Lessons Learned from mAb Development During the COVID-19 Pandemic

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Ian Hirsch and Taylor Cohen are employees of AstraZeneca and have stock ownership and/or stock options or interests in the company.

Rapidly changing variant landscapes necessitates novel approaches for assessing mAb efficacy

Overview

- The predominantly circulating SARS-CoV-2 variant changed every 3-6 months, and in the Omicron era there is often more than one “majority” variant circulating at any given time
- Phase 3 efficacy trials run over a 6-month season do not reflect efficacy against variants in circulation at the time of approval for the next season

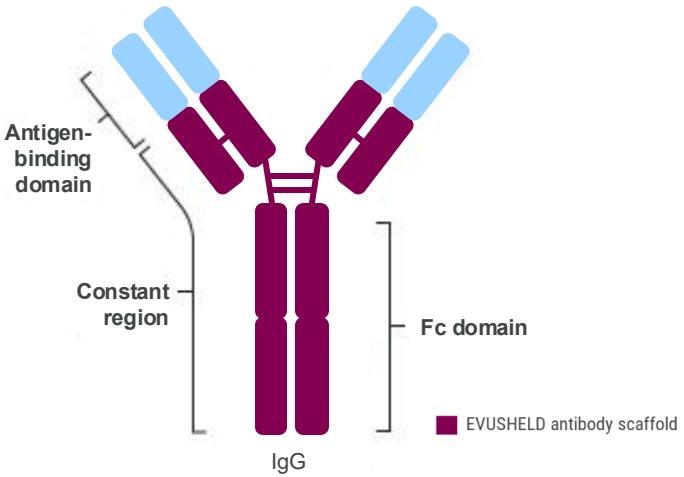
Challenge: Determine expected efficacy against newly emerging variants to 1) give **confidence in the benefit of the antibody** and 2) establish **regulatory pathways for seasonal updates** to antibodies

Solution: Model the relationship between daily predicted serum antibody concentrations, variant IC50 and efficacy established in prior Phase 3 clinical studies, such that efficacy can be predicted for emerging variants or next generation mAbs

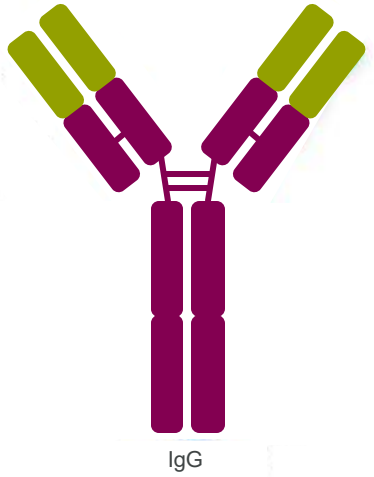
Background on mAbs developed by AstraZeneca for pre-exposure prophylaxis: EVUSHELD and KAVIGALE

EVUSHELD combination of two mAbs

Tixagevimab



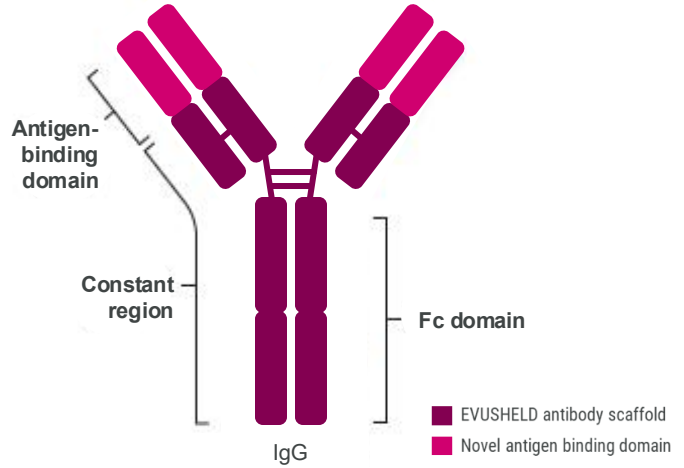
Cilgavimab



- PROVENT, placebo controlled 2:1 randomised study in those at high risk of developing COVID-19
- Pre-exposure prophylaxis
- Primary variants during study (IC50 range 2-400 ng/mL): Wuhan, alpha, delta, omicron

