

A validated model of the neutralising antibody-efficacy relationship for monoclonal antibody pre-exposure prophylaxis against COVID-19

Rhiannon Edge,^{1*} Sam Matthews,^{1*} John Pura,² Bahar Ahani,³ Anastasia A. Aksyuk,⁴ Lindsay Clegg,⁵ John Perez,⁶ Mark T. Esser,⁷ Lee-Jah Chang,⁷ Ian Hirsch,¹ Tonya Villafana,⁷ Oleg Stepanov,⁸ Katie Streicher,⁴ Tom White,¹ Taylor S. Cohen,⁷ Dean Follmann,⁹ Peter B. Gilbert,¹⁰ Seth Seegobin¹

¹Biometrics, Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; ²Biometrics, Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Durham, NC, USA; ³Bioinformatics, Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; ⁴Translational Medicine, Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; ⁵Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; ⁶Late Development, Vaccines and Immune Therapies, BioPharmaceuticals R&D, Gaithersburg, MD, USA; ⁷Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; ⁸Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; ⁹Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; ¹⁰Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA, USA

*Co-first authors

Why did we perform this research?

- The constantly shifting variant landscape of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made development of monoclonal antibodies (mAbs) targeting the virus very challenging
 - New clinical studies evaluating the efficacy of mAbs for pre-exposure prophylaxis (PrEP) of symptomatic COVID-19 cannot keep pace with the emergence of new variants
 - A robust method is needed to rapidly assess expected mAb efficacy against novel variants in high-risk individuals, such as those with immunocompromising conditions^{1–3}
- Here, we developed a model to relate observed efficacy to prevalence-adjusted neutralising antibody (nAb) titres, to facilitate establishment of a threshold of protection for mAb PrEP of COVID-19



Summary

Model development



We developed the ToP model (Figure 1) using data from the PROVENT study (NCT04625725) of tixagevimab-cilgavimab⁴ The model relates prophylactic efficacy against SARS-CoV-2 to nAb titre independent of the variant

Model validation



We showed strong agreement between ToP model predictions and observed efficacies from the sipavibart Phase 3 SUPERNOVA study (NCT05648110) in immunocompromised individuals (Figures 2–4)⁵

