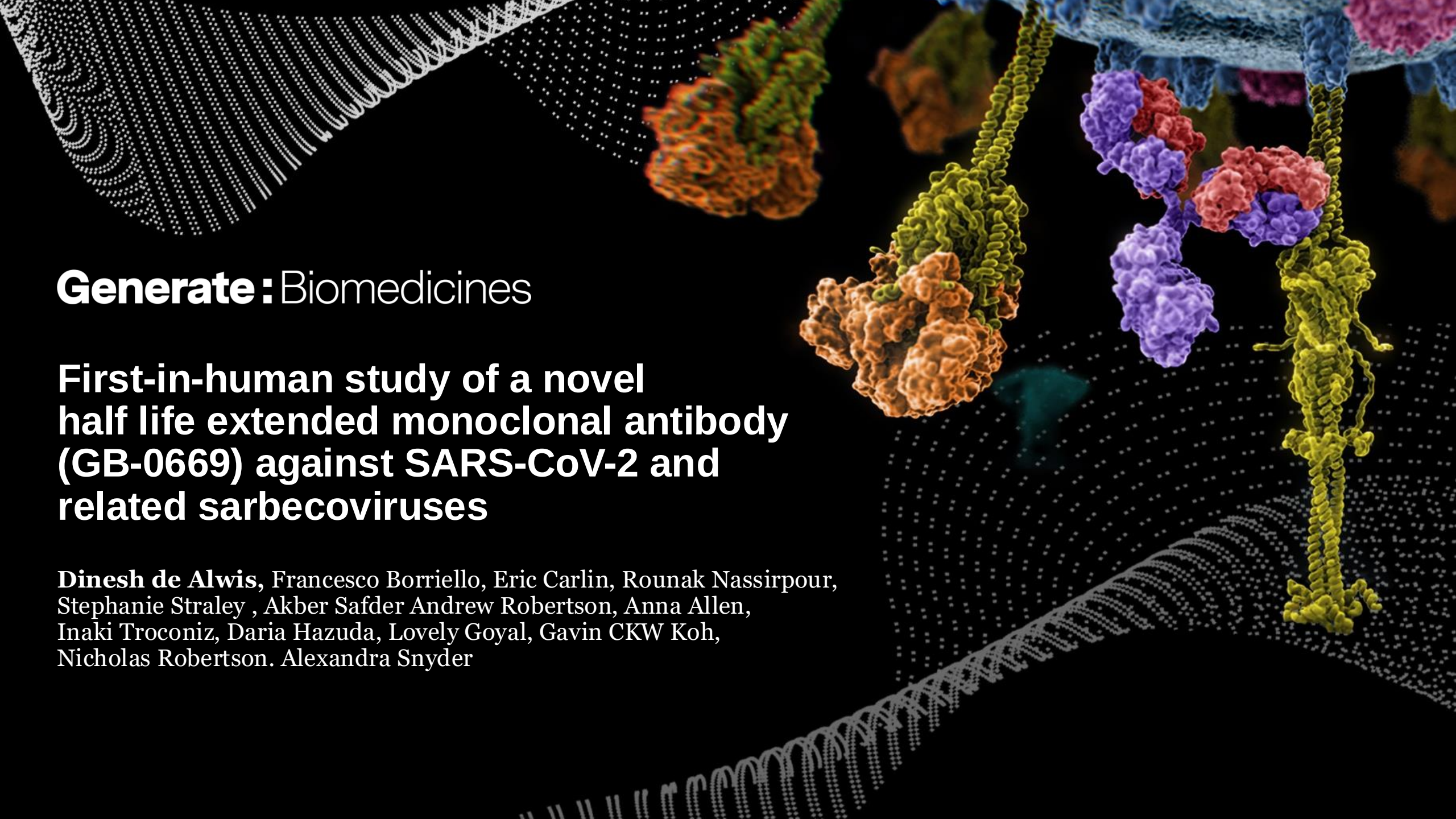


Generate : Biomedicines

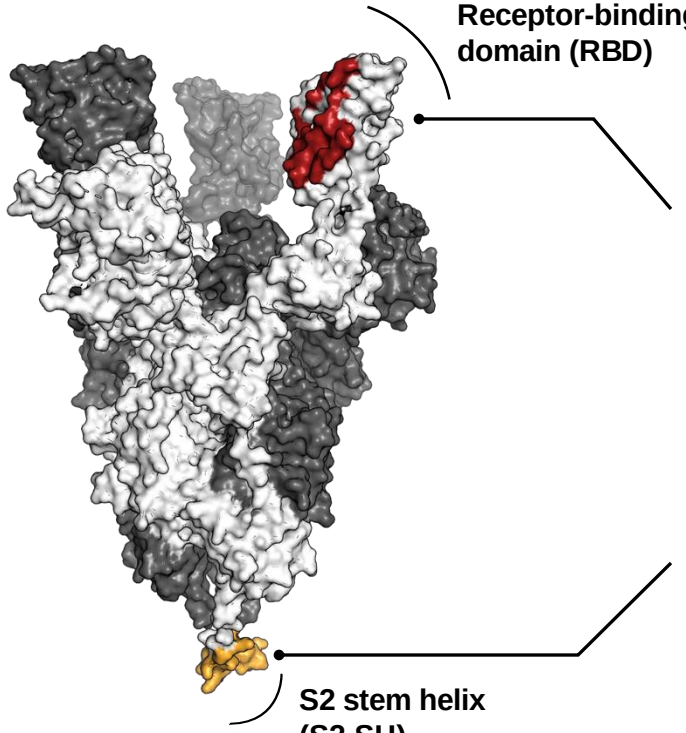
First-in-human study of a novel half life extended monoclonal antibody (GB-0669) against SARS-CoV-2 and related sarbecoviruses

Dinesh de Alwis, Francesco Borriello, Eric Carlin, Rounak Nassirpour, Stephanie Straley , Akber Safder Andrew Robertson, Anna Allen, Inaki Troconiz, Daria Hazuda, Lovely Goyal, Gavin CKW Koh, Nicholas Robertson. Alexandra Snyder

Disclosures

- Dr. De Alwis has stock in Merck Inc.
- Dr. De Alwis is a current employee of Generate Biomedicines

Generate Biomedicines has generated **GB-0669**, **a highly specific, potent, half-life extended therapeutic antibody.** Effective against diverse sarbecoviruses and multiple **SARS-CoV-2 variants** despite continued evolution



All authorized clinical mAbs to date are RBD binders

The RBD is highly immune dominant in human infection, and the normal antibody response drives viral evolution at this site.

Anti-S2-SH mAb (GB-0669):

The epitope of GB-0669 is >99% conserved and subject to limited immune pressure.

Lack of selective pressure at this site means resistance mutations have not been seen to-date.

SARS-CoV-2 variants and other sarbecoviruses	GB-0669 EC50 [ng/ml]	Sotrovimab EC50 [ng/ml]*
SARS-CoV-1	0.2	28[a]
WIV1	1.8	1117[a]
SARS-CoV-2 D614G	18.8	32[b]
SARS-CoV-2 Delta	39.9	42[b]
SARS-CoV-2 BA.4/5	4.8	1120[b]
SARS-CoV-2 BQ.1.1	5.1	4263[b]
SARS-CoV-2 XBB.1.5	8.8	970[c]
SARS-CoV-2 BA.2.86	1.6	1890[c]
SARS-CoV-2 EG.5.1	5.2*	880[c]
SARS-CoV-2 JN.1	16.6*	2300[c]

