Single Technology Appraisal

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

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4. **Comments on the Draft Guidance Document from experts:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Single Technology Appraisal

Response to consultee, commentator and public comments on the draft guidance

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the draft guidance document (if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final draft guidance.

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the draft guidance (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the draft guidance and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the draft guidance when it is posted on NICE's website 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
1	Consultee (company)	AstraZeneca	**AstraZeneca consider that Evusheld should be positioned in a subgroup of its licensed indication where the highest unmet need exists** In response to consultation, AstraZeneca are seeking a recommendation for a specific target population within Evusheld's marketing authorisation. The target population would be for: Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, with high-risk reflecting groups A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the independent advisory group report (1), or • for whom COVID-19 vaccination is not recommended • where Evusheld displays neutralisation activity against a threshold of circulating variants ***Defining the high-risk population*** AstraZeneca agrees with the committee's view that the updated independent advisory group report is appropriate for stratifying the need for preventative treatment, and that groups A1 and A2 represent a highest risk subset among those at the highest risk of developing severe complications from COVID-19. Further to this, within group B of the independent advisory group report, there is a subset of patients who do not achieve a serological response to vaccination determined through serological testing, and these patients are also at high-risk of poor outcomes if contracting COVID-19. These patients would also be considered of equally high-risk of poor outcomes, as the A1 and A2 cohort defined in the independent advisory group report. The company is therefore seeking a recommendation in this highest risk of the high-risk population, that is patients in A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the independent advisory group report.(1) By targeting patients at highest risk, AstraZeneca is ensuring that Evusheld is available to patients with the highest unmet need, who will benefit most from treatment, while also ensuring that Evusheld represents a cost-effective use of NHS resources.	Thank you for your comments. The committee maintained that the eligible population should be all groups covered by the marketing authorisation because it had not seen evidence of differential clinical or cost effectiveness to rule out other groups. Please see section 3.5 of the final draft guidance for further details.
2	Consultee (company)	AstraZeneca	***Recommend Evusheld where there is evidence of neutralisation activity against a threshold of circulating variants.*** A robust, rapid and agile decision-making framework is required in order to ensure that NICE can make responsible decisions for COVID-19 prophylactic treatments given the evolving landscape with respect to	Thank you for your comments. The committee acknowledged the need for a more flexible

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			emerging variants. The need for a robust decision making framework is also recognised by NICE in response to the publication of the draft recommendations for this appraisal, and NICE has announced the development of a new review process to update its recommendations on the clinical and cost-effectiveness of COVID-19 treatments.(2) Further to this, academics, clinicians and patient groups have also reinforced the need for a robust decision making-framework in their responses to the draft negative consultation (see Section 11 for further details). Although it is reassuring to see that NICE is committed to developing an updated decision-making process, and NICE has announced a public consultation on these new processes from the 3rd of April; the appraisal process for Evusheld is currently ongoing. Therefore, there is a need for NICE to adopt an appropriate framework for decision making at the next committee meeting and ahead of the closure of the public consultation. In addition, as outlined in Section 5, AstraZeneca believe that the process adopted by NICE at this present time for this appraisal is not appropriate, highlighting the need for developing a process which can support responsible decision making immediately. In response to this, AstraZeneca has laid out the company's preferred approach to decision making. In summary this process looks to internationally recognised Regulatory Agencies to inform how to best evaluate the clinical appropriateness on the use of Evusheld at any given moment in time with respect to current and future circulating variants. For example, whilst the FDA temporarily suspended the emergency authorisation of Evusheld due to the high proportion of circulating variants to which Evusheld does not neutralise, it has stated that it will reconsider reinstating authorisation of Evusheld if the national prevalence of resistant variants decreases to 90% or less.(3) A signal regarding thresholds is not available from the MHRA; however the FDA are a well-established and robust decision making body; therefore it is appropriate to reference the FDA when determining an appropriate decision making process for the future, until such point the MHRA issue guidance. AstraZeneca would therefore propose that by way of process, NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants. A full discussion of AstraZeneca's preferred decision-making framework is available in Section 11 with relevant economic results available in Section 12 and **Error! Reference source not found.**. However, it should be noted that the proposed process put forward by AstraZeneca supports agile and responsible decision making in the current environment and is aligned with the approach of trusted regulators.	evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
3	Consultee (company)	AstraZeneca	**The dosing assumptions have been updated to reflect a single dose of Evusheld.** The ACD document raises concerns regarding the Company's economic model applying two doses of Evusheld as opposed to single dose. The Committee also concluded that it would be more appropriate to use a single dose in the economic analysis. *"so the committee concluded that the economic analysis should include a single dose of tix–cil only"*	Thank you for your comments.

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			AstraZeneca recognise that the Summary of Product Characteristics (SmPC) recommends a specific dosing criterion, and this criterion does not explicitly prohibit any subsequent dosing or the application of a second dose. However, for the purpose of decision making today, and to align with NICE regarding preferred assumptions for the economic model, the economic modelling has been updated to apply a single dose Evusheld.	
4	Consultee (company)	AstraZeneca	**The patient access scheme (PAS) will be realised by the NHS.** AstraZeneca recognises the committee expressed concern relating to the PAS and specifically commented *"commissioning experts' preference for administering tix–cil in primary care would mean that the benefit of the confidential patient access scheme would not be realised by all parts of the NHS".* The target population for this single technology appraisal (STA) reflects patients who are of the highest risk and therefore this group of patients would be expected to attend hospital regularly by way of routine outpatient visits, to manage their underlying health condition. Alternatively, patients may regularly attend secondary care led community services again with the aim of managing their underlying condition. Given the regular contact between this group of patients and NHS services via routine appointments, it is expected that Evusheld would be administered in this secondary care, or secondary care led community setting, and prescribed upon specialist advice. Furthermore, given the need to make a determination as to the appropriateness to prescribe and administer Evusheld with respect to the patients' eligibility and neutralisation of currently circulating variants, it would be more appropriate to restrict prescribing to secondary care or a secondary care led community service. Therefore, Evusheld would be made available at the PAS price and therefore the benefits realised by the NHS in practice. We have communicated this with NHS England and PASLU, and on this basis, the appropriateness of a PAS for Evusheld has already been assessed and approved by NHS England.	Thank you for your comments. The committee noted that the administration setting was uncertain. Therefore, it took account both the company's and EAG's estimates for the administration cost in its decision making. Please see section 3.18 of the final draft guidance for further details.
5	Consultee (company)	AstraZeneca	**AstraZeneca comments on the *in vitro* data advisory group (IVAG) report and interpretation of neutralisation data.** The ACD acknowledges that given the evolving and changing landscape, variants of COVID-19 that are currently circulating may be different to the prevailing variants when the relevant clinical data (i.e. pivotal trials or real-world evidence) was submitted. *"Although clinical studies of tixagevimab plus cilgavimab suggest a reduction in COVID-19 infection compared with no preventative treatment, these studies were done early in the pandemic when different variants of the COVID-19 virus were circulating."* NICE also go on to suggest that *in vitro* data may provide an insight into how medicines may perform against currently circulating variants,	Thank you for your comments. The committee considered data from the latest technical briefing published by UKHSA in March 2023. This briefing showed that there were only around 3% of circulating variants (BA.2 and BA.5) that tix–cil may be effective against. The committee

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			"In vitro neutralisation assays can be used to assess if treatments neutralise new variants, and therefore if they retain clinical effectiveness over time as the virus evolves. An advantage of in vitro evidence is that it can be generated much faster than it would take to do clinical trials." However NICE also recognise the need for a process to interpret these data, and that the Committees' experience of interpreting such data are limited. Therefore, an advisory panel (IVAG) was established to support the understanding of the *in vitro* evidence. *"But NICE's technology appraisal committees are not used to interpreting and appraising in vitro data. Because of this, NICE commissioned an in vitro data expert advisory group made up of experts in infectious disease, virology, vaccine epidemiology, immunology, and pharmacology. They developed a decision framework to link the in vitro neutralisation data to clinical outcomes, and their report… provided guidance on interpreting in vitro evidence".* AstraZeneca recognise the need for a robust approach in terms of interpreting the *in vitro* data and accept the following conclusions from the IVAG review process. • If the neutralisation activity of a medicine is the same as the previous variants, then similar efficacy can be assumed. • Loss of neutralisation to the current circulating variants does not mean that neutralisation cannot be recovered for future emerging variants. • It is not possible to predict the future with certainty. AstraZeneca also note that the IVAG concluded that if the *in vitro* data reported no evidence of neutralisation, this would imply no efficacy for the treatment against the variant. The company are aware of the challenges and difficulties in interpreting *in vitro* data and therefore accept that in the absence of evidence of clinical effectiveness despite no neutralisation, then for the purpose of decision making today, that it's reasonable to assume that total loss of neutralisation means no clinical effectiveness. (4) However, AstraZeneca would also like to comment that in the event that real world evidence emerges that demonstrates clinical effect in the absence of neutralisation against circulating variants then this data should be factored into decision making. Further to this, AstraZeneca would like to highlight that monoclonal antibodies may have a range of additional functions not directly measured by in-vitro neutralization assays. This may include a range of immunomodulatory functions which may provide protection beyond neutralisation. We do however fully appreciate the challenge that NICE faces in looking to quantify clinical efficacy in such a rapidly evolving environment. However, if such data becomes available and there is evidence of benefit through mechanisms which are beyond neutralisation, then this evidence should also be factored into decision making. It is also worth noting that benefits beyond neutralisation have not been taken into account in the economic modelling and therefore the case put forward by AstraZeneca could be considered to be conservative.	therefore concluded that there was no evidence that tix–cil would neutralise at least 97% of circulating variants as of March 2023. Please see section 3.12 of the final draft guidance for further details. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details. The committee recalled the in vitro assessment group's conclusions that without pharmacokinetic and pharmacodynamic data, it is not possible to

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			AstraZeneca also have additional comments in relation to the level at which neutralisation infers effectiveness. In general, neutralisation ability is assumed to be retained when an IC50 is <10,000 ng/ml and this is a widely accepted threshold for neutralisation activity. (5) Further to this, measurable IC50 values below 10,000 ng/mL implies that the treatment binds to the receptor binding domain of the SARS-CoV-2 Spike Protein which would infer a clinical effect and therefore supports the conclusion that IC50 <10,000 ng/ml is an acceptable threshold for evidence of neutralisation. (6) Given the above AstraZeneca propose that an IC50 of <10,000 ng/ml is utilised by NICE to determine activity against any particular circulating variant and that an IC50 of <10,000 ng/ml would also translate into clinical effect. This position is supported by a recent systematic literature review(7) which provided a summary of the real-world clinical evidence for Evusheld. This review included studies which were conducted in variants which reflected neutralisation across a range of neutralization values, and these studies also reported Evusheld treatment has led to statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation. Therefore, it is appropriate to conclude that an IC50 of <10,000 ng/ml infers clinical effect. A top-line summary of these RWE papers is available in **Error! Reference source not found.Error! Reference source not found.**. Further to this, in terms of changes in neutralisation, there is evidence to suggest that even if there were a decrease in neutralisation for a new variant in relation to older variants, the loss of efficacy would not be diminished in cases of severe COVID-19. This evidence also supports the Company's position of presenting an absolute threshold of effectiveness (IC50 of <10,000 ng/ml) as opposed to focussing on changes in neutralisation.(8)	determine how a change in neutralisation activity may be associated with clinical outcomes. So, the committee did not consider this proposal to be appropriate for decision making. Please see section 3.12 of the final draft guidance for further details. No evidence was submitted to NICE for an immunomodulatory effect outside of neutralisation.
6	Consultee (company)	AstraZeneca	**Conclusions made by NICE in the ACD document are contradictory versus IVAG, or previous NICE advice, and a robust, rapid and agile decision-making process is required.** As part of the ACD, NICE make statements which are contradictory to either the conclusions of IVAG (or previous NICE advice). Examples of which are as follows. ***Neutralisation activity against currently circulating variants is the most useful estimate of effect against future variants.*** *"The effectiveness of tixagevimab plus cilgavimab (tix–cil) over the appropriate time period of the future 6 months would be best indicated by neutralisation potential against currently dominant circulating variants".* This statement is not only incompatible with the unpredictable and evolving nature of the COVID-19 landscape. It also contradicts conclusions drawn by IVAG, e.g., regarding difficulties to predict viral evolution and the shortcomings of *in vitro* neutralisation alone to make decisions. This statement also does not recognise sotrovimab in ID4038(9,10) where sotrovimab demonstrated limited or loss of neutralisation activity, such as the case for BA.2 only to weakly recover and then obtain a positive recommendation from NICE. Another notable example is that of Ronapreve (casirivimab and imdevimab) where in December 2021 it was found that BA.1 fully escaped *in vitro* with no neutralisation at all for the imdevimab component of the medicine. However it was later found that the imdevimab component was able to neutralise omicron BA.2, BA.2.12.2, BA.4 and BA.5 variants.(5)	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based

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			NICE suggest that the relevant time frame for the appraisal is January and the next 6 months. *"But the committee concluded that tix–cil should not be recommended because it is unlikely to be effective against most of the relevant variants in the appropriate time period for this evaluation (January 2023 and the 6 months after)."* AstraZeneca do not agree that it is appropriate to assume a static 6-month window as a timeframe for the appraisal for a number of reasons: A 6-month time period contradicts statements from the IVAG, where, although IVAG suggest major antigenic changes tend to happen every 6-months, changes in variants may occur every 1-2 months. Further to this, the IVAG highlight that 1-2 months is a relevant time period for predicting change in circulating variants, and this point is also recognised on public slide deck (slide 18) for the second ACM for ID4038 which stated *"Predicting change in currently circulating variants limited only to the 'near future' (**1-2 months**)"*(11). Therefore, it would be inaccurate to imply that variants may remain unchanged for 6 months and this is not compatible with the conclusions from the IVAG who suggest that changes in variants can only be predicted for a much shorter time period. In addition, in terms of dominant variants, it is noted that Omicron variant B1.1.529 was dominant for a very short period of time (approximately one month) earlier in the pandemic only to be replaced by other variants as the pandemic progressed (see slide 4 of the public slide deck for the ACM for this appraisal). IVAG also reference that if a variant has a 25% growth advantage and reaches 10% of total samples, then the variant may become dominant. The IVAG do not reference a timescale for this change and therefore it is not time bound. The above are further examples of the shifting and evolving COVID-19 landscape and that it is not appropriate to apply fixed time periods (such as 6-months) to an evolving disease area where there are frequent changes. These examples also highlight the need for continuous surveillance of COVID-19 variants given the rate of change and to inform robust decision making. In the sotrovimab appraisal, NICE initially rejected sotrovimab in the draft guidance(10) and suggested it would not be effective against current variants and most likely would not be effective in the future. However, 3 months later, in the final guidance(9), NICE have revised their decision and recommended sotrovimab for use. Therefore, assuming a 6-month window for the appraisal, where there will be no changes in variants or neutralisation activity, is not consistent with the decision making made by NICE who arrived at two different decisions regarding sotrovimab only 3 months apart. Finally, as referenced by clinical experts in the ACD meeting, even after a decision by the committee, it is likely to take a few months before a medicine is wholly adopted and in use. Therefore, NICE's time frame of 6 months is likely to be an underestimate of the length of time of the appraisal especially if considering a 3-month window for implementation which is assumed for the ongoing MTA. ***A robust, rapid and agile framework for decision making is required.***	on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.

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			It is clear that NICE recognise the need for a process in order to ensure responsible decision making for prophylactic treatments for COVID-19. This is evidenced by NICE commissioning the IVAG to make specific recommendations regarding the interpretation of *in vitro* data. AstraZeneca are also aware that NICE has announced the development of a new review process to update the recommendations on the clinical and cost-effectiveness of COVID-19 treatments, to ensure rapid patient access to potentially effective treatments with emerging evidence against particular variants.(2) However, it is also clear is that the current decision-making process is fundamentally flawed, as for example, NICE are currently applying process or making statements which contradict conclusions made by IVAG or NICE's own advice (see above in Section 5). As such, Section 11 of this response proposes a revised framework for decision making which is underpinned by the outcomes of the IVAG but enables NICE to translate these into practice to support it in making responsible decisions for COVID-19 medicines. This process captures the dynamic nature of the COVID-19 landscape and respective uncertainties with regards to the evidence. In addition, as noted in the ACD and as made unmistakably clear by the patient expert testimonies, there is an urgent and unmet need for preventative therapies. Therefore, the process put forward by AstraZeneca also supports NICE in reaching responsible and robust conclusions to enable access to effective prophylactic therapies for high-risk patients.	
7	Consultee (company)	AstraZeneca	***The sources applied in the economic model are appropriate to reflect the target positioning for Evusheld.*** In the ACD, NICE have noted there is uncertainty around the extent to which the inputs in the economic modelling reflected the target population. *"The external assessment group (EAG) noted that it was not clear from the company submission how the population that is eligible for tix–cil should be defined. It added that many of the inputs in the economic analysis were selected to reflect particular groups, and do not represent the eligible population as a whole, nor do they capture the heterogeneity within the eligible population".* Following the committee meeting, AstraZeneca has clarified that the target population relevant to this appraisal are groups A1, A2 and those in group B without serological response (see Section 1). These patients represent the highest risk subset among those at the highest risk of developing severe complications from COVID-19. To confirm the robustness of the model inputs with respect to the target population, the eligible population and heterogeneity table from the NICE committee meeting slides (slide 26) has been reproduced below and discusses why the company source is appropriate. Where possible, data specific to the target population has been included to ensure the economic evaluation accurately represents the population in scope. However due to the recentness of COVID-19, there is a paucity of data in the specific target population and therefore where this data is not available, AstraZeneca has taken a conservative approach and used data	Thank you for your comments. The committee maintained that the eligible population should be all groups covered by the marketing authorisation because it had not seen evidence of differential clinical or cost effectiveness to rule out other groups. Please see section 3.5 of the final draft guidance for further details.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE response</th></tr>
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from a less immunocompromised or immunocompetent population. AstraZeneca has also provided additional scenario analyses related to infection risk to further quantify the uncertainty in the model inputs and the impact on outcomes (see Section 12).

Table 1. Model inputs and eligible population
<table>
<tr><th>Model parameter</th><th>Company's source</th><th>Population</th><th>IAG cohorts</th><th>Justification</th></tr>
<tr><td>Baseline characteristics (Used to estimate mortality and utility)</td><td>PROVENT trial</td><td>Adults at increased risk of inadequate response to vaccination or at increased risk of SARS-CoV-2 infection</td><td>A1, A2, B, C and uncategorised</td><td>The baseline characteristics, sourced from the PROVENT trial, included individuals that were immunocompromised or had an inadequate immune response to a COVID-19 vaccine. Baseline characteristics used in the model only include age, percentage of males and weight, these characteristics are not specifically linked to defining the IAG cohorts however would be expected to have minimal impact if the population used by the model were broader than the scoped population. Results of the deterministic sensitivity analysis for both the Company and EAG base case showed that when age, percentage male and weight were varied using the standard error, there was not a substantial impact on the ICER.</td></tr>
<tr><td>Risk of COVID-19 infection (without Evusheld)</td><td>UK government</td><td>General population of England between August 2021 and August 2022</td><td>Mostly uncategorised</td><td>The risk of infection was taken from the general population risk of COVID-19 without Evusheld. This risk was used in the economic model for the cohort that had not received Evusheld. Since this risk was taken from a mostly uncategorised risk, it can be assumed that in practice, the risk of COVID-19 to cohorts IAG A1, A2 and seronegative B patients, would be higher. Therefore, the company would like to highlight that this is a conservative estimate of the risk of COVID-19 in the target population. Furthermore, scenario analysis has been run including varying the infection risk by ± 20% and showed limited impact on the ICER (See Table 3: Updated EAG and company scenario analysis post committee using a 10% threshold).</td></tr>
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			Risk of hospitalisation for COVID-19 (without Evusheld)	Shields et al. 2022	Patients with primary and secondary immunodeficiency* in the UK, during Omicron wave (up to April 2022). Subgroup that was not treated in COVID-19 Medicine Delivery Units (CMDUs). *Receiving immunoglobulin replacement therapy or had a serum IgG concentration less than 4g/L and were receiving regular antibiotic prophylaxis to prevent infections.	A2	The risk of hospitalisation is based on Shields et al. (2022) which assess the hospitalisation and mortality risk for immunodeficient individuals (IAG group 2). This population is deemed appropriate since the study was conducted on individuals with primary or secondary immunodeficiency, and would therefore, not mount a sufficient response to vaccination. Whilst the company acknowledges that this population contains individuals with both more severe and less severe immunodeficiency, this source was deemed most appropriate to capture the target population. This source is also most representative of the optimised population in which AstraZeneca seeks reimbursement in i.e. those in A1, A2 and seronegative B patients. These patients represent the highest risk of the high-risk population.	
			Direct utility gain for people receiving Evusheld	Gallop et al. 2022, commissioned by company	Immunocompromised individuals	Majority A2	A study by Gallop et al. 2022 (commissioned by AstraZeneca) determined the direct utility gain for individuals receiving Evusheld. The study was conducted in a population that were largely categorised into the IAG cohort A2. The utility gain could be even greater if it were to include the estimates of QOL impact for the more vulnerable A1 population, who would likely exhibit shielding behaviours. The utility gain, of 0.098, has only been applied to 82% of the model population to reflect the proportion of patients who are either fully or partially shielding according to the ONS survey. (21) Based on the evidence collected in the general population, this utility gain may be considered conservative since:	

