LMAP 2023
LIVERPOOL MASTERCLASS IN ANTIVIRAL PHARMACOLOGY

UNIVERSITY OF LIVERPOOL

New COVID-19 Antiviral Therapies

Saye Khoo

Disclosure & Funding Statement

- *Published on* https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/
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- *The AGILE Platform is funded by the Wellcome Trust, MRC, UKRI, Unitaid*
- *The Liverpool DDI Prescribing tools maintain editorial independence*
- *Speakers fees/honoraria from ViiV, GSK, Merck*

COVID-19: why do we still need antivirals ?

1 Need for greater sterilising potency

- Persistent or relapsing disease in immunosuppressed
- (Rebounds ??)

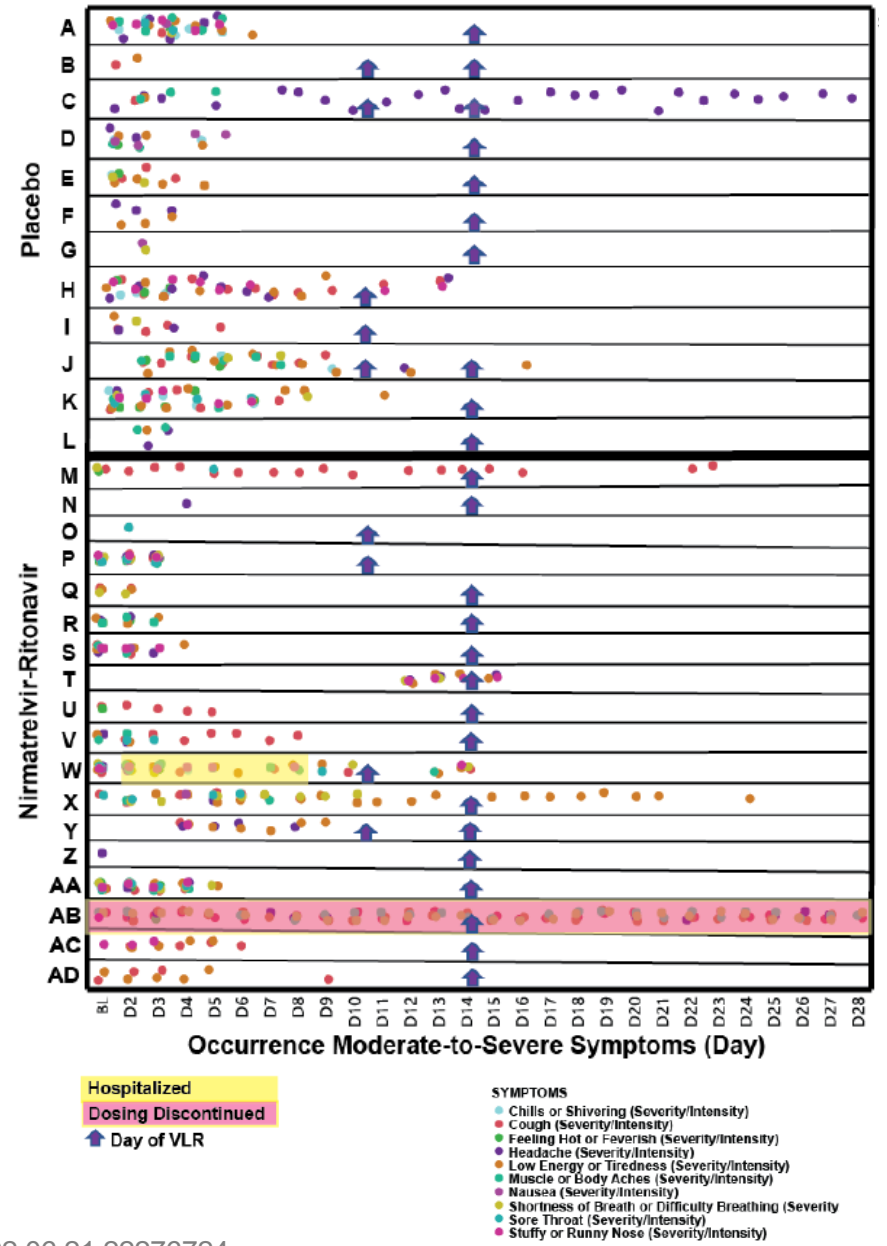
2 Resistance

- mAbs (well-characterised)
- Small molecules (possible)

3 Pandemic Preparedness

- New zoonotic transmissions

		Population	N	Viral rebound	Clinical rebound	
EPIC HR	**RCT**	**NMV/r**	**1106**	**2.3%**		Pre-Omicron, largely unvaccinated
		placebo	**1110**	**1.7%**		Anderson et al
AGILE CST-2	**RCT**	**MOL**	**90**	**3.3%**	**0**	Mixed Omicron
		placebo	**90**	**4.4%**	**0**	
ACTIV-2	**RCT**	**Untreated**	**563**	**31% (↑ level 13%)**	**26%**	Largely unvaccinated, pre Omicron
SCORPIO SR	**RCT**	**ESV**	**590**	**7.8%**		abstract
		placebo	**574**	**4.7%**		
Wang et al*	**cohort**	**NMVr**	**11270**	**5.4%**	**5.87%**	Unpublished
		MOL	**2374**	**8.59%**	**8.21%**	EHR-based data, extracting codes for infection and symptoms
Wang et al *	**cohort**	**NMVr**	**15913**	**2.8-3.4%**	**2.4-2.9%**	Unpublished; Omicron era EHR-based data, extracting codes for infection and symptoms
Hong Kong	**cohort**	**NMVr**	**242**	**6.6%**		Omicron-era (BA2.2)
		MOL	**563**	**4.8%**		
		untreated	**3787**	**4.5%**		
Hong Kong	**cohort**	**NMVr**	**195**	**1.0%**		Hospitalised adults
		MOL	**746**	**0.8%**		CT values
		untreated	**11688**	**0.6%**		



Deo et al. Ann Intern Med. 2023 Mar;176(3):348-354
Anderson et al. N Engl J Med. 2022 Sep 15;387(11):1047-1049
Wong et al. Lancet Infect Dis. 2023 Jun;23(6):683-695
Wong et al. *JAMA Netw Open.* 2022;5(12):e2245086

Wang et al. medRxiv [Preprint]. 2022 Jun 22:2022.06.21.22276724
Wang et al. medRxiv [Preprint]. 2022 Aug 6:2022.08.04.22278450.
Khoo et al. Lancet Infect Dis. 2023 Feb;23(2):183-195
Scorpio SR. ECCMID 2023, Copenhagen, Denmark 15 - 18 April 2023

COVID-19: why do we still need antivirals ?

1 Need for greater sterilising potency

- Persistent or relapsing disease in immunosuppressed
- (Rebounds ??)

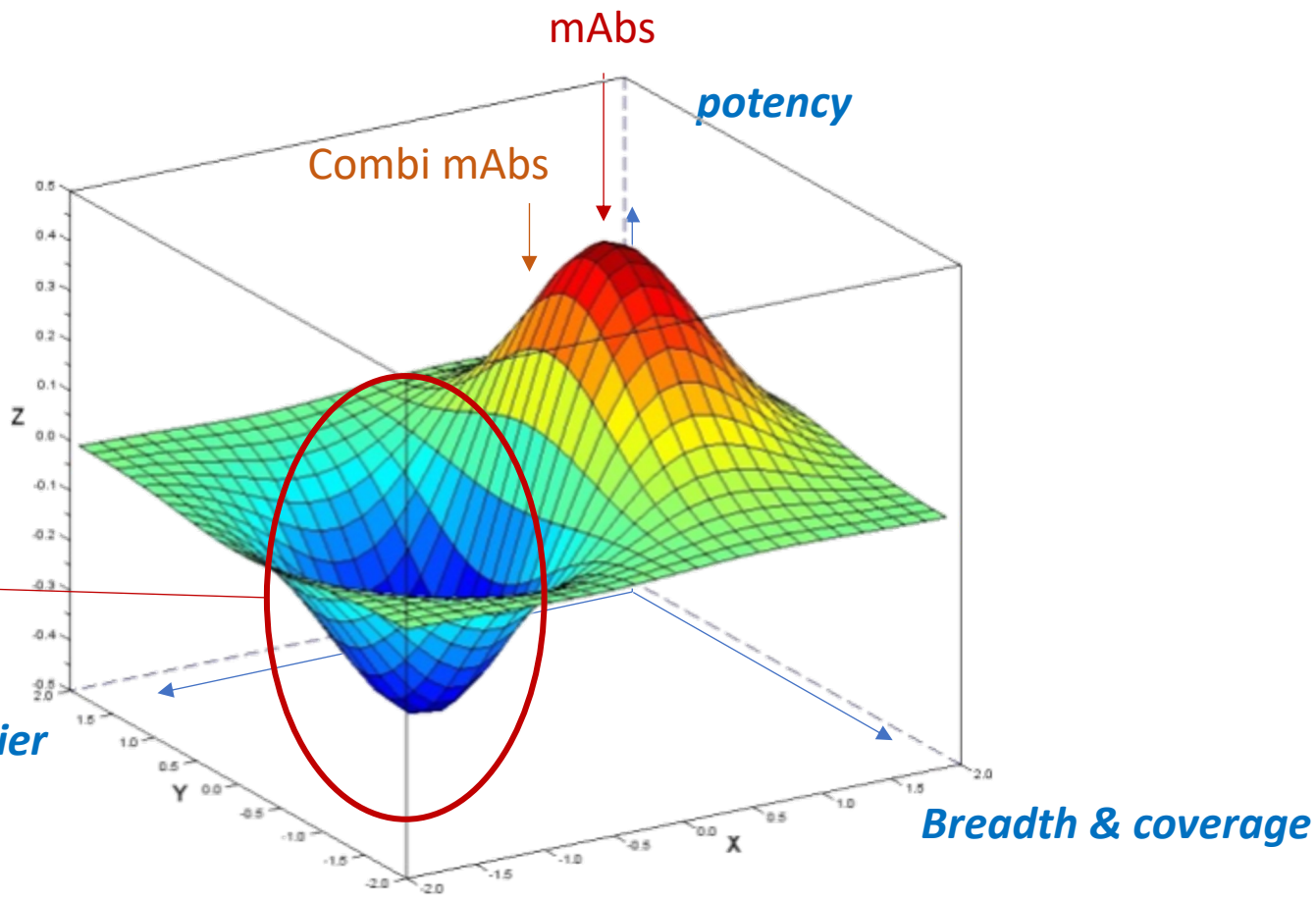
2 Resistance

- mAbs (well-characterised)
- Small molecules (possible)