≤ 50 ng/ml | 51-200 ng/ml | 201-1000 ng/ml | >1000 ng/ml

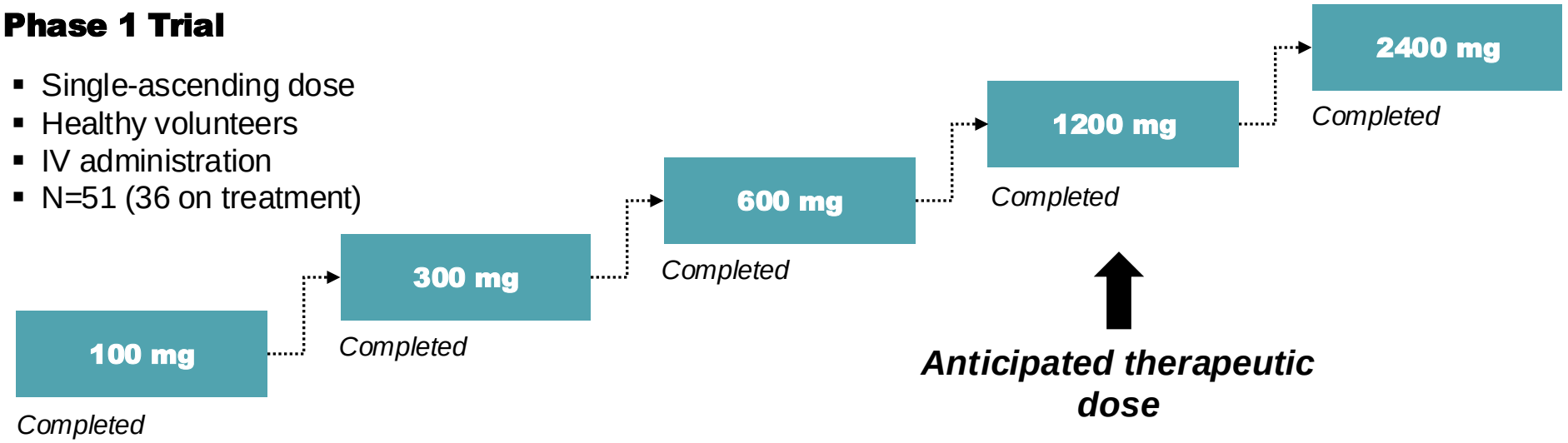
**Live Virus* [a]Liu *Sci Translat Med* 2022; [b]Liu *bioRxiv* 2023; [c]Yang *Lancet Infect Dis* 2023

IDWeek2024 abstract 87 Schmitt

Generate:Biomedicines

The First-In-Human Study of GB-0669 has completed enrolment

GB-0669 has completed enrolment of its Phase 1 HV study



Primary Objective: Safety and Tolerability of GB0669

Other Objectives: Characterize PK and PD (SARS-CoV 2 serum neutralization)

Five sequential cohorts

Each cohort randomized to receive either GB-0669 or placebo in ratios of 3:3, 3:3, 10:3, 10:3, 10:3 respectively

Data is preliminary
(Datacut: 14May2024)

GB-0669-101 Adverse Events were infrequent and mild with no evidence of relationship to dose

Adverse Events - Related

Cohort	# of Subjects	Dose Level	GRADE 1	GRADE 2	GRADE 3	GRADE 4	# of AEs	# of SAEs
Cohort 1	6 (3 active / 3 Placebo)	100 mg/Placebo	1	0	0	0	1	0
Cohort 2	6 (3 active / 3 Placebo)	300 mg/Placebo	0	0	0	0	0	0
Cohort 3	13 (10 active / 3 Placebo)	600 mg/Placebo	0	0	0	0	0	0
Cohort 4	13 (10 active / 3 Placebo)	1200 mg/Placebo	0	1	0	0	1	0
Cohort 5	13 (10 active / 3 Placebo)	2400 mg/Placebo	3	0	0	0	3	0
Total	**51 (36 active / 15 Placebo)**	**Total**	**4**	**1**	**0**	**0**	**5**	**0**

Treatment-related AEs were mild

- No serious AEs
- All related AEs were mild (Grade 1-2)