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			<table><tr><td></td><td></td><td></td><td></td><td>• An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states in the general population, and • An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behaviour health states in the general population (21)</td></tr></table> Finally, a wider overview of the economic model inputs and justification is available in **Error! Reference source not found.**	
8	Consultee (company)	AstraZeneca	**The direct utility gain presented in the evidence and company model appropriately captures the quality-of-life impact for patients treated with Evusheld.** NICE comment on the challenges of capturing the most appropriate direct utility gain for patients treated with Evusheld given the interaction of quality of life with other variables such as infection risk, efficacy of the medicine and pre-existing behaviours. The committee noted uncertainty around whether a direct utility gain should be applied and if so, what size gain is most appropriate and what proportion of people this should apply to. Specific comments from the ACD document are as follows: *"The committee noted that there were additional complexities that needed further attention in addition to the original scope, such as the relationship between risk of infection, shielding behaviours and improvements in health-related quality of life."* *"The committee acknowledged the challenges in relating efficacy of a preventative treatment to reduction in risk of infection, given the importance of behavioural changes leading to increased quality of life. This was made harder by a lack of health-related quality of life data from the trials".* *"The committee considered that there is a trade-off between the extent of shielding and the utility gain from stopping or reducing this, and the level of risk reduction that tix–cil will deliver before and after a decision to stop or reduce shielding. For example, if people's risk of infection reduces such that they interact more with others, the risk of infection would then increase."* While the company appreciates the uncertainty in capturing the impact of individual perceptions of risk on shielding behaviour, the utility gain of 0.098 derived from immunocompromised high-risk patients reported in the utility study (Gallop et al. 2022) is the best available evidence to date to quantify the utility gain associated with the introduction of Evusheld in high-risk patients. [redacted]	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			[redacted] It is noted that the PROVENT trial did not collect quality of life data and therefore no trial data are available to evaluate this potential gain in utility. However, it should be noted that even if quality of life data were collected in PROVENT, given the triple blind nature of PROVENT, it would be unlikely that the trial could collect such data given that patients in both the treatment arm (Evusheld) and the comparator (placebo) would not know if they were receiving active treatment. As the utility gain is dependent on being aware of taking Evusheld, and the benefits this could have, if both sets of patients believe they could be taking the study drug, this would not allow differences in quality of life between Evusheld and placebo to be established. Despite this, it was well recognised at the committee meeting that there is an urgent unmet need for a prophylactic therapy to reduce the risk of COVID-19 infection for those at high-risk. The quality-of-life benefit of an effective treatment was also well established. “Anxiety and fear would be alleviated, and physical health would also improve”. However, it was also noted that despite the availability of an effective prophylactic treatment that did not imply that patients who are at high-risk would not take some precautions, and some modifications would remain in place. “[I would] still continue to take measures to protect myself, such as wearing filtered masks in public places and generally risk assess most situations.” Gallop et al. (2022) elicited utility values from an immunocompromised high-risk population, of which 92% were partially or fully shielding. Therefore, as these patients are reflective of the target population for this submission, it is likely that these patients would share the same views as those testimonies heard at the NICE committee, and when participating in the utility valuation exercises be aware that taking a prophylaxis would not mean all restrictions are lifted. This is also borne out by patient quotes available in Gallop et al. (2022). “I would probably go to the theatre because I miss that like mad, but I would probably be aware of seating and sit on the end where I wasn’t surrounded by people”. “It would provide massive relief, relief at being able to do more and just be happier, more relaxed, I would still be a bit cautious, but you would be happier because it has relaxed you a bit”. Therefore, whilst we acknowledge there is complexity regarding the quality-of-life benefit, as the utility exercise was undertaken in a high-risk immunocompromised population, this complexity is captured in the values derived in Gallop et al. 2022 and applied in the economic model.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			The NICE ACD also suggest that quality of life benefits may not be realised if patients are aware that the medicine may not be effective against all circulating variants. *"There was the potential for some people to resume normal activities and possibly increase their risk of infection; or if they had limited trust in the treatment's effectiveness, they may not realise any quality of life benefit from the ability to reduce shielding behaviour".* *It added that the relationship between these factors was not reflected in the company's analysis, and that no data had been presented on behavioural change. The committee noted the considerable uncertainty and considered this when interpreting the clinical evidence."* This specific issue has been investigated in the Gallop et al. 2022 utility study via the question and response: "Participants were also asked if the change in their behaviour would depend on the variant of COVID-19 that was most common at the time (i.e. if there was a new variant that the treatment was not effective against); half (N=20) of the participants felt that it would and they would return to their pre-treatment behaviour" (Gallop et al, 2022) This demonstrates that 50% of patients would still feel a psychosocial benefit and cautiously modify their behaviour despite the knowledge that prophylaxis would not be effective against the most dominant variant. In order to explore the impact that this may have on the economic model a scenario has been presented where the quality-of-life benefit is only applied to 50% of the patients who receive Evusheld with results available in Section 12. This scenario also took into account patients who were subsequently infected with COVID-19, experiencing a further reduction in their quality of life whereby the duration of direct utility gain for those infected was reduced by 50% (i.e. scenario EA2 in **Error! Reference source not found.**). Further, this analysis may represent an upper bound for the ICER given that patient testimonies communicated in the ACM suggested that there would be a quality-of-life benefit of prophylaxis treatment even if Evusheld did not neutralise all variants, as patients would not be irresponsible in managing their risk and take the necessary precautions to provide them with those layers of protection. The ACD document also discusses that an effective prophylactic may also encourage patients to interact more with others and hence increase their risk of infection. However, it can be seen from the patient quotes above that patients will still take necessary precautions and that patients are still aware of their underlying conditions. Therefore, it would not be expected that the underlying risk of infection would increase, or at least not materially increase, given that patients are well versed and experienced in managing their own condition. It is important for NICE to recognise that the population of patients who are expected to receive treatment with Evusheld, have lived and continue to live with severe immunosuppressive conditions and as such, this population of individuals are well experienced in how to reduce their overall risk of infection in their day-to-day lives.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			The utility value applied in the model is based on data elicited from patients who tend to underestimate quality of life impacts when compared to the general population and therefore represents a conservative estimate. This was observed in Gallop et al. 2022 whereby the utility gain based on evidence collected in the general population was greater compared to the immunocompromised high-risk population: • An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states, and • An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behaviour health states Therefore, the utility value applied in the model based on patient responses of 0.098 may potentially be conservative. Finally, families and carers also experience anxiety around bringing COVID-19 home causing them to modify behaviour or experience guilt if they cannot afford to do so. “As a carer I have had to remain resolutely covid free. This has meant that since mask wearing is no longer required, I have had to give up my job as a massage therapist and now have no income and am not entitled to benefits. I’m very worried.” The psychosocial impact of this has not been considered in the economic analysis and is therefore conservative. As per the NICE reference case, the perspective for outcomes captured in an economic evaluation should include “all direct health effects, whether for patients or, when relevant, carers”. The inclusion of carer disutility into the estimation of cost-effectiveness has been accepted by NICE previously in appraisals for vutrisiran [TA868] and patisiran [HST10]. In reality, the benefit of a prophylactic therapy also extends to those who live with and care for the patient. As such there are potentially significant uncaptured benefits in this particular appraisal. To summarise, the patient testimonies recognise that there is an important quality of life benefit for patients treated with prophylaxis (extending to carers too) and it is imperative that this is included and in the economic model. Whilst we acknowledge the complexity in the interactions between quality-of-life, effectiveness of treatment, and infection, the approach adopted by the Company is evidence based and robust, potentially conservative and uses the best available evidence.	
9	Consultee (company)	AstraZeneca	**The administration cost applied in the model should align to the cost used by NHS England.** The NICE ACD explores which administration cost is most appropriate to apply in the model and suggests that the company estimate of £41 is not reflective of the administration burden and preferred the EAG’s estimate of £410. Specifically, the ACD states	Thank you for your comments. The committee noted that the administration setting was uncertain. Therefore, it took account both the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			"The committee considered that there was a substantial gap between company and CMDU estimates of administration cost but concluded that the more conservative estimate using the CMDU costs was more appropriate, given the uncertainty about how tix–cil would be delivered." AstraZeneca do not believe that applying a cost of £410 is appropriate given that CMDUs are an acute service in which a patient needs to quickly attend a local community centre to receive timely treatment for COVID-19 infection; typically, within 5 days. Therefore, there needs to be multiple centres requiring significant NHS resource and co-ordination beyond the existing infrastructure to facilitate this service. Also, the company maintains since the target populations of A1, A2 and B (who do not have serological response to vaccination), are at greatest risk and have primary or secondary immunodeficiencies, Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services. This is in line with the advice of an integrated care system commissioning expert, as such CMDU costs would not be appropriate to use in the modelling. AstraZeneca also note that a revised budget impact test was received from NICE/NHSE in which NHSE has reduced the administration cost from £410 to £216. On this basis, whilst we believe this is still likely to overestimate the costs, NICE and the EAG should update the costs to align with those used by NHSE.	company's and EAG's estimates for the administration cost in its decision making. Please see section 3.18 of the final draft guidance for further details.
10	Consultee (company)	AstraZeneca	**The hospitalisation rate of 2.8% from Patel et al is not appropriate to use in the economic modelling.** The ACD notes that the risk of hospitalisation from Patel et al. 2022(14), should be used in the economic modelling, and also references that Patel et al. is a preferred source in the ongoing MTA for therapeutics for people treated with COVID-19 which includes Evusheld.(15) Specifically the ACD notes *"The committee preferred to assume a rate of hospitalisation closer to Patel et al. but noted that hospitalisation rate would be dependent on the risk group under consideration".* However, it should be recognised that the target population for Evusheld in the MTA is different, and not the same level of high-risk as the population included within scope of this current STA where Evusheld is assessed as a prophylactic treatment. The population included in Patel et al. closely aligned with the high-risk population as defined by the McInnes report, a report which identified "highest risk clinical subgroups upon community infection with SARS-CoV-2". (1) However, it should be emphasised that the patient group included within the Evusheld STA is narrower in comparison and at significantly greater risk. These patients could be described as "the highest risk of the high risk" and reflect groups A1, A2 and B (who do not have serological response to vaccination) from the independent advisory group report. Therefore, it is not appropriate to use sources such as Patel et al. for the Evusheld STA due to differences in the underlying risk of the population and differences in the respective decision problems. Further to this, there are substantial differences between the 2.8% hospitalisation rate estimated by Patel et al and rates identified in certain subgroups of the McInnes population. This further supports that it would not	Thank you for your comments. The committee acknowledged the higher risk of hospitalisation in specific patient groups. But it had not seen evidence of differential clinical or cost effectiveness to rule out other groups covered by the marketing authorisation. Please see section 3.5 and 3.20 of the final draft guidance for further details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			be appropriate to use data from Patel et al to inform the hospitalisation rate for the highest risk patients, with some hospitalisation rates as high as >30%(16): • **Parry et al. 2022**(17) (chronic lymphocytic leucaemia): 7.7% • **Gleeson et al. 2022**(18) (immunosuppressed kidney transplant recipients): 20.8% • **Bradwell et al. 2022**(19) (haematological malignancy): 26.4% • **Trindade et al. 2022**(20) (lung transplants): 17.9% • **Anjan et al. 2022**(16) (solid organ transplants): 31.9% Further to the above, Lee et al. 2023 (21) conducted a study assessing the association of SARS-CoV-2 spike protein antibody vaccine response with infection severity in cancer patients. The study reported that patients who have cancer are more likely to report an undetectable anti-S antibody response than the general population. In addition, the study also concluded that within the cancer cohort, patients who had an undetectable antibody response were at much greater risk of SARS-CoV-2–related hospitalisation (odd ratio, 6.48; 95% CI, 3.31-12.67; P < .001) than individuals who had a positive antibody response. Lee et al also reported that patients with leukemia or lymphoma had the highest rate of undetectable antibody response and the lowest antibody titres, which implies that leukemia or lymphoma patients are at highest risk of adverse outcomes from COVID-19 such as hospitalisation when compared to other cancer types. AstraZeneca acknowledge it is difficult to directly compare hospitalisation rates from Patel et al with the odds ratios reported in Lee et al. However, the data from Lee et al do support an inference that cancer patients are at a higher risk of hospitalisation, and therefore applying a hospitalisation risk of 2.8% from Patel et al, to a "highest risk of the high risk" group as per the company's positioning, is infeasibly low and not reflective of the available evidence. Finally, Patel et al notes that a surprisingly large proportion (between 39.2%% and 45.7%) of patients had no evidence of having the highest risk conditions where high-risk conditions were identified using SNOMED and ICD-10 codes from patient history. Although the Patel al paper does go on to provide additional context and clarity regarding these figures, given that the target population considered in this appraisal for Evusheld are the highest risk of the high risk, it would not be appropriate to use a paper where a substantial proportion of patients failed to meet a highest risk criterion. Therefore, it is not appropriate to use a value of 2.8% from Patel et al to quantify the risk of hospitalisation in the economic model.	
11	Consultee (company)	AstraZeneca	**The company and EAG base cases have been updated following the comments from the committee.** ***Dosing*** As referenced in Section 2 the economic modelling is aligned to a 6-month single dose treatment duration. In the economic model this update captures the treatment and administration cost reflecting one single	Thank you for your comments.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			dose of Evusheld, reducing the SoC infection rate from a 12 month to 6-month rate, halving treatment-related adverse events to account for a single dose and applying the utility gain associated with Evusheld to only 6 months of protection being provided. All efficacy sources used in the model are based on one dose with a median follow up less than or equal to 6 months, therefore efficacy data were not adjusted. ***Direct Utility*** The original company base case applies a utility gain of 0.098 to 100% of the population administered Evusheld. The company accept the EAG's amendment to apply the utility gain to 82% of the population to reflect the proportion of patients who are either fully or partially shielding according to the ONS survey.(22) ***Administration*** As noted under Section 8, AstraZeneca would like to acknowledge that the administration cost of £410, based on the CDMU in the EAG base case is unsuitable to use as a proxy since the value is too high and not appropriate to include in the model. The company and EAG base case should be guided by the NHSE cost of £216. ***Infection*** The company would like to highlight that the IAG cohorts A1, A2 and B (who do not have serological response to vaccination) represent the 'highest risk of the high-risk population' and a population who are severely immunocompromised. Therefore, the infection rate of the general population is not representative of the target population who will likely remain susceptible to serious infection despite increasing vaccination status. However, since the target population is severely immunocompromised, using data based on general population statistics is considered a conservative estimate for people at the highest risk of poor COVID-19 outcomes or unsuitable to vaccination; particularly since the majority of the general population have either had numerous doses of COVID-19 vaccines in which they do amount an immune response to, or have acquired natural immunity through COVID-19 infection. Based on expert clinical feedback, this population are at a higher risk of infection and severe outcomes compared to the general population, even with shielding methods in place. In addition, the data available for the general population is to date the best available data to populate the economic model since no data specific to the population has been collected. Finally, uncertainty in the underlying risk of infection is explored through scenario analyses (see Section 12). ***Hospitalisation*** The company would like to highlight that the hospitalisation rates captured in Shields et al. are representative of the population in scope of this submission. It is unclear why NICE feel these are over-estimated given the methodology of the study and external evidence to support the conclusions. Also as discussed under Section 9, the hospitalisation rate from Patel et al. 2022 is not suitable to include in the economic modelling and does not address this decision problem, therefore the data from Shields et al. is the most generalisable source of the data available. ***Long COVID***	

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			The company acknowledge the committee's amendment to use the management cost of long COVID of £2,267. In addition, the company accept the use of utility waning in the base case, however, would like to acknowledge that there is no evidence to support this assumption. ***Subgroup analysis*** It is also noted that the NICE committee requested a scenario which focussed on the individual groups in the target positioning (i.e. A1, A2 and B without serological response). It is not possible to run these specific subgroup analyses given the available data. However, scenario analyses have been provided which change the underlying infection risk to proxy results in groups with a higher or lower risk of infection.	
12	Consultee (company)	AstraZeneca	**A suggested framework for robust, agile, and responsible decision making that considers the substantial unmet need and evolving COVID-19 landscape.** **Context** A robust, rapid and agile decision-making framework is required in order to ensure that NICE can make responsible decisions for COVID-19 prophylactic treatments given the evolving landscape with respect to emerging variants. The need for a robust decision making framework is also recognised by NICE in response to the publication of the draft recommendations for this appraisal, and NICE have announced the development of a new review process to update its recommendations on the clinical and cost-effectiveness of COVID-19 treatments.(2) The need for such a framework was reinforced by academics, clinicians and patient groups, who in response to the draft negative recommendation stated: *"NICE recognise that the virus is evolving faster than the evidence can be produced and their assessment process can be undertaken, so that they need to find a way of more rapidly assessing treatments for the immune vulnerable"* *"Evusheld was approved on the 17th of March 2022, and it took 11 months for this decision… We could have provided many months of protection. There is an overwhelming clinical need to give long acting antibodies to protect those who aren't protected from vaccines, because they are immuno-vulnerable. We should and can move much quicker"* *"We believe that Evusheld could have helped vulnerable people over the past year by supporting them to return to normal life, as it has in over 30 countries around the world; but that opportunity was wasted due to the failure to act quickly and decisively… It is clear that the current protracted NICE process is completely inappropriate and has left a huge number of people without protection and reassurance when they needed it most."* It is therefore reassuring to see that NICE recognises this and has announced that it will be developing a process to monitor real-world data and re-evaluate the medicines as needed against that data in a faster way than it currently does for other drugs, and that NICE will be able to respond quickly if evidence emerges that Evusheld or other existing treatments are effective against a particular variant.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			However, the appraisal process for Evusheld is ongoing, and whilst there will a public consultation issued by NICE on 3rd April on these new processes, there is a need for NICE to adopt an appropriate framework for decision making at the next committee meeting and ahead of the closure of the public consultation. **Position of global regulators and AstraZeneca's proposed process** Whilst the company recognises the challenges associated with the evolving landscape, it believes that in the absence of any of guidance or a signal from the MHRA, that NICE should look to other internationally recognised Regulatory Agencies to help inform how to best evaluate the clinical appropriateness on the use of Evusheld at any given moment in time with respect to current and future circulating variants. For example, whilst the FDA temporarily suspended the emergency authorisation of Evusheld due to the high proportion of circulating variants to which Evusheld does not neutralise, it has stated that it will reconsider reinstating authorisation of Evusheld if the national prevalence of resistant variants decreases to 90% or less. The company would therefore propose that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants (please see Section 12 for cost-effectiveness analyses using different variant thresholds). We believe that NICE is in a position to do this; particularly since it was able to rapidly produce an ICER for decision making for sotrovimab in the recently published draft final guidance on the use of therapeutics for people with COVID-19 [ID4038]; despite sotrovimab having a significant reduction in neutralisation ability –against 58.3% of current circulating variants (BQ.1; IC50 = 1709 ng/ml; 51.3% prevalent; BA. 4/5; IC50 = 1055 ng/ml; 7.2% prevalent).(11,23,24) As a final consideration, the company maintains its position that Evusheld offers an important layer of protection against severe COVID-19 in those who continue to remain at the greatest risk due to their underlying health conditions, which severely reduces their ability to amount an immunological response to vaccination or immunity through prior infection. The value conferred by Evusheld, despite the currently reduced number of circulating variants to which it neutralises, has been and continues to be supported by patients across the UK, including those that have received Evusheld through the private clinical settings. Therefore, a process which establishes the clinical need and value for Evusheld through meeting a predetermined threshold of neutralisation against circulating variants (i.e. 10%) is appropriate, in line with internationally recognised Regulatory Agencies such as the FDA, and facilitates patient access to an effective treatment for a high risk and vulnerable population. **Proposed threshold for Evusheld prophylaxis versus COVID-19 treatments** AstraZeneca are proposing that NICE adopt the view of the FDA where Evusheld would be made available if there is evidence of neutralisation against 10% of variants (or conversely where there is no evidence against 90% of variants)(3). It is worth noting that the FDA withdrew the emergency use approval for Bebtolivimab in the treatment setting when the proportion of variants which it was not expected to neutralise reached 57% nationally and was >50% in all regions (but one) (25)	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response
			However, despite this difference in thresholds between COVID-19 prophylactic and treatment applied by the FDA, AstraZeneca believe it is entirely reasonable to use a higher threshold (i.e. a larger proportion where there is no neutralising activity) for the prophylaxis setting. In the treatment indication it is important to understand how efficacious a medicine is in treating those already infected with COVID-19 and at high-risk of poor clinical outcomes. Therefore, those medicines in which there may be greater confidence with respect to the landscape at that particular moment in time should be used ahead of those which have more uncertainty. However, the context with respect to the prophylaxis indication is different. This population has essentially been left behind by society and generally live in significant fear of COVID-19 with the vast majority making lifestyle modifications. In this respect, it is critically important to offer immunocompromised individuals additional layers of protection while they remain not infected. Whilst the level of protection offered by Evusheld is likely to vary with respect to current, emerging, or future variants, any degree of protection is important for these high-risk individuals with high unmet need. Therefore, a threshold of neutralisation against 10% of variants (or conversely where there is no evidence against 90% of variants) for prophylaxis, albeit higher than the FDA's recommendations for COVID-19 treatment, is appropriate. ***Defining neutralisation*** The IVAG report and AstraZeneca's comments on the report are considered under Section 5. As part of that discussion AstraZeneca propose that an IC50 of <10,000 ng/ml is utilised by NICE to determine activity against any particular circulating variant. In addition, AstraZeneca propose that the proportions of circulating variants is informed by the surveillance conducted by the UKHSA. **Conclusion** Utilising a threshold approach would enable NICE to make a positive decision considering both neutralisation data and circulating variants which may be more readily available than trial data or real-world evidence. In addition, it will allow NICE to make flexible and agile decisions that can evolve over time as the disease and variants also changes. Finally, applying a threshold can easily be linked to the economic evaluation as detailed in Section 12.	
13	Consultee (company)	AstraZeneca	**Updated cost-effectiveness results are presented to reflect that Evusheld is cost-effective when Evusheld neutralises different proportions of circulating variants** As discussed in Section 11 above, AstraZeneca propose that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. Therefore, if Evusheld neutralises at least 10% of circulating variants, then the clinical need and value for prophylaxis could be considered met. In terms of decision making, AstraZeneca suggest that the next step for NICE is to consider at what variant threshold Evusheld could be considered cost-effective. Results are presented below which apply a 10%, 15%, 20%, 25% and 30% threshold respectively to the economic modelling. Specifically, Table 2 presents the base case results using a 10% threshold with Table 3 presenting further scenarios at this level of neutralisation. Table 4 presents a summary of ICERs using the 15%, 20%, 25% and 30% thresholds with a full breakdown of each ICER and scenario analysis available in Appendix 4**Error! Reference source not**	Thank you for your comments. The committee's preferred cost-effectiveness estimates are discussed in section 3.23 of the final draft guidance.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE response</th></tr>
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found.. Although it is noted that Evusheld is cost-effective when applying a 10% threshold; utilising different thresholds presents decision makers with a range of options and therefore NICE can choose the threshold that the Committee are most content accepting.

Further to this, Table 2Table 3 andTable 4 and Error! Reference source not found.Error! Reference source not found.present results in terms of “Updated EAG base case” and the “Updated Company base case” for each threshold. To clarify, the updated EAG and Company base case results reflect updates to the EAG and Company base case ICERs that were presented at the first Committee meeting and take in to account the following process:

• Error! Reference source not found.lists the model assumptions which were applied to generate the EAG and company ICERs which were presented at the first NICE committee meeting (ICERs of £18,644 and £5,003 respectively).
• AstraZeneca have updated the EAG base case to take in to account the change above (i.e. reflecting neutralisation activity versus a proportion of variants) in addition to removing scenarios or amendments implemented by the EAG that are factually inaccurate/implausible to arrive at an updated EAG base case. Error! Reference source not found.also lists the model assumptions which are applied in the updated EAG base case.
• Similarly, AstraZeneca have updated the Company base case to take in to account the same variant assumptions as described above and applied additional changes to reflect more appropriate sources/assumptions where relevant. Error! Reference source not found.Error! Reference source not found.also lists the model assumptions which are applied in the updated Company base case.
• Both the updated EAG and Company base cases apply one dose of Evusheld as noted in Section 2.

Computationally, to model Evusheld as able to neutralise a pre-determined threshold of variants, the analysis reduces the symptom infection efficacy of Evusheld to reflect the appropriate threshold/proportion of its original value. For example, in the 10% threshold scenario, the symptom infection efficacy estimate (66% (3)) is reduced to 10% of its original value. This resulted in Evusheld providing a reduced risk of infection of 6.6%.

Table 2: Updated EAG and Company base case results post committee using a 10% threshold
<table>
<tr><th rowspan="2">Technology</th><th rowspan="2">Total costs</th><th rowspan="2">QALYs</th><th colspan="2">Incremental</th><th rowspan="2">ICER</th></tr>
<tr><th>Costs</th><th>QALYs</th></tr>
<tr><td colspan="6">Updated EAG base case – post committee</td></tr>
<tr><td>No prophylaxis</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
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</td><td></td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE response

Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£18,047
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£15,201

Additional scenarios are also presented to explore uncertainty in the model and sensitivity to key model inputs for the 10% threshold analyses. The results of the scenario analyses are presented in Table 3 below.

Table 3: Updated EAG and company scenario analysis post committee using a 10% threshold

Scenario	Updated EAG base case – post committee	Updated company base case – post committee
Base case	£18,047	£15,201
Apply utility gain to 50% of patients	£24,891	£20,143
Increase underling infection rate by 20%	£16,661	£13,668
Reduce underlying infection rate by 20%	£19,583	£16,969
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£22,474	£17,694
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£27,698	£23,110

A top-line summary of the updated EAG base case, and the updated Company base case ICERs for thresholds at 15%, 20%, 25% and 30% respectively are presented below. **Error! Reference source not found.** includes a breakdown of each base case result for each threshold, alongside scenario analyses.

Table 4: Updated EAG and Company base cases using different thresholds for neutralisation

Threshold for neutralisation	Updated EAG base case – post committee	Updated Company base case – post committee
10%	£18,047	£15,201

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment</th><th>NICE response</th></tr>
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<tr><td>15%</td><td>£17,811</td><td>£14,597</td></tr>
<tr><td>20%</td><td>£17,578</td><td>£14,014</td></tr>
<tr><td>25%</td><td>£17,350</td><td>£13,452</td></tr>
<tr><td>30%</td><td>£17,125</td><td>£12,911</td></tr>
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In conclusion, AstraZeneca have presented a framework which proposes that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants.

Cost-effectiveness analyses are presented in this document which utilise thresholds of 10%, 15%, 20%, 25% and 30% respectively. At all these pre-determined thresholds, Evusheld is cost-effective, and this conclusion is confirmed through scenario analyses which tests the uncertainty of the base case result at each given threshold.

Therefore, AstraZeneca have provided NICE with a range of options by presenting cost-effectiveness estimates at a different thresholds and NICE can choose the threshold that the Committee are most content accepting. Given that Evusheld remains a cost-effective use of NHS resources, the high unmet need for an effective prophylaxis treatment and the benefits that such a treatment would bring to patients, it is important that Evusheld be made available for patients and receive a positive recommendation from NICE.</td><td></td></tr>
<tr><td>14</td><td>Consultee (patient/carer groups)</td><td>CLL Support</td><td>NICE agreed that there is an unmet need that needs to be addressed for immunocompromised patients. Many patients are also unable to take post exposure treatments because of their cancer medication.

The draft guidance states that “recent studies done in laboratories report that tixagevimab plus cilgavimab is unlikely to prevent infection with most of the relevant variants in the appropriate time period for this evaluation “</td><td>Thank you for your comments. The committee considered data from the latest technical briefing published by UKHSA in March 2023. This briefing showed that there were only around 3% of circulating variants (BA.2 and BA.5) that tix–</td></tr>
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			Vaccination also does not prevent infection but immunocompromised patients were prioritised for vaccinated as it reduces the likelihood of hospital admission and ICU care by 86% **as would this antibody treatment.** This fact makes the reason for refusal of approval appear unreasonable and this treatment should be considered an extension of the vaccination programme for this vulnerable group.	cil may be effective against. The committee therefore concluded that there was no evidence that tix–cil would neutralise at least 97% of circulating variants as of March 2023. Please see section 3.12 of the final draft guidance for further details.
15	Consultee (patient/carer groups)	CLL Support	No threshold for effectiveness was defined or discussed. This needs to be urgently addressed in this dynamic situation so that future evaluations can be systematically assessed. The FDA have accepted a threshold of effectiveness to be against 10% of circulating variants. Currently the XBB, CH1.1 and BQ1.1 variants are approximately 50% of circulating covid variants meaning that this treatment should be effective against the other 50%.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.

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16	Consultee (patient/carer groups)	CLL Support	The draft guidance states - 'The committee noted the lack of evidence on how the availability of a preventative treatment would impact on shielding behaviours, to determine the impact on both health-related quality of life and efficacy of treatment.' The committee heard from several patient experts' powerful personal testimony regarding their situation re shielding because they are unable to produce antibodies in response to multiple vaccinations. As a group of highly vulnerable patients they are unable to regain their place in society and are permanently in a state of shielding which is a virtual prison for both themselves and their families. The corollary is that, knowing they have covid antibodies, this group can return to a more normal lifestyle with their work, family and friends and that is very precious.	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
17	Consultee (patient/carer groups)	CLL Support	The DHSC have reviewed the data on Evusheld, but they have not published this review. We do not know if this data was or was not part of the NICE evaluation. This situation has not helped patient groups to feel confident in the decision for ID6136	Thank you for your comments. No data were submitted to NICE from DHSC.
18	Consultee (patient/carer groups)	CLL Support	The APPG on Vulnerable Groups to Pandemics recently looked at a systematic review analysing the outcomes of 24,773 immunocompromised patients across 17 clinical studies from around the world. Led by the University of Birmingham with academics from King's College London and the UK Health Security Agency, the findings are the largest meta-analysis of studies about antibody therapies for immunocompromised and immunosuppressed patients to date. The paper also draws on newer studies relating to the effectiveness of treatments such as Evusheld during the widespread Omicron variant of Covid-19, which shows that the therapies **continue to be clinically important as SARS-COV-2 continues to mutate.** **https://appg-vulnerablegroups.org/news/post/antibody-therapies-against-covid-19-for-most-vulnerable-patients-work-new-analysis-finds** **https://appg-vulnerablegroups.org/fileadmin/user_upload/Systematic_review_of_the_clinical_effectiveness_of_Tixagevimab_and_Cilgavimab_for_prophylaxis_of_COVID-19_in_immunocompromised_patients.pdf**	Thank you for your comments. The committee considered data from the latest technical briefing published by UKHSA in March 2023. This briefing showed that there were only around 3% of circulating variants (BA.2 and BA.5) that tix–cil may be effective against. The committee therefore concluded that there was no evidence that tix–cil would neutralise at least 97%

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				of circulating variants as of March 2023. Please see section 3.12 of the final draft guidance for further details.
19	Consultee (patient/carer groups)	Evusheld for the UK	**Effectiveness** We are concerned that in spite of the fact that in vitro data was discussed at the appraisal meeting and the limitations of this information, it is well known that Evusheld performs very differently in the human body. We know from speaking to clinicians in the 32 other countries where Evusheld is still being used, that hospital admissions are significantly reduced and it is still providing protection. There seems to have been little balance in how this real world data has been looked at. Even within members of our patient group, we are seeing numerous real world examples of those who have obtained Evusheld privately having contracted covid, and have low or mild symptoms with good outcomes. For all the discussion regarding perceived neutralisation levels, the protection this is giving to those who have accessed it in this country and abroad is real and significant. When a patient has previously spent 5 months in hospital with covid and 5 weeks in an induced coma, with their family saying goodbye to them twice and then seeing them have a milder insignificant illness than the rest of their family after contracting covid, after having Evusheld privately this year, it is difficult to reconcile its effectiveness in the protection it is giving against severe outcomes compared to the theoretical discussions against its use. It seems such evidence is not being looked at as it is somewhat difficult to assess. This is not a good reason to dismiss it or not look at it further. The decision of the FDA to temporarily withdraw the authorisation for the drug in the US is cited as an example of a reason not to introduce Evusheld, yet the FDA holds the drug in high regard and is willing to re-introduce the drug back into use once the variant mix of certain variants is reduced. This means it will conceivably be reintroduced whilst variants of concern are still circulating, on the basis that it will STILL be offering some level of protection when used in conjunction with other measures. Even at reduced efficacy, this could be the difference between life and death in an immunocompromised patient. We are once again erring on the side of caution for the sake of making the effort to look fully at the real world data. This approach has not been carried out by other bodies such as the JCVI for vaccines. The general population would not have been prepared to wait in these circumstances for vaccines, why then can it be acceptable for the 1.2million that NICE has identified as possibly benefiting from this drug to have their lives restricted for a 4th year as they wait for other drugs to be developed, when this drug is shown worldwide to be making a significant difference in the outcomes for patients.The assumptions being used to make this decision are leaving the people in these cohorts still at total risk with nothing at all to offer them protection. The current draft decision is based on a binary decision and this is simply wrong. It has been accepted by the review that Evusheld has retained neutralisation against some variants. Therefore the drug works, but the basis of the decision is that it doesn't work. It cannot be both.The decision must be made on its effectiveness on what variants it works against, not on what it might not work against. A drug of this type will never work 100%. There therefore needs to be an acceptance of what level of is effective and acceptable otherwise this drug and others following it will never reach a theoretical target of 100%.The draft decision	Thank you for your comments. The evaluation relies on the available evidence submitted to the NICE by stakeholders in line with the NICE health technology evaluations manual. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.