3 Pandemic Preparedness

- New variants
- New zoonotic transmissions

Schematic – the Optimal Antiviral



COVID-19 Guidelines - Use of DAAs in Adults

Community

Standard risk

High risk

Hospitalised

Hypoxia

Critical, ventilated

Strong for / A / Recommended

Conditional or weak for / B or C / alternative

Conditional against / weak aganist

Strong against / not recommended

SARS-CoV-2 test positive within specified window
Symptomatic disease in adult patients

* Avoid in children and pregnancy

https://app.magicapp.org/#/guideline/nBkO1E/rec/LwrMyv
https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/hospitalized-adults--therapeutic-management/
https://app.magicapp.org/#/guideline/L4Qb5n/section/LAJvRn

Clinical Trial Endpoints

1 Death and hospitalisation

- Placebo arms of PINETREE (5.3%), EPIC-HR (7%) → PANORAMIC (1%)
- Difficult/ impossible to include placebo in high-risk populations

2 Participant-reported symptoms

- Open-label designs ?
- Which questionnaires, how and when to evaluate ?

3 Virology

- RNA *vs* infectious virus ?
- Qualitative *vs* titre *vs* elimination rates ?
- Limited value for predicting clinical utility

Virology and clinical endpoints not always concordant

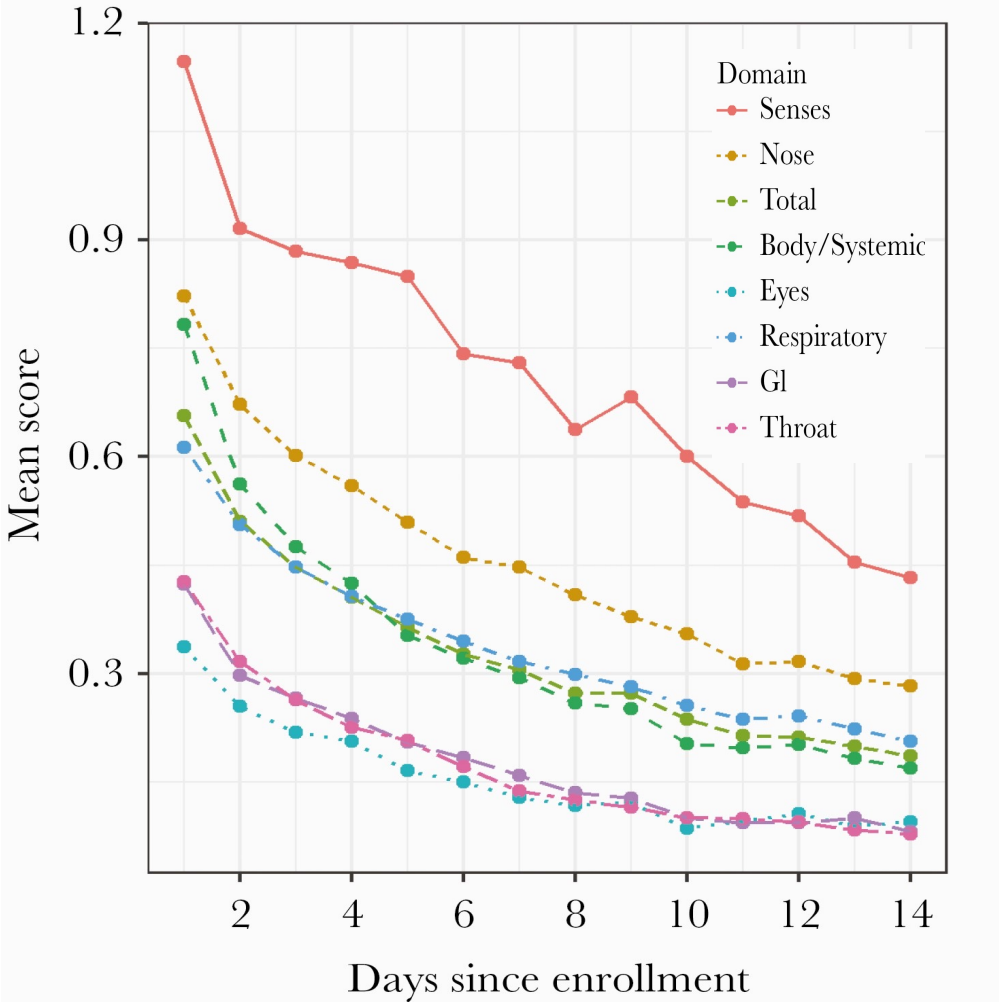
	Drug		N	Population	Clinical benefit	Virological signal
PINETREE	**RDV**	III	562	Outpatient	Y ∇	N [R]
AGILE CST-2	**MOL**	I/II	180	Outpatient	N ∇	Y [R]
MoveOut	**MOL**	III	1433	Outpatient	Y [DHW]	Y [R] (D3, D5 only)
PANORAMIC	**MOL**	IV	26,411	Outpatient	N [DHW] Y [§]	Y [R] (D7; P=0.039)
EPIC-HR	**NMV/r**	III	2246	Outpatient	Y [DHW]	Y [R] (D5 ; 1 log if started in 72h; P<0.001)
SCORPIO-SR	**Ensitrelvir**	II/III	1798	Outpatient	Y ◊	Y [C R]
SPRINT (Enanta)	**EDP-235**	II	231	Outpatient	Y ◊	N [C R]
Pardes	**PBI-0451** **Pomotrelvir**	II	230	Outpatient	N ◊	N [C R]
MOONSONG	**AT-527**	II	100	Outpatient	N	N [C] (all) High Risk - ↓0.5 log D3
MORNINGSKY	**AT-527**	III	207	Outpatient	N [§] ↓ hosp	-

∇ *FLU-PRO Plus*
◊ *FDA instrument*
§ *other symptom scale*

DHW deaths, hospitalisations and/or WHO score

C infectious virus
R RNA titre

Participant-reported Symptoms		Trials
FLU-PRO Plus	Originally severity (5-point scale) & frequency of 34 symptoms over 6 domains - nose, throat, eyes, respiratory, gastrointestinal, systemic Senses (taste & smell) added	COMET-ICE, PINETREE



EPICC cohort (N=226)