Adverse Events - Not Related

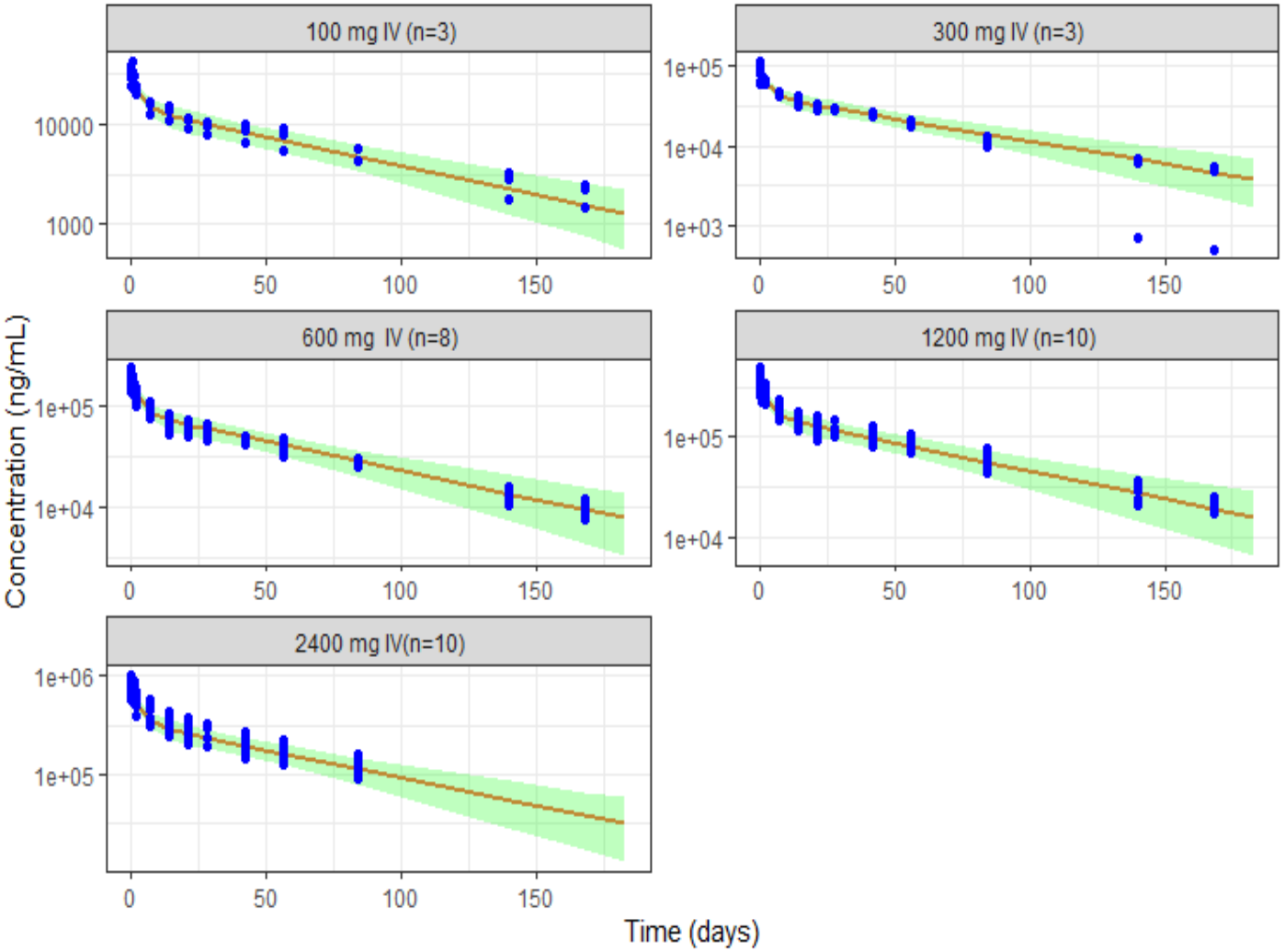
Cohort	# of Subjects	Dose Level	GRADE 1	GRADE 2	GRADE 3	GRADE 4	# of AEs	# of SAEs
Cohort 1	6 (3 active / 3 Placebo)	100 mg/Placebo	7	1	0	1 *	9	0
Cohort 2	6 (3 active / 3 Placebo)	300 mg/Placebo	5	0	0	0	5	0
Cohort 3	13 (10 active / 3 Placebo)	600 mg/Placebo	5	0	1 *	0	6	0
Cohort 4	13 (10 active / 3 Placebo)	1200 mg/Placebo	4	4	0	0	8	0
Cohort 5	13 (10 active / 3 Placebo)	2400 mg/Placebo	10	2	1 *	1 *	14	0
Total	**Total**	**Total**	**31**	**7**	**2**	**2**	**42**	**0**