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			should be reviewed to confirm it works and what needs to be rapidly decided on is the framework and thresholds of when it is used in the face of virus variant levels. The FDA has set a threshold of Evusheld working against 10% of circulating variants. At present the variant mix places this below that threshold, hence the TEMPORARY withdrawal, with the firm intention to place it back into use as the mix alters. The present draft decision quotes that decision, yet at present in the UK we are still above that threshold. That means the FDA would be happy to have it used in the conditions we find ourselves in the UK. As there is no measure set in the Uk, and the decision not to use it is confirmed, what happens in a few months when the variant mix alters and the use of the drug reverts to becoming more effective? This decision sets no threshold on its effectiveness and parameters for its use. It seems implausible and wrong for a drug to be ruled out on perceived effectiveness when no actual threshold has been set. The present decision means the drug would still not be available to allow its use and offer protection. It should also be pointed out that no other country currently using Evusheld has withdrawn its use and is still offering it as a form of protection to their most vulnerable. The decision is simply denying the desperately needed use of what is an essential drug. The decision to deny the access Evusheld is based on a theoretical threshold that hasn't been qualified on theoretical conditions as they stand today, heavily weighted towards the temporary actions of one other country which is in a different situation to here and the rest of Europe, indeed the 'MA has made no such withdrawal. Rather than denying access to this drug, it would be better to authorise its use with an agreement on a review system to monitor the variant mix as the FDA does. If the variant situation changes and NICE decides to re review its use in the future, this will still leave a 3 month window for its implementation by the NHS. By the time this is done the situation may have changed again and more time will be lost, putting more lives at risk. The present draft decision will be a rigid decision based on one point in time and will offer no ability to be flexible and adapt to changes in the virus. This is something we have seen through its history on numerous occasions as the virus evolves. A more agile decision needs to be made to allow reaction and anticipation in the future with the protection this drug can give. If in 2 months time we have a changed picture of the dominant variants and Evusheld is proven to be effective against them (as has happened with Paxlovid) we will have an effective drug that could offer protection, again not able to be used due to a decision made today, with no system in place to review and alter that decision quickly.	
20	Consultee (patient/carer groups)	Evusheld for the UK	**Patient behaviour** We are concerned by the comments regarding how it may change patients behaviour and put them at further unnecessary risk as they take more risks. This is a disingenuous assumption.. Patients dealing with everyday conditions are well aware of their risks and limitations and on the whole are grateful to have the chance to be able to carry on their lives after receiving expensive life saving treatments or treatments just to manage their conditions. Most know their conditions inside out and are risk averse. The use of Evusheld will allow them a semblance of normality, but it is unlikely such patients will put themselves at a greater risk, they value what health they have too much to do this. We therefore refute these assumptions as simply unlikely in the vast majority of patients. We also know from speaking to lots of group members who have privately paid for Evusheld, that they are not going out partying or mixing in large groups, but actually only	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would

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			doing the simple things that most take for granted like being able to see their families and friends and giving them a hug, and attending indoor settings only when not busy.	result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
21	Consultee (patient/carer groups)	Evusheld for the UK	**Mental Health** We are concerned that there has been little evaluation of the mental health impacts on those in this position, who are now facing a 4th year of shielding. The chance to have some return of even a small amount of normality would be a massive release to those facing this long and drawn out situation. The mental impact and its effect on everyday lives and their physical conditions cannot be understated or played down in any way. The damage being caused to people's lives and their families by having to live in this never ending situation is real, severe and with the effects on their physical and mental health long lasting. For this cohort to be left for another year without any freedoms could have untold damage not just now, but for years to come. The recently published study from UWE Bristol on the impact of shielding on immunocompromised patients highlights the serious mental health impact on patients and should be viewed in relation to this decision.	Thank you for your comment. The impact on patient health-related quality of life (including mental health) has been included in the company's model and considered by the committee. Please see section 3.17 of the final draft guidance for further details.
22	Consultee (patient/carer groups)	Evusheld for the UK	**Inequality** By denying this drug to those in these cohorts, it places those in this position in a massive equality debt of treatment compared to the general population. It is inequitable to explain to a person that simply because they are immunosuppressed that they cannot have access to a drug that will give them the same quality of life as the general population obtains from an alternative drug ie covid vaccines. The decision affects their quality of life and also restricts their freedom to have economic independence by returning to work. This is one of the main economic aims of the health service in this country to allow people's health to be improved to allow them the ability to return to work. This is being denied by this decision. Those that are immunosuppressed are those most likely to need to attend care and hospital settings on a regular basis, yet the danger each visit represents to these cohorts, borne out by the covid infection statistics in care settings, means they are placed at an unacceptable risk, leading to an inequality in treatment and in many cases treatments being delayed or cancelled, simply because they do not have the protection. We also know that the wearing of masks in these settings is now significantly reduced, placing them at even more risk	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
23	Consultee (patient/carer groups)	Evusheld for the UK	**Future Evaluation Process** We are very pleased to see that there is a general acceptance that existing systems for evaluating protective MABS and Antivirals for covid 19 are too slow and not effective. We applaud the conclusion that a new system needs to be put in place. It must therefore be a matter of the utmost urgency for NICE to draw up exactly what these new procedures and systems will be, with relevant timescales. However these	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This

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			must be published as a matter of urgency to give a clear and defined process and timeline, so that this can then be applied to the next generation of protective medications which are already in trials. This will allow them to be speedily assessed so that efficacy is maximised. This situation of an inflexible slow process is unfit for the purpose of evaluating Covid drugs in a fast changing pandemic situation and MUST be streamlined quickly. Every day lost in the making of these decision has a real and negative impact on people's lives and their health and unfortunately every delay is simply costing more lives of those in these cohorts	is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
24	Consultee (patient/carer groups)	Evusheld for the UK	**Summary** Evusheld is a drug that has been in use across the globe for over a year and is still showing its effectiveness in the real world, both in the UK and abroad. The view of the JCVI when it comes to vaccines and the immunosuppressed, is that any increase in protection if only by a few percent is better than nothing and should be pursued, yet Evusheld offers the chance of significantly more protection from a severe outcome for patients against many variants still in circulation, but the draft decision is happy to ignore that. We should be giving patients in this exposed position whatever protection we can, not leaving them totally unprotected whilst we await to see what happens. It is proven to have effectiveness against many variants and represents the best option that is currently available for protection of the immunocompromised, if not from neutralisation of all variants, at least from progression to severe outcomes for many. NICE has agreed that there is an unmet need for such protection and there is a large gap in the protection strategy for the most vulnerable that needs plugging. Evusheld is that drug at present that can do this. Whilst other drugs may be in development, at present this represents the ONLY viable option to give protection for the most vulnerable and release from the massive life altering situation they are in. A situation that all members of the UK public have lived through on a much shorter time scale and know how hard it is	Thank you for your comments. Please see NICE's responses above.

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			to live through and adjust from. To not utilise this drug based on a binary decision at one point in time with no flexibility to adapt to changing variant scenarios is wrong and does nothing to fulfil that unmet need By the conclusions of the draft decision Evusheld is below the incremental cost effectiveness ratio (ICER) threshold. That means it is effective and cost effective. A clear demonstration that the use of MABs is a wholly acceptable way to provide protection to what is defined by NICE as nearly 2% of the UK population. The decision is a binary decision and this cannot be the case for a drug that is accepted to work on some variants will some views are harboured regarding its effectiveness on others No threshold of acceptance has been set It is a fixed point decisions offering no ability to allow the decision to be reversed and the drug brought into use at short notice in the future, compounded by the NHS implementation 3 month window The decision compounds the inequality of care for those not in a position to access the drug privately and denies then the ability to return to a more normal life, especially compared to the rest of the general population who have free protection from covid vaccines In light of all the above it is our view that Evusheld should be authorised and it is essential that the new review pathway for future drugs is consulted on with stakeholders as a matter of urgency. We would urge the panel to take on board the points raised and reassess the protection given to patients who are in dire need of protection now. We sadly were relayed this account by the daughters of one of our patients today (8th March 2023) For all we have written, we feel her words sum up the situation more effectively than anything anyone can say on this issue. This is why this drug is so desperately needed in its current form to give some protection and why the fast pathway for the next generation needs to be put in place with extreme urgency. This is not about facts and figures, this is simply about the lives of those affected and their loved ones and for too long they have suffered. “Yesterday my dad, a blood cancer patient, died. I have protected him for the last three years, but he was in hospital as he had cellulitis 7 weeks ago. He caught covid whilst he was in hospital. I can't help thinking if he had been given Evusheld I might still have had my Dad here. Although too late for my wonderful Dad I hope you win this battle and get it for people . Yes Dad caught covid in hospital. I tested positive Sunday, the first time having covid. So they tested dad and he was positive. I pleaded for antivirals for Dad from that moment, but he didn't get connected to antiviral iv until 11pm Monday night. He was sleepy Monday night, but no temperature and his pulse was strong and regular. Strange it was strange he was so bad after iv antivirals, maybe just a coincidence. So it fills me with horror that I may have it given to him.	

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			Although the hospital is full of it at the moment and Dad or staff could have given it to me. Maybe best I don't know. For three years we haven't been in supermarkets or anywhere etc. We always still wear ffp2 and 3 masks out. Anything we had to do to protect my Dad. They called us to come to the hospital Tuesday morning and the scene in the room was horrific. They had waited for me to arrive before giving him morphine. Thankfully Dad's breathing was more settled once he had the morphine. But it will haunt me forever what I saw beforehand. Sorry for going on, I think I'm just so shocked. But thank you all so much . God bless you" Every day this drug is denied we will continue to hear more accounts like this, and more people will die. Evusheld For The UK	
25	Consultee (professional groups)	Faculty of Pharmaceutical Medicine, endorsed by the Royal College of Physicians	**Has all of the relevant evidence been taken into account?** The Faculty of Pharmaceutical Medicine (FPM) has noted that patient perspectives, in vitro and clinical data were considered by the Committee and particularly welcomed the consideration of the patient perspective from this group of vulnerable individuals. FPM notes that two trials with different antibodies have successfully demonstrated that monoclonal antibodies can prevent infection and illness due to SARS-CoV-2 infection: the BLAZE 2 trial with bamlanivimab (Cohen MS et al. JAMA. 2021 Jul 6;326(1):46-55. doi: 10.1001/jama.2021.8828. PMID: 34081073; PMCID: PMC8176388) and the PROVENT trial with tix-cil (Levin MJ et al N Engl J Med. 2022 Jun 9;386(23):2188-2200. doi: 10.1056/NEJMoa2116620. Epub 2022 Apr 20. PMID: 35443106; PMCID: PMC9069994). These trials documented that clinical activity followed successful demonstration of antiviral effect from in vitro and in vivo animal studies. Antiviral medications that have shown inhibitory activity in vitro and efficacy in animal models can be anticipated to be effective in human diseases. This has been confirmed recently with the clinical use of tecovirimat, which was conditionally approved based on documented efficacy in an animal model of monkeypox, accompanied by human studies documenting the dose required to match exposure in humans to those achieved in the successful animal model. Recent confirmatory clinical evidence has been amassed during the monkey pox outbreak in the UK and elsewhere. If this approach was considered appropriate for COVID-19 antivirals, permitting earlier access by high-risk patients during an outbreak when confirmatory proof of clinical efficacy can be collected from treated patients, then all parties – MHRA, DHSC, UKHSA and NICE – should work together to enable accelerated access. Early human studies should demonstrate that adequate exposure can be achieved with acceptable safety.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft

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				guidance for further details.
26	Consultee (professional groups)	Faculty of Pharmaceutical Medicine, endorsed by the Royal College of Physicians	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** FPM concurs that the product is not anticipated to be efficacious in preventing or treating COVID-19 caused by current circulating variants and should not be approved for use in the NHS.	Thank you for your comment
27	Consultee (professional groups)	Faculty of Pharmaceutical Medicine, endorsed by the Royal College of Physicians	**Are the recommendations sound and a suitable basis for guidance to the NHS?** As the product being considered is currently not anticipated to be efficacious from the data, the recommendation is sound. FPM would like to note that it has had representations from multiple patient organisations representing some of the >500,000 immunosuppressed patients in the UK, which overwhelmingly confirm the patient perspectives in the report, stating predominantly that shielding has placed patients and their families at great strain, with constant anxiety and reduced mobility. This has interfered with everyday life and has contributed to some carers having to stop work during the ongoing epidemic in order to protect their immunosuppressed relative. The patient perspectives have reflected that for some patients e.g. those being treated for cancer or receiving dialysis, there is a necessity to travel to hospital centres for treatment, which places them at greater risk of infection, given the considerably higher rate of infection in healthcare facilities than in the general community. Patients that have undergone organ transplantation cannot take the NICE recommended Paxlovid treatment for covid infection and those recently transplanted cannot respond to vaccination. This puts them at greater risk of infection and death from disease. Taken in context with the MTA guidance this is problematic for them. Access to passive protection offered by new monoclonal combinations would enable these individuals to live a more normal life free from fear and protect the considerable investment made in giving them a transplant.	Thank you for your comments. Patient perspectives were considered alongside the evidence for effectiveness. Please see section 3.3 and 3.4 of the final draft guidance.
28	Consultee (professional groups)	Faculty of Pharmaceutical Medicine, endorsed by the Royal College of Physicians	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** None.	Thank you for your comment
29	Consultee (patient/carer groups)	Immunodeficiency UK	It is important for this and future evaluations that NICE define what is considered the effectiveness threshold against COVID-19 variants as the FDA have done. This would add some transparency to the process and help define the scenario by which Evusheld may become a suitable treatment option.	Thank you for your comments. The committee acknowledged the need for a more flexible

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				evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
30	Consultee (patient/carer groups)	Kidney Care UK	It is not reasonable to apply the utility gain only to people fully or partially shielding. There are many people who do not have the option of fully or partially shielding – reasons being retaining employment and therefore income, fulfilling caring or parental duties. These individuals may experience significant distress and anxiety because they know they are exposing themselves to the risk of Covid-19 infection but cannot choose to stay at home. A treatment that offered protection would therefore provide substantial utility benefits in terms of reducing anxiety and distress in this group, and its vital that the model is able to capture this. Failing to capture the benefits for people who cannot choose to shield risks exacerbating inequalities that have been present throughout the Covid-19 pandemic, as ONS data to Jan '23 shows, those with the lowest incomes and education levels in elementary occupations are the least likely to work from home. The data also showed some slight differences between ethnicities -workers in the "Black or Black British" ethnic group reported the highest levels of travelling to work without the option to work from home (60%) compared with workers in the "White British/Irish" ethnic group (46%).	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.

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31	Consultee (patient/carer groups)	Kidney Care UK	We do not believe it is reasonable to use a cost based on administration in the CDMU, given that we know CDMUs will no longer be in place after April 2023. Local arrangements will be made in each ICB for the delivery of Covid treatments. It may be more appropriate to base costs on the administration of other preventative treatments, such as Hep B vaccination for kidney patients.	Thank you for your comments. The committee noted that the administration setting was uncertain. Therefore, it took account both the company's and EAG's estimates for the administration cost in its decision making. Please see section 3.18 of the final draft guidance for further details.
32	Consultee (patient/carer groups)	Kidney Care UK	The draft guidance states that there is uncertainty about how people's behaviour would change after having tix-cil. We suggest that a NICE appraisal of prophylactic Covid-19 treatment is an opportunity to develop guidance that optimises the benefits of a preventative treatment in terms of quality of life and clinical effectiveness, by ensuring people at high risk are offered advice and guidance on appropriate levels of activity/social mixing following preventative treatment (taking a similar approach to that used in the PrEP guidance). This advice would support people to maximise their quality of life as far as possible while avoiding significant increases in their risk of infection. The model should incorporate these assumptions of how people would behave.	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
33	Consultee (patient/carer groups)	Kidney Care UK	We do not think it is reasonable to use a hospitalisation rate close to the 2.8% reported by Patel for people with renal disease, given that the OpenSAFELY study found a hospitalisation rate among this group of about 4%. We suggest NICE consider a subgroup analysis of this group, using this more appropriate hospitalisation rate.	Thank you for your comments. The committee considered the data from OpenSAFELY. Please see section 3.20 of the final draft guidance for further details.
34	Consultee (patient/carer groups)	Kidney Care UK	We very much welcome NICE's announcement of ongoing surveillance of the disease and available evidence and rapid review of Covid treatments as required, but it is vital that problems with the current	Thank you for your comments. The committee

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			model are addressed promptly to enable the rapid review and fair, timely access to effective preventative treatment.	acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
35	Consultee (patient/carer groups)	Kidney Care UK	There is an unmet (and not fully understood) need in a population which remains at risk from Covid-19 and it is not fair that the burden of protection relies solely on the individual's behaviour. We very much want to work with NICE to understand and develop plans to address a future for living with Covid-19.	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.

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36	Consultee (patient/carer groups)	Kidney Research UK	We are concerned that the process that has been followed for providing this draft guidance cannot be relied upon to give sound and suitable guidance for the NHS. While we have confidence that relevant evidence has been considered, our key issue is that that evidence has been assessed far too slowly. This draft guidance has been published far too late. The guidance itself acknowledges that studies analysed were from earlier in the pandemic when different variants of the Covid-19 virus were circulating. Omicron subvariants BQ.1 and CH.1.1 and XBB lineages were not dominant variants in the summer of 2022. By July 2022, when the NICE's consultation began after licensing was approved in the March, Evusheld had already been procured across 32 other countries. In August 2022, while those at high-risk of Covid could have benefited from the drug, the NICE HTA process was only just being formally referred to NICE by the Department of Health and Social Care – with no end in sight for eight more months. This process was slow to start, unsuitable for assessing a rapidly evolving virus, and has been incredibly protracted. The draft guidance acknowledges these key points throughout its summation. The committee 'considered that SARS-CoV-2 is rapidly evolving and acknowledged that this makes assessing neutralising monoclonal antibodies difficult'. In future, a faster, more adaptive, and flexible process must be considered for assessing the efficacy of new treatments for Covid-19. We welcome the decision to introduce a new mechanism for reviewing new evidence for existing treatments, but this must be extended to future new appraisals.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
37	Consultee (patient/carer groups)	Kidney Research UK	We are concerned that parts of the rationale provided for recommendations would set an unfair precedent that will exacerbate health inequalities. Those shielding face great unmet treatment need. Shielding has taken a significant toll on the physical, emotional, and financial well-being of kidney patients. Addressing the risk of COVID-19 to those who are immunocompromised must be prioritised. As the evidence shows, vaccination can be less effective in transplant recipients. The importance of the vaccination and booster programme is clear, but we must continue to push for more effective strategies and review new data promptly. No utility gain from the technology was considered as arising from the increased confidence of vulnerable people to resume normal activities as the Draft Guidance suggests that it could increase the risk of infection. This is a perverse reading of potential outcomes. There is a significant underestimation of the effect of shielding if it is to be implied that patients "may not realise any quality-of-life benefit from the ability to reduce shielding behaviour". We know from kidney patients that shielding has had a direct impact on social isolation, on input into the economy, on loved ones and carers. We outlined in our previous evidence	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft

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			submission how kidney disease is known to be associated with an increased risk of mental ill-heath, and how the mental health impact of shielding has been shown to have a significant effect on health-related anxieties compared to the rest of the population.	guidance for further details. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model.

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				Please see section 3.17 of the final draft guidance for further details.
38	Consultee (patient/carer groups)	Kidney Research UK	The binary recommendation that tixagevimab plus cilgavimab (tix-cil) is considered not clinically effective is too inflexible considering the ever-evolving nature of the Covid-19 virus. The summary of evidence clearly indicates that assessments made of the tix-cil's efficacy was based on the prevalence of particular variants. Given that the prevalence of said variants are ever-changing, it may be unwise to make such a black and white declaration of a medicine's efficacy. Antibody treatments must be assessed against different variants to assess where there is efficacy, and where there is not. As noted by clinical experts, tix–cil may not be clinically effective against many new variants but could still be effective against some of them. It is also possible that tix–cil may regain efficacy against future variants. In the United States, the FDA has decided upon a threshold of effectiveness of antibody treatments. They have decided upon a threshold of efficacy of 10% against circulating variants. It would be prescient for NICE to consider this as an appropriate way forward.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
39	Consultee (patient/carer groups)	Leukaemia Care	We are concerned about the committee's inability to make a reliable cost-effectiveness estimate due to the uncertainty in the clinical evidence. Whilst we appreciate the challenge of translating the in vitro data into estimates of efficacy in humans, the treatment does show neutralisation activity against some variants. Additionally, the treatment remains licensed by the MHRA. We therefore ask the committee to consider this treatments' suitability for the Innovative Medicines Fund (IMF). This would grant a period of managed access to patients who want this treatment to be available on the NHS and would enable NICE to gather more real-world evidence for the committee to make a more accurate decision on the treatments' clinical and cost-effectiveness.	Thank you for your comment. The company have not submitted a proposal for the innovative medicines fund (IMF). The feasibility of the IMF was considered by NICE as part of the appraisal process, however NICE

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				concluded that tix-cil was not a suitable candidate for managed access. Please see document 10 of the draft guidance committee papers and section 3.27 of the final draft guidance for further details.
40	Consultee (patient/carer groups)	LUPUS UK	Evusheld was effective and cost-effective, and therefore likely to have been approved, when previous Omicron variants were more dominant. It is both frustrating and concerning that an opportunity was missed to address an urgent unmet need for people who are at high risk from COVID-19, particularly those who do not have a good response to, or are unable to receive, vaccinations. If Evusheld had been appraised more rapidly, these vulnerable patients may have been able to have some protection from COVID-19 when previous variants were dominant during the second half of 2022. In addition to providing vital protection by reducing risk of severe illness, this treatment could have drastically improved quality of life for a group of people continuing to experience the adverse impact of shielding. We welcome the recommendation to create a new fast-track system for updating recommendations for COVID-19 treatments, particularly in the case of monoclonal antibodies which are most effective against particular variants. However, as we understand it, this process is for updating existing recommendations, and not for the evaluation of new treatments. This means potential future prophylaxis preventative treatments will not be included. Therefore, the rapid review scheme will not solve the problem of appraising novel treatments in a timely manner. It is essential that new and novel COVID-19 treatments are included in a fast-track system, so that another effective treatment is not wasted due to the appraisal process taking place after the window of opportunity for its effective use is passed.	The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
41	Consultee (patient/carer groups)	LUPUS UK	We are concerned that the recommendations imply that NICE requires a threshold of evidence which is too high for medicines such as these to be approved in a timely manner. In section 3.23, the committee recommends that "further data collection through clinical trial would be a more appropriate way to resolve key uncertainties". Given the long timescales of clinical trials, and the issues of changes in circulating variants, waiting for the outcome of a clinical trial will likely delay appraisal	Thank you for your comments. The text on clinical trials has been removed. The committee noted the limitations of replying solely on in vitro

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			to a point at which the variants have changed and the treatment becomes less effective (as discussed above). The reliance on in-vitro evidence alone is problematic, as this approach makes significant assumptions regarding tissue penetration and mechanism of action of monoclonal antibodies, as research has indicated that in-vitro studies analysing the neutralising effect of monoclonal antibodies on different variants of SARS-Cov-2 do not accurately demonstrate the real-world, clinical efficacy of treatments. In some cases a monoclonal antibody developed for a historic variant could regain activity against the spike protein of a future variant. As such, the recommendations should not be reliant on in-vitro analyses. Uraki et al. (2022) demonstrated that another monoclonal antibody treatment, sotrovimab, can restrict viral replication in the lungs of hamsters infected with Omicron BA.2 in an in-vivo experiment, despite in-vitro experiments suggesting that Omicron BA.2 had resistance to sotrovimab. The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, especially due to the rapid changes in circulating variants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities mean they have little response to, or are unable to receive, vaccination. A wider range of evidence needs to be synthesised for rapid and accurate assessment of the efficacy of monoclonal antibody treatments.	evidence. It would have preferred to triangulate the data with real-world evidence. However, in the context of changing variants, it considered the in vitro data for current variants more relevant to decision making than the older real-world studies in the company's submission. Please see section 3.12 of the final draft guidance for details. No evidence was submitted to NICE for an immunomodulatory effect outside of neutralisation.
42	Consultee (patient/carer groups)	LUPUS UK	We are concerned that evidence used by the committee for this recommendation implies that, because (some) people at higher risk from COVID-19 continue to modify their behaviour by shielding, their true risk cannot be fully considered in cost-effectiveness modelling. Section 3.16 of the draft recommendations states that: "…data for the general population [on infection risk] may not be generalisable to those likely to have Evusheld. The committee considered it likely that the risk of infection in those eligible for Evusheld would be lower than the general population. This is because those eligible for Evusheld modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden." The committee then considered that the model should be sensitive to changes or differences in background levels of risk. It is unreasonable to expect people in the eligible group to continue to modify their behaviour to reduce risk of infection. Using this as evidence of a lower level of risk than the general population could mean recommendations require people to continue to shield and does not account for the large number of eligible people unable to do this. The committee may need to review any stereotypes of a person who is shielding. We cannot assume that those at risk can reduce their risk of exposure to the virus by modifying just their own behaviour. Many in the at-risk group do not live alone. It is more likely that someone is in a household with family or friends whose behaviour would also need to be modified. This becomes increasingly unlikely due to the lack of precautionary measures and governmental support such as widespread testing. We must also consider the reduced opportunities for at-risk people to practice shielding. Most people in this group are living with a disease and/or treatment which requires attendance to medical settings for medication administration and/or monitoring. Even if an at-risk person can stay safe traveling to and from appointments, the	Thank you for your comments. The committee considered that further research is needed to understand the background risk of infection in different populations. The committee noted that the company had not provided any new data for the target population for the risk of infection in people not having tix–cil, so the risk was still uncertain. It concluded that both of the EAG's scenarios (halving and doubling the risk) should be considered in decision making. Please see section 3.19 of the final draft guidance for further details.

