OFFICIAL-SENSITIVE

Summary and initial interpretation of Evusheld data

UKHSA Porton Down have been commissioned by the Vaccine Task Force to establish a programme of viral neutralisation studies to help understand the potential threats from variants of SARS-CoV2. As part of this commission, UKHSA Porton have developed live virus neutralisation assays (VNA) to test the ability of serum samples to neutralise the biological activity of SARS-CoV-2.

UKHSA Porton have also been commissioned by ATTF and commercial organisations including Astra Zeneca to utilise this VNA assay to test the functional activity of anti-virals and therapeutics.

This document summarises data from assays performed on a number of monoclonal antibodies and small molecules and a commentary and interpretation of the data so far after discussions with [redacted]).

Monoclonal Antibodies

SARS-CoV-2 Variant	Immunostain: antibody used	Evusheld IC_{50} ng/ml	Sotrovimab IC_{50} ng/ml	Ronapreve IC_{50} ng/ml	Imdevimab IC_{50} ng/ml	Casirivimab IC_{50} ng/ml
Victoria (wild-type)	Spike	7.27	6.60	ND	7.71	2.38
Alpha (Kent)	Spike	10.50	ND	ND	5.96	2.85
Beta (South Africa)	Spike	6.45	41.4	ND	4.57	923.36
Gamma (P1)	Spike	3.19	ND	ND	1.30	>1000
Delta (B.1.617.2)	Spike	7.54	67.0	ND	32.82	7.20
Omicron BA.1	Nucleocapsid	223*	596	> 20,000	> 20,000 (>1,000***)	> 20,000 (>1,000***)
Omicron BA.2	Nucleocapsid	103*	3,343*	CBA	CBA	CBA
Victoria (repeat)	Nucleocapsid	1.53*	16*	CBA	CBA	CBA

Ronapreve is an antibody cocktail containing a 1:1 mixture of Imdevimab and asirivimab

New batch of Evusheld tested week of 9th May 2022. The following table summarises preliminary data, on newly supplied Evusheld, generated during assay optimisation and development.

SARS-CoV-2 Variant	Immunostain: antibody used	Evusheld AZD7442 IC_{50} ng/ml	Cilgavimab AZD1061 IC_{50} ng/ml	Tixavimab AZD8895 IC_{50} ng/ml
Victoria	Nucleocapsid	17.81*	13.30*	2.80*
Omicron BA.2	Nucleocapsid	24.88*	16.73*	>500*

Small molecule antivirals

SARS-CoV-2 Variant	Immunostain: antibody used	Remdesivir IC_{50} ng/ml	Paxlovid# IC_{50} ng/ml
Victoria (wild-type)	Spike	5,050	ND
Beta (South Africa)	Spike	830	ND
Delta (B.1.617.2)	Spike/Nucleocapsid	2,050 (s)	465* (nc)
Omicron BA.1	Nucleocapsid	1,780	1,389*
Omicron BA.2	Nucleocapsid	CBA	4,495**
Victoria (repeat)	Nucleocapsid	12,390*	1,189*

CBA: currently being analysed
ND: not done
s: antibody to the spike was used
nc: antibody to the nucleocapsid was used
* Preliminary data generated during assay set-up and optimisation,
** only one pilot run
*** initial separate assays
IC_{50} The concentration of an antiviral or antibody required to inhibit 50% of SARS-CoV-2 viral foci in a VeroE6 cell micro-neutralisation assay.
Paxlovid# data is provided in the absence of an efflux pump inhibitor (EPI). Data on efficacy with an EPI added to the micro-neutralisation assay, as suggested by the company, is currently being generated

1) These are relatively small data sets, and so should not be overinterpreted at the absolute VNA result / value level, but the relative orders of magnitude of the results are strongly suggestive of differential effects;
2) We cannot make direct comparisons / derive likely clinical benefit as easily as we could with vaccines as we realistically only have one comparative benchmark to reference known clinical outcomes (trials on Sotrovimab);
3) We cannot from these VNA studies make any determinants of clinical suitability, recommend likely therapeutic ranges, or identify potential idiosyncratic effects of these medicine. These elements can only be determined from clinical trial data and ongoing surveillance;
4) These results and their interpretation are made in respect to, and limited to, VNA experiments conducted on wild-type, alpha, beta, gamma, delta and omicron (BA.1 and BA.2 as proxies for the BA.x lineage);
5) However, we think it reasonable to conclude that these VNA results support the following conclusions:
    a. There is broad concordance of VNA results for Evushield and Sotrovimab against wild strain, alpha, beta, gamma, and delta variants of SARS-CoV2; and where there is clinical evidence for the prophylactic and therapeutic effects of Sotrovimab it is scientifically plausible that the prophylactic and therapeutic effects of Evushield ought to be directly comparative for these genotypes;
    b. In respect to BA.x variants, compared to the rest of the variant panel tested, we note that there is a 1-2 log order reduction in neutralisation activity by reference to dilution effects for Sotrovimab. Given the limits of experimental accuracy, and noting that VNAs can be very sensitive to relatively small differences in neutralisation matching, we would suggest that these findings are unlikely to correlate with an impairment of clinical benefit for use of this medicine (Sotrovimab) against the BA.x variants of SARS-CoV2;
    c. The differential in neutralisation concentrations in the studies performed on Evushield against the BA.x variants compared to neutralisation concentrations reported for the other variants tested is in practice small[1]; and we suggest that these results are interpreted as evidence that Evushield is likely to have equivalent clinical effect against all the panel of variants tested, including the BA.x series;
    d. It cannot be determined, or assumed, from these results that Evushield will be therapeutically superior to Sotrovimab *in vivo* against BA.x variants. Any relative benefits need to be determined by clinical trial.

[1] clinically significant changes in neutralisation effects are usually associated with 100-1,000+ fold increases in concentrations needed for neutralisation effects to be seen (changes in the ND_{50} / IC_{50}). Smaller changes may indicate differences of fitness in a medicine that are unlikely to be clinically apparent, and may also, in part, be due to the natural variation that is inherent in tests on biological medicines that use biological assays.

6) Broadly speaking, therefore, we believe that these VNA studies suggest that there is no evidence to suggest that Evushield is likely to have any therapeutic advantage, or disadvantage, for prophylactic or therapeutic use against the known strains of SARS-CoV2, including the emerging BA.x strains. The benefit of use of one of these medicines over the other is most likely to lie in effectiveness data from clinical trial, and experiential data from clinical use.

[redacted] UKHSA/VTF 10-05-2022