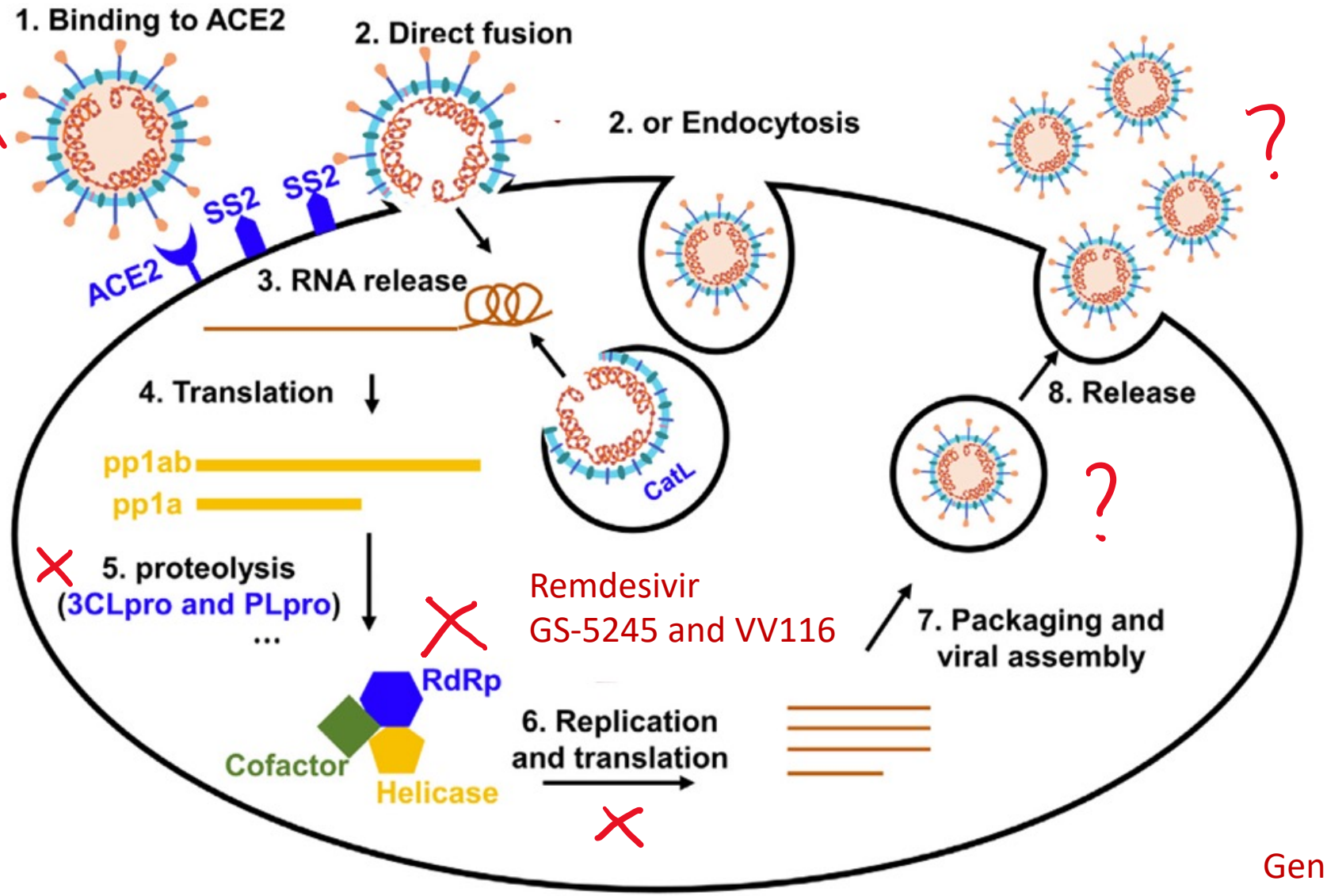
Mar 2020- Jun 2021

mean domain and total scores

Richard et al. Open Forum Infect Dis, 2021;8:ofab517,

Antiviral Therapy – potential targets

mAbs
Ab-like molecules



Nirmaltrelvir/r
Ensitrelvir (S-217622)
PBI-0451
EDP-235
ALG 097558
CDI-45205
others

Remdesivir
GS-5245 and VV116

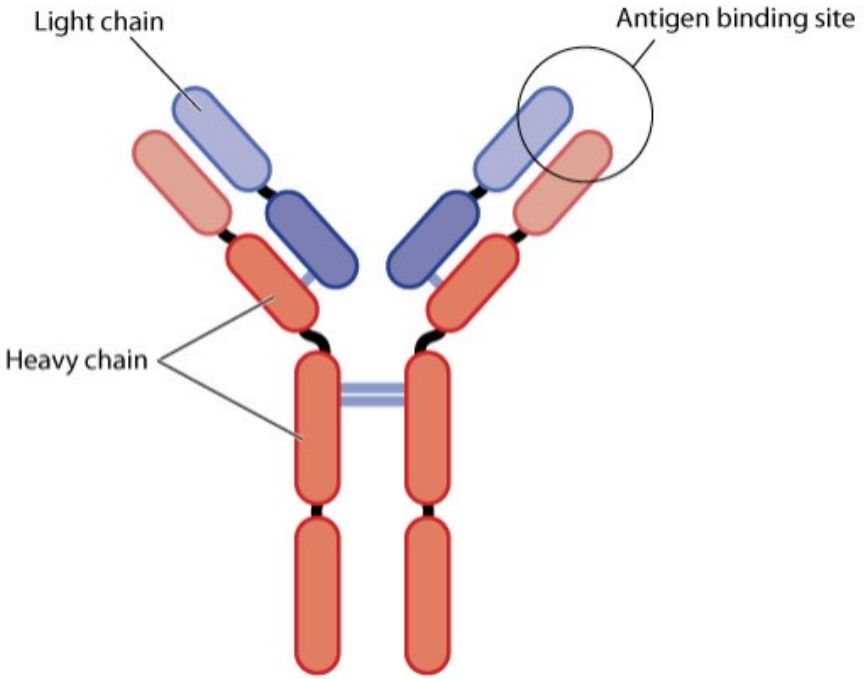
Molnupiravir
Favipiravir

Others:
siRNA
Gene therapy
etc, etc

Su et al. Fundamental Research 2021;1(2): 151-165

Antibodies – not all the same

- **Convalescent plasma** *vs* **mAbs** *vs* **bnAbs**
- **Binding sites**
- **Neutralising activity – neutralising potency** *vs* **breadth**
- **Route, dose and indication** *(treatment vs prophylaxis)*
- **Pharmacokinetics**
- **ADE and ADCC**



Bamlanivimab/ Etesevimab

Casirivimab/ Imdevimab

Regdanvimab

Bebtelovimab

Tixagevimab/ Cilgavimab

Sotrovimab

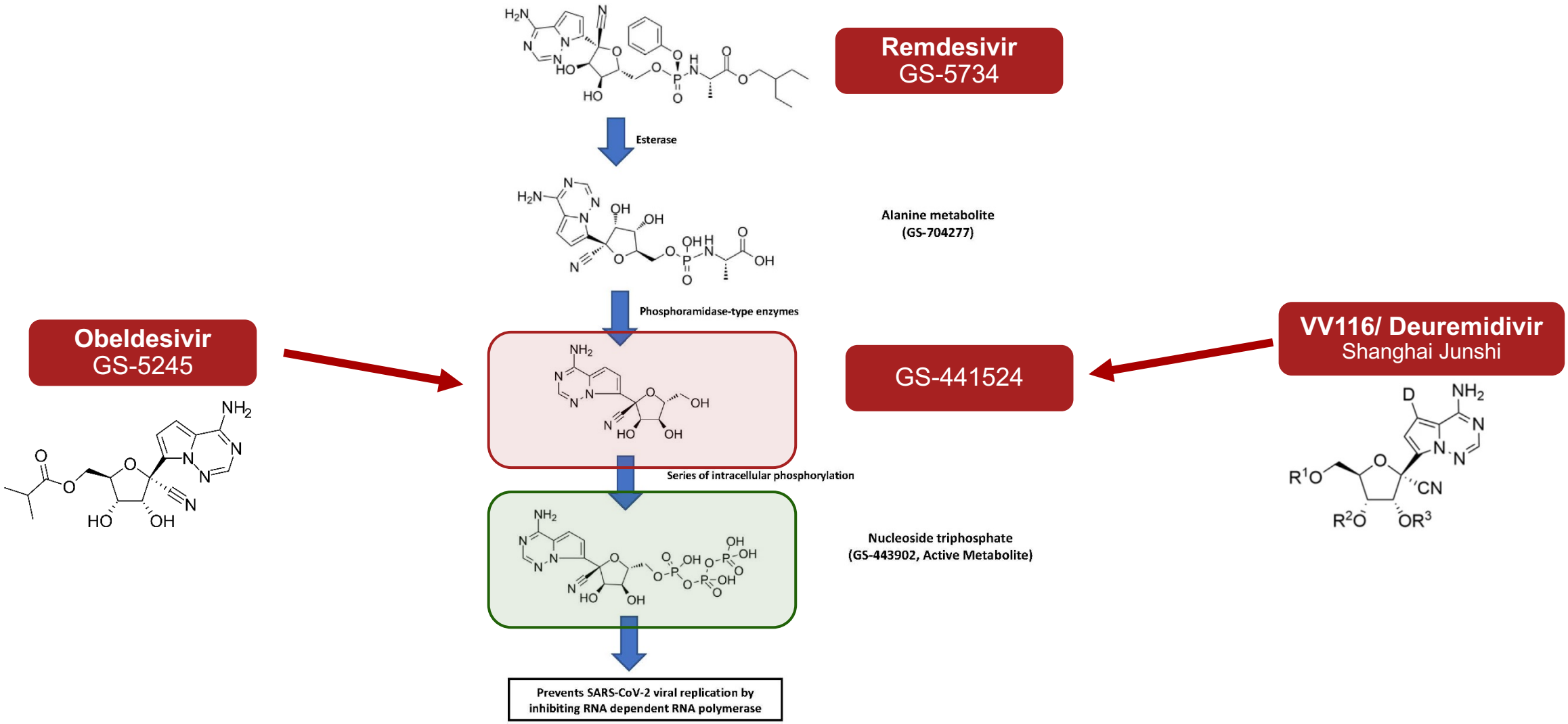
AZD5156/AZD3152

SA-58

Nanobodies

Sherpabodies (mimetic) (eg TriSb92)

Oral versions of Remdesivir ?



Deb et al. Pharmaceuticals. 2021; 14(7):655

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19

Z. Cao, W. Gao, H. Bao, H. Feng, S. Mei, P. Chen, Yueqiu Gao, Z. Cui, Q. Zhang, X. Meng, H. Gui, W. Wang, Y. Jiang, Z. Song, Y. Shi, J. Sun, Y. Zhang, Q. Xie, Y. Xu, G. Ning, Yuan Gao, and R. Zhao

RESULTS

A total of 822 participants underwent randomization, and 771 received VV116 (384 participants) or nirmatrelvir–ritonavir (387 participants). The noninferiority of VV116 to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery was established in the primary analysis (hazard ratio, 1.17; 95% confidence interval [CI], 1.01 to 1.35) substantially between the two groups. No participants in either group had died or had had progression to severe Covid-19 by day 28. The incidence of adverse events was lower in the VV116 group than in the nirmatrelvir–ritonavir group (67.4% vs. 77.3%).