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			precautionary measures in medical settings are being increasingly abandoned. It is not reasonable to use lower risk values to model cost-effectiveness for this group, because it is not reasonable to assume that all at-risk people and their households are able to adequately modify their behaviour, nor is it reasonable to expect those that are able to, to continue shielding given the difficulties and well-documented mental and physical health impacts of this (e.g. Sloan et al, 2021; Ryan et al, 2022; Maldonado et al, 2021). This is also a matter of health inequalities. A disproportionate number of those unable to shield are from minority ethnic groups, due to the higher likelihood that they are in employment without remote working options, higher likelihood to work in occupations with higher risk of exposure to COVID-19, and higher likelihood of needing to use public transport to travel to work (POST, 2020). Lupus also disproportionately affects those from African-Caribbean or Asian heritage, who also tend to have more severe disease (e.g. Hasan et al, 2022), and so would likely be a high proportion of those eligible for Evusheld.	The committee considered that these were important equalities issues. However, its decision was based on a lack of expected clinical effectiveness and consequently very high ICERs. The committee did not expect its conclusions to differ across these groups. Please see section 3.24 of the final draft guidance for further details.
43	Consultee (patient/carer groups)	LUPUS UK	We are concerned that the committee has underestimated the direct utility gain to shielding patients. The committee suggests that the evidence submitted by patient experts implies a lower direct utility gain due to more limited behaviour change in shielding behaviours than the Company submitted in evidence. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for almost three years, to immediately return to pre-pandemic behaviour, even if a treatment was able to provide 100% protection. Patients in recent research (as referenced in point 3 above) have discussed impacts to their mental and physical health, including a loss of confidence and physical decline. Given these impacts, it is unrealistic to expect these patients to immediately or fully return to pre-pandemic behaviours. Additionally, COVID-19 is not the only viral risk for this group, so many would have been practicing enhanced precautionary measures to reduce risk of exposure to viral and bacterial threats before the pandemic. Therefore, it is likely patients will continue to modify their behaviour in some form due to the very real need to reduce risk from infections of all kinds. Additionally, in the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients, patients were not necessarily requesting a complete return to their pre-pandemic life, but a desire and need to have more of life open to them (even if that still includes some precautions like masking, for example), and that this could make huge improvements to their mental and physical health. When considering direct utility gains related to changes in shielding behaviours, the committee should consider change over time as people re-gain confidence and physical strength, rather than just immediate changes in behaviour. Continuing some shielding or protective behaviours should also not be viewed as a lack of impact, as there can still be a significant impact on mental and physical health if people feel able to do more whilst still masking, for example, and some protective behaviours are likely due to increased risk from other viral or bacterial infection for this group.	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
44	Consultee (patient/carer groups)	LUPUS UK	We are concerned that the recommendations do not include or imply a defined threshold of accepted effectiveness.	Thank you for your comments. The committee

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			The landscape of the pandemic has changed dramatically since the clinical trials for Evusheld. We are no longer experiencing a single dominant variant in circulation at one time but instead there are several dominant variants. It is unclear how this could change in the future, but it may not return to a pattern of single variants at a time. Monoclonal antibodies such as Evusheld usually work most effectively against one particular variant. As there will be more than one variant circulating, it is imperative that NICE develops a definition for the threshold of effectiveness to support rapid appraisal and deployment of effective treatments. This must include a threshold related to the estimated prevalence of variants the monoclonal antibody is likely to be effective at neutralising. If a monoclonal antibody is appraised to be effective (and cost-effective) against particular variants (such as is the case with Evusheld), then a threshold must be set for it being appraised as effective and cost-effective in the context of there always being multiple variants in circulation (for example, the FDA have accepted a threshold of using a monoclonal preventative treatment if the variant it works against is estimated to be responsible for greater than 10% of cases; FDA, 2023). Setting a clearly defined threshold will support rapid and transparent appraisal and updating of recommendations as variants change within the UK.	acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
45	Consultee (patient/carer groups)	LUPUS UK	References: - FDA (26th January 2023). Emergency use update open letter to AstraZeneca. https://www.fda.gov/media/154704/download - Hasan, B., Fike, A., & Hasni, S. (2022). Health disparities in systemic lupus erythematosus – a narrative review. *Clinical Rheumatology, 41(11)*, 3299-3311 - Maldonado et al (2021). Association of medication access difficulty and COVID-19-related distress with disease flares in rheumatology patients during the COVID-19 pandemic. *Arthritis Care & Research, 73(8)*, 1162-1170 - POST (2020). Impact of COVID-19 on different ethnic minority groups. Rapid response report. https://post.parliament.uk/impact-of-covid-19-on-different-ethnic-minority-groups - Ryan et al (2022). Exploring the physical, psychological and social well-being of people with rheumatoid arthritis during the coronavirus pandemic: a single-centre, longitudinal, qualitative interview study in the UK. *BMJ Open, 12(7)*, e056555 - Sloan et al (2021). COVID-19 and shielding: experiences of UK patients with lupus and related diseases. *Rheumatology advances in practice, 5(1)*, rkab003	N/A

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			- Uraki, R., Kiso, M., Iida, S., Imai, M., Takashita, E., Kuroda, M., ... & Kawaoka, Y. (2022). Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA. 2. *Nature*, *607*(7917), 119-127.	
46	Patient expert	Jill Nicholson	Discrimination and inequality has occurred.	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
47	Patient expert	Jill Nicholson	NICE's objective and that of our society is to be inclusive. The legislation that Evusheld has undergone means the "bench mark" for this product has been set higher than other vaccinations in circulation. There is no proof that the longevity and efficacy of Evusheld is any worse than our current vaccines which we know give NO protection to the immunosuppressed community.	Thank you for your comment. NICE considers topics referred to it by the Department of Health and Social Care. Vaccines are approved via a different route (the Joint Committee on Vaccination and Immunisation).
48	Patient expert	Jill Nicholson	It is of great concern to discover, that if Evusheld was not available two antiviral post exposure treatments have been withdrawn further limiting lifestyle options for the immunocompromised. Many of these people have contra indications against some of the anti virals, but not so for Evusheld.	Thank you for your comment.
49	Patient expert	Jill Nicholson	The mental health of the immune compromised (and that of their dependants) would take another back step without Evusheld. (for example I have actually paid out for this vaccine and travelled on the bus for the first time in 3 years. I now visit my elderly in laws with a mask inside, but don`t ask that they wear theirs) Life quality has this improved with Evusheld for all concerned.	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain

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				through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
50	Patient expert	Jill Nicholson	We are in the same position as that of 3 years ago, but by ourselves – abandoned and without a government/medical plan.	Thank you for your comments. Patient perspectives were considered alongside the evidence for effectiveness. Please see section 3.3 and 3.4 of the final draft guidance.
51	Patient expert	Jill Nicholson	There could be problems in the future. Every single person in the CEV community is DEEPLY CONCERNED that in future this long winded process will yet again leave us cast aside. Whilst this is not necessarily connected to Evusheld evaluation in itself we are utterly terrified about the future, even though we are living in a first world country in the 21st century.	Thank you for your comments. Patient perspectives were considered alongside the evidence for effectiveness. Please see section 3.3 and 3.4 of the final draft guidance.
52	Public (web comment)	Web commenter 1	• Has all of the relevant evidence been taken into account? There is no mention of any evidence being sought from the 30+ other countries who have already been administering Evusheld or indeed any evidence as to why these other countries have decided that, unlike the United Kingdom, it is appropriate to administer Evusheld. The evidence also does not take account of a lack of United Kingdom Government messaging on the severity of COVID. In particular the United Kingdom Government has not highlighted the significant risks relating to potential cardiovascular, blood vessel, lung, brain, immune system and Long COVID disorders associated with COVID infections. If the United Kingdom Government highlighted the significant risks in each of these areas to the general population there would be a twofold impact. Firstly Immunocompromised non-shielders would potentially change their behavioural patterns and secondly the general population would potentially engage in more	Thank you for your comments. The evaluation relies on the available evidence submitted to the NICE by stakeholders and that retrieved from the published literature by the external assessment group. It is unclear if this evidence if the same as presented to health technology assessment agencies and regulators

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			mitigations against COVID. The impact of proper COVID messaging is therefore likely to be that some of the Immunocompromised non-shielders would shield as at the moment they are in an “ignorance is bliss” bubble. There would therefore be an increased requirement for a preventative treatment such as Evusheld as more people would be shielding. The other outcome would be a reduction in the spread of COVID as the general population would engage in more mitigations against COVID. This would have the knock on impact that the Immunocompromised population would feel more able to move about as the ongoing COVID levels would drop and especially if they were administered a preventative treatment against COVID . This all assumes proper messaging as to the severity of COVID by the United Kingdom Government in the first place.	globally.
53	Public (web comment)	Web commenter 1	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Although it is accepted that there is a need for sophisticated cost modelling with regard to Evusheld there is also a need for a “helicopter view” of the costings. The percentage of Immunocompromised people who are hospitalised by COVID is disproportionately high compared to the percentage of Immunocompromised people in the general population by a significant amount. Immunocompromised people who are hospitalised are, in general, in hospital for longer and therefore the associated cost is significantly higher. A high level exercise should be carried out to compare the cost saved by the non-hospitalisation of a proportion of Immunocompromised people because of protection from a treatment like Evusheld against the cost of administering preventative treatments such as Evusheld. Since the beginning of COVID tens of thousands of Immunocompromised people have been hospitalised. This exercise would show that the hospitalisation costs which would be saved are significantly higher than the cost of administering Evusheld or an equivalent. If a preventative treatment was administered to the Immunocompromised group it would significantly reduce the number of Immunocompromised people hospitalised and would also free up valuable resource within the NHS. Effectively a significant hidden cost would also be removed.	Thank you for your comment. The committee considered the model that was submitted to NICE by the company. The model included the cost offsets for hospitalisation.
54	Public (web comment)	Web commenter 1	• Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations do not stress enough the need for a speedy approval process for potential future preventative treatments for the Immunocompromised population. It is imperative that future treatments such as Evusheld 2 are approved rapidly to ensure they are administered to the Immunocompromised population when they are effective as has been the case with COVID vaccines to date. The irony of the current consideration of Evusheld is that a treatment which was created in the United Kingdom was authorised for emergency use in the United States in December 2021 and was administered	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are

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			to patients up until recently. However, in the United Kingdom the review of Evusheld has not been completed close to 15 months after it was approved for use in the United States. This cannot be allowed to happen for future preventative treatments or else the Immunocompromised population will have to continue to shield indefinitely.	provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.
55	Public (web comment)	Web commenter 1	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? All Immunocompromised people should be given the right to future preventative treatments not just those at highest risk. If this were not to be the case then there would still be a significant minority of the Immunocompromised population who would feel discriminated against.	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
56	Public (web comment)	Web commenter 2	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil

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			This draft guidance discriminates on the grounds of disability – people who have had no/poor response to covid vaccines are not offered any protection against covid, despite being more vulnerable. As such, there should have been more patient experts and the afternoon session should have been held earlier in the day - at least one patient was exhausted - or the session held in the morning, or patient experts allowed to pre-record responses to set questions. Patient engagement must be realistic and respectful of patients' needs to be valid.	could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
57	Public (web comment)	Web commenter 2	• Section 1 – Recommendations, point 1.1 'The limitations in the clinical evidence mean it is not possible to make a reliable cost-effectiveness estimate.' Given that Evusheld was effective against previous dominant Omicron variants, and probably cost-effective on that basis, it is devastating that an opportunity was missed to address an urgent unmet need for people who are at high risk from COVID-19 - those who have no/inadequate response to, or unable to receive, vaccinations. If Evusheld had been appraised more rapidly, vulnerable patients, including those like me with severe SLE, may have been able to have some protection from COVID-19 when previous variants were dominant during the second half of 2022. In addition to providing vital protection, reducing risk of severe illness, this treatment could have drastically improved quality of life for a group of people continuing to experience the adverse impact of shielding. As it was since getting covid in August I have ongoing lung damage and aside from participating in the Rapid Protection trial where I have had one dose of Evusheld in January 2023, I still can't leave the flat because, apart from the fact that current variants aren't well covered, I'm now too unwell. No one really understands what has happened to my lungs post-Covid, six months on there is no diagnosis or prognosis. I am concerned about what will happen if I get Covid, or any other respiratory illness on top of this damage. My days are dominated by a hideous productive cough that hasn't responded to several courses of antibiotics, and sleeping. I am now on yet another course of antibiotics. I don't have anything like a life. First I was robbed of the opportunity for protection by the incredible decision to put Evusheld through a lengthy NICE process, then I was led to believe that there would be antivirals. I had the letter, the phone number etc, but due to bureaucratic delays got the wrong antiviral, too late, then got rebound and nobody knew what to do. Like many patients, I feel let down and abandoned at every turn. While I welcome the recommendation to create a new fast-track system for updating recommendations for Covid treatments, I am concerned to understand if this a process for updating existing recommendations, or the evaluation of new treatments.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details.

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			It is essential that new and novel COVID-19 treatments are included in a fast-track appraisal system, so as not to waste future treatments and opportunities to protect vulnerable people. 1. When is NICE going to get an appropriate process in place to deal with pandemic-related medications, especially for the vulnerable? 2. Will it be ready when the next Supernova version of Evusheld that covers new and current variants and is expected in the second half of this year? 3. Failing this, what improved antiviral delivery is being arranged for vulnerable people? •	
58	Public (web comment)	Web commenter 2	• Section 2 – Information about tixagevimab plus cilgavimab 2. I am concerned that the recommendations suggest a required threshold of evidence that is too high for medicines such as these to ever be approved in a timely manner. In section 3.23, the committee recommends that "further data collection through clinical trial would be a more appropriate way to resolve key uncertainties". Given NHS constraints on clinical trials in general, the length of time it takes to establish and run clinical trials, and the rapidity of variant mutations, this all conspires to bring us to the same point – the moment when a treatment could have been effective will have passed. The reliance on in-vitro evidence alone is strange, as in this case it does not seem to accurately demonstrate real-world, clinical efficacy of the treatment. I may have missed it, but I didn't see/hear any references to the use of Evusheld in other countries and their view of efficacy/cost-benefit. The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high given the rapid changes in circulating variants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities mean they have no/little response to, or are unable to receive, vaccination. A wider range of evidence needs to be synthesised to more rapidly and accurately assess the efficacy of monoclonal antibody treatments.	Thank you for your comments. The text on research recommendations has now been revised. Please see section 4 of the final draft guidance. The efficacy evidence presented to NICE and the committees conclusions on this are discussed in sections 3.7-3.13 of the final draft guidance.
59	Public (web comment)	Web commenter 2	• Section 3 – Committee discussion The evidence used by the committee for this recommendation implies that, because (some) people at higher risk from COVID-19 continue to modify their behaviour by shielding, their true risk cannot be fully considered in cost-effectiveness modelling. Section 3.16 of the draft recommendations states that: "…data for the general population [on infection risk] may not be generalisable to those likely to have tix-cil. The committee considered it likely that the risk of infection in those eligible for tix-cil would be lower than the general population. This is because those eligible for tix-cil modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden." The committee then considered that the model should be sensitive to changes or differences in background levels of risk.	Thank you for your comments. The committee considered that further research is needed to understand the background risk of infection in different populations. The committee noted that the company had not provided any new data for the target population for the risk of infection in

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			This implies that because (some) are able to take that burden, their true risk (should they not modify their behaviour) is not an accurate measure. Can I suggest that the committee review stereotypes of a shielding person? You cannot assume that those at risk can reduce their risk of exposure to the virus by modifying just their own behaviour, but also that of family, friends, carers. Behaviour modifications aside from shielding are increasingly difficult due to the withdrawal of general precautionary measures and governmental support, including widespread testing. Also, it is now more difficult for at-risk people to shield. Most people in this group are living with a disease and/or treatment that requires hospital attendance and medical monitoring. Even if an at-risk person can stay safe travelling to and from appointments, the precautionary measures in these settings are being increasingly abandoned. It is not reasonable to use lower risk values to model cost-effectiveness for this group, because it is not reasonable to assume that all at-risk people and their households are able to adequately modify their behaviour, nor is it reasonable to expect those that are able to, to continue shielding given the difficulties and well-documented mental and physical health impacts of this.	people not having tix–cil, so the risk was still uncertain. It concluded that both of the EAG's scenarios (halving and doubling the risk) should be considered in decision making. Please see section 3.19 of the final draft guidance for further details.
60	Public (web comment)	Web commenter 2	• Section 3 – Committee discussion, point 3.2 'Patient perspectives' The committee appears to have underestimated the direct utility gain to shielding patients. The committee suggests that the evidence submitted by patient experts implies a lower direct utility gain due to more limited behaviour change in shielding behaviours than the Company submitted in evidence. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for almost three years, to immediately return to pre-pandemic behaviour, even if a treatment was able to provide 100% protection. Due to decline in mental and physical health, it is unrealistic to expect these patients to immediately or fully return to pre-pandemic behaviours. Additionally, in the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients, patients were not necessarily requesting a complete return to their pre-pandemic life, but a desire and need to have more of life open to them (even if that still includes some precautions like masking, for example), and that this could make huge improvements to their mental and physical health. When considering direct utility gains related to changes in shielding behaviours, the committee should consider change over time as people regain confidence and physical strength, rather than just immediate changes in behaviour. Continuing some shielding or protective behaviours should also not be viewed as a lack of impact, as there can still be a significant impact on mental and physical health if people feel able to do more whilst still masking, for example. Finally, on a personal note, while an at-risk person living alone might be able to manage to avoid Covid, the toll of the social isolation over the years of the pandemic puts them at very real risk of a collapse of their mental state. They might not have Covid, but they don't have a life either. Like most at-risk people who are also at risk of other infectious diseases, I am habituated to avoiding crowds and other aspects of shielding. Nevertheless, when I was given Evusheld as part of the Rapid Protection trial, I did experience a reduction in the sense of abandonment and a greater hopefulness for the future. My days have been very bleak, and I've wondered what I'm going through all of this for. If I got	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.

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			nothing else from Evusheld, this was worth it and will hopefully keep me going until the more timely approval of the next Supernova version of Evusheld or another prophylactic treatment.	
61	Public (web comment)	Web commenter 3	Re section 4.3 It's my anecdotal experience that a good proportion of these patients are actually very poorly informed of their situation. A significant proportion have never heard of Evusheld and many don't even realise they are not well protected by vaccination. I spoke to a transplant patient recently who has only had 3 vaccines for example, he thought he was well protected, and no one told him otherwise. He hadn't had a booster for well over a year. Another whom I discussed the situation with recently had no idea there was anything else out their apart from vaccines, she was shocked when i told her about Evusheld and the fact other countries had protected their transplant communities many months ago. The communication to these vulnerable groups from government has been exceptionally poor in my opinion. Many people do not seek out information, it has to be put in front of them. It's a mistake to assume that just because someone has a serious medical condition that they all take a deep active interest in their situation. Therefore, an ONS type study would be of limited use. Asking people if they are still shielding when a fair proportion don't actually realise they are still at high risk is meaningless. It's a disgraceful situation in my view and exacerbated with the false and deluded narrative that "it's all over". Vulnerable groups are not immune to this narrative and also suffer a lot of ill-informed peer pressure from "friends" and family.	Thank you for your comments. The committee acknowledged the need for a better communication of the risks of COVID-19. Text referring to the ONS survey has been removed.
62	Public (web comment)	Web commenter 3	Re section 3.3 My own situation is similar to the patient experts who appeared at the committee meeting. I have been effectively shielding since the beginning of March 2020, soon to be three years. During that time, I have not been in a shop or a restaurant. I have had no one inside my house and have been in no indoor spaces aside from medical facilities. If we need petrol I "pay at pump" while wearing a mask, my medication is delivered and left at the door, likewise my supermarket deliveries. Everything I do is risk assessed. Accessing safe health care is increasingly difficult, I wear an FFP3 mask at all times outside my home. I have transplant friends who have been abused in the street and even in a pharmacy for wearing a mask and trying to navigate a dystopian world safely. We are discriminated against. I can't even see my own father in his nursing home, I am restricted to window visits from the car park and an occasional garden visit in PPE in the summer. The staff in the home no longer wear masks, nobody is testing, they have had multiple outbreaks one of which very nearly caused my father’s demise last year. It's a high-risk environment which is not safe for me to enter. I and my husband are retired, he has shielded with me throughout and hence has not seen his family in Yorkshire since 2019.We have economic spending power but can't use it, we have been effectively excluded from society and the economy by government Covid policy and the lack of preventative drugs. I have looked after my transplant fiercely for many years and will not gamble with my health when i am not adequately protected. We desperately need effective preventative drugs and rapid action on procurement when they are available.	Thank you for your comments. Patient perspectives were considered alongside the evidence for effectiveness. Please see section 3.3 and 3.4 of the final draft guidance. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and

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			The availability of post infection treatments is absolutely no solace to me. Firstly, the provision is hit and miss, I know a number of people who have had a dreadful battle to access treatment, some failing entirely. Other people have been told "they aren't ill enough " at the time to be given them, absolutely ludicrous. Even if the system worked properly, it's not a risk to be a taken. If I may use the analogy of a car accident it's much better not to have it than get treatment for the damage afterwards. I have not had Evusheld, I had a virtual private consultation for it around Christmas time at a proposed cost of £1500. It was apparent to me by that time that it was probably approaching the end of its useful life, so I didn't proceed. I will be waiting and shielding until the updated version is available, hopefully on the NHS but privately if not. This protection should be provided by the state, no question of that. We don't have the tools to "live with Covid". I am a former medical professional in the transplant field and also a transplant patient with multiple comorbidities, perhaps a near unique situation. I believe NICE have made a reasonable decision on Evusheld given the situation on the ground by the time this drug reached the committee. However, the fact that this has taken so long is appalling, Evusheld did have proven effectiveness earlier in its life and UK patients have missed out on a years' worth of protection sinch MHRA approval. I am heartened by NICE acknowledging the need for rapid appraisal of preventative Covid drugs such as these. We cannot carry on with the status quo, these drugs have a limited useful life against a moving target, they need rapid rollout as soon as efficacy is proven. The current system means nobody would ever get anything, the drug would be past it's "use by date" or approaching it before it even reaches a decision-making process. I hope we now have a window for NICE to instigate the rapid evaluation process in time for the updated version of Evusheld which is due for release in the second half of this year. I think this is a reasonable decision given the current variant mix in the UK. However, it does not excuse the lamentable time it has taken to get to this stage during which these cohorts have missed out on many months' worth of protection. I am however heartened by the committee's acknowledgment of the urgent clinical need and the wish to act much faster with similar future preventative drugs.	3.24 of the final draft guidance for further details.
63	Public (web comment)	Web commenter 3	• Has all of the relevant evidence been taken into account? Given so much evidence around current efficacy of Evusheld is anecdotal then the NICE decision is understandable. It is however a great shame that it has taken so long to get to this stage.	Thank you for your comment.
64	Public (web comment)	Web commenter 3	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I believe NICE has made a fair appraisal of the situation given the current situation on the ground in terms of variant mix etc.	Thank you for your comment.

