Use of neutralizing antibody or PK/IC50 threshold to expedite clinical development for prophylactic monoclonal antibodies

EMA/FDA workshop on monoclonal antibodies against SARS-CoV-2

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Prophylactic Monoclonal Antibody Executive Summary

1. Prophylactic extended half-life monoclonal antibodies (mAb) fulfil a critical unmet medical need in the immunocompromised population, by providing protection in those not protected by vaccines.
2. Randomized Clinical Trial (RCT) efficacy cannot be generated against every new variant. In vitro and ex vivo data, together with immunobridging approaches, are needed for rapid clinical development.
3. International standard for neutralization antibody (nAb) and IC50 assays are urgently needed
4. mAb exhibit extremely consistent and predictable PK, and ex vivo neutralizing activity correlates well with drug levels.
5. Expedited clinical development must go hand-in-hand with expedited CMC review processes.
6. Brand names for next generation products must be consistent with brand names of first-generation products to avoid confusion in the marketplace.

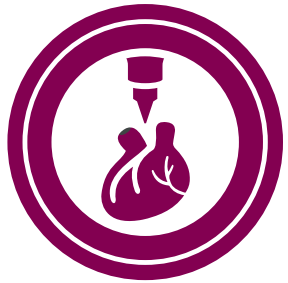
Immunocompromized populations are not protected by vaccination & require prophylaxis with long-acting monoclonal antibodies

In the US and EU about 3%

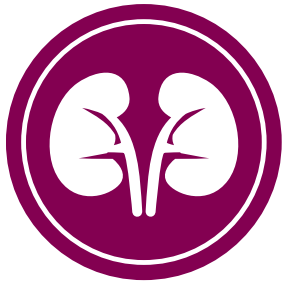
of the adult population is moderately to severely immunocompromised, leading to increased vulnerability to COVID-19[1-4]

Blood cancers[3]

Active chemotherapy[3]

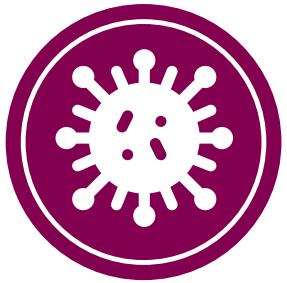


Transplant[3]



Dialysis[5]

Taking immunosuppressants[a]



Primary immune deficiency

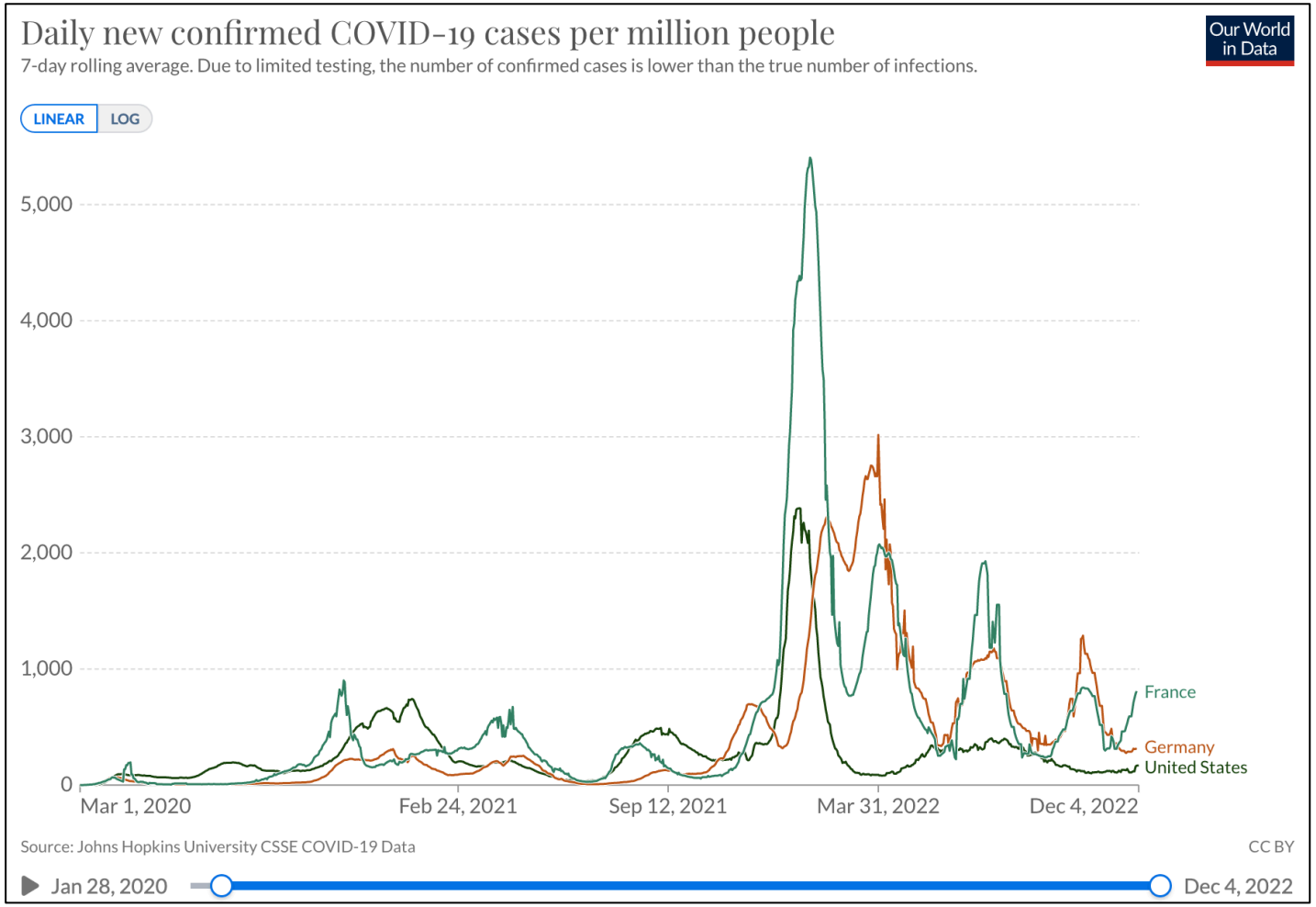
[a]Immunosuppressants could include medicines for non-Hodgkin's lymphoma, lupus, multiple sclerosis, rheumatoid arthritis.[3,6]

