Skyddsnivå:

Sätt ett kryss (X) framför rätt skyddsnivå!

(K0) Ingen/låg
(K1) Grundläggande
(K2) Utökad
(K3) Hög

# Challenges in evidence generation for COVID-19 mAbs

## A regulatory perspective

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# Problem statement

Monoclonal antibodies (mAbs) targeting the receptor-binding domain of the Sars-CoV-2 spike protein have demonstrated the ability to:

- decrease the risk of symptomatic SARS-CoV-2 infection in the context of pre- or post-exposure prophylaxis
- reduce the risk of progression to severe disease in patients with early disease not requiring supplemental oxygen

However:

- The time-frame of utility of mAbs has been short-lived due to viral evolution
- Studies to directly capture the impact on clinical outcome of a new variant mAb need to be relatively large and are time-consuming, resulting in mAbs being obsolete at the time of approval
- In future situations, equipoise for randomization to a placebo or an ineffective comparator may be questionable

# 15th Dec 2022: Joint EMA-FDA workshop on the efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants

- It was agreed that the prevention of COVID-19 in immunocompromised patients should be a primary target of future mAb development
- There was agreement on the need to expedite the development of new mAb products against emerging variants of concern (VOC)

# The immunobridging approach

- There was general support for the use of an immunobridging approach based on geometric mean titres (GMT) of neutralizing antibodies (nAb) at specific timepoints, preferably with a confirmation of clinical efficacy post-approval/post-authorisation
- Overall, participants did not believe that a cross-variant comparison would be significantly impacted by assay constraints, if it is ensured that assay performance criteria, i.e., linearity, range, precision, slope and response, are comparable

# Example of corresponding regulatory Scientific Advice

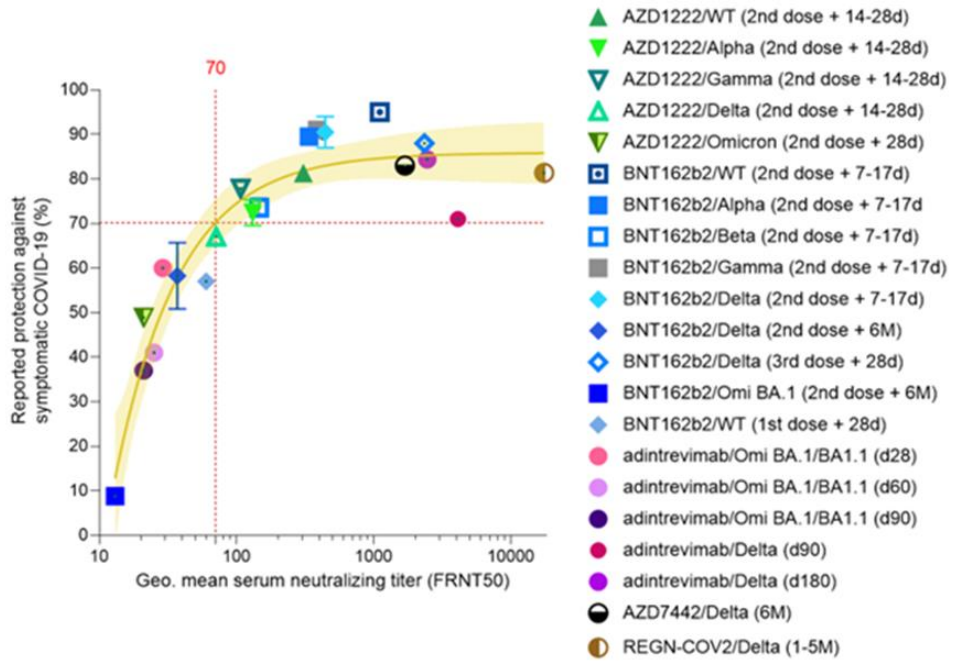
- “It is assumed that the ultimate basis for approval of (*medicine)* will be based on immunobridging to the prophylactic efficacy of an approved mAb.
- This will require selection and justification of a licensed comparator and a prospective randomised study with a clear primary hypothesis.
- In a prophylaxis setting, it could be appropriate that the primary analysis seeks to demonstrate that day 28 nAb GMT provided by (*medicine*) against a relevant VOC selected based on epidemiological data, is non-inferior to the day 28 neutralizing GMT provided by the comparator against the VOC that was predominant in the pivotal efficacy study that supported its approval for prophylaxis.”