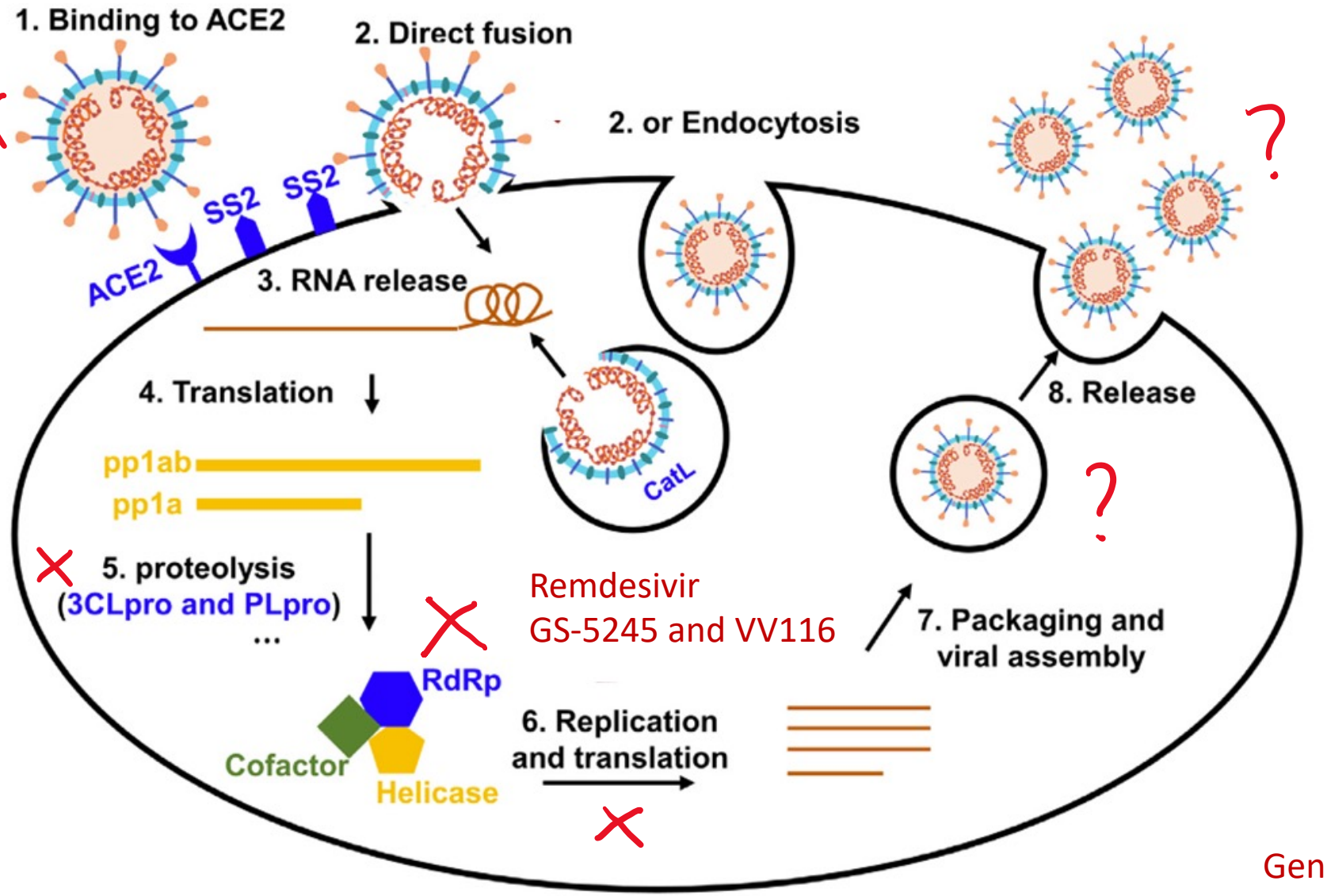
Gilead Sciences Statement on Phase 3 Obeldesivir Clinical Trials in COVID-19: BIRCH Study to Stop Enrollment While OAKTREE Study Nears Full Enrollment

Foster City, Calif., September 28, 2023 – Gilead Sciences, Inc. (Nasdaq: GILD) today announced that it has stopped patient enrollment in BIRCH (Study GS-US-611-6273), a Phase 3 study evaluating the efficacy and safety of obeldesivir compared with placebo in non-hospitalized participants who are at high risk for developing severe COVID-19. This decision is based on lower-than-expected COVID-19 incidence rates and related hospitalizations or all-cause death by Day 29, which are primary endpoints in the study. The decision does not reflect any safety or efficacy concerns. Patients already enrolled will continue in the study which remains blinded.

The decision to stop enrolling patients in the BIRCH study does not impact the OAKTREE study (GS-US-611-6549), a Phase 3 study evaluating the safety and efficacy of obeldesivir compared with placebo in non-hospitalized participants without risk factors for developing severe COVID-19. OAKTREE is rapidly approaching full enrollment and will continue to enroll patients in the United States and Japan. Data from

Antiviral Therapy – potential targets

mAbs
Ab-like molecules



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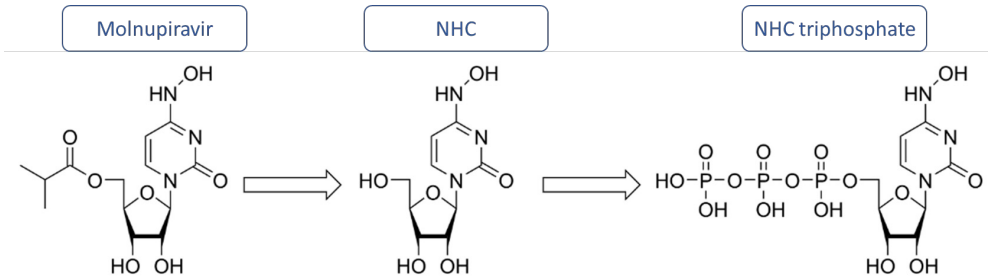
Molnupiravir
Favipiravir

Others:
siRNA
Gene therapy
etc, etc

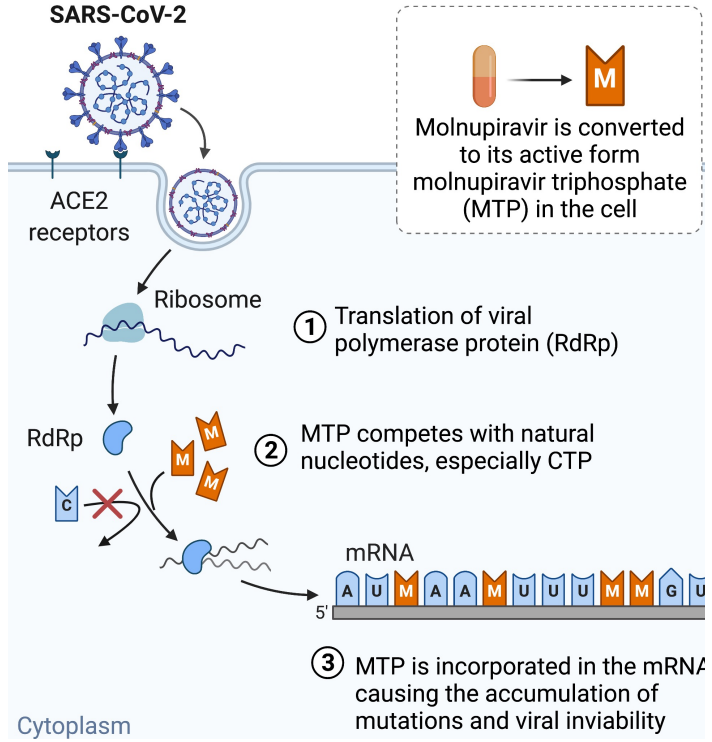
Su et al. Fundamental Research 2021;1(2): 151-165

