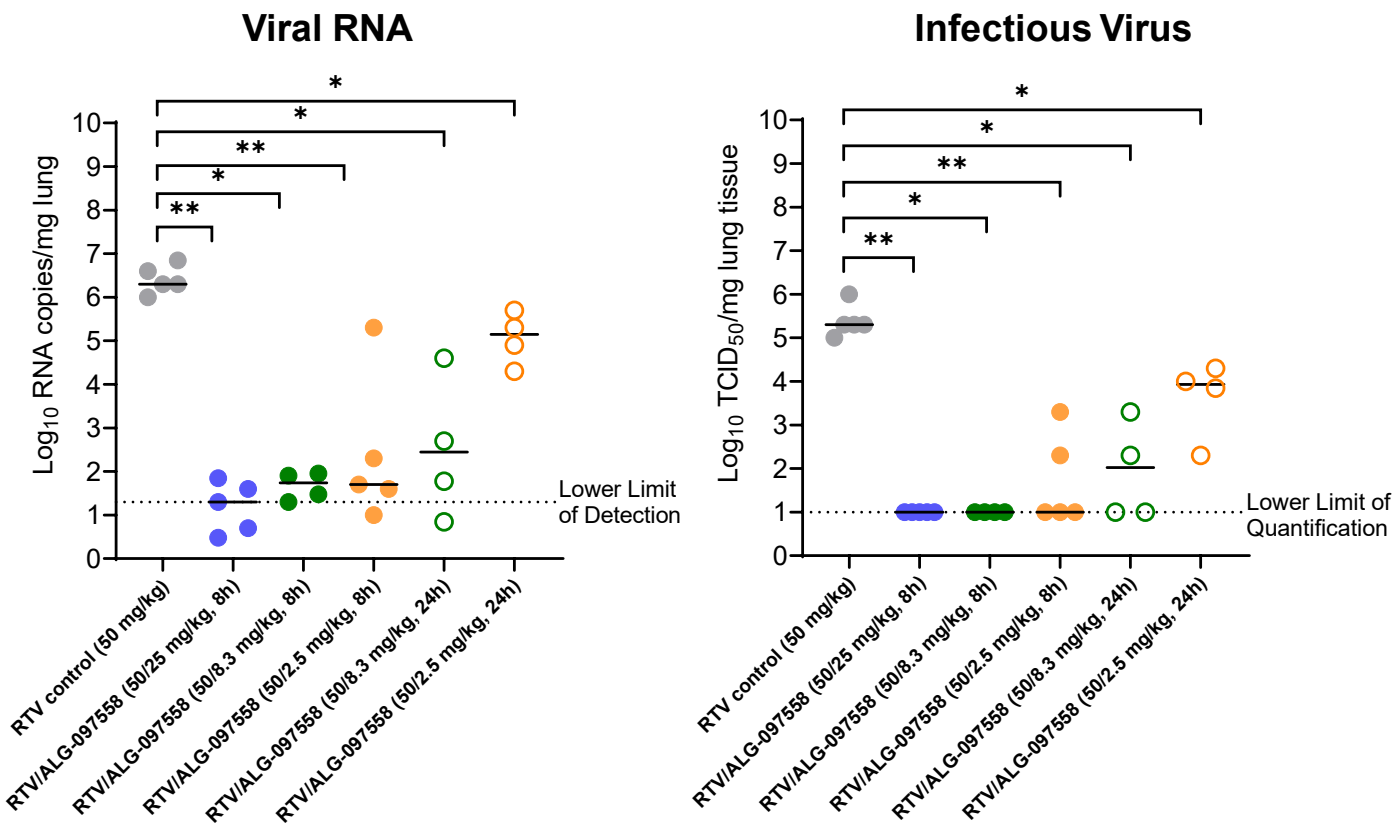
RTV administered 1 h before ALG-097431, RTV and ALG-097431 formulated as a solution in 43% Ethanol + 27% PG in water.
3105H22-097558-PO-PH.

ALG-097558
SARS-CoV-2 Hamster Model: Efficacy After Therapeutic Dosing

- In a therapeutic setting, low doses of ALG-097558 significantly reduced lung viral RNA and infectious titer
  - ~5 log_{10} vRNA reduction with 8h p.i dosing start
  - At limit of quantification for vRNA and infectious titer with 8h p.i. dosing start
  - Significant reductions in vRNA and infectious titer at 24 h p.i.
  - Dosing initiation as late as 24h post-infection improves body weight loss due to infection (not shown)



Significant reduction in lung vRNA and infectious virus titers after therapeutic treatment with ALG-097558

RTV administered 1 h before ALG-097431, RTV and ALG-097431 formulated as a solution in 43% Ethanol + 27% PG in water.
3117H22-097558-PO-PH.