*PT: Blood creatine phosphokinase increased. No associated symptoms, related to physical activity.

Unrelated AEs were mild

- No serious AEs
- All unrelated AEs were mild (Grade 1-2) excluding those related to physical activity (CK elevations)

PK is well behaved and dose proportional with low inter-subject variability and is consistent with PK predicted from non-human primates



Half-life 55 days

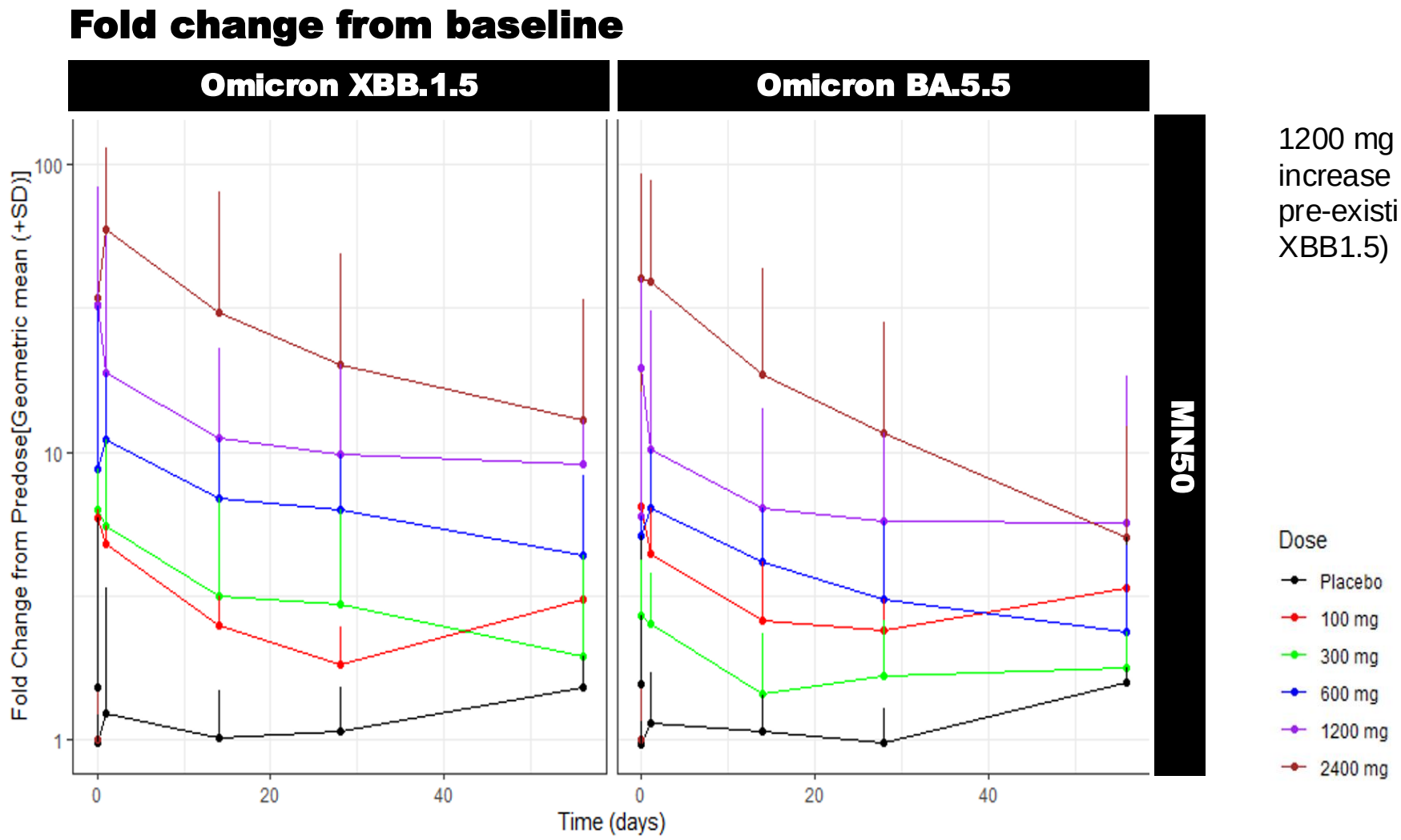
Median Predicted C_{max} of 1200 mg dose is 368,875 ng/ml

