The Rt Hon Dr Thérèse Coffey MP
Secretary of State for Health and Social Care
Department of Health and Social Care
39 Victoria Street
London SW1H 0EU

5 October 2022

Dear Secretary of State,

I am writing in response to a letter sent by your predecessor, to myself and colleagues in other patient support organisations on 05 September. We were in conversation with the Rt Hon Steve Barclay MP concerning the procurement of Evusheld, a prophylactic COVID-19 treatment used to prevent infection and ameliorate severity of illness in people who are severely immunocompromised. Such a treatment is urgently needed for those who do not mount an adequate immune response from the COVID-19 vaccines.

In his letter to us, your predecessor outlined the reasons that your Department has chosen not to decide whether to procure Evusheld until a NICE appraisal has been completed in summer 2023. Since the Department's decision is highly unusual in the context of COVID therapeutics – which are normally procured before a full appraisal is conducted via the RAPID C-19 pathway – it is vital that the decision-making process is transparent. To this end, I appreciate the comprehensive and detailed nature of his letter; we have shared it with our community, who have keenly followed Evusheld's progress since the success of its clinical trials last year.

We have considered his response and have sought clinical advice on each of his points to ensure that we remain evidence-led. We are also grateful to the Faculty of Pharmaceutical Medicine for providing expert input on the process of medicines development. I have outlined our response to his key points below.

<u>Real-world evidence</u>

While there is clinical uncertainty (as referenced in the letter), the risks from COVID-19 to our community outweigh the risks of potentially reduced efficacy of Evusheld against future variants. Evusheld, were it to be rolled out, could be monitored and withdrawn if proven ineffective against future variants. Further, while there are limitations concerning real-world studies, as cited in the letter, limitations also exist in in vitro studies. One key limitation is outlined in a further section below.

Citing limitations for those studies which demonstrate Evusheld's effectiveness, while not referencing the limitations of lab-based studies is misleading. It is a basic requirement of

manuscript authors to appraise the strengths and weaknesses of their studies; the stated limitations do not reduce the significance of their research findings, but rather acknowledge the potential shortcomings of the study to ensure integrity and honesty. Indeed, the Oxford COVID Vaccine Trial Group publication[1] that helped lead to the rapid clinical introduction of the AstraZeneca Oxford Covid vaccine cited limitations including a short follow-up, small participant numbers in the prime-boost group, the single-blinded design, and the fact that the findings are not easily generalisable due to the relative youth and health of participants, as well as that they were majority white. Despite these methodological limitations, the vaccine was – quite rightly – rolled out at speed.

Regulators, including the MHRA, often use real-world data to confirm or refute results produced by lab testing and clinical trials, and to ensure that these results are replicable and scalable to a wider group of patients. Discounting real-world evidence for the reasons cited by your predecessor is incongruent with the prevailing opinion among regulators.

Peer-review

In addition, that many of the real-world study publications have yet to be peer-reviewed is also, we believe, not a legitimate reason to prematurely dismiss them. Albeit a rigorous and important mechanism in the publication process, it is widely accepted that peer-review is not a perfect mechanism for managing research integrity[2] and that it is possible to review and make judgment on evidence before it is peer-reviewed. The argument, therefore, that evidence published in pre-prints is fundamentally flawed because they have yet to undergo the peer-review process is one with which we disagree. Indeed, the Department itself used data which, at the time, was presented in pre-prints to inform their public-facing communications outlining the efficacy of the COVID-19 vaccines in the UK population. One of the largest pre-print servers for health sciences research – medRvix – was established by Yale University, the British Medical Journal, and others specifically to "improve the openness and accessibility of scientific findings, enhance collaboration among researchers…through more timely reporting of completed research."[3] While pre-prints are not intended to guide clinical practice, they played – and continue to play – a crucial role in the public health response to the pandemic where key information would have otherwise been slow to reach publication.

Lab-based testing

Further, while I acknowledge that there are methodological concerns in some of the real-world studies, including the retrospective nature of some, and challenges in matching control groups, there are methodological limitations to in vitro testing of SARS CoV2 that should also be

[1] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext
[2] See, e.g., Richard Smith in the Journal of the Royal Society of Medicine 99(4), pp.178-182: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1420798/
[3] https://www.medrxiv.org/content/about-medrxiv

considered. There is, as yet, no international standard for in vitro testing of SARS CoV2. This has led to considerable discrepancies in the drug concentration values required to neutralise the virus, as there are no internationally agreed-upon designs ensuring that each lab uses the same model system.

Some laboratories, therefore, have reported unusually high concentration requirements to prevent and/or treat infection with subvariants of Omicron when testing Evusheld. The FDA examined this issue in June, in relation to the dose and dosing interval of Evusheld in light of Omicron. Their updated emergency use authorisation for Evusheld[4] explains that they discounted several outlier values from some labs for this reason, which led to the dosage increase from 300mg to 600mg given every six months. In the UK, it is unusual that the UKHSA and NIBSC have yet to publish such data on the testing of SARS CoV2; if that testing has been conducted, I ask that this data be published.

Eligibility

Lastly, on eligibility and cohort identification, we agree that not all 500,000 immunosuppressed people will benefit from Evusheld or are in equal need of Evusheld. However, the need to identify the cohort at greatest need is not a reason, we believe, to refuse its procurement. We welcome a programme that would enable immunocompromised people to test for antibodies if it is also paired with clear communications enabling them to interpret the results and incorporate them into their personal methods of risk management. This includes, for instance, educational materials that outline the role of cellular versus humoral immunity. I would like to note, however, that the MELODY study team have been involved with such testing in a group of 36,000 patients. They would be in a position to assist in any such antibody testing pilot programme, as Dr Michelle Willicombe expressed to you in a letter dated 8 September.

I appreciate that much of this letter is a response to one sent by your predecessor, and therefore request to meet so that we can continue this discussion in further detail.

Yours sincerely,

Gemma Peters

Gemma Peters
Chief Executive of Blood Cancer UK

[4] https://www.fda.gov/media/159767/download