KAVIGALE is built on EVUSHELD Scaffold

Sipavibart



- Antibody shares EVUSHELD scaffold
- Binding domain also within spike protein RBD
- SUPERNOVA, placebo controlled 1:1 randomized study in immunocompromised individuals
- Pre-exposure prophylaxis
- Primary variants during study (IC50 range 2- >1000 ng/mL): XBB, BA.2.86, JN.1 and F456L containing

Approach to build and validate a model relating nAb titre to efficacy

Objective: To characterise the association between the probability of symptomatic infection as a function of estimated daily plasma concentration (derived from the sipavibart popPK model), adjusting for variant IC50 values and local variant prevalence over time

Steps Taken:

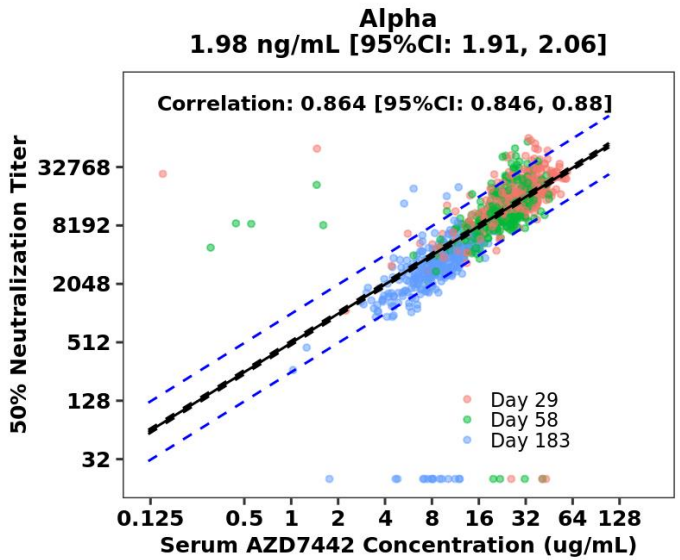
1. Develop model using data from the Phase III **PROVENT** study, a randomized, double blind, placebo-controlled, multi-centre phase 3 study to assess the efficacy of **EVUSHELD (tixagevimab/cilgavimab)** compared to placebo for the prevention of COVID-19.

2. Validate the model using observed efficacy data in the **SUPERNOVA** study for the next-generation mAb, **KAVIGALE (sipavibart**)

Use of predicted serum nAbs titres as an endpoint is supported by strong correlation between PK and measured nAbs

- Measured PK vs. measured nAb correlations across variants, using samples from EVUSHELD Phase 3 study, PROVENT, participants

Correlation between EVUSHELD PK and nAb titers for the Alpha variant



Comparison of EVUSHELD Estimated Ex Vivo IC50 Values and In Vitro IC50 Measurements from Monogram for 5 SARS-CoV-2 VOCs

Variant	ng/mL ex vivo IC50 estimate (95%CI)	in vitro IC50[a]
Wuhan	1.74 (1.67, 1.80)	2.2
Alpha	1.98 (1.91, 2.06)	2.1
Delta	1.66 (1.60, 1.72)	2.2
BA.2	15.49 (14.75, 16.26)	9.8
BA.4/5	65.85 (62.68, 69.19)	69.5

[a] Source: Monogram Biosciences (reported through FDA/BARDA)

In-vitro IC50 are consistent with ex-vivo IC50 based on measured nAb titres (both measured in the same assay)

Methodology for estimating momentaneous plasma concentration adjusting for variant prevalence and IC50

1. Prevalence of individual variants estimated based on GISAID variant surveillance data mapped to study data

2. Determine standardised nAb titres for each participant (PK/weighted IC50) by using surveillance data to weight in vitro IC50 values for each variant over time

3. Prevalence-standardised titres can be used in a model to relate time-varying prevalence-standardised titres to observed efficacy data