Molnupiravir

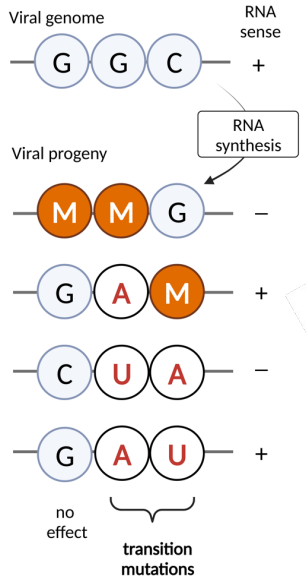
Molnupiravir is a prodrug



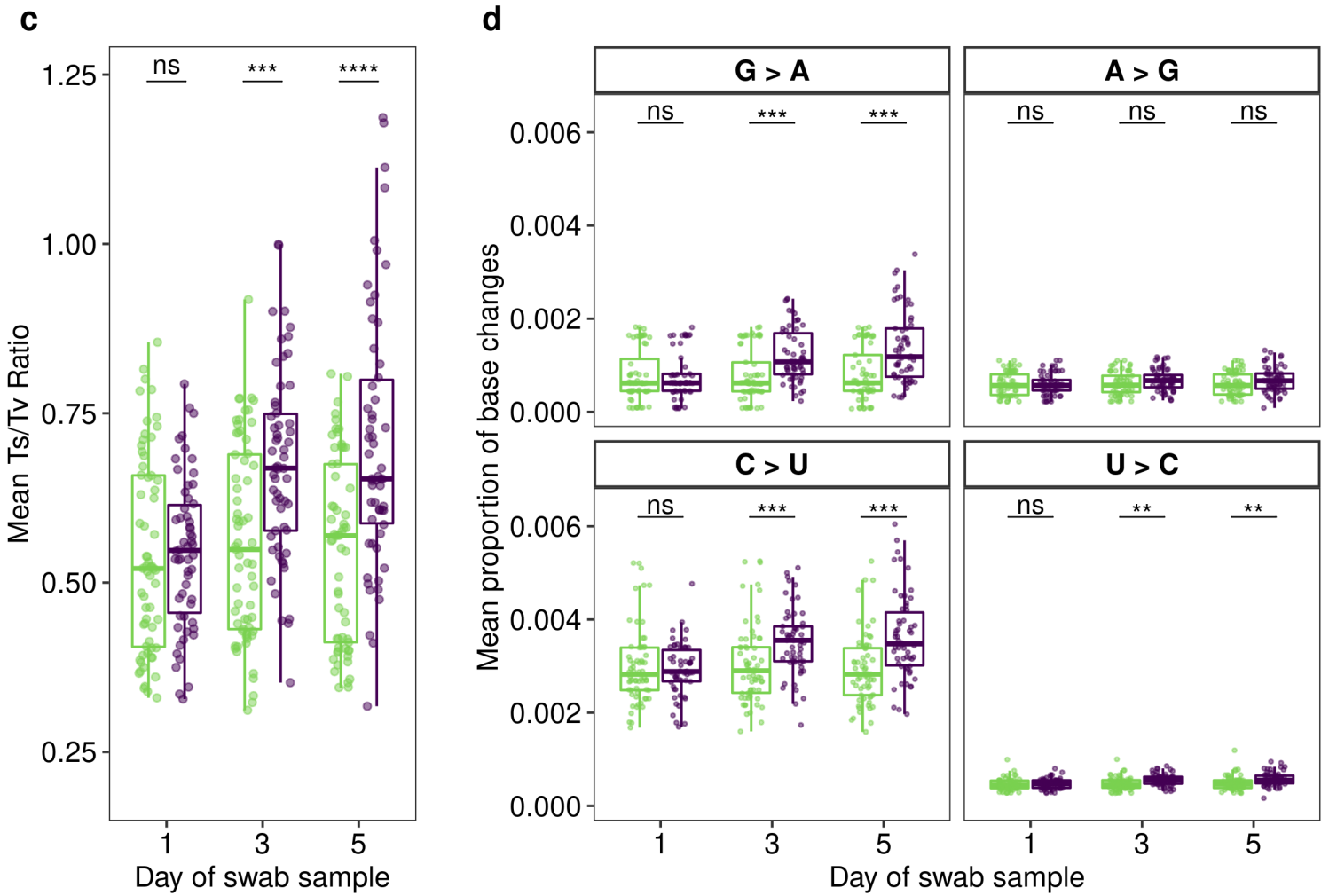
.. incorporated into mRNA ….



.. and inducing error catastrophe….



Hallmark of molnupiravir treatment detectable *in vivo*



Treatment allocation

placebo n = 65

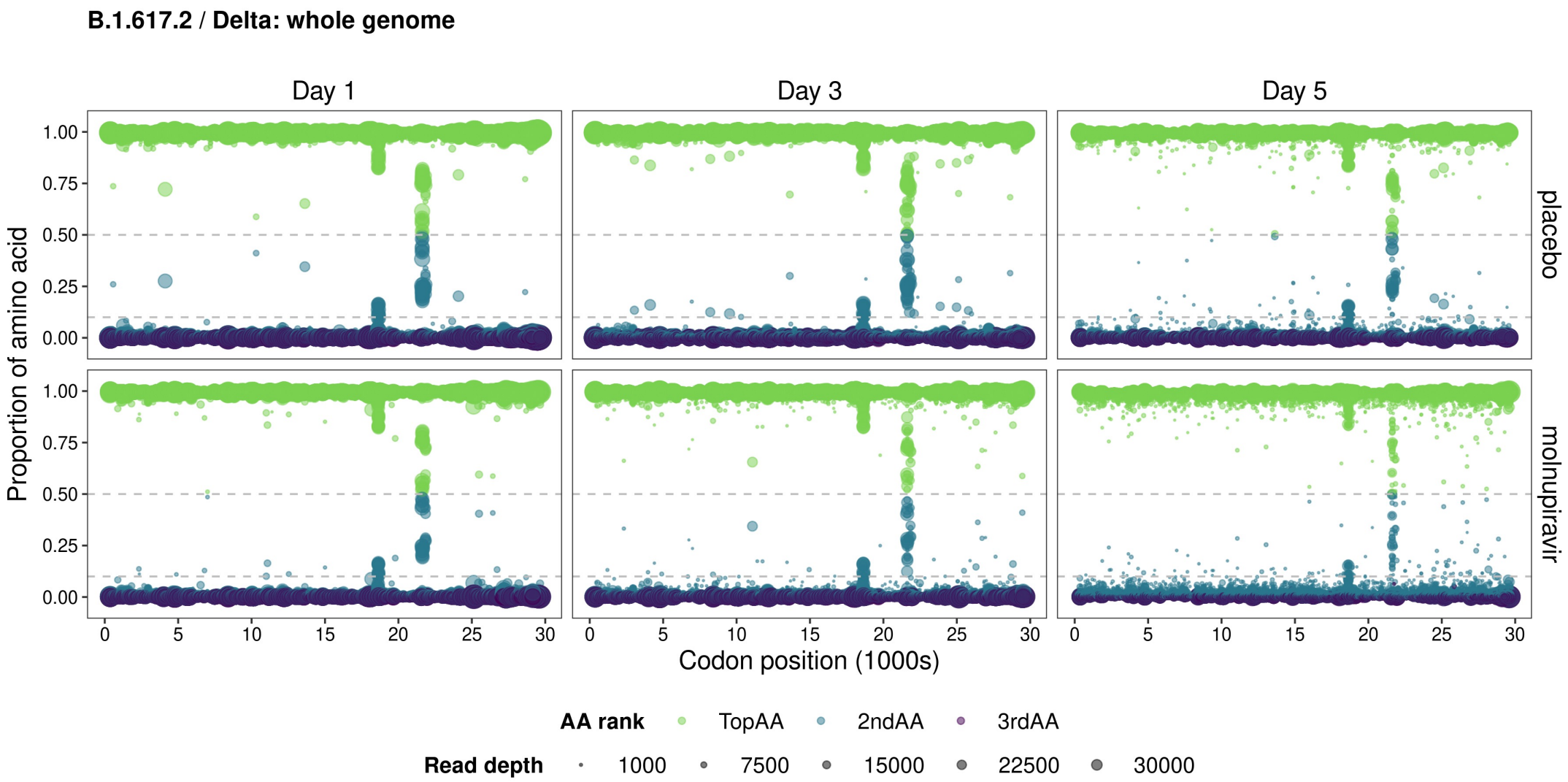
molnupiravir n = 59

****$P \leq 0.0001$, ***$P \leq 0.001$, ns = $P > 0.05$

Mean transition/transversion ratio of SARS-CoV-2 significantly increases over time with molnupiravir but not placebo

