The National Expert Group for tixagevimab/cilgavimab (Evusheld) pre-exposure prophylaxis of COVID-19

26 April 2022 10:00-11:30

Via Teams

NOTES OF MEETING

Attendees

Professor Anthony Kessel (Chair) (AK)	Clinical Director, National Clinical Policy, NHS England and NHS Improvement
[redacted]	[redacted] Ider Hey Children's Hospital
[redacted]	[redacted] UCLH NHS Foundation Trust
[redacted]	[redacted] Royal Free Hospital
[redacted]	[redacted] University of Liverpool
[redacted]	[redacted] Royal Liverpool University Hospital, [redacted] University of Liverpool
[redacted]	[redacted] University of Glasgow
[redacted]	[redacted] Llywodraeth Cymru/ Welsh Government
[redacted]	[redacted] he Newcastle Upon Tyne Hospitals NHS Foundation Trust
[redacted]	[redacted] Crick Institute
[redacted]	[redacted] UKHSA [redacted]
[redacted]	[redacted] University of Oxford
[redacted]	[redacted] North Bristol NHS Trust
[redacted]	Department of Health, Northern Ireland
[redacted]	[redacted] Department of Health, Northern Ireland
[redacted]	[redacted] Welsh Government
[redacted]	[redacted] The Scottish Government

[redacted]	[redacted] Llywodraeth Cymru/Welsh Government
[redacted]	[redacted] Department of Health & Social Care
Professor James Palmer (JP)	National Medical Director, Specialised Commissioning, NHS England and Improvement
[redacted]	[redacted] Specialised Commissioning, NHS England and NHS Improvement
[redacted]	[redacted] NHS England and NHS Improvement
[redacted]	[redacted] Specialised Commissioning, NHS England and NHS Improvement
[redacted]	[redacted] Specialised Commissioning, NHS England and NHS Improvement
[redacted]	[redacted] Specialised Commissioning, NHS England and NHS Improvement

Item	Description	Actions

1	**Welcome, apologies and introduction**
	• The chair welcomed the attendees and noted apologies.
	• The chair ensured attendees from all four UK nations were present
	• The chair provided a brief overview of the RAPID-C19 process for COVID-19 therapies and the role of national expert groups in the development of COVID-19 UK Clinical Commissioning Policies.
	• The chair discussed the background and purpose of the expert group meeting.
	• In advance of this meeting, circulated documents included:
	  ○ an agenda
	  ○ terms of reference and briefing documents
	  ○ relevant papers including the draft Independent Advisory Group report.
	• Attendees agreed not to circulate documents as they are official sensitive.
	
	Apologies received from [redacted]	

2	**Declarations of interest and review of TOR** The following interests were declared: • [redacted]: Chief Investigator for an observational study of sotrovimab (sponsored by GSK) • [redacted] Historical research funding from Astrazeneca, historical consultancy and current research funding from GSK (all not related to COVID-19) • [redacted] lab has made a number of SARS-CoV-2 antibodies (IP helped by Oxford University); founder of RQ Bio which is developing and recently licensed antibodies for human use; lab has recently also tested the AZ antibodies currently licensed for PrEP; sits on the GSK vaccines Senior Advisory Board and has in the past performed consulting with GSK for SARS-CoV-2 • [redacted] member of UKRI-funded pandemic ethics accelerator	

3	**Opening comments** The chair read out a statement from [redacted] (DHSC) and [redacted] at the Liverpool School of Tropical Medicine [redacted] Liverpool School of Tropical Medicine. The statement can be found in Appendix 1.	

4	**Pre-exposure prophylaxis (PrEP) cohorts**
	
	• [redacted], a member of the DHSC-commissioned independent advisory group (IAG), introduced the report by the IAG on cohorts suitable for PrEP.
	• The role of the IAG was briefly discussed: to determine suitable cohorts for treatment with novel antivirals and neutralising monoclonal antibodies. The IAG was additionally commissioned by DHSC to determine the cohorts in which PrEP would be indicated.
	• These cohorts were developed based on risk of severe outcomes from COVID-19 and capacity to benefit from PrEP due to poor humoral response to vaccination.
	• The groups have been stratified according to the following
	  ○ Group A1: unable to complete vaccination or known vaccine failure (as indicated by severe disease/hospitalisation despite completing the recommended vaccinations)
	  ○ Group A2: Anticipated failure of humoral response to vaccination
	  ○ Group B: significant immunocompromise but with variable response to vaccination
	• Other members of the IAG at the meeting highlighted that the original development of cohorts was done in a largely evidence-free area and the recommendations made are mainly theoretical. However, good evidence now exists for the antibody response to vaccinations in many vulnerable cohorts.
	• The expert group was advised that the ethics of individuals opting out of vaccination was not part of today's discussion, which was primarily centred around the risk levels in various cohorts. However, vaccination status is captured by the phrase 'unable to complete vaccination' in Group A1.
	• The IAG's recommendation is that, if prophylaxis is approved, patients in group A should receive PrEP irrespective of serum antibody status, and the eligibility of those in Group B may be subject to serum antibody status.	