Model application

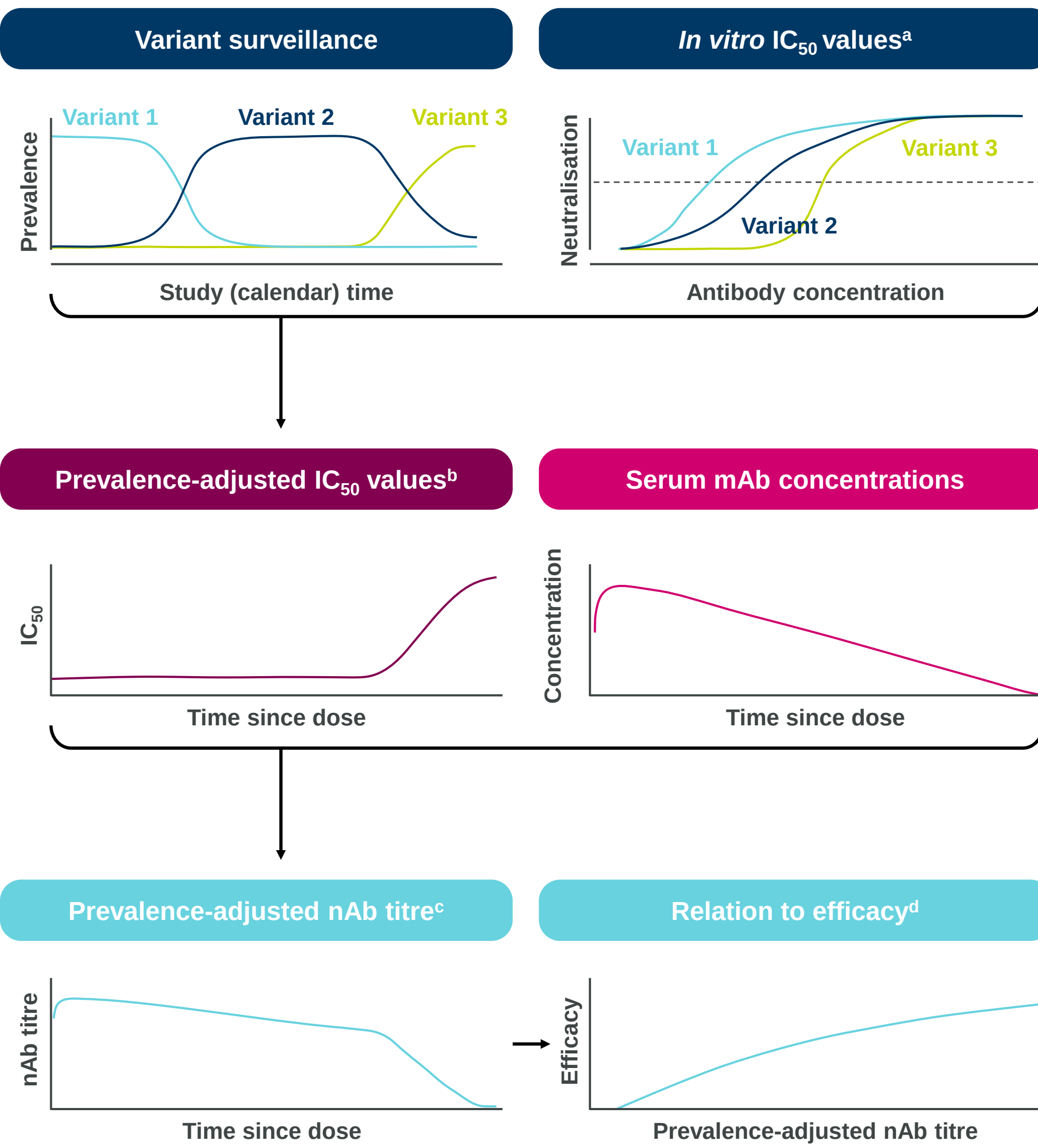


For any SARS-CoV-2 variant(s), we can expedite clinical evaluation through rapidly immunobridging new mAbs against a model-defined benchmark (Figure 5) We can evaluate proposed dosing regimens by estimating the duration of protection

Model development



Figure 1. Development of the ToP model



^aPotency against circulating variants. ^bWeighted against the variant landscape. ^cDaily serum mAb concentration divided by adjusted IC₅₀ value. ^dUsing time-varying Cox model. IC₅₀, 50% inhibitory concentration; mAb, monoclonal antibody; nAb, neutralising antibody; ToP, threshold of protection.

Model validation



PROVENT ToP model predictions provide strong agreement with observed efficacies in SUPERNOVA

- Figure 2 compares PROVENT ToP model predictions (corresponding to prespecified endpoints in SUPERNOVA) with observed efficacies in SUPERNOVA⁵
- Agreement is shown using Lin's concordance correlation coefficient (Figure 3)

PROVENT ToP model was robust to inclusion of the SUPERNOVA data

- Inclusion of PROVENT and SUPERNOVA data in the ToP model increases precision, with small model differences between the geometric mean nAb titre required to achieve 40% efficacy (Figure 4)
- The updated ToP model, based on the pooled study results, could be used to determine efficacy against future variants and variant landscapes (Figure 5)