Donovan-Banfield *et al.*, ResearchSquare 2022

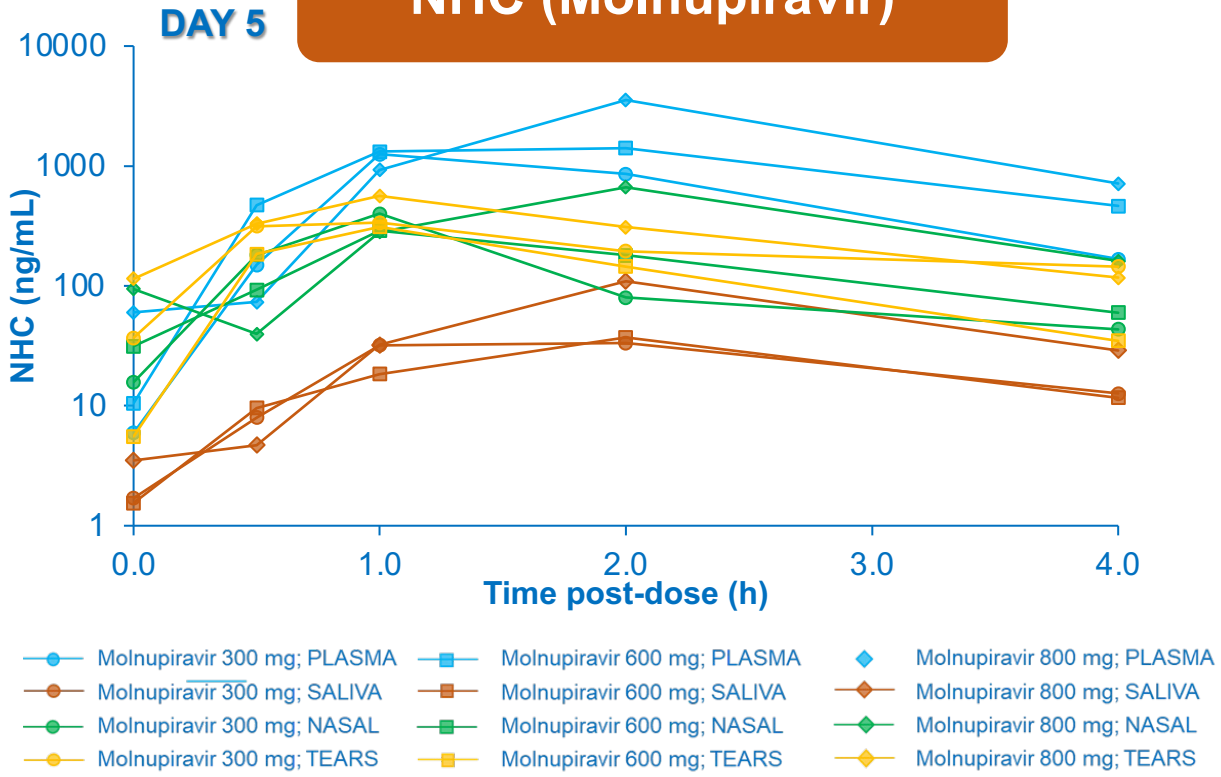
Predicted amino acid profile shows increased diversity over time



Donovan-Banfield *et al.*, Nat Comm 2022; 2022 Nov 26;13(1):7284

PK : Non-plasma:Plasma Ratios ($R_{NP:P}$)

NHC (Molnupiravir)

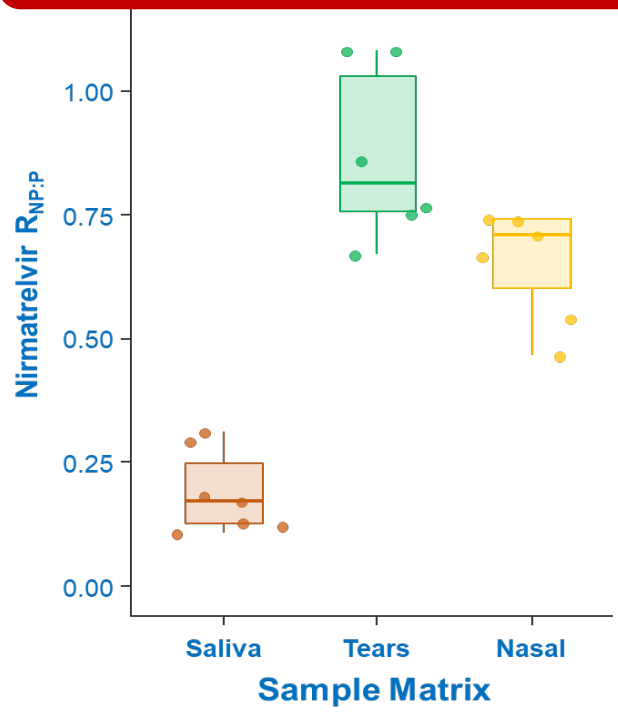


$R_{NP:P}$	Overall [median (range)]
Saliva	0.03 (0.01-0.11, 60%; n=16)
Nasal secretions	0.21 (0.05-0.73, 70%; n=17)
Tears	0.22 (0.09-1.05, 92%; n=12)

* n=3, # n=2, § n=1

NHC $R_{NP:P}$, expressed as geometric mean (CV%) unless stated otherwise

Nirmatrelvir

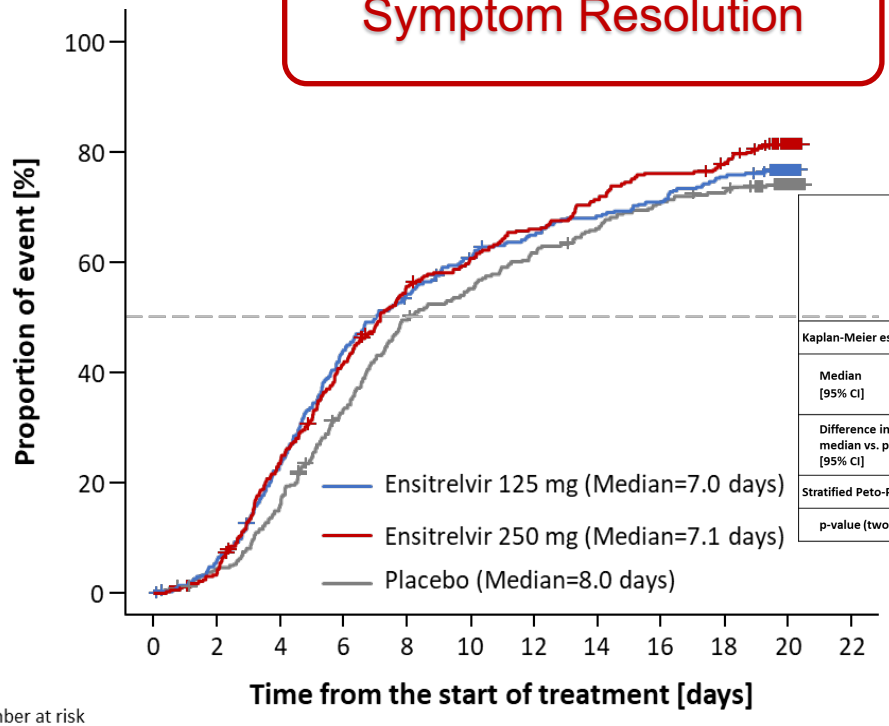


Drug	$R_{NP:P}$ Saliva	Tears	Nasal
n	7	6	7
Nirmatrelvir	**0.18 (45)**	**0.86 (20)**	**0.70 (33)**
Ritonavir	0.008 (20)	-	-

Fitzgerald et al CID 2022 Aug 24;75(1):e525-e528
Dickinson et al. Int Workshop Clin Pharm Antiviral Ther Sept 2023 Rome

Ensitrelvir – Scorpio SR

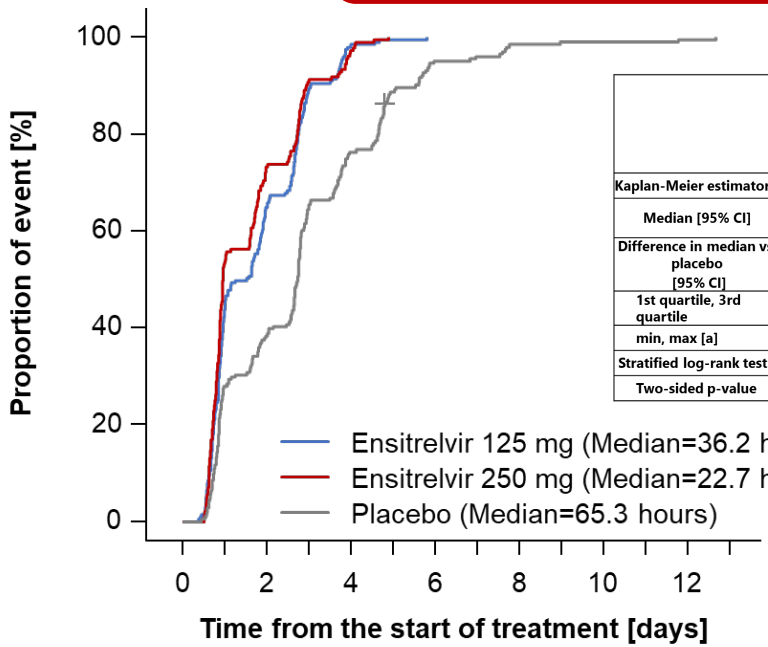
Symptom Resolution



	COVID-19 onset to randomization : <72 hours (Primary analysis)		
	Ensitrelvir 125 mg (n=347)	Ensitrelvir 250 mg (n=340)	Placebo (n=343)
Kaplan-Meier estimates (hours)			
Median [95% CI]	167.9 [145.0, 197.6]	171.2 [150.8, 190.3]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]	-24.3 [-78.7, 11.7]	-21.0 [-73.8, 7.2]	---
Stratified Peto-Prentice's generalized Wilcoxon test [a]			
p-value (two-sided)	0.0407	0.0203	---

Number at risk											
Ensitrelvir 125 mg	336	314	255	186	151	128	113	102	94	79	55
Ensitrelvir 250 mg	329	315	247	188	141	124	107	90	75	67	37
Placebo	321	304	265	208	158	139	119	104	89	83	52

Infectious Virus



	COVID-19 onset to randomization : <72hr (Primary analysis)		
	Ensitrelvir 125 mg group (n=199)	Ensitrelvir 250 mg group (n=183)	Placebo group (n=211)
Kaplan-Meier estimator (hours)			
Median [95% CI]	36.2 [23.4, 43.2]	22.7 [21.2, 37.9]	65.3 [62.0, 66.8]
Difference in median vs. placebo [95% CI]	-29.1 [-42.3, -21.1]	-42.6 [-44.6, -27.4]	---
1st quartile, 3rd quartile	19.5, 64.0	18.2, 60.6	21.8, 93.6
min, max [a]	8.8, 139.3	11.9, 116.8	10.5, 303.8
Stratified log-rank test [b]			
Two-sided p-value	<.0001	<.0001	---