5	**Evidence for tixagevimab and cilgavimab** • The group discussed the evidence for the efficacy of tixagevimab and cilgavimab. • The group highlighted that the outcome numbers of interest from the PROVENT trial were too small to draw a definitive conclusion [symptomatic COVID-19 occurred in 8/3441 (0.2%) and 17/1731 (1.0%) participants in the Evusheld and placebo groups, respectively] and that the decision to proceed with a policy should also be based on biological plausibility • The group noted that the STORM-CHASER trial, which studied tixagevimab and cilgavimab in the post-exposure prophylactic setting, did not meet its primary endpoint • The group discussed the potential benefits of any neutralising antibody in patients with absent immune responses at baseline • The group noted that there is scarce evidence from the PROVENT trial of efficacy in the cohorts of interest, and reiterated that the event numbers/rates in the study population were very low	

6	**Activity against Omicron** [redacted] provided a pharmakinetic overview of tixagevimab and cilgavimab in the context of in vitro neutralising activity against Omicron (and subvariants). A detailed statement is available in Appendix 2. The following key points were raised: • The properties of tixagevimab and cilgavimab with regards to recruitment of effector function and direct neutralisation activity were discussed. • Published in-vitro data has demonstrated significantly compromised activity against the BA.1 subvariant of Omicron, i.e. a >100-fold decrease in neutralisation. • The neutralisation activity of cilgavimab against BA.2 was restored to levels comparable to that against pre-Omicron variants. However, the activity of tixagevimab remained compromised. • The efficacy of tixagevimab and cilgavimab has been reported to be augmented by the synergistic activity between the two antibodies. In the case of BA.2, the product works as a monoprophylactic agent (on the basis of reduced neutralisation activity by tixagevimab). Therefore reduced neutralisation activity overall should be expected for the combination. • All neutralising monoclonal antibodies (nMABs) have been progressed as combinations due to the resistance risk (with exception of sotrovimab due to its high epitope conservation) • The activity profile against other Omicron sublineages is unknown as yet. • The concluding impression was: it is a reasonable assumption that doubling the licensed dose of tixagevimab and cilgavimab will produce comparable neutralising activities against the BA.2 subvariant but that it would be driven by one antibody rather than two as studied in PROVENT. This would effectively represent monoprophylaxis with cilgavimab, which may have implications for the development of resistant/escape variants. The group highlighted the following: • There is no evidence that definitively indicates that tixagevimab and cilgavimab will be ineffective against BA.2 but there is also no definitive evidence that it will be effective against BA.2. • Knowledge of emerging variants will be important in anticipating potential impacts of these variants on the neutralisation activities of nMABs.	
7	**Cost-effectiveness analysis** [redacted] presented DHSC analysis on cost effectiveness. Key points included: • The outcome of interest in the cost-effectiveness analysis by the DHSC was based on hospitalisation rather than development of symptomatic COVID-19 which was the primary endpoint in the PROVENT trial. • This outcome depends on the attack rate in the population of rates and their vulnerability.	
8	**Role of antibody testing** It was discussed that serology may be of benefit in group B in the IAG report due to the variability of vaccine response in this group.	
9	**Conclusions:** The group discussed all the relevant issues at length. A vote was then held in the Microsoft Teams chat facility and the majority (all members bar one),	

	concluded that there was insufficient evidence at present to progress a clinical policy, and new academic research in the UK setting was strongly needed. In summary: • In the absence of clinical data, in-vitro data is insufficient to provide guidance towards deployment decisions. • There is at present insufficient evidence and significant scientific uncertainty such that it is not possible to progress to the development of a clinical policy for access to tixagevimab and cilgavimab. • An NIHR-sponsored research study of PrEP with tixagevimab and cilgavimab in the cohorts outlined in the IAG report is the most appropriate course of action. • Variables studied may include: dosing, combination versus monotherapy, pharmacokinetic and pharmacodynamic outcomes • Such an academic study should ideally be a randomised controlled trial rather than an observational study. • Any research study should be designed such that its outcomes are generalisable and applicable towards all new/emerging variants i.e. future-proofing the research platform and approach against the changing pandemic context as best as possible.	
	Next steps and close • Minutes will be developed and circulated for comment. • A report and recommendation will be prepared for the CMO. • Next steps to be discussed with DHSC.	