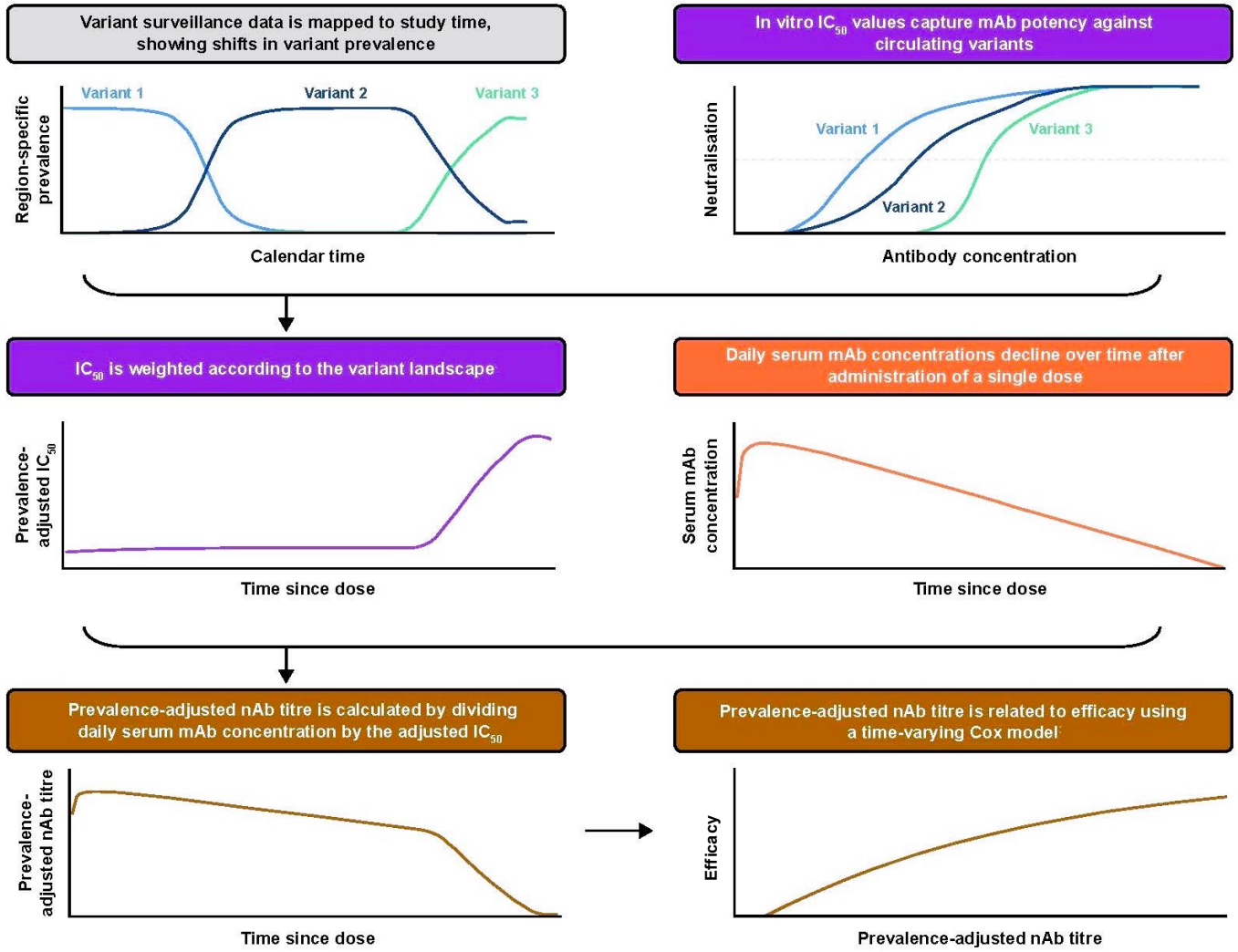
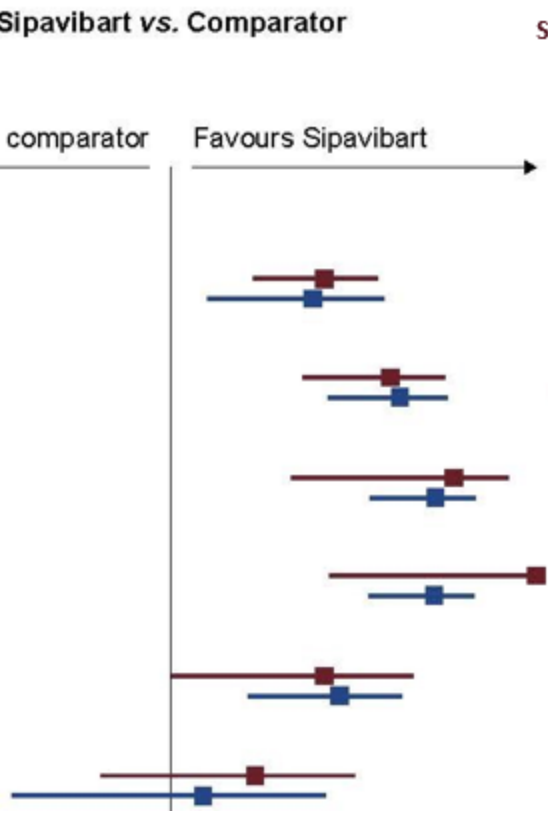