Primary Endpoint – symptom resolution

5 symptoms (prespecified)

Subgroup within 72h of symptom onset

Ensitrelvir 125mg - approx 1 day faster

Ensitrelvir 125mg - 29h faster

Uehara et al CROI 2023 OA-9

Long COVID Symptoms, ≤120 hours

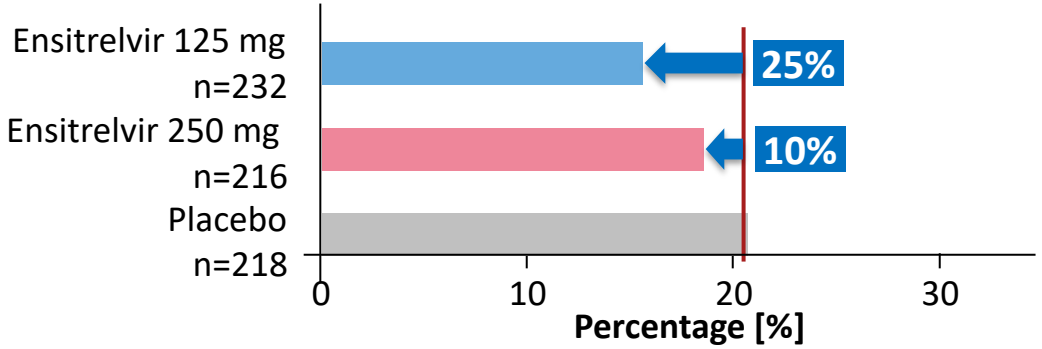
Definition for presence of Long COVID symptoms in post-hoc analysis

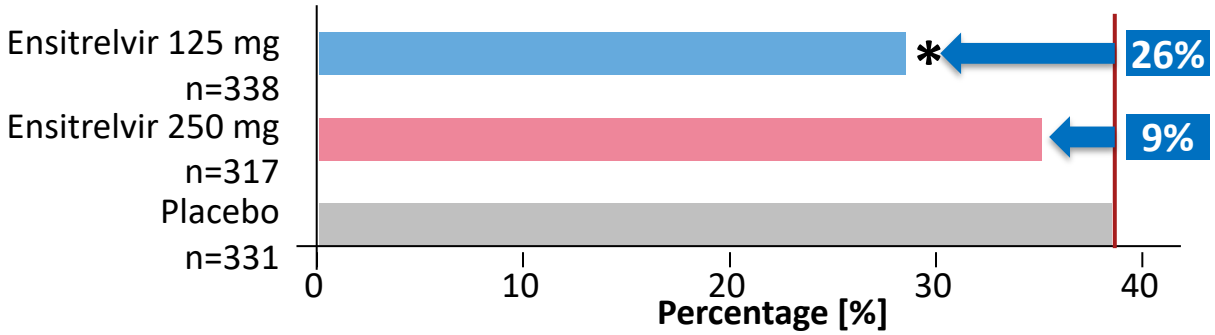
- Symptoms listed in 14 COVID-19 symptom questionnaire
  - ✓At least 2 consecutive time points with a mild or more severe symptom continuing from the last observation in the follow up (e.g., Day 21) to Day 169
- Symptoms listed only in PASC questionnaire
  - ✓One mild or more severe symptom at Day 85 OR Day 169
- Relationship with COVID-19: Yes (related) or unknown symptoms (exclude No (not related))

Proportion with ongoing symptoms (14 COVID-19 symptoms)

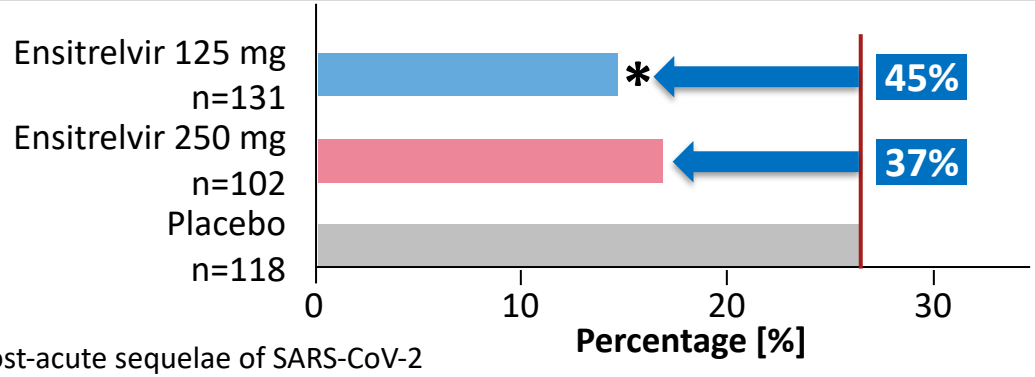
Proportion of 4 neurological symptoms in PASC Questionnaire

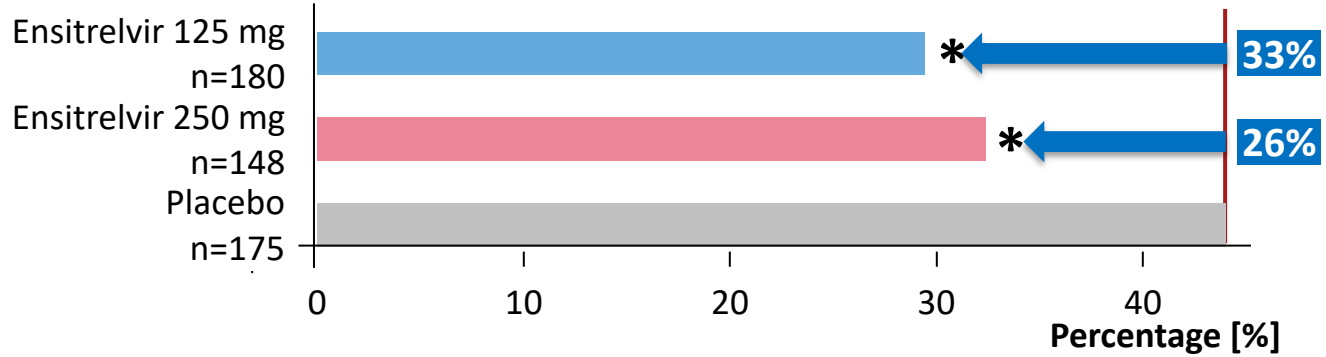
Overall population





Subpopulation of patients who have high symptom score for 14 symptoms at baseline[a]





PASC= post-acute sequelae of SARS-CoV-2

*: P value by Fisher's exact test <0.05 [a]high symptom score is defined as the total score of 14 symptoms at baseline ≥ 9