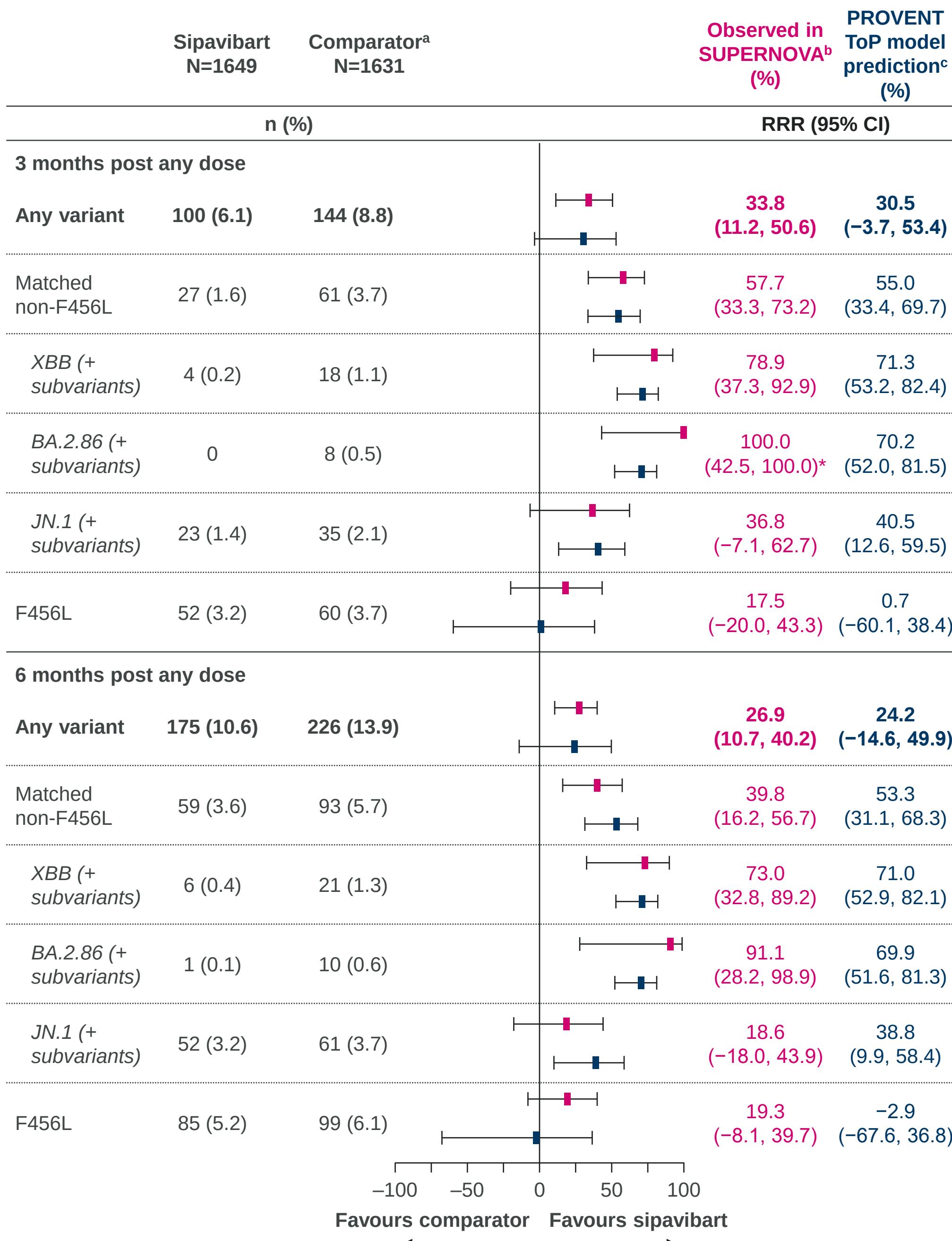
Key takeaway

The ToP model provides robust prediction of variant-specific mAb efficacy in PrEP of COVID-19 based on two Phase 3 trials