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65	Public (web comment)	Web commenter 3	• Are the recommendations sound and a suitable basis for guidance to the NHS? I believe so, I am heartened by the recommendation for a rapid assessment committee and the acceptance of the urgent clinical need for Covid preventative drugs. I am less convinced by the stated need for an ONS type survey of the highly vulnerable cohorts. It's my opinion that too many do not understand they are still at high risk and would act differently if they were properly informed.	Thank you for your comment. Text referring to the ONS survey has been removed.
66	Public (web comment)	Web commenter 3	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? I don't believe the NICE decision in isolation is discriminatory in any way, it is fair and balanced. However, these groups are most certainly being discriminated against or even persecuted in day-to-day life in a way which is not acceptable in a modern Western nation. They have been constructively excluded from society because of their medical vulnerabilities.	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
67	Public (web comment)	Web commenter 4	• Has all of the relevant evidence been taken into account? No. There are problems with the studies used in evidence and the arguments used in justification of preventing access to this treatment. There was a lack of evidence as to the effectiveness of covid vaccination when first given and for new variants, but mass vaccination was provided. We know the risk to immunocompromised and those groups not able to access vaccination. We know the impact on lives although underestimated. In reality many people are impacted other than the person shielding or vulnerable. QUALYs are hugely impacted for those who are in need of this health care provision. To prevent it is discriminatory when available and is prevention of basic healthcare need. There is a need to look at alternative treatments such as infusions for those who need Covid treatment after catching it who are immunocompromised - further immunity impact for 3 months - hardly appropriate against the use of Evusheld. To prevent this preventative is unethical. It is a choice to leave people at risk of death when this is preventable. It is discriminatory as due to our health care needs, we are placed at higher risk and this choice to prevent lowering risk is a choice against the most vulnerable in certain groups of society based on certain characteristics.	Thank you for your comment. NICE considers topics referred to it by the Department of Health and Social Care. Vaccines are approved via a different route (the Joint Committee on Vaccination and Immunisation). The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need

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				as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
68	Public (web comment)	Web commenter 4	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. The cost to health and social care of failure to give this treatment is outweighed massively by vulnerable people who are immunocompromised if they should contract COVID. A transplant patient may lose their transplant. The ongoing costs of this are huge and would massively outweigh treatment with prevention. The treatment of covid once contracted are more likely to need more intensive costs for the population groups being discussed. The summaries detract from the ethical reality which is that most vulnerable people are not able to shield in reality as they cannot remove themselves from risk if they live with family or are cared/carers for/by someone else and are having contact with medical services, food from shops, mail, parcels and all other sources of possible sources of infection. To say that people who take responsibility for their healthcare and do everything to minimise their risk would take more risk if access to prevention is given is both insulting and naïve. For many it would be lowering risk in everyday life circumstances within their home or work which they cannot do anything about whilst doing everything possible to mitigate these risks. They took vaccination and still shielded. They fought to keep the 8-week gap between vaccinations as recommended in little green vaccination book for immunocompromised despite the government deciding against advice on a 12-week gap for all members of society. The arguments do not stack up in reality. To treat certain groups as unvalued members of society not provided with equality of protection is a failure of the government to keep its citizens safe and protected. If our risk is heightened by measures to relax lock down for other members of society, then we need other measures to protect us due to our health characteristics.	Thank you for your comments. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.
69	Public (web comment)	Web commenter 4	• Are the recommendations sound and a suitable basis for guidance to the NHS? No. It holds the same negligence and disregarding attitude when decisions were taken to start discharging people from hospital back to nursing homes without a known COVID status at the start of the pandemic. Same as not ensuring vulnerable were vaccinated according to guidance at 8-week internals due to lack of immune response and antibody death after this period. We know the risk, we know how we could prevent harm and vulnerable people are put at additional preventable risk of severe illness, harm and even death as a result of a decision to continue to fail to protect. It is an unethical decision against a vulnerable at-risk group. It is as though society would rather reduce their burden of the vulnerable rather than the vulnerable's burden of risk. It is discriminatory and not sound or suitable to recommend as guidance to the NHS if we are a modern moral society measured by how we take care of our most vulnerable.	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see

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				section 3.3, 3.12 and 3.24 of the final draft guidance for further details.
70	Public (web comment)	Web commenter 4	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? prevention of access to equitable healthcare is an issue and this is discriminatory to those with long term health conditions and or disabilities for which this treatment has been developed. Groups affected should have been contacted and views given as part of equality impact assessment. In itself the wording in the impact assessment acknowledges the groups likely to be affected most but personally I find the wording offensive...it might as well say but it only affects...the less contributing members of society. Personally, the document appears as skewed towards declining this treatment for the most vulnerable and leaving them at the mercy of living in society with no protection or interest in protecting them against Covid. The whole decision is appalling and unethical. Cost effective decision - well it may ultimately reduce benefits and pensions budgets, and free up hospital and social care places if the risk is left high for vulnerable groups to succumb to COVID? What is the political motivation to provide this protection? morals? well vulnerable were all given priority in vaccination roll out weren't we? or were we the first guinea pigs subjected to a vaccination program that was hailed a success but in reality did very little for the protection of the most vulnerable immunocompromised groups as the 8 week interval was not carried out as clinically advised by JVCI to be effective...civilised moral society? I do wonder.	Thank you for your comments – please see the above response.
71	Public (web comment)	Web commenter 5	• Has all of the relevant evidence been taken into account? No, real life data was not taken into account and the effect of delay on the human beings involved. These are real people and the delay has seriously affected peoples quality of life!	Thank you for your comment. The committee considered the real-word evidence for Evusheld. Please see section 3.9 of the final draft guidance.
72	Public (web comment)	Web commenter 5	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No, real life data was not included and the whole process was unfair!	Thank you for your comment – please see the above response.
73	Public (web comment)	Web commenter 5	• Are the recommendations sound and a suitable basis for guidance to the NHS? No, it was based on insufficient holistic data, a lot of valuable time has been lost and the questions asked on the 24th of January should have been asked months ago!	Thank you for your comments. The evaluation relies on the available evidence submitted to the NICE by stakeholders and that

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				retrieved from the published literature by the external assessment group. The efficacy evidence presented to NICE and the committees conclusions on this are discussed in sections 3.7-3.13 of the final draft guidance.
74	Public (web comment)	Web commenter 5	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity Yes, you were aware that Evusheld had some effect against covid in the early stages, yet you still took this length of time to make a decision, the government and NICE discriminated against immunosuppressed patients compared to the general population and you have already disabled them by your inaction!	The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. Topics were selected in line with the NICE health technology evaluation topic selection manual
75	Public (web comment)	Web commenter 6	The Cardiothoracic Transplant Patient Group appreciates that the clinical evidence suggests that tix-cil is unlikely to be effective against the current relevant Covid 19 variants. The Cardiothoracic Transplant Patient Group believe that the extreme length of the assessment process has directly led to a missed opportunity of tix-cil's window of effectiveness. The Medicines and Healthcare products Regulatory Agency approved tix-cil on 17 March 2022. At this time Omicron BA.2 was the dominant UK variant and remained so until approximately June 2022. Omicron BA.5 then succeeded in becoming the dominant variant until approximately Nov 2022. The In Vitro Advisory Group report demonstrated tix-cil had neutralising activity against Omicron BA.2 and to a lesser extent Omicron BA.5 which were the dominant strains for the 8 months preceding the drug's authorisation. Additionally, the observational study Young-Xu et al was conducted when Omicron BA.2 was one of the dominant variants.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology

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			If approval and delivery of tix-cil had been given as close as possible to 17 March 2022, then the Cardiothoracic Transplant Patient Group believe that some of its patient population could have gained a material benefit. As a direct consequence of the length of assessment process some patients who have received a heart and / or lung transplant will have experienced avoidable morbidity and mortality. Whilst the preliminary recommendations have not been discriminatory, the speed at which they have been produced has discriminated against people whose life is sustained by either a donated heart or lung. The Cardiothoracic Transplant Patient Group appreciate further organisations in addition to NICE were involved during the whole decision process for tix-cil. These include commissioners and the Medicines and Healthcare products Regulatory Agency. The Cardiothoracic Transplant Patient Group would encourage all relevant bodies to work collaboratively in the future to ensure appraisals and approvals of any treatments to prevent Covid 19 in high-risk groups are conducted rapidly. The Cardiothoracic Transplant Patient Group is concerned that the committee may have not received all relevant evidence related to cardiothoracic transplant recipients due to the lack of professional inclusion and engagement from the cardiothoracic transplant clinical community. The Cardiothoracic Transplant Patient Group are extremely concerned that the list of professional groups does not include The British Transplantation Society, or any cardiac related group such as The British Society for Heart Failure. The Cardiothoracic Transplant Patient Group is further concerned by the relative lack of stakeholder engagement from cardiac related patient / carer groups. Other relevant groups could include, British Heart Foundation, Somerville Heart Foundation, Pumping Marvellous and Pulmonary Hypertension Association UK. The Cardiothoracic Transplant patient Group consider that the NICE appraisal process should place patients at the centre of their decision making. To achieve this patient engagement could be enhanced. Representative patients from NHS formally appointed bodies should be considered preferential to those from other organisations. The Cardiothoracic Transplant Patient Group (part of NHSBT) would be a good example of such a body. The Group has formal processes to ensure that the views it gives are representative of a whole patient population rather than that of an individual patient.	appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details. Web comments from the Cardiothoracic Transplant Patient Group were considered by committee in response to consultation.
76	Public (web comment)	Web commenter 6	• Has all of the relevant evidence been taken into account? No – please see comments made within the relevant document sections.	N/A
77	Public (web comment)	Web commenter 6	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes at a higher level, but insufficient analysis at a defined patient group analysis.	Thank you for your comments. Thank you for your comments. The committee acknowledged the higher

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				risk of hospitalisation and mortality in specific patient groups. But it had not seen evidence of differential clinical or cost effectiveness to rule out other groups covered by the marketing authorisation. Please see section 3.5 and 3.20 of the final draft guidance for further details.
78	Public (web comment)	Web commenter 6	• Are the recommendations sound and a suitable basis for guidance to the NHS? Yes, but the speed of the process has deficiencies which are acknowledged in the recommendations.	Thank you for your comments. The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft

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				guidance for further details. Web comments from the Cardiothoracic Transplant Patient Group were considered by committee in response to consultation.
79	Public (web comment)	Web commenter 6	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes, please see relevant comments within the relevant body of the document.	N/A
80	Public (web comment)	Web commenter 6	• Section 3 – Committee discussion, point 3.17 'Hospitalisation risk (without tix-cil) The Cardiothoracic Transplant Patient Group recognise the challenges the NICE Appraisal Committee have with estimating Covid-19 hospitalisation risk. The Group, however, considers that the Appraisal Committee need to improve engagement with stakeholder groups to facilitate this process. Whilst NICE acknowledge that the benefit gain will vary within the selected eligible population the only defined sub patient group which has a hospitalisation rate tested by NICE is that within Shield et al. (2022). More proactive engagement with stakeholder groups on this specific matter may yield further useful information. The Cardiothoracic Transplant Patient Group wish to highlight several pieces of additional information, all of which indicate that NICE may have underestimated hospitalisation risk in certain high-risk patient groups, with some specific references to risk within solid organ transplant recipients and cardiothoracic transplant recipients. 1) Callaghan et al (2023) (Vaccine Effectiveness Against the SARS-CoV-2 B.1.1.529 Omicr… : Transplantation (lww.com)) measured vaccine effectiveness against the Covid 19 Omicron B.1.1.529 variant in solid organ or islet transplant recipients. This revealed an overall hospitalisation or death risk of 5.8% in this patient population. Further interrogation of the information provided, showed a Covid 19 mortality rate of 6.2% and 12.0% for heart and lung recipients respectively in the whole study period (Dec 20 – March 22 – which is post UK vaccine deployment). Every solid organ transplant study demonstrates heart and particularly lungs transplant recipients to be at higher risk of severe Covid 19 than the whole transplant population. It is thus reasonable to assume that the risk of hospitalisation or death risk to heart and lung transplant recipients was much higher than 5.8% in the Covid 19 Omicron B.1.1.529 variant era.	Thank you for your comments. The committee acknowledged the higher risk of hospitalisation in specific patient groups. But it had not seen evidence of differential clinical or cost effectiveness to rule out other groups covered by the marketing authorisation. Please see section 3.5 and 3.20 of the final draft guidance for further details.

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			2) The first results of the MELODY study have been published, Pearce et al (2023) (Antibody prevalence after 3 or more COVID-19 vaccine doses in 23,000 immunosuppressed individuals: a cross-sectional study from MELODY | medRxiv). This investigated the prevalence of spike-protein antibodies following at least 3 Covid 19 vaccinations in immunocompromised individuals. Three patient groups were included, solid organ transplants, rare autoimmune rheumatic diseases, and lymphoid malignancies. The headline results revealed that solid organ transplant recipients had the highest levels (23.3%) of no detectable IgG spike protein antibodies in the three patient cohorts. Further interrogation of the data reveals that heart (25.7%) and lung (35.4%) have the highest percentage of undetectable antibodies of the solid organ transplant cohort. 3) Evans et al (2023) (Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study | medRxiv) undertook a retrospective study on high risk patients in Wales eligible for out of hospital Covid 19 therapies. This study revealed an all-cause hospitalisation or death risk within 28 days of 10.9% of those who had not received any treatment. 4) Radcliffe et al (2022) (Real-world experience with available, outpatient COVID-19 therapies in solid organ transplant recipients during the omicron surge – American Journal of Transplantation (amjtransplant.org)) conducted a single centre retrospective study on the effectiveness of out of hospital Covid therapies on reducing the risk of hospitalisation. This showed that of the patient cohort which did not receive any treatment, 27% were hospitalised within 30 days of Covid 19 diagnosis. It should be noted that the study group did not contain any lung transplant recipients and 18% were heart transplant recipients. 5) The latest Covid 19 mortality figures published by NHS Blood and Transplant (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)), reveals mortality rates of 15.5% and 7.5% for lung and heart transplant recipients respectively.	
81	Public (web comment)	Web commenter 6	In summary The Cardiothoracic Transplant Patient Group believe that future NICE appraisals must, where information is available, analyse benefit at a defined patient cohort level. This is especially relevant where the patient cohort is congruent with a single identifiable protected characteristic such as individuals with donated heart or lungs. The Cardiothoracic Transplant Patient group is concerned that the focus on hospitalisation risk underestimates the risk of severe covid 19. Data provided by Callaghan et al (2023) revealed that in solid organ or islet transplant recipients 0.71% of patients died within 28 days of a positive Covid 19 test who were not admitted to hospital for a noninjury. As such The Cardiothoracic Transplant Patient Group believe that in future calculations of severe Covid 19 NICE should utilise hospitalisation and mortality statistics. Alternatively, a multiplier on hospitalisation risk could be used to estimate the additional patient cohort – based on Callaghan et all, for solid organ or islet transplants this would be 1.14.	Thank you for your comments – please see responses above.

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			• Section 3 – Committee discussion, point 3.23 'Recommendation' The Cardiothoracic Transplant Patient Group commend the NICE Evaluation Committee for recognising the urgent need for an effective prophylactic treatment for people who do not have an adequate response to vaccination. The Cardiothoracic Transplant Patient Group believe that the NHS need to commit to all members of the public receiving an equitable opportunity for protection from Covid 19 regardless of their disability. • Section 4 – Recommendations for research, point 4.1 The Cardiothoracic Transplant Patient Group welcome the NICE Evaluation Committee acknowledging the need for tix-cil to be evaluated quickly against all new variants. The Cardiothoracic Transplant Patient Group would also encourage the company to enter tix-cil into the suggested ongoing platform trials. • Section 4 – Recommendations for research, point 4.2 The Cardiothoracic Transplant Patient Group supports the recommendation outlined in 4.2. In the stakeholder meeting of 15 February 2023, a potential quicker assessment timeframe of 90 days was suggested. The Cardiothoracic Transplant Patient Group does not consider this aim to be sufficiently ambitious. Covid variant evolution is rapid and variant domination can easily pass within such a time duration. As such the Cardiothoracic Transplant Patient Group would recommend a pre-emptive approval and delivery model. Such a model could establish pre agreed in vitro efficacy achievement levels at which the required cost effectiveness estimates are delivered. This could grant automatic (or very rapid authorisation) and trigger pre planned delivery methods. The model and delivery could be tailored at patient group levels, with different authorisation points depending on benefit gained by each group. The Cardiothoracic Transplant Patient Group, post-transplant patients, would be an excellent example of a known defined, very high-risk patient group.	
82	Public (web comment)	Web commenter 7	• Has all of the relevant evidence been taken into account? I believe that there a two main issues with respect to relevant evidence. The first issue is the disparity with which prophylactic protection for the disabled immunocompromised (Evusheld) was forced down a different process than that of the prophylactic protection for the immunocompetent (vaccines). This caused a vastly elongated timescale, 15 months longer than in other countries such as the USA, in which Covid-19 naturally mutated many times, to the point where Evusheld	Thank you for your comment. NICE considers topics referred to it by the Department of Health and Social Care. Vaccines are approved via a different route (the Joint Committee on

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			naturally became less effective against current variants. Hence, the immunocompromised in the UK missing out on at least 15 months of protection that many other countries took advantage of. The second issue is the fact that NICE took too little notice of the real world clinical data, that proved Evusheld was effective in many countries, and put too much of an emphasis on in vitro studies that have been proven by medical experts to have little or no bearing on the clinical effectiveness of a medicine. Whilst the experts do say that where there is no reaction at all of the medicine on the Covid-19 variant, it is safe to say that the medicine will not be effective, they go on to say that where there is some effect of the medicine at whatever level on the Covid-19 variant, that there will be some clinical effectiveness, however there is no collation of the percentage effectiveness from in vitro to real world effectiveness. In fact low in vitro percentages have been proven not to be an indicator in the real world, where higher effectiveness has been demonstrated.	Vaccination and Immunisation). Real world-evidence for Evusheld was submitted to the committee and considered alongside the in vitro evidence. The committees conclusions on this are discussed in sections 3.7-3.13 of the final draft guidance.
83	Public (web comment)	Web commenter 7	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I do not believe the summaries of the clinical or cost effectiveness reasonably interpret the evidence. For example, in the clinical effectiveness it is stated that Evusheld is not effective against the current variants nor those likely in the next 6 months. The effectiveness against the current variants is largely based on the flawed conclusions drawn from the in vitro studies, as outlined above in question 1. The exact knowledge of the variants that will be prevalent in 6 months' time can be little more than guess work, given the evidence of how Covid-19 has mutated over the last 3 years. Therefore, the conclusion that Evusheld will not be clinically effective on the variants that will be prevalent in 6 months' time, is clearly flawed. A much better approach would have been to approve Evusheld or similar medicines against future variant, but to hold the distribution until it is probable that they would be more clinically effective against the imminently future variants, similar to what the USA has done. On cost effectiveness I believe the interpretations of the evidence were fundamentally flawed on a number of accounts. For example, a large amount of the cost/ benefit analysis was weighted on the number of people shielding, and to base the number of people shielding on a Gallop survey of 48 people was fundamentally and statistically flawed. In addition, the utility study was based on the total population estimates of those shielding, which are heavily based on the estimates of those people who are immunocompromised. There is strong evidence that the numbers shielding does not only include those who are immunocompromised, but also the family members that they live with. This would greatly increase the utility population numbers, and the associated impact. Also, on this impact, I do not believe the cost effectiveness has truly factored in the full economic cost of making so many immunocompromised and their loved ones economically inactive. For example, in my own case I have had to give up my business, not only losing my income, but my employees also losing their income. In itself this has cost the UK economy not only in lost employment, lost corporate tax, lost income and NI tax, but also lost VAT as there is a reduced spending power, and a reduced spending opportunity for myself and my wife. This tax cost alone is more than a dozen times the cost of Evusheld per annum. In addition, my wife had to give up her profession as a nurse, at a much-needed time for nurses. In terms of ongoing costs, we have been living off our retirement savings, and at some point, these will run	Thank you for your comments. The committee can only evaluate a treatment based on the evidence available at the time of the committee meeting. The committee considered data from the latest technical briefing published by UKHSA in March 2023. This briefing showed that there were only around 3% of circulating variants (BA.2 and BA.5) that tix–cil may be effective against. The committee therefore concluded that there was no evidence that tix–cil would neutralise at least 97% of circulating variants as of March 2023. Please see section 3.12 of the final draft guidance for further details. The committee

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			out and then we will have to turn to the State for support, which we would not have had to do if we could have carried on working. My wife and I are not alone in the community of the unprotected shielding immunocompromised, where the relatively low cost of Evusheld would be more than made up for in direct tax income to the economy. Also none of the lost income to the economy of forcing the immunocompromised to continue shielding seems to take notice of the multiplier effect that those lost jobs, income and expenditure that has been lost to our economy through shielding. For example, in my business I worked many companies delivering value to them, and spent much more than I can whilst shielding with UK businesses, on holidays, eating out, etc. All the above cost benefit to the economy have been lost and needs to be factored in the cost effectiveness calculation.	acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. For the current single technology appraisal, the committee considered it could only make decisions based on the data available at the time of the committee meeting. Please see section 3.13 of the final draft guidance for further details. The committee considered that there is a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding, that had not been accounted for in the company's model. Please see section 3.17 of the final draft guidance for further details.

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84	Public (web comment)	Web commenter 7	• Are the recommendations sound and a suitable basis for guidance to the NHS? For the above reasons in the answers to question 1 and 2, the recommendations for guidance to the NHS, and indeed to the British economy, are not sound. The evaluation process used is not fit for purpose to use in a case like Covid-19, and the clinical and cost effectiveness interpretations of the narrow field of evidence are neither medically nor economically sound or complete. As a result, the recommendation to the NHS are not sound.	Thank you for your comments – please see the responses above.
85	Public (web comment)	Web commenter 7	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The population that Covid-19 impacts the greatest are the CEV disabled immunocompromised. For this group the effectiveness of the prophylactic vaccines that were rolled out through a fit for purpose rapid evaluation process is close to no existence, due to the fact that vaccines need a working immune system to produce the antibodies. When medical science caught up and AZ developed an effective prophylactic for the immunocompromised, Evusheld, that was delivered to people in the USA and 30+ other countries from December 2021, it was at this point or before that the same rapid evaluation process used for the immunocompetent vaccines should have been used for the disabled immunocompromised on Evusheld. This did not happen in the UK and the immunocompromised prophylactic, Evusheld, was forced by our government to go down a different, elongated, and not fit for purpose evaluation process. As a result, the disabled immunocompromised, and their loved ones, have been forced to shield for an additional 15 months plus more than others. I believe this to have been unlawful discrimination against a disabled group of people.	The committee acknowledged the need for a more flexible evaluation process. This is currently being developed by NICE. Further details of the proposed process are provided in the consultation document on NICE's website: COVID-19 technology appraisal recommendations: surveillance and rapid update process. Topics were selected in line with the NICE health technology evaluation topic selection manual.
86	Public (web comment)	Web commenter 8	• Has all of the relevant evidence been taken into account? I do not believe that the devastating impact on patients and their close family has been taken into account sufficiently. It is well past the point that the permanent damage done to shielders and their loved ones needs to be fully recognised and action taken immediately to release us from purgatory. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Thank you for your comments. Patient perspectives were considered alongside the evidence for effectiveness. Please see section 3.3 and 3.4

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			What cost can be put on releasing us from a life sentence in solitary confinement, which prevents us from being able to live rather than exist? I have paid several hundred thousand in taxes but now when we don't have access to funds. we are cast aside, the computer says NO. Tell my beautiful granddaughter that she doesn't matter. That we don't matter after 3 years in solitary confinement for no crime other than my partner having leukaemia.	of the final draft guidance.
87	Public (web comment)	Web commenter 8	• Are the recommendations sound and a suitable basis for guidance to the NHS? I really don't know.	Thank you for your comment.
88	Public (web comment)	Web commenter 8	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? For people like my partner and I, we will never have a post Covid era. We, like millions of others, are stuck in permanent exclusion from life. A life sentence in solitary with no prospect of a release date. It is not just the extremely clinically vulnerable who stay shut away from real life, it is all of their friends and family. [redacted] oldest daughter has a beautiful daughter, born on [redacted], who we have only seen in photos or video calls. She lives in the South West of England, but we can't smell her hair, hold her hand, throw her up and catch her in fits of giggles. Knowing what you are prevented from doing because our governments have decided that we and our granddaughter just don't matter, is absolute torture. We were shut up, locked away and they have lost the key and have no interest in buying a key to release us from this existing Hell, for it can't be called a living Hell. Could any one of the politicians look that beautiful little girl in the face and say "You don't matter, your need to know where you come from, who your grandparents are, doesn't matter. For her and her parents' privacy I can't share her photo, but I can tell you that every person who has seen the sheer joy in that little girl's eyes will tell you, she is a girl who deserves everything the world can provide. The politicians all stood up and justified lock down as Protecting the NHS and protecting the vulnerable. Both in Westminster and Holyrood, they got their hours of faked concern in front of the world's cameras, when we all know it was fake. Meanwhile they ruined lives not then begun without a second of consideration. How has their plan worked out? The NHS is, across all parts of the UK, broken beyond repair. The vulnerable are forgotten, left to rot in torture with their nearest if not always dearest, amputated from life as they knew it. I am neurodiverse and heartbroken, I live with the searing heartachingly sad knowledge that my man, the	Thank you for your comments. The committee noted there was an unmet need for an effective prophylactic treatment. However, it considered that tix-cil could not meet this need as there is no evidence it works against 97% of circulating variants at the time guidance was produced. Please see section 3.3, 3.12 and 3.24 of the final draft guidance for further details.

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			person I love more than anyone I have ever known, is in decline, his spirit is broken, he has given up any hope of being alive. He exists. He committed no crime but together with myself, his daughters and his beautiful granddaughter, we are all serving a life sentence in solitary from each other, never mind all the other things we could be doing. Were he a criminal it would be a breach of law in every country in the world to be treated this way. I doubt even North Korea would imprison a man's spirit in this way. We cannot and will not remain silent any longer. This is abuse of the worst kind. I returned home from a work trip, having worn a mask, sanitised throughout, just 2 weeks ago, desperate to see [redacted], hug and kiss him. But I couldn't, I left the train, walked to the car, wearing a mask, he was wearing his mask, exhausted from a drive of 20 minutes, we passed each other with barely a look. drove home with the windows down on a chilly late evening in February. Little was said. Why, because hugs, kisses and excited sharing has to wait until I know it is safe. It became clear the following day that I had contracted a very nasty virus, most likely Influenza A. So my quarantine continues, I am still very unwell, with no GP able to tell me when it will be safe to escape from my bedroom. As I type this, the evening before his birthday, [redacted] has just put a flask of tea and a chocolate biscuit outside the door, although I only asked for tea, he showed his love for me in the only way he can until my quarantine is over, a chocolate biscuit. If anyone thinks that what I have shared is acceptable, please ask them to contact me and explain why they think it is fine for us to "just wait, be patient". We have had enough, it is cruel beyond measure to expect anyone to live like this, when you have in your hands the means to release us all. It may not be perfect but 32 other countries have enabled their citizens to have the opportunity to live. I fail to see why this cannot be provided for us.	