COVID-19 = coronavirus disease 2019; US = United States.

1. Harpaz R et al. *JAMA*. 2016;316:2547-2448; 2. Centers for Disease Control and Prevention. COVID-19 vaccines for people who are moderately or severely immunocompromised. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html; 3. Abbasi J. *JAMA*. 2021;325:2033-2035; 4. https://ecpc.org/joint-statement-on-the-protection-of-immunocompromised-patients/; 5. Rincon-Arevalo H et al. *Sci Immunol.* 2021;6:eabj1031; 6. Richard-Eaglin A et al. *Nurs Clin N Am*. 2018;53:319-334.

Clinical trial efficacy cannot be generated against every new variant; Real Work Effectiveness (RWE) data always lags behind the changing variant landscape

- New variants of concern emerge approximately every three months; each wave lasting about two months
- Clinical data is generally only available after the wave has passed
- RWE data is compiled after a wave has passed & will not be available in time for prescribers to make timely decisions
- Long acting mAb provide protection across multiple variant waves



International Standards for neutralizing antibody (nAb) and IC50 assays are urgently needed

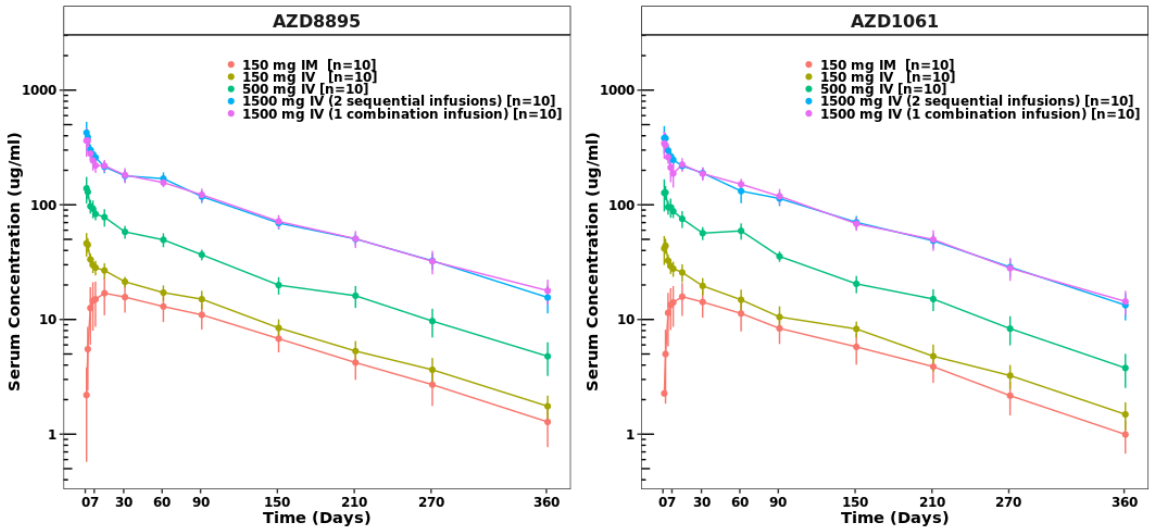
- Pseudovirus neutralization assays and authentic virus assays do not produce comparable results.
  - Pseudovirus assays: **Fast** (only requires published sequence to initiate work). Results available in first part of the wave when clinical decisions need to be made.
  - Authentic virus assays: **Gold standard but slower**. Requires Biosafety Level-3 laboratory. Virus obtained from patients and the resulting sequence may differ from published sequence.

- Variability in cell-based neutralizing assays are amplified when comparing data across laboratories with different levels of validation/qualification of the assay.

- Both assays, however, have a role in understanding how well mAb work against new VOC.

- An international standard for neutralization antibody (nAb) and IC50 assays would permit **rapid, actionable** interpretation of results from clinical trials.

PK of mAb are generally consistent and predictable by PK modelling



The PK profiles of AZD8895 and AZD1061 are superimposable despite having different variable regions

Arithmetic Mean (± SD) Serum concentrations of AZD8895, AZD1061 following single dose IM or IV administration to healthy participants, through day 361

https://www.ema.europa.eu/en/documents/assessment-report/evusheld-epar-public-assessment-report_en.pdf

- PK profile is mostly determined by the constant region of the antibody (F_c) not the variable region (F_v)
- Given a known target drug concentration, the duration of protection provided by an mAb may be predicted by PK modelling and neutralizing titer/IC50 data.