Acknowledgements

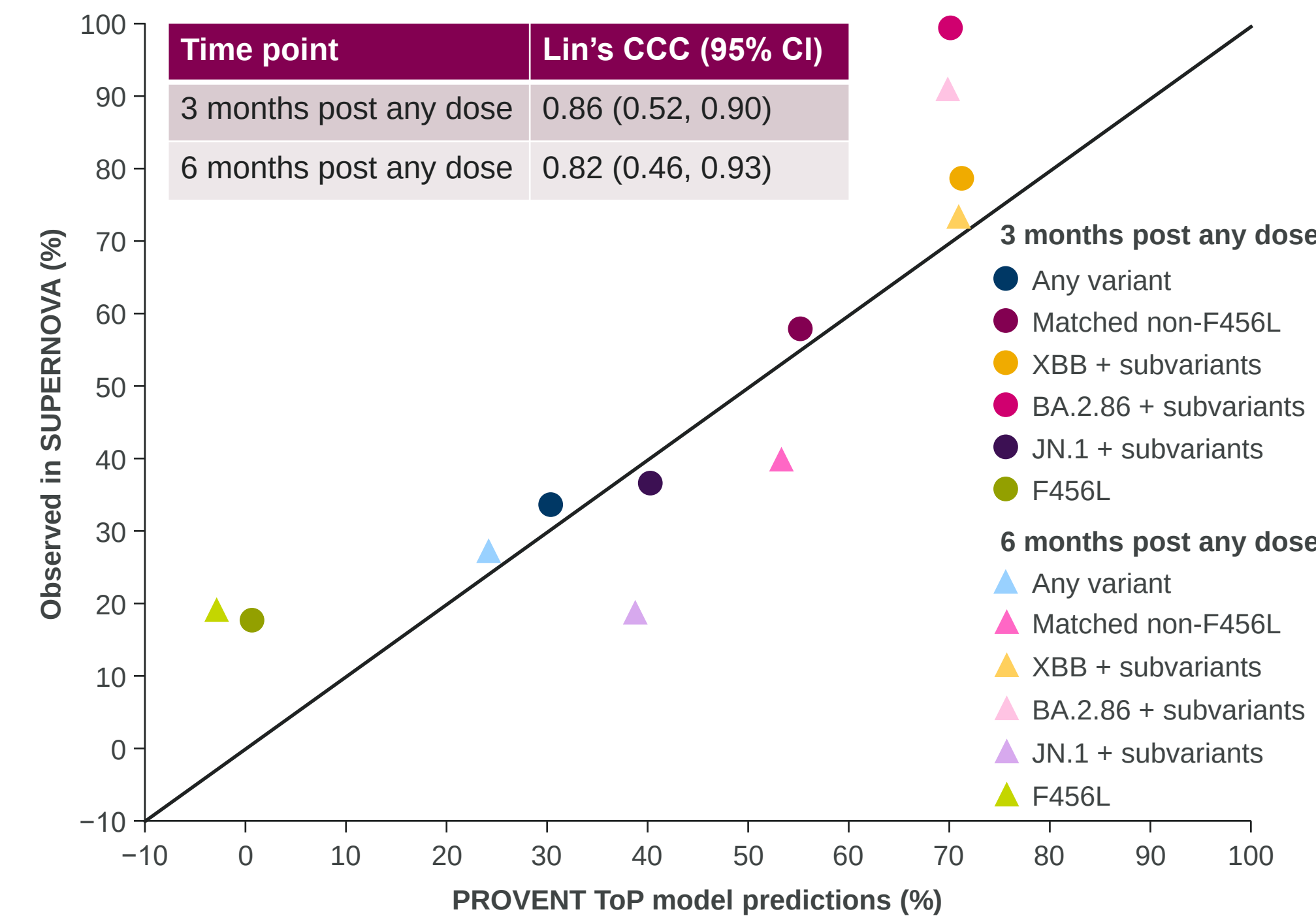
This analysis was funded by AstraZeneca and includes data from the PROVENT trials that was funded by AstraZeneca and the United States Government. This project has been supported in whole or in part with from federal funds from the Department of Health and Human Services, Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority in partnership with the Department of Defense, and Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense, under Contract No. W911QY-21-9-0001. The findings and conclusions in this presentation have not been formally disseminated by the Department of Health and Human Services and should not be construed to represent any agency determination or policy

