Focus: Neutralising antibodies for the treatment of ambulatory (outpatient) patients

Future Scenario: Use an EC90/PopPK framework to derive the effective dose as new viral variants emerge with moderate loss in susceptibility

Due to the fast-evolving nature of SARS-CoV-2 virus, <u>it is not</u> <u>possible to generate relevant clinical evidence in a timely</u> <u>manner</u> and therefore alternative approaches to assess the effectiveness of the available nAbs are needed.

Key outputs regarding variable dosing for the treatment of ambulatory patients

- Variants with a moderate loss in susceptibility, and where dose changes are within a range known to be safe, there is a need to use an EC90/PopPK framework to predict clinically effective doses
- This approach needs to be <u>compatible with a timeframe</u> where variants emerge/circulate
- In the treatment setting, there is a need to establish a minimum efficacious neutralising titer (threshold) linked to clinical outcome
- One approach that would fit with the necessary timeframe and refine the EC90/PopPK framework is <u>ex vivo neutralisation data</u>
- Under the assumption that the evidence generated refines the framework, future dose changes could be achieved by the EC90/PopPK framework alone

Viral variants with moderate loss of activity - potential for higher dose

Viral Variant	nAb susceptibility	Dose used
Α	Full activity	Approved dose
В	Moderate loss of activity	Potential for higher dose (assuming safety data are available)
С	No activity	No dose appropriate

In vitro EC90 and PopPK methodology data suggests certain viral variants with moderate loss of activity could be inhibited by increased doses

Important considerations when predicting clinically effective dose against new variants



These considerations can be used to develop an EC90/PopPK framework to derive doses

We have the "tools" to adjust doses based on a EC90/PopPK framework



Other data may prove challenging:

• Clinical outcome data would not be feasible to collect (during the period of variant circulation) in an informative timeframe