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**AstraZeneca**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments
1	**AstraZeneca consider that Evusheld should be positioned in a subgroup of its licensed indication where the highest unmet need exists** In response to consultation, AstraZeneca are seeking a recommendation for a specific target population within Evusheld's marketing authorisation. The target population would be for: Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and: • are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, with high-risk reflecting groups A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the independent advisory group report (1), or • for whom COVID-19 vaccination is not recommended • where Evusheld displays neutralisation activity against a threshold of circulating variants ***Defining the high-risk population*** AstraZeneca agrees with the committee's view that the updated independent advisory group report is appropriate for stratifying the need for preventative treatment, and that groups A1 and A2 represent a highest risk subset among those at the highest risk of developing severe complications from COVID-19. Further to this, within group B of the independent advisory group report, there is a subset of patients who do not achieve a serological response to vaccination determined through serological testing, and these patients are also at high-risk of poor outcomes if contracting COVID-19. These patients would also be considered of equally high-risk of poor outcomes, as the A1 and A2 cohort defined in the independent advisory group report. The company is therefore seeking a recommendation in this highest risk of the high-risk population, that is patients in A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the independent advisory group report.(1) By targeting patients at highest risk, AstraZeneca is ensuring that Evusheld is available to patients with the highest unmet need, who will benefit most from treatment, while also ensuring that Evusheld represents a cost-effective use of NHS resources. ***Recommend Evusheld where there is evidence of neutralisation activity against a threshold of circulating variants.*** A robust, rapid and agile decision-making framework is required in order to ensure that NICE can make responsible decisions for COVID-19 prophylactic treatments given the evolving landscape with respect to emerging variants. The need for a robust decision

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	making framework is also recognised by NICE in response to the publication of the draft recommendations for this appraisal, and NICE has announced the development of a new review process to update its recommendations on the clinical and cost-effectiveness of COVID-19 treatments.(2) Further to this, academics, clinicians and patient groups have also reinforced the need for a robust decision making-framework in their responses to the draft negative consultation (see Section 11 for further details). Although it is reassuring to see that NICE is committed to developing an updated decision-making process, and NICE has announced a public consultation on these new processes from the 3rd of April; the appraisal process for Evusheld is currently ongoing. Therefore, there is a need for NICE to adopt an appropriate framework for decision making at the next committee meeting and ahead of the closure of the public consultation. In addition, as outlined in Section 5, AstraZeneca believe that the process adopted by NICE at this present time for this appraisal is not appropriate, highlighting the need for developing a process which can support responsible decision making immediately. In response to this, AstraZeneca has laid out the company's preferred approach to decision making. In summary this process looks to internationally recognised Regulatory Agencies to inform how to best evaluate the clinical appropriateness on the use of Evusheld at any given moment in time with respect to current and future circulating variants. For example, whilst the FDA temporarily suspended the emergency authorisation of Evusheld due to the high proportion of circulating variants to which Evusheld does not neutralise, it has stated that it will reconsider reinstating authorisation of Evusheld if the national prevalence of resistant variants decreases to 90% or less.(3) A signal regarding thresholds is not available from the MHRA; however the FDA are a well-established and robust decision making body; therefore it is appropriate to reference the FDA when determining an appropriate decision making process for the future, until such point the MHRA issue guidance. AstraZeneca would therefore propose that by way of process, NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants. A full discussion of AstraZeneca's preferred decision-making framework is available in Section 11 with relevant economic results available in Section 12 and Appendix 4 – Full model results and scenarios for varying levels of neutralising ability. However, it should be noted that the proposed process put forward by AstraZeneca supports agile and responsible decision making in the current environment and is aligned with the approach of trusted regulators.
2	**The dosing assumptions have been updated to reflect a single dose of Evusheld.** The ACD document raises concerns regarding the Company's economic model applying two doses of Evusheld as opposed to single dose. The Committee also concluded that it would be more appropriate to use a single dose in the economic analysis.

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	"so the committee concluded that the economic analysis should include a single dose of tix–cil only" AstraZeneca recognise that the Summary of Product Characteristics (SmPC) recommends a specific dosing criterion, and this criterion does not explicitly prohibit any subsequent dosing or the application of a second dose. However, for the purpose of decision making today, and to align with NICE regarding preferred assumptions for the economic model, the economic modelling has been updated to apply a single dose Evusheld.
3	**The patient access scheme (PAS) will be realised by the NHS.** AstraZeneca recognises the committee expressed concern relating to the PAS and specifically commented *"commissioning experts' preference for administering tix–cil in primary care would mean that the benefit of the confidential patient access scheme would not be realised by all parts of the NHS".* The target population for this single technology appraisal (STA) reflects patients who are of the highest risk and therefore this group of patients would be expected to attend hospital regularly by way of routine outpatient visits, to manage their underlying health condition. Alternatively, patients may regularly attend secondary care led community services again with the aim of managing their underlying condition. Given the regular contact between this group of patients and NHS services via routine appointments, it is expected that Evusheld would be administered in this secondary care, or secondary care led community setting, and prescribed upon specialist advice. Furthermore, given the need to make a determination as to the appropriateness to prescribe and administer Evusheld with respect to the patients' eligibility and neutralisation of currently circulating variants, it would be more appropriate to restrict prescribing to secondary care or a secondary care led community service. Therefore, Evusheld would be made available at the PAS price and therefore the benefits realised by the NHS in practice. We have communicated this with NHS England and PASLU, and on this basis, the appropriateness of a PAS for Evusheld has already been assessed and approved by NHS England.
4	**AstraZeneca comments on the *in vitro* data advisory group (IVAG) report and interpretation of neutralisation data.** The ACD acknowledges that given the evolving and changing landscape, variants of COVID-19 that are currently circulating may be different to the prevailing variants when the relevant clinical data (i.e. pivotal trials or real-world evidence) was submitted. *"Although clinical studies of tixagevimab plus cilgavimab suggest a reduction in COVID-19 infection compared with no preventative treatment, these studies were done early in the pandemic when different variants of the COVID-19 virus were circulating."*

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	NICE also go on to suggest that *in vitro* data may provide an insight into how medicines may perform against currently circulating variants, *"In vitro neutralisation assays can be used to assess if treatments neutralise new variants, and therefore if they retain clinical effectiveness over time as the virus evolves. An advantage of in vitro evidence is that it can be generated much faster than it would take to do clinical trials."* However NICE also recognise the need for a process to interpret these data, and that the Committees' experience of interpreting such data are limited. Therefore, an advisory panel (IVAG) was established to support the understanding of the *in vitro* evidence. *"But NICE's technology appraisal committees are not used to interpreting and appraising in vitro data. Because of this, NICE commissioned an in vitro data expert advisory group made up of experts in infectious disease, virology, vaccine epidemiology, immunology, and pharmacology. They developed a decision framework to link the in vitro neutralisation data to clinical outcomes, and their report… provided guidance on interpreting in vitro evidence".* AstraZeneca recognise the need for a robust approach in terms of interpreting the *in vitro* data and accept the following conclusions from the IVAG review process. • If the neutralisation activity of a medicine is the same as the previous variants, then similar efficacy can be assumed. • Loss of neutralisation to the current circulating variants does not mean that neutralisation cannot be recovered for future emerging variants. • It is not possible to predict the future with certainty. AstraZeneca also note that the IVAG concluded that if the *in vitro* data reported no evidence of neutralisation, this would imply no efficacy for the treatment against the variant. The company are aware of the challenges and difficulties in interpreting *in vitro* data and therefore accept that in the absence of evidence of clinical effectiveness despite no neutralisation, then for the purpose of decision making today, that it's reasonable to assume that total loss of neutralisation means no clinical effectiveness. (4) However, AstraZeneca would also like to comment that in the event that real world evidence emerges that demonstrates clinical effect in the absence of neutralisation against circulating variants then this data should be factored into decision making. Further to this, AstraZeneca would like to highlight that monoclonal antibodies may have a range of additional functions not directly measured by in-vitro neutralization assays. This may include a range of immunomodulatory functions which may provide protection beyond neutralisation. We do however fully appreciate the challenge that NICE faces in looking to quantify clinical efficacy in such a rapidly evolving environment. However, if such data becomes available and there is evidence of benefit through mechanisms which are beyond neutralisation, then this evidence should also be factored into decision making. It is also worth noting that benefits beyond neutralisation have not been taken

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	into account in the economic modelling and therefore the case put forward by AstraZeneca could be considered to be conservative. AstraZeneca also have additional comments in relation to the level at which neutralisation infers effectiveness. In general, neutralisation ability is assumed to be retained when an IC50 is <10,000 ng/ml and this is a widely accepted threshold for neutralisation activity. (5) Further to this, measurable IC50 values below 10,000 ng/mL implies that the treatment binds to the receptor binding domain of the SARS-CoV-2 Spike Protein which would infer a clinical effect and therefore supports the conclusion that IC50 <10,000 ng/ml is an acceptable threshold for evidence of neutralisation. (6) Given the above AstraZeneca propose that an IC50 of <10,000 ng/ml is utilised by NICE to determine activity against any particular circulating variant and that an IC50 of <10,000 ng/ml would also translate into clinical effect. This position is supported by a recent systematic literature review(7) which provided a summary of the real-world clinical evidence for Evusheld. This review included studies which were conducted in variants which reflected neutralisation across a range of neutralization values, and these studies also reported Evusheld treatment has led to statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation. Therefore, it is appropriate to conclude that an IC50 of <10,000 ng/ml infers clinical effect. A top-line summary of these RWE papers is available in Appendix 1 – Summary of RWE studiesAppendix 1 – Summary of RWE studies. Further to this, in terms of changes in neutralisation, there is evidence to suggest that even if there were a decrease in neutralisation for a new variant in relation to older variants, the loss of efficacy would not be diminished in cases of severe COVID-19. This evidence also supports the Company's position of presenting an absolute threshold of effectiveness (IC50 of <10,000 ng/ml) as opposed to focussing on changes in neutralisation.(8)
5	**Conclusions made by NICE in the ACD document are contradictory versus IVAG, or previous NICE advice, and a robust, rapid and agile decision-making process is required.** As part of the ACD, NICE make statements which are contradictory to either the conclusions of IVAG (or previous NICE advice). Examples of which are as follows. ***Neutralisation activity against currently circulating variants is the most useful estimate of effect against future variants.*** *"The effectiveness of tixagevimab plus cilgavimab (tix–cil) over the appropriate time period of the future 6 months would be best indicated by neutralisation potential against currently dominant circulating variants".* This statement is not only incompatible with the unpredictable and evolving nature of the COVID-19 landscape. It also contradicts conclusions drawn by IVAG, e.g., regarding difficulties to predict viral evolution and the shortcomings of *in vitro* neutralisation alone to make decisions. This statement also does not recognise sotrovimab in ID4038(9,10) where sotrovimab demonstrated limited or loss of neutralisation activity, such as the case for BA.2 only to weakly recover and then obtain a positive recommendation from NICE.

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	Another notable example is that of Ronapreve (casirivimab and imdevimab) where in December 2021 it was found that BA.1 fully escaped *in vitro* with no neutralisation at all for the imdevimab component of the medicine. However it was later found that the imdevimab component was able to neutralise omicron BA.2, BA.2.12.2, BA.4 and BA.5 variants.(5) ***NICE suggest that the relevant time frame for the appraisal is January and the next 6 months.*** *"But the committee concluded that tix–cil should not be recommended because it is unlikely to be effective against most of the relevant variants in the appropriate time period for this evaluation (January 2023 and the 6 months after)."* AstraZeneca do not agree that it is appropriate to assume a static 6-month window as a timeframe for the appraisal for a number of reasons: A 6-month time period contradicts statements from the IVAG, where, although IVAG suggest major antigenic changes tend to happen every 6-months, changes in variants may occur every 1-2 months. Further to this, the IVAG highlight that 1-2 months is a relevant time period for predicting change in circulating variants, and this point is also recognised on public slide deck (slide 18) for the second ACM for ID4038 which stated *"Predicting change in currently circulating variants limited only to the 'near future' (**1-2 months**)"*(11). Therefore, it would be inaccurate to imply that variants may remain unchanged for 6 months and this is not compatible with the conclusions from the IVAG who suggest that changes in variants can only be predicted for a much shorter time period. In addition, in terms of dominant variants, it is noted that Omicron variant B1.1.529 was dominant for a very short period of time (approximately one month) earlier in the pandemic only to be replaced by other variants as the pandemic progressed (see slide 4 of the public slide deck for the ACM for this appraisal). IVAG also reference that if a variant has a 25% growth advantage and reaches 10% of total samples, then the variant may become dominant. The IVAG do not reference a timescale for this change and therefore it is not time bound. The above are further examples of the shifting and evolving COVID-19 landscape and that it is not appropriate to apply fixed time periods (such as 6-months) to an evolving disease area where there are frequent changes. These examples also highlight the need for continuous surveillance of COVID-19 variants given the rate of change and to inform robust decision making. In the sotrovimab appraisal, NICE initially rejected sotrovimab in the draft guidance(10) and suggested it would not be effective against current variants and most likely would not be effective in the future. However, 3 months later, in the final guidance(9), NICE have revised their decision and recommended sotrovimab for use. Therefore, assuming a 6-month window for the appraisal, where there will be no changes in variants or

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	neutralisation activity, is not consistent with the decision making made by NICE who arrived at two different decisions regarding sotrovimab only 3 months apart. Finally, as referenced by clinical experts in the ACD meeting, even after a decision by the committee, it is likely to take a few months before a medicine is wholly adopted and in use. Therefore, NICE's time frame of 6 months is likely to be an underestimate of the length of time of the appraisal especially if considering a 3-month window for implementation which is assumed for the ongoing MTA. ***A robust, rapid and agile framework for decision making is required.*** It is clear that NICE recognise the need for a process in order to ensure responsible decision making for prophylactic treatments for COVID-19. This is evidenced by NICE commissioning the IVAG to make specific recommendations regarding the interpretation of *in vitro* data. AstraZeneca are also aware that NICE has announced the development of a new review process to update the recommendations on the clinical and cost-effectiveness of COVID-19 treatments, to ensure rapid patient access to potentially effective treatments with emerging evidence against particular variants.(2) However, it is also clear is that the current decision-making process is fundamentally flawed, as for example, NICE are currently applying process or making statements which contradict conclusions made by IVAG or NICE's own advice (see above in Section 5). As such, Section 11 of this response proposes a revised framework for decision making which is underpinned by the outcomes of the IVAG but enables NICE to translate these into practice to support it in making responsible decisions for COVID-19 medicines. This process captures the dynamic nature of the COVID-19 landscape and respective uncertainties with regards to the evidence. In addition, as noted in the ACD and as made unmistakably clear by the patient expert testimonies, there is an urgent and unmet need for preventative therapies. Therefore, the process put forward by AstraZeneca also supports NICE in reaching responsible and robust conclusions to enable access to effective prophylactic therapies for high-risk patients.
6	***The sources applied in the economic model are appropriate to reflect the target positioning for Evusheld.*** In the ACD, NICE have noted there is uncertainty around the extent to which the inputs in the economic modelling reflected the target population. *"The external assessment group (EAG) noted that it was not clear from the company submission how the population that is eligible for tix–cil should be defined. It added that many of the inputs in the economic analysis were selected to reflect particular groups, and do not represent the eligible population as a whole, nor do they capture the heterogeneity within the eligible population".* Following the committee meeting, AstraZeneca has clarified that the target population relevant to this appraisal are groups A1, A2 and those in group B without serological

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response (see Section 1). These patients represent the highest risk subset among those at the highest risk of developing severe complications from COVID-19.

To confirm the robustness of the model inputs with respect to the target population, the eligible population and heterogeneity table from the NICE committee meeting slides (slide 26) has been reproduced below and discusses why the company source is appropriate. Where possible, data specific to the target population has been included to ensure the economic evaluation accurately represents the population in scope. However due to the recentness of COVID-19, there is a paucity of data in the specific target population and therefore where this data is not available, AstraZeneca has taken a conservative approach and used data from a less immunocompromised or immunocompetent population. AstraZeneca has also provided additional scenario analyses related to infection risk to further quantify the uncertainty in the model inputs and the impact on outcomes (see Section 12).

Table 1. Model inputs and eligible population

Model parameter	Company's source	Population	IAG cohorts	Justification
Baseline characteristics (Used to estimate mortality and utility)	PROVENT trial	Adults at increased risk of inadequate response to vaccination or at increased risk of SARS-CoV-2 infection	A1, A2, B, C and uncategorised	The baseline characteristics, sourced from the PROVENT trial, included individuals that were immunocompromised or had an inadequate immune response to a COVID-19 vaccine. Baseline characteristics used in the model only include age, percentage of males and weight, these characteristics are not specifically linked to defining the IAG cohorts however would be expected to have minimal impact if the population used by the model were broader than the scoped population. Results of the deterministic sensitivity analysis for both the Company and EAG base case showed that when age, percentage male and weight were varied using the standard error, there was not a substantial impact on the ICER.
Risk of COVID-19 infection (without Evusheld)	UK government	General population of England between August 2021 and August 2022	Mostly uncategorised	The risk of infection was taken from the general population risk of COVID-19 without Evusheld. This risk was used in the economic model for the cohort that had not received Evusheld. Since this risk was taken from a mostly uncategorised risk, it can be assumed that in practice, the risk of COVID-19 to cohorts IAG A1, A2 and seronegative B patients, would be higher. Therefore, the company

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					would like to highlight that this is a conservative estimate of the risk of COVID-19 in the target population. Furthermore, scenario analysis has been run including varying the infection risk by ± 20% and showed limited impact on the ICER (See Table 3: Updated EAG and company scenario analysis post committee using a 10% threshold).
	Risk of hospitalisation for COVID-19 (without Evusheld)	Shields et al. 2022	Patients with primary and secondary immunodeficiency* in the UK, during Omicron wave (up to April 2022). Subgroup that was not treated in COVID-19 Medicine Delivery Units (CMDUs). *Receiving immunoglobulin replacement therapy or had a serum IgG concentration less than 4g/L and were receiving regular antibiotic prophylaxis to prevent infections.	A2	The risk of hospitalisation is based on Shields et al. (2022) which assess the hospitalisation and mortality risk for immunodeficient individuals (IAG group 2). This population is deemed appropriate since the study was conducted on individuals with primary or secondary immunodeficiency, and would therefore, not mount a sufficient response to vaccination. Whilst the company acknowledges that this population contains individuals with both more severe and less severe immunodeficiency, this source was deemed most appropriate to capture the target population. This source is also most representative of the optimised population in which AstraZeneca seeks reimbursement in i.e. those in A1, A2 and seronegative B patients. These patients represent the highest risk of the high-risk population.
	Direct utility gain for people receiving Evusheld	Gallop et al. 2022, commissioned by company	Immunocompromised individuals	Majority A2	A study by Gallop et al. 2022 (commissioned by AstraZeneca) determined the direct utility gain for individuals receiving Evusheld. The study was conducted in a population that were largely categorised into the IAG cohort A2. The utility gain could be even greater if it were to include the estimates of QOL impact for the more vulnerable A1 population, who would likely exhibit shielding behaviours. The utility gain, of 0.098, has only been applied to 82% of the model

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Based on the evidence collected in the general population, this utility gain may be considered conservative since:
• An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states in the general population, and
• An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behaviour health states in the general population (21)</td></tr>
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Finally, a wider overview of the economic model inputs and justification is available in Appendix 2 – Summary of model inputs and relevance to target population.</td></tr>
<tr><td>7</td><td>The direct utility gain presented in the evidence and company model appropriately captures the quality-of-life impact for patients treated with Evusheld.

NICE comment on the challenges of capturing the most appropriate direct utility gain for patients treated with Evusheld given the interaction of quality of life with other variables such as infection risk, efficacy of the medicine and pre-existing behaviours. The committee noted uncertainty around whether a direct utility gain should be applied and if so, what size gain is most appropriate and what proportion of people this should apply to. Specific comments from the ACD document are as follows:

“The committee noted that there were additional complexities that needed further attention in addition to the original scope, such as the relationship between risk of infection, shielding behaviours and improvements in health-related quality of life.”

“The committee acknowledged the challenges in relating efficacy of a preventative treatment to reduction in risk of infection, given the importance of behavioural changes leading to increased quality of life. This was made harder by a lack of health-related quality of life data from the trials”.

“The committee considered that there is a trade-off between the extent of shielding and the utility gain from stopping or reducing this, and the level of risk reduction that tix–cil will deliver before and after a decision to stop or reduce shielding. For example, if people’s risk of infection reduces such that they interact more with others, the risk of infection would then increase.”</td></tr>
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	While the company appreciates the uncertainty in capturing the impact of individual perceptions of risk on shielding behaviour, the utility gain of 0.098 derived from immunocompromised high-risk patients reported in the utility study (Gallop et al. 2022) is the best available evidence to date to quantify the utility gain associated with the introduction of Evusheld in high-risk patients. [redacted] It is noted that the PROVENT trial did not collect quality of life data and therefore no trial data are available to evaluate this potential gain in utility. However, it should be noted that even if quality of life data were collected in PROVENT, given the triple blind nature of PROVENT, it would be unlikely that the trial could collect such data given that patients in both the treatment arm (Evusheld) and the comparator (placebo) would not know if they were receiving active treatment. As the utility gain is dependent on being aware of taking Evusheld, and the benefits this could have, if both sets of patients believe they could be taking the study drug, this would not allow differences in quality of life between Evusheld and placebo to be established. Despite this, it was well recognised at the committee meeting that there is an urgent unmet need for a prophylactic therapy to reduce the risk of COVID-19 infection for those at high-risk. The quality-of-life benefit of an effective treatment was also well established. “Anxiety and fear would be alleviated, and physical health would also improve”. However, it was also noted that despite the availability of an effective prophylactic treatment that did not imply that patients who are at high-risk would not take some precautions, and some modifications would remain in place. “[I would] still continue to take measures to protect myself, such as wearing filtered masks in public places and generally risk assess most situations.”

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	Gallop et al. (2022) elicited utility values from an immunocompromised high-risk population, of which 92% were partially or fully shielding. Therefore, as these patients are reflective of the target population for this submission, it is likely that these patients would share the same views as those testimonies heard at the NICE committee, and when participating in the utility valuation exercises be aware that taking a prophylaxis would not mean all restrictions are lifted. This is also borne out by patient quotes available in Gallop et al. (2022). "I would probably go to the theatre because I miss that like mad, but I would probably be aware of seating and sit on the end where I wasn't surrounded by people". "It would provide massive relief, relief at being able to do more and just be happier, more relaxed, I would still be a bit cautious, but you would be happier because it has relaxed you a bit". Therefore, whilst we acknowledge there is complexity regarding the quality-of-life benefit, as the utility exercise was undertaken in a high-risk immunocompromised population, this complexity is captured in the values derived in Gallop et al. 2022 and applied in the economic model. The NICE ACD also suggest that quality of life benefits may not be realised if patients are aware that the medicine may not be effective against all circulating variants. *"There was the potential for some people to resume normal activities and possibly increase their risk of infection; or if they had limited trust in the treatment's effectiveness, they may not realise any quality of life benefit from the ability to reduce shielding behaviour".* *It added that the relationship between these factors was not reflected in the company's analysis, and that no data had been presented on behavioural change. The committee noted the considerable uncertainty and considered this when interpreting the clinical evidence."* This specific issue has been investigated in the Gallop et al. 2022 utility study via the question and response: "Participants were also asked if the change in their behaviour would depend on the variant of COVID-19 that was most common at the time (i.e. if there was a new variant that the treatment was not effective against); half (N=20) of the participants felt that it would and they would return to their pre-treatment behaviour" (Gallop et al, 2022) This demonstrates that 50% of patients would still feel a psychosocial benefit and cautiously modify their behaviour despite the knowledge that prophylaxis would not be effective against the most dominant variant. In order to explore the impact that this may have on the economic model a scenario has been presented where the quality-of-life benefit is only applied to 50% of the patients who receive Evusheld with results available in Section 12. This scenario also took into account patients who were subsequently

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	infected with COVID-19, experiencing a further reduction in their quality of life whereby the duration of direct utility gain for those infected was reduced by 50% (i.e. scenario EA2 in Appendix 3 **– Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committee**). Further, this analysis may represent an upper bound for the ICER given that patient testimonies communicated in the ACM suggested that there would be a quality-of-life benefit of prophylaxis treatment even if Evusheld did not neutralise all variants, as patients would not be irresponsible in managing their risk and take the necessary precautions to provide them with those layers of protection. The ACD document also discusses that an effective prophylactic may also encourage patients to interact more with others and hence increase their risk of infection. However, it can be seen from the patient quotes above that patients will still take necessary precautions and that patients are still aware of their underlying conditions. Therefore, it would not be expected that the underlying risk of infection would increase, or at least not materially increase, given that patients are well versed and experienced in managing their own condition. It is important for NICE to recognise that the population of patients who are expected to receive treatment with Evusheld, have lived and continue to live with severe immunosuppressive conditions and as such, this population of individuals are well experienced in how to reduce their overall risk of infection in their day-to-day lives. The utility value applied in the model is based on data elicited from patients who tend to underestimate quality of life impacts when compared to the general population and therefore represents a conservative estimate. This was observed in Gallop et al. 2022 whereby the utility gain based on evidence collected in the general population was greater compared to the immunocompromised high-risk population: • An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states, and • An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behaviour health states Therefore, the utility value applied in the model based on patient responses of 0.098 may potentially be conservative. Finally, families and carers also experience anxiety around bringing COVID-19 home causing them to modify behaviour or experience guilt if they cannot afford to do so. “As a carer I have had to remain resolutely covid free. This has meant that since mask wearing is no longer required, I have had to give up my job as a massage therapist and now have no income and am not entitled to benefits. I’m very worried.”

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	The psychosocial impact of this has not been considered in the economic analysis and is therefore conservative. As per the NICE reference case, the perspective for outcomes captured in an economic evaluation should include "all direct health effects, whether for patients or, when relevant, carers". The inclusion of carer disutility into the estimation of cost-effectiveness has been accepted by NICE previously in appraisals for vutrisiran [TA868] and patisiran [HST10]. In reality, the benefit of a prophylactic therapy also extends to those who live with and care for the patient. As such there are potentially significant uncaptured benefits in this particular appraisal. To summarise, the patient testimonies recognise that there is an important quality of life benefit for patients treated with prophylaxis (extending to carers too) and it is imperative that this is included and in the economic model. Whilst we acknowledge the complexity in the interactions between quality-of-life, effectiveness of treatment, and infection, the approach adopted by the Company is evidence based and robust, potentially conservative and uses the best available evidence.
8	**The administration cost applied in the model should align to the cost used by NHS England.** The NICE ACD explores which administration cost is most appropriate to apply in the model and suggests that the company estimate of £41 is not reflective of the administration burden and preferred the EAG's estimate of £410. Specifically, the ACD states *"The committee considered that there was a substantial gap between company and CMDU estimates of administration cost but concluded that the more conservative estimate using the CMDU costs was more appropriate, given the uncertainty about how tix–cil would be delivered."* AstraZeneca do not believe that applying a cost of £410 is appropriate given that CMDUs are an acute service in which a patient needs to quickly attend a local community centre to receive timely treatment for COVID-19 infection; typically, within 5 days. Therefore, there needs to be multiple centres requiring significant NHS resource and co-ordination beyond the existing infrastructure to facilitate this service. Also, the company maintains since the target populations of A1, A2 and B (who do not have serological response to vaccination), are at greatest risk and have primary or secondary immunodeficiencies, Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services. This is in line with the advice of an integrated care system commissioning expert, as such CMDU costs would not be appropriate to use in the modelling. AstraZeneca also note that a revised budget impact test was received from NICE/NHSE in which NHSE has reduced the administration cost from £410 to £216. On this basis, whilst we believe this is still likely to overestimate the costs, NICE and the EAG should update the costs to align with those used by NHSE.