Figure 2. Forest plot of observed SUPERNOVA efficacies and PROVENT ToP model predictions



^aTixagevimab/cilgavimab then placebo, or two placebo doses. ^bRRR (95% CI) are presented for symptomatic COVID-19 endpoints in SUPERNOVA.⁵ ^cPROVENT ToP model was defined as a time-varying Cox model adjusting for treatment and its interaction with an intercept term and log₁₀(prevalence-adjusted titres + 1). Efficacy was calculated as 1 – hazard ratio. Prediction of efficacy (95% CI) by evaluating average nAb titres over 90 or 180 days post any dose (any variant, average prevalence-adjusted nAb titres were considered after mapping GISAID prevalence data to at-risk participants for variants with ≥5% prevalence; for matched non-F456L and XBB (+ subvariants) a similar approach was taken excluding F456X variants [assumed IC₅₀ 1000 ng/mL] and including only hedgehog variants with XBB Pango lineage, respectively; serum mAb concentrations estimated from population pharmacokinetics model used to predict nAb titres in at-risk participants based on sipavibart IC₅₀ 3.8, 83.1 and 1000 ng/mL for BA.2.86, JN.1 and F456L-containing variants, respectively). CI, confidence interval; GISAID, Global Initiative on Sharing All Influenza Data; IC₅₀, 50% inhibitory concentration; N, number of SUPERNOVA participants without a positive SARS-CoV-2 RT-PCR test at baseline; n, number with events; RRR, relative risk reduction; RT-PCR, reverse transcription-polymerase chain reaction; ToP, threshold of protection.