Areas in green cover the 95% prediction intervals of thousand simulated profiles

Solid lines represent the median of the predictions

Solid blue circles show observed concentrations

PD : GB-0669 boosts neutralizing titer in a dose-dependent fashion (MN50 live virus)



1200 mg dose provides a ~10-fold increase in titers in subjects with pre-existing SARS-CoV-2 titers (e.g XBB1.5)

There remains a significant need to treat persistent SARS-CoV-2 infection in B-cell depleted oncology patients

Nature Medicine 2024;30:2413–14

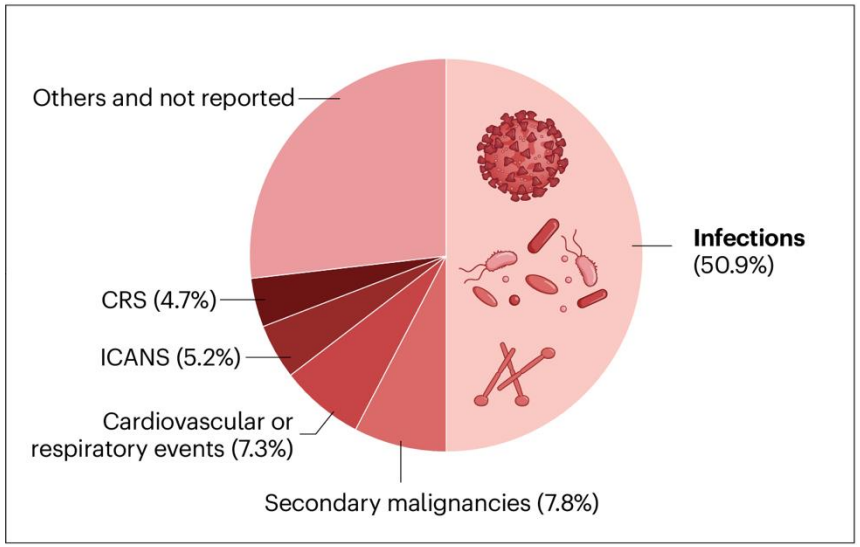
Cancer therapy

https://doi.org/10.1038/s41591-024-03212-2

Tracking non-relapse mortality after CAR T cell therapy

Viktoria Blumenberg & Marcela V. Maus

Top five non-relapse-related causes of death

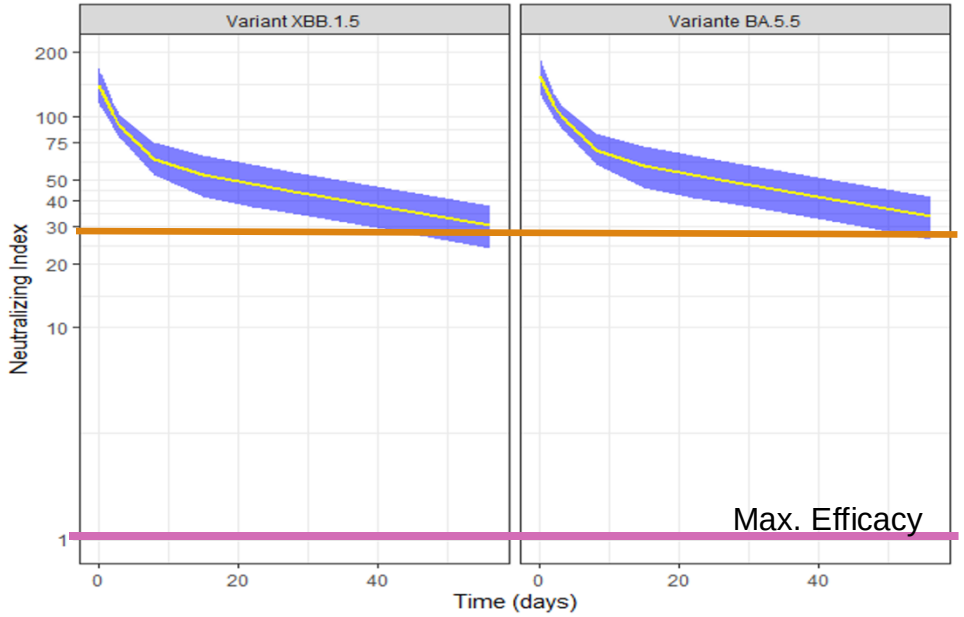


B-cell lymphoma patients