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9	**The hospitalisation rate of 2.8% from Patel et al is not appropriate to use in the economic modelling.** The ACD notes that the risk of hospitalisation from Patel et al. 2022(14), should be used in the economic modelling, and also references that Patel et al. is a preferred source in the ongoing MTA for therapeutics for people treated with COVID-19 which includes Evusheld.(15) Specifically the ACD notes *"The committee preferred to assume a rate of hospitalisation closer to Patel et al. but noted that hospitalisation rate would be dependent on the risk group under consideration".* However, it should be recognised that the target population for Evusheld in the MTA is different, and not the same level of high-risk as the population included within scope of this current STA where Evusheld is assessed as a prophylactic treatment. The population included in Patel et al. closely aligned with the high-risk population as defined by the McInnes report, a report which identified "highest risk clinical subgroups upon community infection with SARS-CoV-2". (1) However, it should be emphasised that the patient group included within the Evusheld STA is narrower in comparison and at significantly greater risk. These patients could be described as "the highest risk of the high risk" and reflect groups A1, A2 and B (who do not have serological response to vaccination) from the independent advisory group report. Therefore, it is not appropriate to use sources such as Patel et al. for the Evusheld STA due to differences in the underlying risk of the population and differences in the respective decision problems. Further to this, there are substantial differences between the 2.8% hospitalisation rate estimated by Patel et al and rates identified in certain subgroups of the McInnes population. This further supports that it would not be appropriate to use data from Patel et al to inform the hospitalisation rate for the highest risk patients, with some hospitalisation rates as high as >30%(16): • **Parry et al. 2022**(17) (chronic lymphocytic leucaemia): 7.7% • **Gleeson et al. 2022**(18) (immunosuppressed kidney transplant recipients): 20.8% • **Bradwell et al. 2022**(19) (haematological malignancy): 26.4% • **Trindade et al. 2022**(20) (lung transplants): 17.9% • **Anjan et al. 2022**(16) (solid organ transplants): 31.9% Further to the above, Lee et al. 2023 (21) conducted a study assessing the association of SARS-CoV-2 spike protein antibody vaccine response with infection severity in cancer patients. The study reported that patients who have cancer are more likely to report an undetectable anti-S antibody response than the general population. In addition, the study also concluded that within the cancer cohort, patients who had an undetectable antibody response were at much greater risk of SARS-CoV-2–related hospitalisation (odd ratio,

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	6.48; 95% CI, 3.31-12.67; P < .001) than individuals who had a positive antibody response. Lee et al also reported that patients with leukemia or lymphoma had the highest rate of undetectable antibody response and the lowest antibody titres, which implies that leukemia or lymphoma patients are at highest risk of adverse outcomes from COVID-19 such as hospitalisation when compared to other cancer types. AstraZeneca acknowledge it is difficult to directly compare hospitalisation rates from Patel et al with the odds ratios reported in Lee et al. However, the data from Lee et al do support an inference that cancer patients are at a higher risk of hospitalisation, and therefore applying a hospitalisation risk of 2.8% from Patel et al, to a "highest risk of the high risk" group as per the company's positioning, is infeasibly low and not reflective of the available evidence. Finally, Patel et al notes that a surprisingly large proportion (between 39.2%% and 45.7%) of patients had no evidence of having the highest risk conditions where high-risk conditions were identified using SNOMED and ICD-10 codes from patient history. Although the Patel al paper does go on to provide additional context and clarity regarding these figures, given that the target population considered in this appraisal for Evusheld are the highest risk of the high risk, it would not be appropriate to use a paper where a substantial proportion of patients failed to meet a highest risk criterion. Therefore, it is not appropriate to use a value of 2.8% from Patel et al to quantify the risk of hospitalisation in the economic model.
10	**The company and EAG base cases have been updated following the comments from the committee.** ***Dosing*** As referenced in Section 2 the economic modelling is aligned to a 6-month single dose treatment duration. In the economic model this update captures the treatment and administration cost reflecting one single dose of Evusheld, reducing the SoC infection rate from a 12 month to 6-month rate, halving treatment-related adverse events to account for a single dose and applying the utility gain associated with Evusheld to only 6 months of protection being provided. All efficacy sources used in the model are based on one dose with a median follow up less than or equal to 6 months, therefore efficacy data were not adjusted. ***Direct Utility*** The original company base case applies a utility gain of 0.098 to 100% of the population administered Evusheld. The company accept the EAG's amendment to apply the utility gain to 82% of the population to reflect the proportion of patients who are either fully or partially shielding according to the ONS survey.(22) ***Administration*** As noted under Section 8, AstraZeneca would like to acknowledge that the administration cost of £410, based on the CDMU in the EAG base case is unsuitable to use as a proxy since the value is too high and not appropriate to include in the model. The company and EAG base case should be guided by the NHSE cost of £216.

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	Infection The company would like to highlight that the IAG cohorts A1, A2 and B (who do not have serological response to vaccination) represent the 'highest risk of the high-risk population' and a population who are severely immunocompromised. Therefore, the infection rate of the general population is not representative of the target population who will likely remain susceptible to serious infection despite increasing vaccination status. However, since the target population is severely immunocompromised, using data based on general population statistics is considered a conservative estimate for people at the highest risk of poor COVID-19 outcomes or unsuitable to vaccination; particularly since the majority of the general population have either had numerous doses of COVID-19 vaccines in which they do amount an immune response to, or have acquired natural immunity through COVID-19 infection. Based on expert clinical feedback, this population are at a higher risk of infection and severe outcomes compared to the general population, even with shielding methods in place. In addition, the data available for the general population is to date the best available data to populate the economic model since no data specific to the population has been collected. Finally, uncertainty in the underlying risk of infection is explored through scenario analyses (see Section 12). ***Hospitalisation*** The company would like to highlight that the hospitalisation rates captured in Shields et al. are representative of the population in scope of this submission. It is unclear why NICE feel these are over-estimated given the methodology of the study and external evidence to support the conclusions. Also as discussed under Section 9, the hospitalisation rate from Patel et al. 2022 is not suitable to include in the economic modelling and does not address this decision problem, therefore the data from Shields et al. is the most generalisable source of the data available. ***Long COVID*** The company acknowledge the committee's amendment to use the management cost of long COVID of £2,267. In addition, the company accept the use of utility waning in the base case, however, would like to acknowledge that there is no evidence to support this assumption. ***Subgroup analysis*** It is also noted that the NICE committee requested a scenario which focussed on the individual groups in the target positioning (i.e. A1, A2 and B without serological response). It is not possible to run these specific subgroup analyses given the available data. However, scenario analyses have been provided which change the underlying infection risk to proxy results in groups with a higher or lower risk of infection.
11	**A suggested framework for robust, agile, and responsible decision making that considers the substantial unmet need and evolving COVID-19 landscape.** **Context**

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	A robust, rapid and agile decision-making framework is required in order to ensure that NICE can make responsible decisions for COVID-19 prophylactic treatments given the evolving landscape with respect to emerging variants. The need for a robust decision making framework is also recognised by NICE in response to the publication of the draft recommendations for this appraisal, and NICE have announced the development of a new review process to update its recommendations on the clinical and cost-effectiveness of COVID-19 treatments.(2) The need for such a framework was reinforced by academics, clinicians and patient groups, who in response to the draft negative recommendation stated: *"NICE recognise that the virus is evolving faster than the evidence can be produced and their assessment process can be undertaken, so that they need to find a way of more rapidly assessing treatments for the immune vulnerable"* *"Evusheld was approved on the 17th of March 2022, and it took 11 months for this decision… We could have provided many months of protection. There is an overwhelming clinical need to give long acting antibodies to protect those who aren't protected from vaccines, because they are immuno-vulnerable. We should and can move much quicker"* *"We believe that Evusheld could have helped vulnerable people over the past year by supporting them to return to normal life, as it has in over 30 countries around the world; but that opportunity was wasted due to the failure to act quickly and decisively… It is clear that the current protracted NICE process is completely inappropriate and has left a huge number of people without protection and reassurance when they needed it most."* It is therefore reassuring to see that NICE recognises this and has announced that it will be developing a process to monitor real-world data and re-evaluate the medicines as needed against that data in a faster way than it currently does for other drugs, and that NICE will be able to respond quickly if evidence emerges that Evusheld or other existing treatments are effective against a particular variant. However, the appraisal process for Evusheld is ongoing, and whilst there will a public consultation issued by NICE on 3rd April on these new processes, there is a need for NICE to adopt an appropriate framework for decision making at the next committee meeting and ahead of the closure of the public consultation. **Position of global regulators and AstraZeneca's proposed process** Whilst the company recognises the challenges associated with the evolving landscape, it believes that in the absence of any of guidance or a signal from the MHRA, that NICE should look to other internationally recognised Regulatory Agencies to help inform how to best evaluate the clinical appropriateness on the use of Evusheld at any given moment in time with respect to current and future circulating variants. For example, whilst the FDA temporarily suspended the emergency authorisation of Evusheld due to the high proportion of circulating variants to which Evusheld does not neutralise, it has stated that it will reconsider reinstating authorisation of Evusheld if the national prevalence of resistant variants decreases to 90% or less.

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	The company would therefore propose that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants (please see Section 12 for cost-effectiveness analyses using different variant thresholds). We believe that NICE is in a position to do this; particularly since it was able to rapidly produce an ICER for decision making for sotrovimab in the recently published draft final guidance on the use of therapeutics for people with COVID-19 [ID4038]; despite sotrovimab having a significant reduction in neutralisation ability –against 58.3% of current circulating variants (BQ.1; IC50 = 1709 ng/ml; 51.3% prevalent; BA. 4/5; IC50 = 1055 ng/ml; 7.2% prevalent).(11,23,24) As a final consideration, the company maintains its position that Evusheld offers an important layer of protection against severe COVID-19 in those who continue to remain at the greatest risk due to their underlying health conditions, which severely reduces their ability to amount an immunological response to vaccination or immunity through prior infection. The value conferred by Evusheld, despite the currently reduced number of circulating variants to which it neutralises, has been and continues to be supported by patients across the UK, including those that have received Evusheld through the private clinical settings. Therefore, a process which establishes the clinical need and value for Evusheld through meeting a predetermined threshold of neutralisation against circulating variants (i.e. 10%) is appropriate, in line with internationally recognised Regulatory Agencies such as the FDA, and facilitates patient access to an effective treatment for a high risk and vulnerable population. **Proposed threshold for Evusheld prophylaxis versus COVID-19 treatments** AstraZeneca are proposing that NICE adopt the view of the FDA where Evusheld would be made available if there is evidence of neutralisation against 10% of variants (or conversely where there is no evidence against 90% of variants)(3). It is worth noting that the FDA withdrew the emergency use approval for Bebtolivimab in the treatment setting when the proportion of variants which it was not expected to neutralise reached 57% nationally and was >50% in all regions (but one) (25) However, despite this difference in thresholds between COVID-19 prophylactic and treatment applied by the FDA, AstraZeneca believe it is entirely reasonable to use a higher threshold (i.e. a larger proportion where there is no neutralising activity) for the prophylaxis setting. In the treatment indication it is important to understand how efficacious a medicine is in treating those already infected with COVID-19 and at high-risk of poor clinical outcomes. Therefore, those medicines in which there may be greater confidence with respect to the landscape at that particular moment in time should be used ahead of those which have more uncertainty. However, the context with respect to the prophylaxis indication is different. This population has essentially been left behind by society and generally live in significant fear of COVID-19 with the vast majority making lifestyle modifications. In this respect, it is critically important to offer immunocompromised individuals additional layers of protection while they remain not

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	infected. Whilst the level of protection offered by Evusheld is likely to vary with respect to current, emerging, or future variants, any degree of protection is important for these high-risk individuals with high unmet need. Therefore, a threshold of neutralisation against 10% of variants (or conversely where there is no evidence against 90% of variants) for prophylaxis, albeit higher than the FDA's recommendations for COVID-19 treatment, is appropriate. ***Defining neutralisation*** The IVAG report and AstraZeneca's comments on the report are considered under Section 5. As part of that discussion AstraZeneca propose that an IC50 of <10,000 ng/ml is utilised by NICE to determine activity against any particular circulating variant. In addition, AstraZeneca propose that the proportions of circulating variants is informed by the surveillance conducted by the UKHSA. **Conclusion** Utilising a threshold approach would enable NICE to make a positive decision considering both neutralisation data and circulating variants which may be more readily available than trial data or real-world evidence. In addition, it will allow NICE to make flexible and agile decisions that can evolve over time as the disease and variants also changes. Finally, applying a threshold can easily be linked to the economic evaluation as detailed in Section 12.
12	**Updated cost-effectiveness results are presented to reflect that Evusheld is cost-effective when Evusheld neutralises different proportions of circulating variants** As discussed in Section 11 above, AstraZeneca propose that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld PrEP, so long as it neutralises at least 10% of circulating variants. Therefore, if Evusheld neutralises at least 10% of circulating variants, then the clinical need and value for prophylaxis could be considered met. In terms of decision making, AstraZeneca suggest that the next step for NICE is to consider at what variant threshold Evusheld could be considered cost-effective. Results are presented below which apply a 10%, 15%, 20%, 25% and 30% threshold respectively to the economic modelling. Specifically, Table 2 presents the base case results using a 10% threshold with Table 3 presenting further scenarios at this level of neutralisation. Table 4 presents a summary of ICERs using the 15%, 20%, 25% and 30% thresholds with a full breakdown of each ICER and scenario analysis available in Appendix 4Appendix 4 – Full model results and scenarios for varying levels of neutralising ability. Although it is noted that Evusheld is cost-effective when applying a 10% threshold; utilising different thresholds presents decision makers with a range of options and therefore NICE can choose the threshold that the Committee are most content accepting. Further to this, Table 2Table 3 andTable 4 and Appendix 4 – Full model results and scenarios for varying levels of neutralising abilityAppendix 4 – Full model results and scenarios for varying levels of neutralising abilitypresent results in terms of "Updated EAG base case" and the "Updated Company base case" for each threshold. To clarify,

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the updated EAG and Company base case results reflect updates to the EAG and Company base case ICERs that were presented at the first Committee meeting and take in to account the following process:

- – Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committeelists the model assumptions which were applied to generate the EAG and company ICERs which were presented at the first NICE committee meeting (ICERs of £18,644 and £5,003 respectively).
- AstraZeneca have updated the EAG base case to take in to account the change above (i.e. reflecting neutralisation activity versus a proportion of variants) in addition to removing scenarios or amendments implemented by the EAG that are factually inaccurate/implausible to arrive at an updated EAG base case. – Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committeealso lists the model assumptions which are applied in the updated EAG base case.
- Similarly, AstraZeneca have updated the Company base case to take in to account the same variant assumptions as described above and applied additional changes to reflect more appropriate sources/assumptions where relevant. – Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committee – Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committeealso lists the model assumptions which are applied in the updated Company base case.
- Both the updated EAG and Company base cases apply one dose of Evusheld as noted in Section 2.

Computationally, to model Evusheld as able to neutralise a pre-determined threshold of variants, the analysis reduces the symptom infection efficacy of Evusheld to reflect the appropriate threshold/proportion of its original value. For example, in the 10% threshold scenario, the symptom infection efficacy estimate (66% (3)) is reduced to 10% of its original value. This resulted in Evusheld providing a reduced risk of infection of 6.6%.

Table 2: Updated EAG and Company base case results post committee using a 10% threshold

Technology	Total costs	QALYs	Incremental		ICER
			Costs	QALYs	
Updated EAG base case – post committee					
No prophylaxis	[redacted]	[redacted]			

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Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£18,047
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£15,201

Additional scenarios are also presented to explore uncertainty in the model and sensitivity to key model inputs for the 10% threshold analyses. The results of the scenario analyses are presented in Table 3 below.

Table 3: Updated EAG and company scenario analysis post committee using a 10% threshold

Scenario	Updated EAG base case – post committee	Updated company base case – post committee
Base case	£18,047	£15,201
Apply utility gain to 50% of patients	£24,891	£20,143
Increase underling infection rate by 20%	£16,661	£13,668
Reduce underlying infection rate by 20%	£19,583	£16,969
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£22,474	£17,694
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£27,698	£23,110

A top-line summary of the updated EAG base case, and the updated Company base case ICERs for thresholds at 15%, 20%, 25% and 30% respectively are presented below. Appendix 4 – Full model results and scenarios for varying levels of neutralising ability includes a breakdown of each base case result for each threshold, alongside scenario analyses.

Table 4: Updated EAG and Company base cases using different thresholds for neutralisation

Threshold for neutralisation	Updated EAG base case – post committee	Updated Company base case – post committee
10%	£18,047	£15,201
15%	£17,811	£14,597

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	20%	£17,578	£14,014
	25%	£17,350	£13,452
	30%	£17,125	£12,911

In conclusion, AstraZeneca have presented a framework which proposes that NICE should adopt the view of the FDA and acknowledge the importance of offering Evusheld, so long as it neutralises at least 10% of circulating variants. If this criterion is met, then the committee should appropriately consider the cost-effectiveness of Evusheld in scenarios in which it neutralises differing levels of currently circulating variants.

Cost-effectiveness analyses are presented in this document which utilise thresholds of 10%, 15%, 20%, 25% and 30% respectively. At all these pre-determined thresholds, Evusheld is cost-effective, and this conclusion is confirmed through scenario analyses which tests the uncertainty of the base case result at each given threshold.

Therefore, AstraZeneca have provided NICE with a range of options by presenting cost-effectiveness estimates at a different thresholds and NICE can choose the threshold that the Committee are most content accepting. Given that Evusheld remains a cost-effective use of NHS resources, the high unmet need for an effective prophylaxis treatment and the benefits that such a treatment would bring to patients, it is important that Evusheld be made available for patients and receive a positive recommendation from NICE.

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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References

1. UK Government. Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report [Internet]. [cited 2022 Jul 14]. Available from: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies

2. NICE recommends 3 treatments for COVID-19 in final draft guidance | News | News [Internet]. NICE. NICE; 2023 [cited 2023 Feb 24]. Available from: https://www.nice.org.uk/news/article/nice-recommends-3-treatments-for-covid-19-in-final-draft-guidance

3. Research C for DE and. FDA announces Evusheld is not currently authorized for emergency use in the U.S. FDA [Internet]. 2023 Jan 25 [cited 2023 Feb 24]; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us

4. NICE (Technology appraisal committee C). Tixagevimab cilgavimab (tix cil) for preventing COVID 19 [ID6136]- ACD Slides [Internet]. 2023. Available from: https://www.nice.org.uk/guidance/gid-ta11102/documents/1

5. Wu MY, Carr EJ, Harvey R, Mears HV, Kjaer S, Townsley H, et al. WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. Lancet [Internet]. 2022 Oct 6 [cited 2022 Oct 21]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9536776/

6. Wu M, Wall EC, Carr EJ, Harvey R, Townsley H, Mears HV, et al. Three-dose vaccination elicits neutralising antibodies against omicron. Lancet. 2022 Feb 19;399(10326):715–7.

Please return to: **NICE DOCS**

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

7. Suribhatla R, Starkey T, Ionescu MC, Pagliuca A, Richter A, Lee LY. Systematic review of the clinical effectiveness of Tixagevimab/Cilgavimab for prophylaxis of COVID-19 in immunocompromised patients. medRxiv. 2022;

8. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021 Jul;27(7):1205–11.

9. Therapeutics for people with COVID-19 [ID4038] | Guidance | NICE | Final draft guidance [Internet]. NICE; 2023 [cited 2023 Feb 24]. Available from: https://www.nice.org.uk/guidance/gid-ta10936/documents/html-content-10

10. Therapeutics for people with COVID-19 [ID4038] | Guidance | NICE | Draft guidance - Committee papers [Internet]. NICE; 2023 [cited 2023 Feb 24]. Available from: https://www.nice.org.uk/guidance/gid-ta10936/documents/html-content-2

11. NICE (Technology appraisal committee C). ID4038 COVID PART 2- MTA slides to PM for public observers [redacted]. Therapeutics for people with COVID 19 Multiple Technology Appraisal. [Internet]. 2023 Jan. Available from: https://www.nice.org.uk/guidance/gid-ta10936/documents/1-2

12. Follows A, Clark C, Dye C, King L, Follows G. Evusheld prophylaxis increases social interactions and improves anxiety, depression, agoraphobia and quality of life scores in blood cancer patients (AIC). MDPI.

13. UK Health Security Agency. Technical briefing 48 - SARSCoV2 variants of concern and variants under investigation in England [Internet]. 2022 Nov [cited 2023 Feb 3]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1120304/technical-briefing-48-25-november-2022-final.pdf

14. Patel V, Yarwood MJ, Levick B, Gibbons DC, Drysdale M, Kerr W, et al. Characteristics and outcomes of patients with COVID-19 at high-risk of disease progression receiving sotrovimab, oral antivirals or no treatment in England [Internet]. medRxiv; 2022 [cited 2023 Feb 23]. p. 2022.11.28.22282808. Available from: https://www.medrxiv.org/content/10.1101/2022.11.28.22282808v1

15. NICE (Technology appraisal committee C). ID4038 COVID PART 1- MTA slides to PM for public observers [redacted]. Therapeutics for people with COVID 19 Multiple Technology Appraisal. 2022 Oct 18.

16. Anjan S, Khatri A, Viotti JB, Cheung T, Garcia LAC, Simkins J, et al. Is the Omicron variant truly less virulent in solid organ transplant recipients? Transpl Infect Dis. 2022 Aug 12;e13923.

17. Parry H, Bruton R, Roberts T, McIlroy G, Damery S, Sylla P, et al. COVID-19 vaccines elicit robust cellular immunity and clinical protection in chronic lymphocytic leukemia. Cancer Cell. 2022 Jun 13;40(6):584–6.

18. Gleeson S, Martin P, Thomson T, Thind A, Prendecki M, Spensley KJ, et al. Kidney Transplant Recipients and Omicron: Outcomes, effect of vaccines and the efficacy and safety of novel

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

treatments [Internet]. medRxiv; 2022 [cited 2022 Nov 29]. p. 2022.05.03.22274524. Available from: https://www.medrxiv.org/content/10.1101/2022.05.03.22274524v1

19. Bradwell S, Hone L, Thorneycroft K, Lambourne J, Aries JA, Davies JK, et al. 2022 update on the clinical outcome of coronavirus disease 2019 in haemato-oncology patients. Leuk Res. 2022 Aug;119:106908.

20. Trindade AJ, Chapin KC, Gannon WD, Hoy H, Demarest CT, Lambright ES, et al. Clinical course of SARS-CoV-2 infection and recovery in lung transplant recipients. Transpl Infect Dis. 2022 Oct 21;e13967.

21. Lee LYW, Tilby M, Starkey T, Ionescu MC, Burnett A, Hattersley R, et al. Association of SARS-CoV-2 Spike Protein Antibody Vaccine Response With Infection Severity in Patients With Cancer: A National COVID Cancer Cross-sectional Evaluation. JAMA Oncology. 2023 Feb 1;9(2):188–96.

22. Office for National Statistics. Coronavirus and clinically extremely vulnerable (CEV) people in England - Office for National Statistics [Internet]. [cited 2022 Jul 14]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronavirusandclinicallyextremelyvulnerablepeopleinengland/latest

23. Cao Y, Jian F, Wang J, Yu Y, Song W, Yisimayi A, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. Nature. 2023 Feb;614(7948):521–9.

24. UK Health Security Agency. Technical briefing 49 - SARSCoV2 variants of concern and variants under investigation in England [Internet]. 2023 Jan [cited 2023 Feb 3]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1129169/variant-technical-briefing-49-11-january-2023.pdf

25. Research C for DE and. FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region. FDA [Internet]. 2022 Nov 30 [cited 2023 Mar 2]; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region

26. Young-Xu Y, Epstein L, Marconi V. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data. medRxiv [Internet]. 2022 May 29; Available from: https://www.medrxiv.org/content/10.1101/2022.05.28.22275716v1

27. Bruel T, Hadjadj J, Maes P. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies | Nature Medicine [Internet]. [cited 2022 Oct 27]. Available from: https://www.nature.com/articles/s41591-022-01792-5

28. Dejnirattisai W, Huo J, Zhou D, Zahradník J, Supasa P, Liu C, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. Cell. 2022 Feb 3;185(3):467-484.e15.

29. VanBlargan L, Errico J, Halfmann P, Zost S. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nature Medicine. 2022 Jan 19;28:490–5.

Please return to: **NICE DOCS**

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

30. Case J, Mackin S, Errico J. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. Nature Communications. 2022 Jul 2;13:3824.

31. Cao Y, Yisimayi A, Jian F, Song W, Xiao T, Wang L, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. Nature. 2022 Aug;608(7923):593–602.

32. Yamasoba D, Kimura I, Kosugi Y, Uriu K, Fujita S, Ito J, et al. Neutralization sensitivity of Omicron BA.2.75 to therapeutic monoclonal antibodies [Internet]. bioRxiv; 2022 [cited 2022 Oct 27]. p. 2022.07.14.500041. Available from: https://www.biorxiv.org/content/10.1101/2022.07.14.500041v1

33. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave. American Journal of Transplantation [Internet]. [cited 2022 Sep 10];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.17128

34. Kertes J, David S, Engel-Zohar N. Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality. Clinical Infectious Diseases. 2022 Jul;ciac625.

35. Kaminski H, Gigan M, Vermorel A, Charrier M, Guirle L, Jambon F, et al. COVID-19 morbidity decreases with tixagevimab–cilgavimab preexposure prophylaxis in kidney transplant recipient nonresponders or low-vaccine responders. Kidney International [Internet]. 2022 Jul 20 [cited 2022 Sep 10];0(0). Available from: https://www.kidney-international.org/article/S0085-2538(22)00550-6/fulltext

36. Chen B, Haste N, Binkin N, Law N, Horton LE, Yam N, et al. Real World Effectiveness of Tixagevimab/cilgavimab (Evusheld) in the Omicron Era [Internet]. medRxiv; 2022 [cited 2022 Nov 26]. p. 2022.09.16.22280034. Available from: https://www.medrxiv.org/content/10.1101/2022.09.16.22280034v1

37. Takashita E. Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. New England Journal of Medicine. 2022 Aug 4;387:468–70.