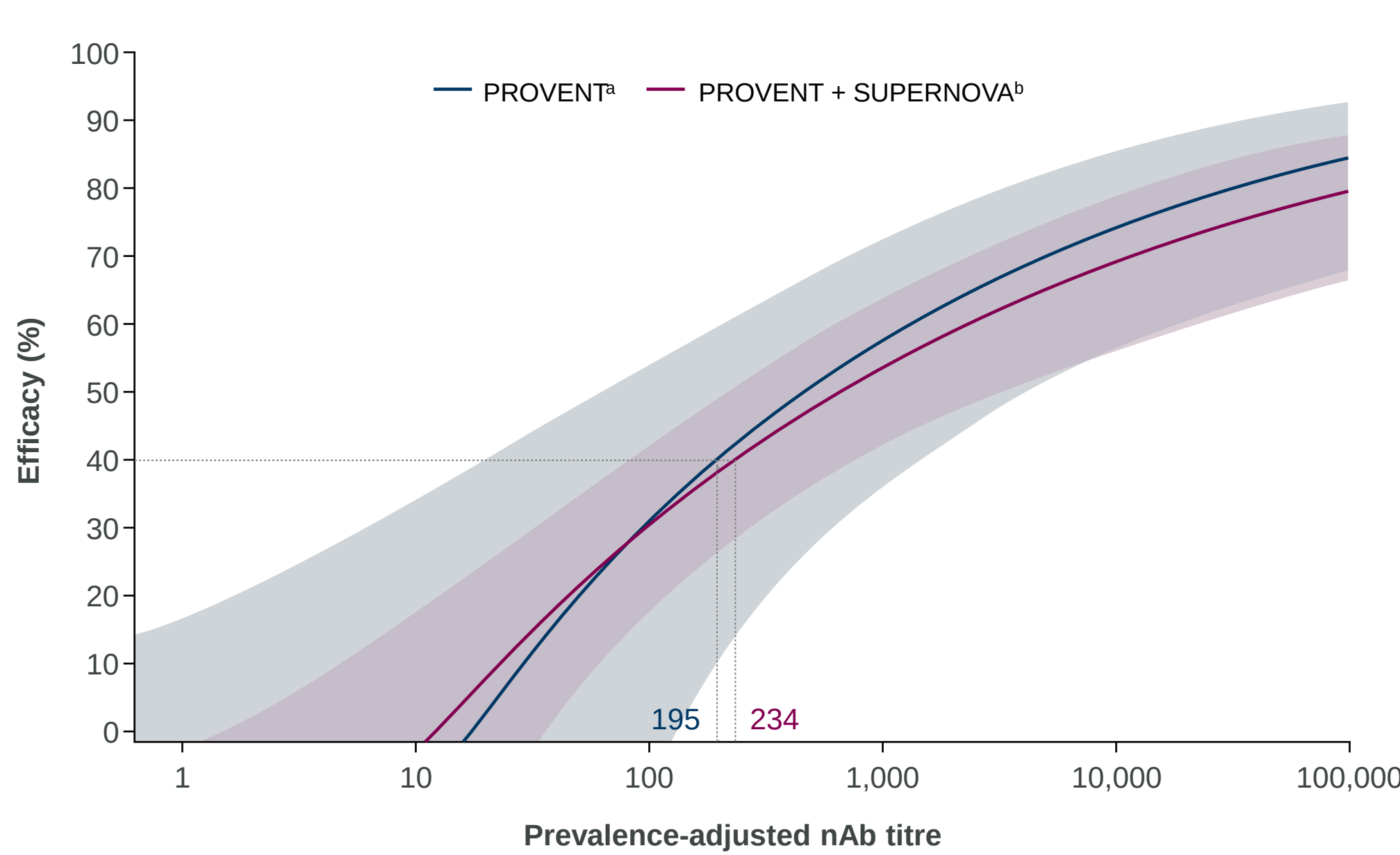
Figure 3. Agreement between observed SUPERNOVA efficacies and PROVENT ToP model predictions



The observed SUPERNOVA efficacies and the respective PROVENT ToP model predictions from Figure 2 show strong agreement using Lin's CCC. CIs are bootstrapped from 1000 resamples. CCC, concordance correlation coefficient; CI, confidence interval; ToP, threshold of protection.

We gratefully acknowledge all authors from the laboratories responsible for obtaining the specimens and the submitting laboratories where genetic sequence data were generated and shared via GISAID, upon which this research is based. The authors thank Jonathan Toma, Paul Theobald, Carmeliza Santos and others at Monogram Biosciences (San Francisco, CA, USA) for continuous support on the next-generation sequencing analysis. A version of this poster was previously presented at the Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), 11–15 April 2025, held in Vienna, Austria. Medical writing and editorial support, including formatting, proofreading and submission was provided by Shaun Foley, BSc (Hons) and Isabella Cannava, BA, both of Core (a division of Prime, London, UK), supported by AstraZeneca according to Good Publication Practice guidelines.

Figure 4. ToP analyses of efficacy against confirmed symptomatic COVID-19 by prevalence-adjusted nAb titre



The PROVENT + SUPERNOVA^b ToP model was defined similarly to the PROVENT ToP model^a with additional stratification of the baseline hazard by study. The two-sided 90% CIs were bootstrapped using 1000 resamples. The 40% thresholds are aligned with the predefined go criteria from SUPERNOVA based on efficacy against any variant. The nAb titre can be converted to IU/mL by multiplying by 0.1428. CI, confidence interval; IU, international unit; nAb, neutralising antibody; ToP, threshold of protection.