Action	**Actionee**
Develop minutes from this meeting	[redacted]
Discussion with DHSC	AK

Appendix 1

[redacted] (DHSC) and [redacted] Liverpool School of Tropical Medicine

1. NmAbs are particularly susceptible to mutations in the spike protein of the SARS-CoV-2 virus and can be rendered partially or completely ineffective against new VoCs, as in the case of Ronapreve which is now withdrawn from clinical policy.
2. Although the company have confidence that Evusheld retains efficacy against the Omicron variants, independent experts and the Prophylaxis Oversight Group have expressed concern about the reduction in efficacy as per in vitro testing. There is a risk that a suboptimal neutralising response against a variant can place selection pressure on the virus and create new variants. While in vitro neutralisation data are not a substitute for clinical evidence, in vitro neutralisation data were used by AZ as the basis for dose selection in clinical trials in which Evusheld was only studied against pre-omicron variants.
3. UKHSA are currently carrying out in vitro testing of Astronaut against BA.1 and BA.2. Initial results from BA.1 testing show it to have markedly reduced neutralisation activity against BA.1. Other independently generated data indicate that while one of the two antibodies in the Evusheld (cilgavimab) combination has neutralising activity against BA.2 that is comparable to that against pre-omicron variants, the other antibody (tixagevimab) remains compromised (https://www.nature.com/articles/s41591-022-01792-5). UKHSA testing against BA.2 is underway but there are currently no timelines for the availability of results.
4. The key question is whether the beneficial clinical results seen in the initial clinical trials can still be assumed to exist against omicron variants. It is challenging to determine conclusively whether Evusheld retains efficacy against Omicron sub-lineages (and future variants), as this is reliant upon extrapolation from in vitro neutralisation assays and PKPD modelling of how the product will work in vivo. The Prophylaxis Oversight Group continues to have concerns over some of the modelling assumptions set out by the company and does not consider that there is currently adequate preclinical evidence to conclude clinical efficacy against Omicron variants or to justify widespread deployment.

Appendix 2

[redacted] University of Liverpool

Differences in mechanism of action between Evusheld and Sotrovimab:

- Like sotrovimab, both antibodies in Evusheld have Fc modifications to extend pharmacokinetic half-life.
- Evusheld antibodies have additional modifications to obviate the effector functions. Therefore, for Evusheld direct neutralization is the only mechanism of action.

Both antibodies in Evusheld were substantively compromised with respect to BA.1 Omicron to an extent that there could be no reasonable expectation of parity with pre-omicron variants.
However, for one of the two antibodies (cilgavimab) the neutralisation activity against BA.2 Omicron was restored such that it maintains neutralisation activity comparable to that against the pre-Omicron variants for which it was clinically studied. However, for the other antibody in the combination (tixagevimab), neutralisation of BA.2 Omicron remains compromised.
There are several implications of this that the panel should consider:

1. Existing clinical data for Evusheld reflect the efficacy of a combination of monoclonal antibodies for which AZ have argued exhibit a synergy in neutralization. In the context of BA.2 Omicron, Evusheld represents a mono-prophylactic. Published data show that the combination exhibits reduced neutralization of BA.2 in vitro relative to pre-Omicron variants which is broadly consistent with absence of any contribution from the compromised antibody.
2. With the exception of sotrovimab, antiviral monoclonal antibodies have been progressed as combinations because of the resistance risk with single antibodies (which has been empirically demonstrated to be a liability for other monoclonals such as bamlanivumab and well as antiretroviral monoclonals). Sotrovimab monotherapy was argued on the basis that the epitope was "highly" conserved and sotrovimab resistance mutations have been documented clinically despite the conserved epitope.
3. Notwithstanding, doubling the dose of Evusheld may be expected to provide neutralizing activities for BA.2 Omicron broadly comparable to the conditionally approved dose against pre-Omicron variants if synergy was not important.
4. The profile against other Omicron sub-lineages currently on the rise in the UK is unknown.

Final point that even with full neutralization activity against pre-Omicron variants, headline data presented in the FDA EUA indicate that Evusheld failed its primary endpoint in STORMCHASER which was a PEP trial.
I am not a clinical trialist, so have the panel reviewed the STORM CHASER data to ascertain whether there were reasons for this other than the potential that Evusheld was already very close to its PK-PD threshold at the original dose against the variants for which it was originally developed? It should be noted that for intramuscular administration (e.g. Evusheld), there is a delayed absorption compared to intravenous administration (e.g. sotrovimab). This means therapeutic concentrations take longer to achieve for IM than for IV, which could be important in post exposure where rapid attainment of therapeutic concentrations may be more important.