- B-cell depleting therapy is commonly employed for curative intent in patients with B-cell lymphoma
- Meta-analysis of 7,604 patients on B-cell depleting CAR-T therapy
- Over 50% of non-relapse deaths in these patients are due to infections, of which COVID-19 is the main cause
- Infection is also a major cause of morbidity/mortality in patients treated with T-cell engagers [*Nooka 2023*].
- Vaccine responses are sub-optimal to non-existent in these patients and chronic covid infection is often unresponsive to monotherapy anti-viral treatments

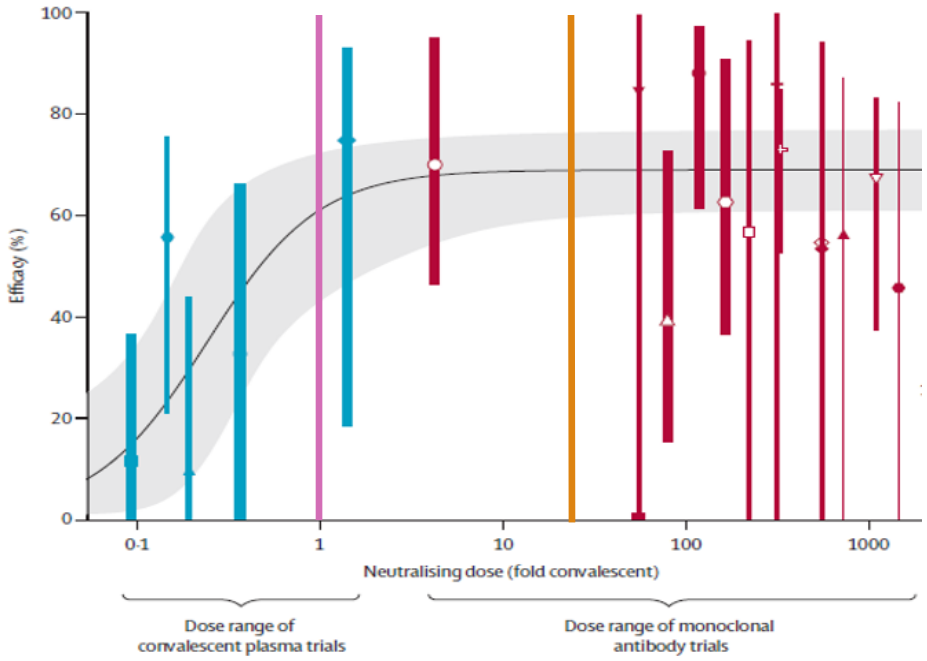
Based on this threshold index established with multiple mABs and convalescent plasma, a single dose of GB-0669 should provide maximal protection from hospitalization against XBB1.5 and BA5.5 for over 60 days in subjects with low baseline titer levels