Model application

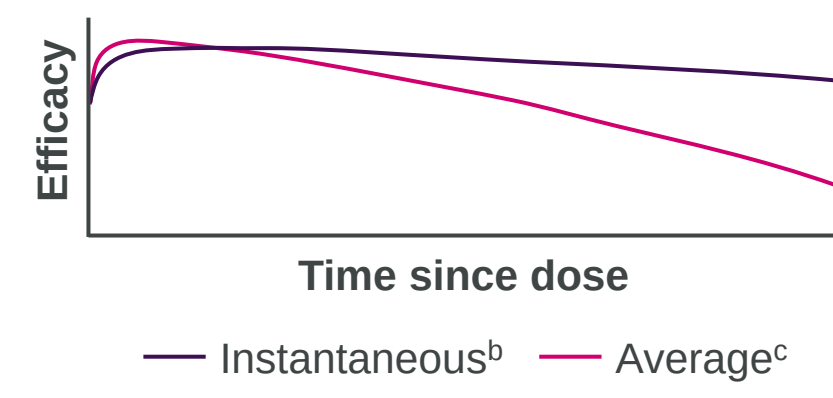


Figure 5. Application of the ToP model

To evaluate expected efficacy of a proposed mAb dosing regimen:

- Use popPK model to generate predicted serum mAb concentrations over time
- Calculate nAb titres over time against variant of interest from serum mAb concentrations and *in vitro* IC₅₀
- Input geometric mean nAb titre over time into ToP model to predict efficacy

Application of model to predict efficacy^a



To leverage ToP model for immunobridging to a new mAb:

- Identify target level of efficacy and duration of protection
- Use ToP model to determine associated nAb titre target
- Assess non-inferiority of nAb titre (based on serum mAb concentration and *in vitro* IC₅₀ value) to target nAb titre at appropriate time point

^aFor new mAb dosing regimen. ^bEvaluation of ToP model at the geometric average prevalence-adjusted nAb titre at each study day to provide a snapshot of current efficacy at a given time point. ^cEvaluation of ToP model at the geometric average prevalence-adjusted nAb titre up to each study day to provide assessment of the efficacy post-dose through to the given time point. IC₅₀, 50% inhibitory concentration; popPK, population pharmacokinetic; mAb, monoclonal antibody; nAb, neutralising antibody; ToP, threshold of protection.

What is the significance of these data?



- This provides the first externally validated, quantified relationship between SARS-CoV-2 nAb titres and protection against COVID-19 using individual participant data
- This approach innovatively adjusts against changing variant prevalence using *in vitro* IC₅₀ values
- Prior immunobridging authorisations have relied on the observed efficacy level for a mAb from a historic study⁶
- Flexibility to identify nAb titre targets associated with different levels of efficacy represents a significant advance enabling rapid benefit assessment of mAbs

Limitations

- Several sources of error reduce precision, but are not expected to introduce systematic bias of the model:
- Model variability in population pharmacokinetic predictions of serum mAb concentration are not propagated through to the final ToP model
 - Viral prevalence data are not adjusted to account for the delay between individual viral exposure and sample collection time, and regional viral prevalence data may not reflect individual exposures
 - As many SARS-CoV-2 variants co-circulated during SUPERNOVA, not all IC₅₀ values could be measured, and assumptions were made from available IC₅₀ data

Disclosures

D.F. and P.B.G. serve as unpaid members of scientific advisory boards for AstraZeneca. P.B.G. has a contract to his institution. S.M. is employed by MMS Holdings Inc. All other authors are employees of, and may hold stock and/or stock options in, AstraZeneca

References

- Kertes J et al. *Clin Infect Dis.* 2023;76:e126–e132.
- Al Jundi A et al. *Am J Transplant.* 2022;22:3130–3136.
- Young-Xu Y et al. *mBio.* 2023;14:e0102423.
- Edge R et al. Poster presented at ECCMID 2024, Barcelona, Spain. Poster BES0303.
- Haidar G et al. *Lancet Infect Dis.* 2025;S1473-3099(24)00804-1.
- Schmidt P et al. *N Engl J Med.* 2024;391:1860–1862.