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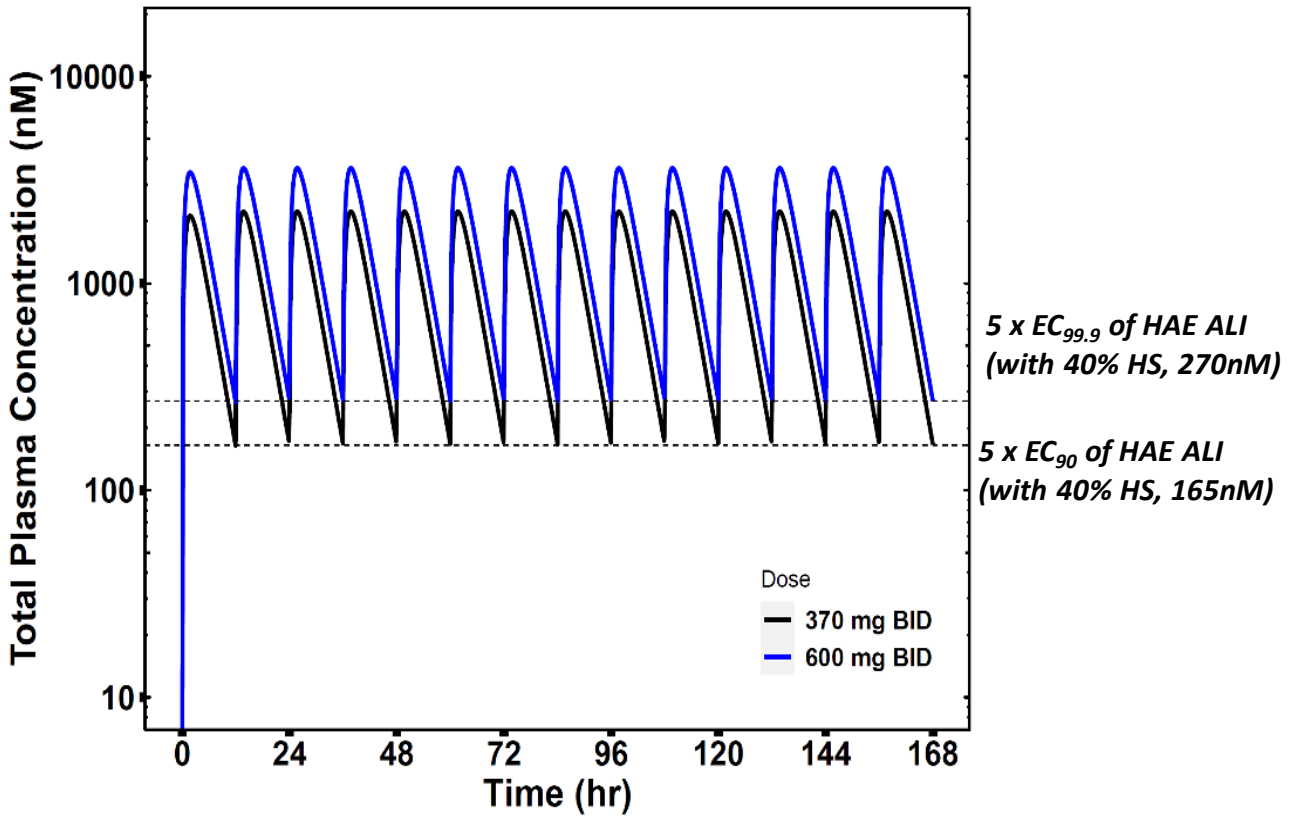
Human Efficacious Dose Projection

- C_{min} targeted as 5x of serum-shifted EC_{90} or serum-shifted $EC_{99.9}$ in the *in vitro* HAE ALI assays
- Methods validated based on comparable clearance and volume of distribution predicted by these methods vs. the parameters derived from reported human PK for nirmatrelvir [1]



Projected efficacious human dose 370 to 600 mg BID without need for ritonavir

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[1] Owen DR et al., Science 374:6575:1586-93

ALG-097558
Summary and Outlook

- Pan-coronavirus inhibitor, nanomolar antiviral activity in biochemical and cellular assays
- Efficient inhibition of viral replication in human airway epithelium ALI cultures with $EC_{99.9}$ of 5.3 and 54 nM, respectively, with or without 40% human serum
- Efficient reduction of viral replication in the SARS-CoV-2 hamster model using low, oral doses and a therapeutic dosing regimen
- Favorable, preliminary resistance profile
- Favorable ADME profile indicates a 370-600 mg BID dosing regimen in humans without the need of ritonavir boosting
- IND enabling non-clinical studies in progress
- First-in-human clinical trials expected to start in first half of 2023

Thank you !

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