Figure reproduced from: Edge et al. A threshold of protection model for monoclonal antibody pre-exposure prophylaxis against COVID-19 enabling rapid development for future SARS-CoV-2 variants. ESCMID 2025

The Thresholds of Protection model built on PK and IC50 values predicted COVID-19 efficacy

Endpoint	Sipavibart N = 1649 n (%)	Comparator N = 1631 n (%)	SUPERNOVA observed *	ToP predicted ‡
3 months post any dose				
Overall	75 (4.5)	124 (7.6)	41.9 (22.5, 56.5)	38.9 (10.1, 58.5)
Matched non-F456L	25 (1.5)	60 (3.7)	60.0 (36.2, 74.9)	62.7 (43.1, 75.6)
XBB + subvariants	4 (0.2)	17 (1.0)	77.6 (33.1, 92.5)	72.5 (54.6, 83.3)
BA.2.86 + subvariants	0	8 (0.5)	100.0 (43.3, 100.0)†	72.2 (54.3, 83.1)
JN.1 + subvariants	21 (1.3)	35 (2.1)	42.0 (0.4, 66.2)	46.1 (21.1, 63.3)
F456L	37 (2.2)	46 (2.8)	23.0 (–19.0, 50.2)	8.8 (–43.7, 42.1)



The ToP model using only **PK and IC50s** predicted the **observed efficacy** in SUPERNOVA

*RRR (95% CI) are presented for symptomatic COVID-19 endpoints in SUPERNOVA. †When events are not present in at least one arm, an exact approach is followed and the 97.5% two-sided CI presented (Haidar G, et al. Lancet Infect Dis. 2025;10.1016/S1473-3099(24)00804-1). ‡PROVENT ToP model was defined as a time-varying Cox model adjusting for treatment and its interaction with an intercept term and $\log_{10}$ (prevalence-adjusted titres + 1). Efficacy was calculated as 1 – hazard ratio. Prediction of efficacy (95% CI) by evaluating average nAb titres over 90 days post any dose. Comparator was tixagevimab/cilgavimab then placebo, or two placebo doses.
CI, confidence interval; 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 reproduced from: Edge et al. A threshold of protection model for monoclonal antibody pre-exposure prophylaxis against COVID-19 enabling rapid development for future SARS-CoV-2 variants. ESCMID 2025

Conclusions: Lessons learned and path forward

Pathogens with high rates of mutation, or associated with seasonal strain shifts, **necessitate a robust, data driven method for predicting efficacy** of long-acting monoclonal antibodies

- Duration of traditional efficacy studies limits utility in this setting

Once efficacy is established for a well characterised monoclonal antibody, modelling can be utilized to rapidly **predict efficacy for emerging variants** or **immunobridge to next generation antibodies** that utilize the same scaffold

- PK and variant IC50 used to determine neutralizing mAb titre
- mAb titre predicts efficacy through Threshold of Protection model