Uehara et al CROI 2023

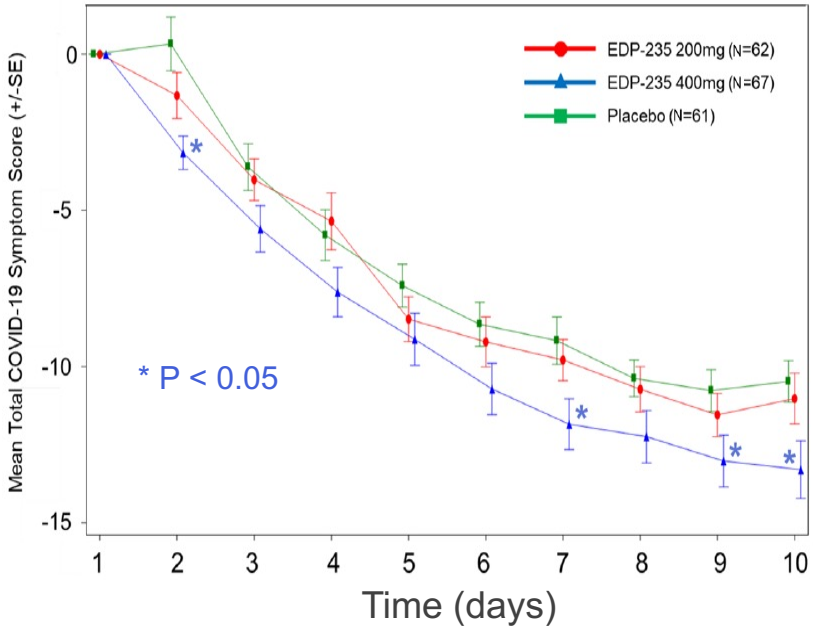
EDP-235 : Change in Symptom Scores

3CL^{pro} inhibitor

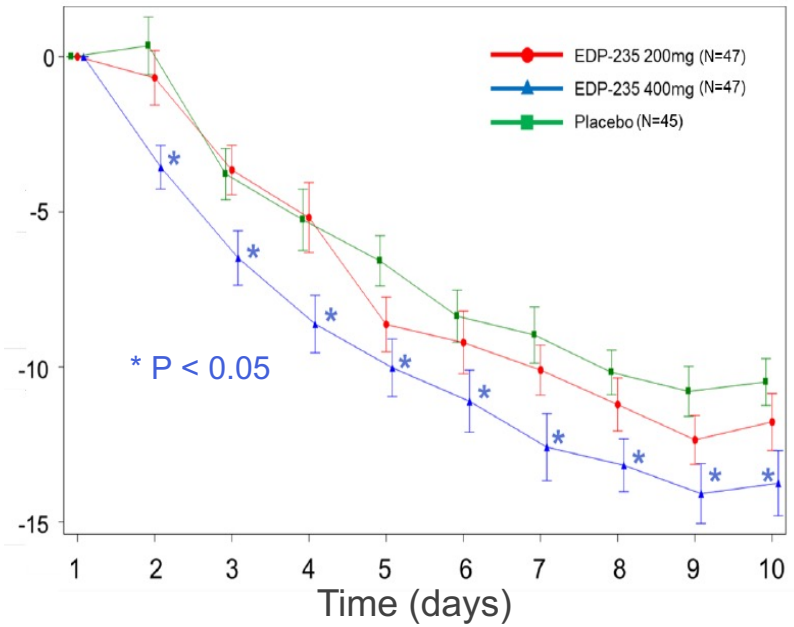
SPRINT study (Phase II); N ~ 200

EDP-235 200mg vs 400mg vs placebo

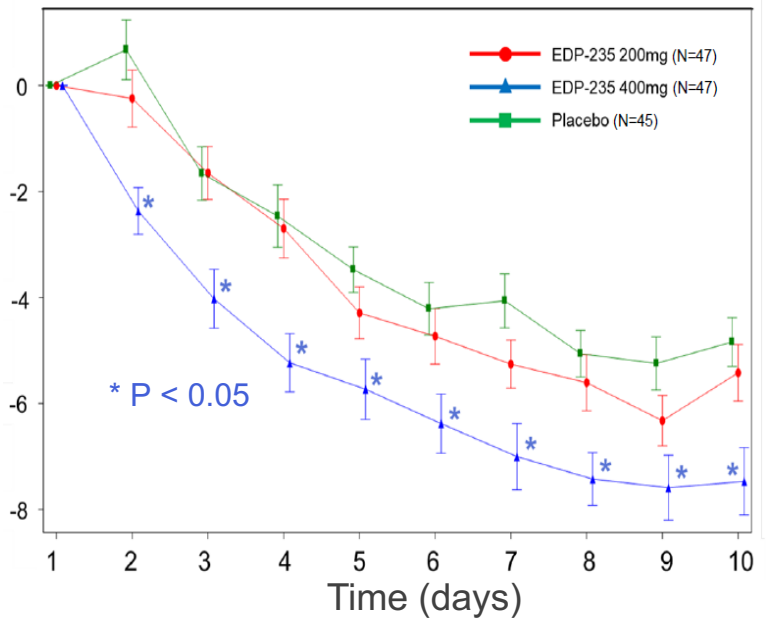
14 symptoms
Within 5d onset



14 symptoms
Within 3d onset



6 symptoms
Within 3d onset



No difference in VL reduction between treatment arms and placebo
(subgroup with BL VL >5 log had reduction of 0.4 log over placebo at 3d)

https://ir.enanta.com/events-presentations
May 8 2023 and Sept 12 2023

Pomotrelvir (PBI-0451) :

- 3CL^{pro} inhibitor
- Phase II, mild-moderate disease (N = 242), non-hospitalised
- Within 5d of symptoms

Virology

- Negative infectious virus at D3 * - pomotrelvir (70%) vs placebo (63%)
- No difference in infectious virus or RNA at D2, 3, or 5

Symptoms

- No difference in FDA symptom score (14) or (12) or (5)

Viral titres lower, clearance and symptom resolution more rapid than anticipated

Clinical Development halted

* Primary endpoint

Kearney et al CROI 2022 (LB470)
https://ir.pardesbio.com/news-releases/news-release-details/pardes-biosciences-announces-top-line-results-phase-2-trial

Bemnifosbuvir (AT-527)

- RdRp inhibitor (guanosine analogue)
- Broad spectrum

MOONSONG (Phase 2, non-hospitalised)

- No difference in viral (RNA) clearance between 2 doses of AT-527 and placebo
- Potential signal in (prespecified) subgroup of participants with underlying medical conditions

MORNINGSKY (Phase 3, non-hospitalised)

- Closed early – bemnifosbuvir (137) vs placebo (70)
- Time-to-symptom alleviation (primary endpoint) not met
- Exploratory analysis (unadjusted) – 71% reduction in hospitalisations

- **SUNRISE-3**

Good et al. AAC 2021 Mar 18;65(4):e02479-20
Shannon et al. Nat Commun. 2022 Feb 2;13(1):621
https://ateapharma.com/covid-19/bemnifosbuvir/

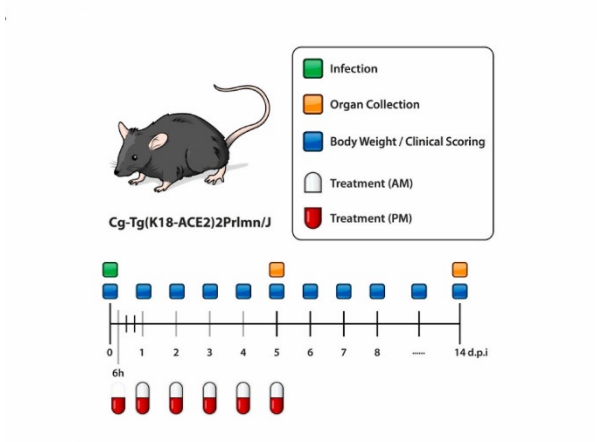
Rational Selection of Combinations

- **Small molecule + small molecule**
- **mAb + small molecule**
- **Antiviral + Host-targeted**

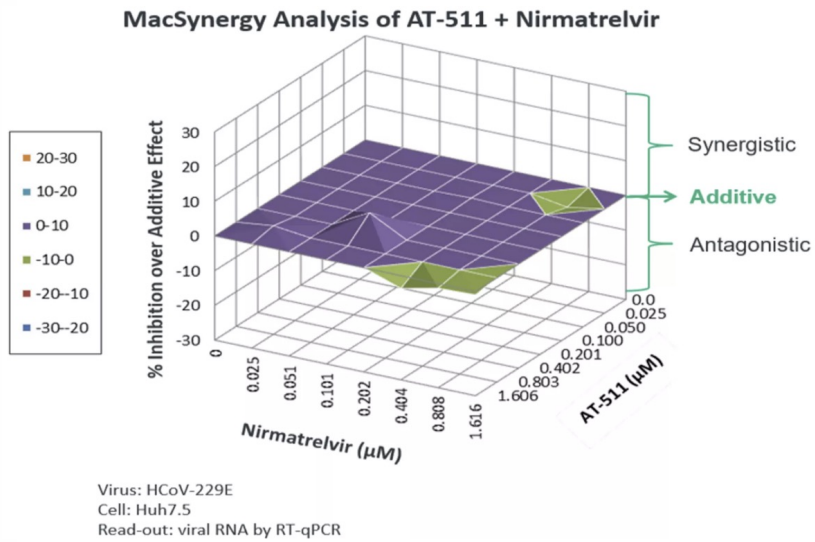
Rational design of regimens, based on:
- Additivity, synergy
- Parity of evidence
- Operational deployment

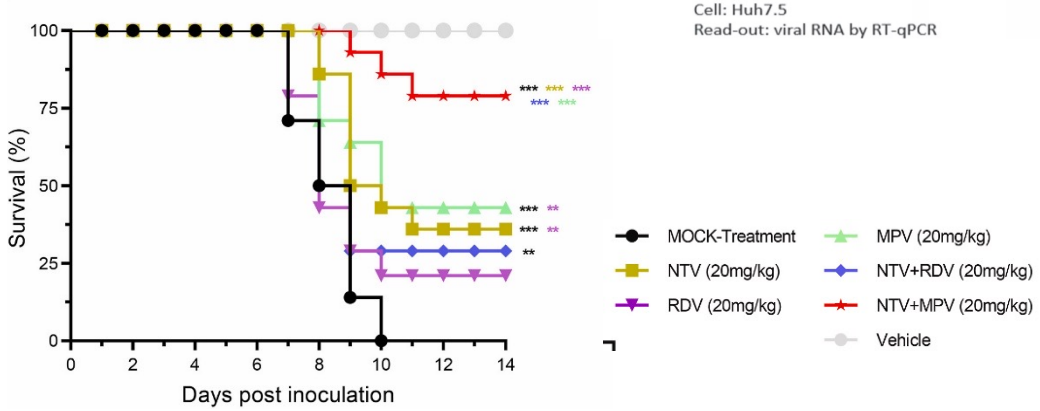
Argues for publicly-funded platforms !

NMV + MOL



NMV + Bemnifosbuvir





Jeong et al. Antiviral Res 2022;208:105430

https://ateapharma.com/covid-19/bemnifosbuvir/

New SARS-CoV-2 Antivirals

- **Continued need for better drugs**
  - *greater potency*
  - *fewer DDIs*
- **Case for evaluating combinations**
- **Importance of publicly-funded trial platforms**
  - *able to develop protocols 'at-risk'*
  - *access candidates from academia and small-medium biotech*
  - *rational design and timely evaluation of combinations*
- **Access, access, access**
  - *testing*
  - *participation in clinical trials*
  - *affordable treatments*

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