# Limitations to immunobridging

- The immunobridging approach (if needed) is, arguably, relevant when when (a) the MoA of test and reference mAb's is similar, (b) Fc receptor function is similar, and (c) plasma half-life is therefore similar
- The immunobridging study design requires a control group treated with an obsolete mAb

# Can efficacy be inferred based on absolute Nab titres?

**Figure 2** Relationship Between Median Serum Neutralisation Titre (Measured by Authentic Virus Assay) and Protective Efficacy Against Symptomatic COVID-19




Adapted from Schmidt et al. (2023).

But: can similar PK/PD really be assumed given, e.g., different cellular tropism/clinical presentation of omicron disease, as well as the different patient populations (immunocompetent versus immunocompromised)?

# Example: sipavibart

- mAb based on the Evusheld scaffold
- Designed to be effective against early omicron strains, with pseudovirus neutralization IC50 values ranging from 3.6 ng/mL (XBB.1) to 25.0 ng/mL (BA.2.75).
- “A 300 mg dose of sipavibart was predicted to maintain nasal lining fluid concentrations above the IC80 for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.”

# The pivotal study for sipavibart

- SUPERNOVA was a randomised double blinded study in adolescents ≥12 year of age or adults with clinically significant immunocompromise
- Subjects were allocated either to receive sipavibart 300 mg i.m or a comparator not deemed active given circulating variants (Evusheld or placebo)
- After a first dose, subjects were to receive a second dose of sipavibart or comparator 6 months later
- The primary endpoints were (a) RT-PCR confirmed symptomatic Sars-Cov-2 infection due to any viral variant, and (b) the same counting only events due to “matched” viral variants

# The study period was characterised by a changing landscape of circulating viral variants

In vitro neutralisation (pseudovirus assay):

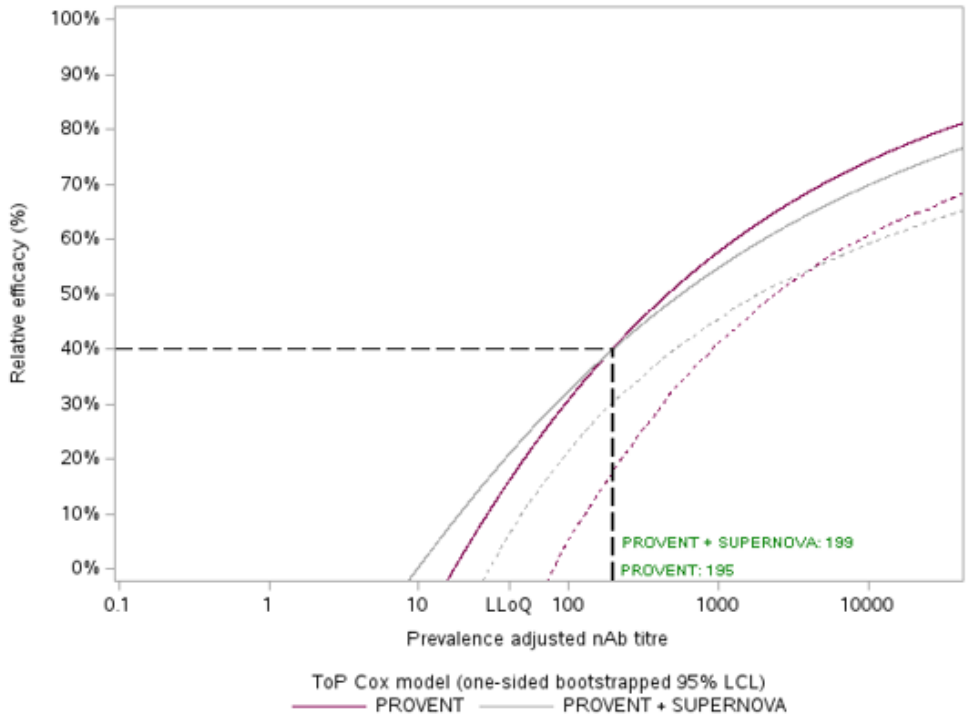
1. BA.2, BA4/5, BQ.1, XBB etc (without F456L mutation): IC50 <15 ng/mL
2. JN.1: IC50 = 83 ng/mL
3. FLiRT variants are not anticipated to be susceptible to sipavibart, as these exhibit the F456L mutation (IC50 >1000 ng/mL)