Neutralizing Index against omicron variants following a 1200 mg dose of GB0669 (depicted as median & 90 % CI)



$$Neutralizing\ Index_{(t)} = \frac{Predicted\ Concentration_{(t)}}{Pre-dose\ (titers) \times InVitro\_EC_{50}}$$

Dose–response curve for treatment with neutralizing antibodies from symptomatic infection to hospitalization



Determinants of passive antibody efficacy in SARS-CoV-2 infection: a systematic review and meta-analysis

Eva Stadler, Khai Li Chai, Timothy E Schlub, Deborah Cromer, Shanchita R Khan, Mark N Polizzotto, Stephen J Kent, Claire Beecher, Heath White, Tari Turner, Nicole Skoetz, Lise Estcourt, Zoe K McQuilten, Erica M Wood, David S Khoury, Miles P Davenport

Stadler et al., 2023, *Lancet Microbe*

Interim analysis of first-in-human data supports advancement to phase 2

- No dose-limiting toxicity observed
- Dose-proportional increases in pharmacokinetics. PK Half-life ~55 days
- Dose dependent fold increase in viral neutralizing titres. Viral neutralizing titres increased 10-fold from baseline at 1200mg dose in subjects with pre-dose titres
- Estimated neutralizing index (Stadler et al.,2023) in subjects with low titres results in an index of >100 to 30 over a 60-day period, indicating maximal efficacy as treatment against hospitalization
- Data supports advancement of GB-0669 to phase 2 especially highly immune compromised patient populations with greatest need

Acknowledgements

Pre-clinical
Grace Marden
Eric Carlin
Hongru Li
Geetika Sharma
Leslee Morrow
Giovanni Tosi
Ross Federman
Nicole Leon Vargas
Alan Leung
Jon Fallon
Amarendra Pegu
Heather Van Epps
Kristen Hopson
Daria Hazuda

DNA Team
Robin Green
Brian Patuto
Babu Ram
Prasad Saravanan

Protein Sciences
Nadine Shaban
Monica Menzenski
Yanyan Lu
Avery Farnham
Darren Ferguson
Brett Blakely
Ben Manning
Sandra Sipsey
Adi Ravipati
Lucy Xu
Alexandra Gurney
Atreyi Bhattacharya
Lyle McPherson
Ramsey Fadlalla
Nathan Wong
Alex Ayoub
Patrick Brophy
Mark Benhaim
Nate Joh
Adam Root

Clinical
Francesco Borriello
Dinesh De Alwis
Gavin Koh
Nicholas Robertson
Anna Allen
Lovely Goyal
Loona Borgohain
Syam Chandrala
Pam Farmer
Stephanie Straley
Rounak Nassirpour
Smita Clements
Alex Synder

Tech Ops
Lisa Wyman
Tyson Fetzer
Vikram Sadineni
Guy DelloRusso
Farrah Chaudhary

Regulatory
Andrew Robertson
Irene Figari

Compliance
Leo Dodds
Sarah Hurley

Project Management
Denise Murphy

Novel Therapeutics
Anne Jecrois
Joe Garlick
Claudio Perez
Max Zimmerman
Eugene Palovcak
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Comp Sci.
Alex Ramos
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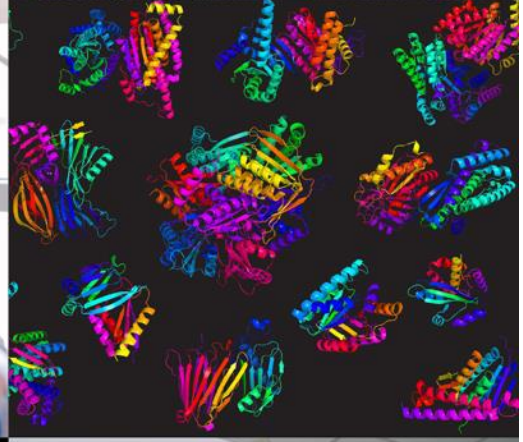

Generate: *Now we can*