# Efficacy by viral variant

**Table 16** **Incidence of Symptomatic COVID-19 Cases Up to Day 361 Attributable to Specific Variants - While-on-Treatment Strategy - Main Cohort (SARS-CoV-2-Negative Set)**

| Variant | Planned intervention (Day 1/Day 181) | | Relative risk reduction (%) [b] | 95% CI (%) |
|---|---|---|---|---|
| | AZD3152/AZD3152 N = 1649 | Comparator [a] N = 1631 | | |
| | n (%) | n (%) | | |
| Any (sequenced) | 101 (6.1) | 154 (9.4) | 37.6 | 19.6, 51.6 |
| Matched | 54 (3.3) | 90 (5.5) | 42.9 | 19.9, 59.3 |
| BA.2.86 + subvariants | 1 (0.1) | 10 (0.6) | 90.9 | 27.4, 98.9 |
| XBB + subvariants | 6 (0.4) | 20 (1.2) | 71.6 | 29.0, 88.7 |
| JN.1 + subvariants | 47 (2.9) | 60 (3.7) | 25.1 | -9.7, 48.8 |
| F456L (sequenced) | 47 (2.9) | 64 (3.9) | 30.4 | -1.8, 52.5 |

# Cox Model Estimates of Efficacy as a Function of "Prevalence-Adjusted nAb titres" – PROVENT (Evusheld pivotal trial) + SUPERNOVA data




The solid lines represent the point estimate from each model (PROVENT – purple; PROVENT and SUPERNOVA – grey) showing the change in efficacy as a function of prevalence adjusted nAb titre level. The dotted lines show the lower bound of the confidence intervals for each model. The PROVENT only model indicates that a threshold of 195 corresponds with 40% efficacy. The updated model incorporating data form both PROVENT and SUPERNOVA indicates that a threshold of 199 corresponds with 40% efficacy

# What are ”Prevalence-Adjusted nAb titres”?

- The GISAID database was used to infer region-specific variant prevalence of SARS-CoV-2 by calendar date. Variants with at least 5% prevalence were included
- Where the IC50 values of variants were unable to be determined in vitro due to reduced binding of sipavibart to the spike protein, the values were imputed to 1000 ng/mL (upper LoQ for assay)
- Variant prevalence data were combined with individual-level predicted nAb titre data by country and calendar date
- For each participant and day, a prevalence-adjusted nAb titre level was calculated as a weighted geometric mean of predicted nAb titres, based on regional variant prevalence (country-level)

# Reflections

- A regular Emax model plotting a steady state plasma concentration over IC50 as dependent variable does not work in this scenario, due to the time-dependency in SUPERNOVA of plasma concentrations as well as IC50
- Events indicate the failure of a nAb-titre. There are no data illustrating the success of a nAb-titre
- Therefore, the prevalence adjusted nAb-titre approach has a rationale
- However, this is based on hypothetical IC50's of non-existing viral strains

# Concerns

- The actual viruses of the SUPERNOVA study had IC50s that were either <15 ng/mL *OR* 83.1 ng/mL *OR* >1000 ng/mL
- A large part of the [nAb titre vs % protection] curves correspond to no empirical facts. The soundness of this intrapolation is uncertain
- The imputation of IC50 to 1000 ng/mL for F456L, given an observed protection rate of 30%, which in reality would be zero, probably results in an under-estimation of the titre required for a given level of protection

# Resulting labeling language (SmPC section 4.4.)

"Sipavibart was designed to be effective against early omicron strains, with pseudovirus neutralisation IC50 values ranging from 3.6 ng/ml (XBB.1 variant) to 25.0 ng/ml (BA.2.75 variant).

*The extent and duration of protective efficacy against viruses with moderately increased IC50 (e.g. JN.1, IC50 83.1 ng/ml) is reduced and the clinical relevance of any prophylactic effect unclear.*

Due to the absence of in vitro neutralising activity, sipavibart is not anticipated to provide any protection against symptomatic COVID-19 due to viral variants containing F456L mutations in the spike protein (see section 5.1)."

# For discussion

Given the relevant practicality / feasibility issues with directly demonstrating clinical efficacy as well as with the immunobridging approach:

- Is there a path towards robustly defining a generalizable relation between [plasma mAb concentration / IC50] and protective efficacy, on which basis mAbs for pre-exposure prophylaxis of Covid-19 could be approved (e.g, primary endpoint day 28 nAb titre)?