38. Wang Q, Li Z, Ho J, Guo Y, Yeh AY, Liu M, et al. Resistance of SARS-CoV-2 Omicron Subvariant BA.4.6 to Antibody Neutralization [Internet]. bioRxiv; 2022 [cited 2022 Oct 27]. p. 2022.09.05.506628. Available from: https://www.biorxiv.org/content/10.1101/2022.09.05.506628v1

39. Touret F, Baronti C, Pastorino B, Villarroel PMS, Ninove L, Nougairède A, et al. In vitro activity of therapeutic antibodies against SARS-CoV-2 Omicron BA.1, BA.2 and BA.5 [Internet]. In Review; 2022 Jul [cited 2022 Aug 11]. Available from: https://www.researchsquare.com/article/rs-1415749/v2

40. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, et al. Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. New England Journal of Medicine. 2022 Jun 9;386(23):2188–200.

41. Shields A. Data on file (Shields et al- in press). 2022;

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

42. Cusinato M, Gates J, Jajbhay D, Planche T. Increased risk of death in COVID-19 hospital admissions during the second wave as compared to the first epidemic wave: a prospective, single-centre cohort study in London, UK. Infection. 2021 Oct;50(2):457–65.

43. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine [Internet]. 2022 Jun 7 [cited 2022 Aug 28];0(0). Available from: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00180-1/fulltext

44. Rafia R, Martyn-St James M, Harnan S, Metry A, Hamilton J. A Cost-Effectiveness Analysis of Remdesivir for the Treatment of Hospitalised Patients With COVID-19 in England and Wales. Value in Health. 2022 Feb 20;

45. Evans R, McAuley H, Harrison E, Shikotra A. Physical, cognitive and mental health impacts of COVID-19 following hospitalisation: a multi-centre prospective cohort study. The Lancet Respiratory Medicine [Internet]. 2021 Oct; Available from: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00383-0/fulltext

Appendix 1 – Summary of RWE studies

Young-Xu et al. 2022(26)

- Retrospective observational study comparing Evusheld 600 mg and 300 mg (n=1,733) with a control group (n=251,756).
- Population considered US veterans (aged ≥18 years), immunocompromised or otherwise at high-risk for COVID-19.
- Dominating variants were BA.1, BA.2, and BA.2.12.1.
    - Estimated IC_{50} ranges from 147-715 ng/mL in BA.1(27–31), from 8.2-42 ng/mL in BA.2(27,30–32) and 18 ng/mL in BA.2.12.1(31).
- COVID-19 vaccination was received in 95% of patients.
- Propensity-score matched study undertaken, which matched Evusheld (n=1,733) to the control (n=6,354 post matching).

Al Jurdi et al. 2022(33)

- Retrospective cohort study comparing Evusheld 300 mg, 600 mg, and 900 mg (n=222) in vaccinated solid organ transplant recipients to age-matched, vaccinated solid organ transplant recipients (n=222).
- Population considered US kidney, liver, and lung transplant recipients.

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- Dominating strains were BA.1.1.529, BA.2 and BA.2.12.1.
    - Estimated IC_{50} ranges from 8.2-42 ng/mL in BA.2(27,30–32) and 18 ng/mL in BA.2.12.1(31).
- The patient population was focused on vaccinated patients.

Kertes et al. 2022(34)

- Large retrospective study in members of the of the Maccabi HealthCare Services in Israel which compared Evusheld 300mg (n=825) to unmatched controls (n=4,299).
- Population considered severely immunocompromised patients aged 12 and over.
- Dominating strains were BA.1 and BA.2.

Estimated IC_{50} ranges from 147-715 ng/mL in BA.1(27–31), from 8.2-42 ng/mL in BA.2(27,30–32).

- The majority were vaccinated. In the Evusheld group, 98.8% had received at least one vaccine dose and 91.3% had received 3–4 doses. In the control group, 88.0% had received at least one vaccine dose, and 76.3% 3–4 doses.

Kaminski et al. 2022(35)

- Retrospective study comparing Evusheld 300 mg (n=333) to controls (n=97).
- The population reflected kidney transplant recipients from Bordeaux University Hospital in France with no or low response to COVID-19 vaccines.
- Dominating strains were BA.1 and BA.2.
- Estimated IC50 ranges from 147-715 ng/mL in BA.1(27–31), from 8.2-42 ng/mL in BA.2(27,30–32).

Chen et al. 2022(36)

- Comparison before and after receiving Evusheld in n=1,295 patients.
- Patients received treatment at the University of California San Diego's Health System in the US, a quaternary referral centre, serving many patients who require complex subspecialty care.
- Dominating strains were BA.1, BA.1.1, BA.2.12 and BA.5.
    - Estimated IC_{50} ranges from 147-715 ng/mL in BA.1(27–31), from 4.7-8090 ng/mL in BA.1.1(30–32), from 18 ng/mL in BA.2.12.1(31) and from 40-586 ng/mL in BA.5(31,32,37–39).

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- The majority were vaccinated. Of the 121 patients who developed COVID-19 infection prior to receipt of Evusheld, 84.3% had received at least one dose, 57.0% had received 3–4 doses. The corresponding figures for those who had COVID-19 infection following receipt of Evusheld was 97% and 72.2% respectively.

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Appendix 2 – Summary of model inputs and relevance to target population.

Table 5: Summary of model inputs

Model Input		Source		Justification
		No prophylaxis	Evusheld	
Baseline Characteristics		PROVENT trial (40)		The baseline characteristics, sourced from the PROVENT trial, included individuals that were immunocompromised, had an inadequate immune response to a COVID-19 vaccine or, at increased risk for SARS-CoV-2 infection categorised as IAG cohort A1, A2, B, C and uncategorised . Baseline characteristics used in the model only include age, percentage of males and weight, these characteristics are not specifically linked to defining the IAG cohorts however would be expected to have minimal impact if the population used by the model were broader than the scoped population. Results of the deterministic sensitivity analysis for both the company and EAG base case showed that when age, percentage male and weight were varied using the standard error, there was not a substantial impact on the ICER.
Efficacy	**Risk of infection**	22.58% annually, general population England, Aug 21-22	66% reduction based on Young-Xu et al. 2022 (26)	The risk of infection was taken from the general population risk of COVID-19 without Evusheld. This risk was used in the economic model for the cohort that had not received Evusheld. Since this risk was taken from a mostly uncategorised risk, it can be assumed that in practice, the risk of COVID-19 to cohorts IAG A1, A2 and the proportion of B (those who are seronegative B patients) would be higher. Therefore, the company would like to highlight that this is a conservative estimate of the risk of COVID-19 in the target population. Furthermore, scenario analysis has been run including varying the infection risk by ± 20% and showed minimal impacts on the ICER (See Table 3: Updated EAG and company scenario analysis post committee using a 10% threshold).

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	Risk of hospitalisation	15.9% - Shields et al. 2022 (41)	N/A	The risk of hospitalisation is based on Shields et al. (2022) which assess the hospitalisation and mortality risk for immunodeficient individuals (IAG group 2). This population is deemed appropriate since the study was conducted on individuals with primary or secondary immunodeficiency, and would therefore, not mount a sufficient response to vaccination. Whilst the company acknowledges that this population contains individuals with both more severe and less severe immunodeficiency, this source was deemed most appropriate to capture the target population. This source is also most representative of the optimised population in which AstraZeneca seeks reimbursement in i.e. those in A1, A2 and seronegative B patients. These patients represent the highest risk of the high-risk population.
	Level of hospital ventilation	Same distribution for both arms (Cusinato et al. 2022)(42)		Cusinato et al.2022 utilised a UK based population to derive hospital ventilation levels. The company acknowledges that the population of Cusinato et al. is not specific to immunocompromised patients and thus may underestimate the true severity of hospitalisation associated with COVID-19 infection in the high-risk cohort, however it was the only UK based study identified at the time and the data captured reflected the model structure chosen for the evaluation. (42)
Adverse events		TACKLE trial (Montgomery et al. 2022) (43)		The TACKLE trial utilises the higher dose of 600mg and was therefore used to assess the safety profile of 600mg Evusheld. The TACKLE trial was conducted in immunocompetent outpatient individuals with COVID-19. Since the population was immunocompetent, it may

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				be considered a conservative estimate of adverse events for Evusheld. (43)
Mortality	**All-cause**	All-cause mortality in the general population taken from UK life tables with standardised mortality ratio of 1.7 applied for common variable immunodeficiency disorders, based on Odnoletkova et al. 2018		Odnoletkova et al. 2018 derived a standardised mortality ratio for patients with CVID. CVID is a primary immunodeficiency typically characterised by significantly decreased levels of IgG, in combination with decreased IgA and/or IgM, poor vaccine response, and increased susceptibility to bacterial infections. This population largely aligns with **IAG cohort A1 and A2**, with reduced vaccine response.
	Acute	Based on Ohsfeldt et al. 2022 (35) and ICNARC data		Ohsfeldt et al. 2022 (35) does not require eligible population to be immunocompromised. Whilst this data was deemed most appropriate for the economic evaluation, it could be a conservative estimate when applied to the immunocompromised population.
Utility	**Utility in target population**	A baseline disutility of 0.1160 is applied to all patients to reflect baseline comorbidities in line with the utility value applied from Rafia et al. 2022, for people with heart conditions. (44)		The company acknowledges that the utility decrement is not directly from the IAG cohorts IA1 or IA2, however, this data was not available. This disutility was used to reflect the comorbidities of patients hospitalised with COVID-19 at study entry and is based on UK tariff EQ-5D-3L data. Furthermore, since the IA1 and IA2 populations are considered "the highest risk of the high-risk population", this is likely to be a conservative estimate.
	Direct utility gain due to Evusheld treatment	N/A	Utility gain of 0.082 for 82% of patients based on the company's utility study	A study by Gallop et al. 2022 (commissioned by AstraZeneca) determined the direct utility gain for individuals receiving Evusheld. The study was conducted in a population that were largely categorised into the IAG cohort A2. The utility gain could be even greater if it were to include the estimates of QOL impact for the more vulnerable A1 population, who would likely exhibit shielding behaviours. The utility gain, of 0.098, has only been applied to 82% of the model population to

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				reflect the proportion of patients who are either fully or partially shielding according to the ONS survey. (21) Based on the evidence collected in the general population, this utility gain may be considered conservative since: • An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states in the general population, and • An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behaviour health states in the general population (21)
Long COVID	**Proportion**	Non-hospitalised patients: 34.% (Augustin et al. 2022) Hospitalised patients 100% (assumed)		In the model the proportion non-hospitalised patients who suffer with long-COVID is 34.8%, based on a study by Augustin et al. (2021). At the time of the study, patients were unvaccinated. Given the target population are known, anticipated to fail vaccination or expect a weak immune response, the company believe this study to be a good approximation of the long COVID rate in non-hospitalised patients and can be assumed to be equivalent to those who are unable to mount a vaccine response (**IAG cohort A1, A2 and a proportion of B**). It was assumed all of the hospitalised patients develop long COVID. A study Evans et al. found that only 20-30% of the general population in most severe health states had recovered at 6 months.(45) The target populations are expected to have a significantly worse outcomes and therefore a slower recovery.
	Cost	£2,267		The cost of managing long COVID is based on the Hunter et al. study which estimated the annual healthcare cost of long covid as a weighted average of

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				resources from four published studies. This was agreed with the EAG as an appropriate estimate.
	Disutility	0.1330 long COVID disutility		In the absence of available disutility data specific to long COVID patients, long-term post discharge disutility values were calculated from Evans et al. 2021. (45) Since Evans used a largely immunocompetent population, this disutility value could be considered a conservative estimate when applied to the IAG cohort IA1, IA2 and part of B.
Costs	**Administration**	N/A	NHSE (£216)	The committee noted a lot of uncertainty in the cost of administration, revolving around if it would be administered in primary care or in Covid-19 medical delivery units (CDMUs). The company maintains since the populations are A1, A2 and a proportion of B, are at greatest risk and have primary or secondary immunodeficiencies, Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services. To align with the budget impact assessment from NHSE a cost of £216 should be used. The company believes this is the most appropriate cost to use to account for the uncertainty around administration. The committee itself noted a serious gap between the company's original costs (£41) and the EAG admin costs but choose to favour the far too high CDMU cost of £410 in order to take a conservative approach. This does not capture the likely efficiencies that would be gained over the 1:1 patient nurse ratio. By using the cost recommend by NHSE, rather than a proxy, it possible to reduce this uncertainty and align with the budget impact assessment.

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*Note: A report has been produced for prophylaxis by IAG/McInnes to stratify cohorts in terms of risk of COVID-19. Group A1 have known failure of vaccination. Group A2 have anticipated failure of vaccination. Group B have anticipated sub-optimal vaccination response: physician discretion advised. Group C have anticipated food vaccination response (therefore not eligible for Evusheld according to the market authorisation)

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Appendix 3 – Comparison of model settings for EAG and company base case presented at NICE committee alongside updated EAG base case and Company base case post Committee

Table 6: Summary of settings for EAG and Company ICER at Committee and post Committee

Aspect of model	EAG base case - committee	Company based case - Committee	Updated EAG base case – post committee	Updated company base case – Post Committee
ICER	£18,644*	£5,003**	-	-
Modelling reflects that Evusheld would be effective versus a proportion of circulating variants	No	No	Yes	Yes
Dosing reflects 6 months treatment	No	No	Yes	Yes
EAG corrections to the company's base case (partially amended in response to the FAC)	Yes	Yes	Yes	Yes
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	New evidence included to update utility gain to 0.098 but applied to only 82% of target population	New evidence included to update utility gain to 0.098 but applied to 100% of target population	New evidence included to update utility gain to 0.098 for 82% of target population	New evidence included to update utility gain to 0.098 for 82% of target population
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Yes	Yes	Yes	Yes
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Yes	No – 34.8% as per company's original base case	Yes	No – 34.8% as per company's original base case
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	Yes, maintained CMDU costs	£41 per administration	£216 per administration based on NHSE cost	£216 per administration based on NHSE cost
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Yes	No, maintained company's original preferred approach using original calibrated lognormal from ScHARR MTA	Yes	No, maintained company's original preferred approach using original calibrated lognormal from ScHARR MTA

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EA6: Using the long COVID annual costs of £1,128 assuming chronic fatigue as proxy	Amended to £2,267 using an updated estimate of chronic fatigue cost	No, maintained company's original long covid cost of £2,500	Amended to £2,267 using an updated estimate of chronic fatigue cost	Amended to £2,267 using an updated estimate of chronic fatigue cost
EA7: Recalculating disutility values due to long COVID and assuming linear HRQoL improvement by time for 5 years	Applied EAG's preferred disutility values and assumed linear improvement over 5 years but also corrected an error in which company preferred utilities were applied to non-hospitalised patients	No – applied company's original disutility values which are assumed constant for the duration of long COVID	Applied EAG's preferred disutility values and assumed linear improvement over 5 years but also corrected an error in which company preferred utilities were applied to non-hospitalised patients	Applied EAG's preferred disutility values and assumed linear improvement over 5 years but also corrected an error in which company preferred utilities were applied to non-hospitalised patients
EA8: Using 15.9% as the risk estimate of hospitalisation for infected patients. (amended from 9.9% in response to FAC)	Yes	Yes	Yes	Yes
EA9: Updating hospitalisation reference costs associated with acute admissions	Yes	Yes	Yes	Yes
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventilation (IMV)	Yes	No – original company base case value retained	Yes	No – original company base case value retained
EA11: Applying long COVID to new infections after 1 year. • partially amended in response to the FAC	Yes	Yes	Yes	Yes

*Note the EAG ICER displayed on the committee slides is £18,646. This difference is likely due to a rounding issue of one of the inputs.

** Note the company ICER displayed on the committee slides is £5,004. This difference is likely due to a rounding issue of one of the inputs.

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Appendix 4 – Full model results and scenarios for varying levels of neutralising ability

Table 7: Updated EAG and company base case results post committee using a 15% threshold

Technology	Total costs	QALYs	Incremental		ICER
			Costs	QALYs	
Updated EAG base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£17,811
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£14,597

Table 7.1: Updated EAG and company scenario analysis post committee using a 15% threshold

Scenario	Updated EAG base case – post committee	Updated Company base case – post committee
Base case	£17,811	£14,597
Apply utility gain to 50% of patients	£24,503	£19,237
Increase underling infection rate by 20%	£16,408	£13,043
Reduce underlying infection rate by 20%	£19,369	£16,402
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£22,077	£16,796
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£27,330	£22,217

Table 8: Updated EAG and company base case results post committee using a 20% threshold

Technology	Total costs	QALYs	Incremental		ICER
			Costs	QALYs	
Updated EAG base case – post committee					
No prophylaxis	[redacted]	[redacted]			

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Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£17,578
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£14,014

Table 8.1: Updated EAG and company scenario analysis post committee using a 20% threshold

Scenario	Updated EAG base case – post committee	Updated Company base case – post committee
Base case	£17,578	£14,014
Apply utility gain to 50% of patients	£24,123	£18,374
Increase underling infection rate by 20%	£16,161	£12,444
Reduce underlying infection rate by 20%	£19,159	£15,853
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£21,689	£15,943
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£26,969	£21,363

Table 9: Updated EAG and company base case results post committee using a 25% threshold

Technology	Total costs	QALYs	Incremental		ICER
			Costs	QALYs	
Updated EAG base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£17,350
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£13,452

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Table 9.1: Updated EAG and company scenario analysis post committee using a 25% threshold

Scenario	Updated EAG base case – post committee	Updated Company base case – post committee
Base case	£17,350	£13,452
Apply utility gain to 50% of patients	£23,752	£17,550
Increase underling infection rate by 20%	£15,918	£11,868
Reduce underlying infection rate by 20%	£18,951	£15,323
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£21,311	£15,132
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£26,615	£20,545

Table 10: Updated EAG and company base case results post committee using a 30% threshold

Technology	Total costs	QALYs	Incremental		ICER
			Costs	QALYs	
Updated EAG base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£17,125
Updated company base case – post committee					
No prophylaxis	[redacted]	[redacted]			
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	£12,911

Table 10.1: Updated EAG and company scenario analysis post committee using a 30% threshold

Scenario	Updated EAG base case – post committee	Updated Company base case – post committee
Base case	£17,125	£12,911

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Apply utility gain to 50% of patients	£23,389	£16,763
Increase underling infection rate by 20%	£15,680	£11,314
Reduce underlying infection rate by 20%	£18,747	£14,809
Increase underling infection rate by 20% and apply utility gain to 50% of patients	£20,942	£14,360
Reduce underlying infection rate by 20% and apply utility gain to 50% of patients	£26,268	£19,760

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**CLL Support Charity**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	NICE agreed that there is an unmet need that needs to be addressed for immunocompromised patients. Many patients are also unable to take post exposure treatments because of their cancer medication. The draft guidance states that "recent studies done in laboratories report that tixagevimab plus cilgavimab is unlikely to prevent infection with most of the relevant variants in the appropriate time period for this evaluation " Vaccination also does not prevent infection but immunocompromised patients were prioritised for vaccinated as it reduces the likelihood of hospital admission and ICU care by 86% **as would this antibody treatment.** This fact makes the reason for refusal of approval appear unreasonable and this treatment should be considered an extension of the vaccination programme for this vulnerable group.
2	No threshold for effectiveness was defined or discussed. This needs to be urgently addressed in this dynamic situation so that future evaluations can be systematically assessed. The FDA have accepted a threshold of effectiveness to be against 10% of circulating variants. Currently the XBB, CH1.1 and BQ1.1 variants are approximately 50% of circulating covid variants meaning that this treatment should be effective against the other 50%.
3	The draft guidance states - 'The committee noted the lack of evidence on how the availability of a preventative treatment would impact on shielding behaviours, to determine the impact on both health-related quality of life and efficacy of treatment.' The committee heard from several patient experts' powerful personal testimony regarding their situation re shielding because they are unable to produce antibodies in response to multiple vaccinations. As a group of highly vulnerable patients they are unable to regain their place in society and are permanently in a state of shielding which is a virtual prison for both themselves and their families. The corollary is that, knowing they have covid antibodies, this group can return to a more normal lifestyle with their work, family and friends and that is very precious.

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4	The DHSC have reviewed the data on Evusheld, but they have not published this review. We do not know if this data was or was not part of the NICE evaluation. This situation has not helped patient groups to feel confident in the decision for ID6136
5	The APPG on Vulnerable Groups to Pandemics recently looked at a systematic review analysing the outcomes of 24,773 immunocompromised patients across 17 clinical studies from around the world. Led by the University of Birmingham with academics from King's College London and the UK Health Security Agency, the findings are the largest meta-analysis of studies about antibody therapies for immunocompromised and immunosuppressed patients to date. The paper also draws on newer studies relating to the effectiveness of treatments such as Evusheld during the widespread Omicron variant of Covid-19, which shows that the therapies **continue to be clinically important as SARS-COV-2 continues to mutate.** **https://appg-vulnerablegroups.org/news/post/antibody-therapies-against-covid-19-for-most-vulnerable-patients-work-new-analysis-finds** **https://appg-vulnerablegroups.org/fileadmin/user_upload/Systematic_review_of_the_clinical_effectiveness_of_Tixagevimab_and_Cilgavimab_for_prophylaxis_of_COVID-19_in_immunocompromised_patients.pdf**
6	

Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Evusheld for the UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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Example 1	We are concerned that this recommendation may imply that ……..
1	**Effectiveness** We are concerned that in spite of the fact that in vitro data was discussed at the appraisal meeting and the limitations of this information, it is well known that Evusheld performs very differently in the human body. We know from speaking to clinicians in the 32 other countries where Evusheld is still being used, that hospital admissions are significantly reduced and it is still providing protection. There seems to have been little balance in how this real world data has been looked at. Even within members of our patient group, we are seeing numerous real world examples of those who have obtained Evusheld privately having contracted covid, and have low or mild symptoms with good outcomes. For all the discussion regarding perceived neutralisation levels, the protection this is giving to those who have accessed it in this country and abroad is real and significant. When a patient has previously spent 5 months in hospital with covid and 5 weeks in an induced coma, with their family saying goodbye to them twice and then seeing them have a milder insignificant illness than the rest of their family after contracting covid, after having Evusheld privately this year, it is difficult to reconcile its effectiveness in the protection it is giving against severe outcomes compared to the theoretical discussions against its use. It seems such evidence is not being looked at as it is somewhat difficult to assess. This is not a good reason to dismiss it or not look at it further. The decision of the FDA to temporarily withdraw the authorisation for the drug in the US is cited as an example of a reason not to introduce Evusheld, yet the FDA holds the drug in high regard and is willing to re-introduce the drug back into use once the variant mix of certain variants is reduced. This means it will conceivably be reintroduced whilst variants of concern are still circulating, on the basis that it will STILL be offering some level of protection when used in conjunction with other measures. Even at reduced efficacy, this could be the difference between life and death in an immunocompromised patient. We are once again erring on the side of caution for the sake of making the effort to look fully at the real world data. This approach has not been carried out by other bodies such as the JCVI for vaccines. The general population would not have been prepared to wait in these circumstances for vaccines, why then can it be acceptable for the 1.2million that NICE has identified as possibly benefiting from this drug to have their lives restricted for a 4th year as they wait for other drugs to be developed, when this drug is shown worldwide to be making a significant difference in the outcomes for patients.The assumptions being used to make this decision are leaving the people in these cohorts still at total risk with nothing at all to offer them protection.

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	The current draft decision is based on a binary decision and this is simply wrong. It has been accepted by the review that Evusheld has retained neutralisation against some variants. Therefore the drug works, but the basis of the decision is that it doesn't work. It cannot be both.The decision must be made on its effectiveness on what variants it works against, not on what it might not work against. A drug of this type will never work 100%. There therefore needs to be an acceptance of what level of is effective and acceptable otherwise this drug and others following it will never reach a theoretical target of 100%.The draft decision should be reviewed to confirm it works and what needs to be rapidly decided on is the framework and thresholds of when it is used in the face of virus variant levels. The FDA has set a threshold of Evusheld working against 10% of circulating variants. At present the variant mix places this below that threshold, hence the TEMPORARY withdrawal, with the firm intention to place it back into use as the mix alters. The present draft decision quotes that decision, yet at present in the UK we are still above that threshold. That means the FDA would be happy to have it used in the conditions we find ourselves in the UK. As there is no measure set in the Uk, and the decision not to use it is confirmed, what happens in a few months when the variant mix alters and the use of the drug reverts to becoming more effective? This decision sets no threshold on its effectiveness and parameters for its use. It seems implausible and wrong for a drug to be ruled out on perceived effectiveness when no actual threshold has been set. The present decision means the drug would still not be available to allow its use and offer protection. It should also be pointed out that no other country currently using Evusheld has withdrawn its use and is still offering it as a form of protection to their most vulnerable. The decision is simply denying the desperately needed use of what is an essential drug. The decision to deny the access Evusheld is based on a theoretical threshold that hasn't been qualified on theoretical conditions as they stand today, heavily weighted towards the temporary actions of one other country which is in a different situation to here and the rest of Europe, indeed the EMA has made no such withdrawal. Rather than denying access to this drug, it would be better to authorise its use with an agreement on a review system to monitor the variant mix as the FDA does. If the variant situation changes and NICE decides to re review its use in the future, this will still leave a 3 month window for its implementation by the NHS. By the time this is done the situation may have changed again and more time will be lost, putting more lives at risk. The present draft decision will be a rigid decision based on one point in time and will offer no ability to be flexible and adapt to changes in the virus. This is something we have seen through its history on numerous occasions as the virus evolves. A more agile decision needs to be made to allow reaction and anticipation in the future with the protection this drug can give. If in 2 months time we have a changed picture of the dominant variants and Evusheld is proven to be effective against them (as has happened with Paxlovid) we will have an effective drug that could offer protection, again not able to be used due to a decision made today, with no system in place to review and alter that decision quickly.

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2	**Patient behaviour** We are concerned by the comments regarding how it may change patients behaviour and put them at further unnecessary risk as they take more risks. This is a disingenuous assumption.. Patients dealing with everyday conditions are well aware of their risks and limitations and on the whole are grateful to have the chance to be able to carry on their lives after receiving expensive life saving treatments or treatments just to manage their conditions. Most know their conditions inside out and are risk averse. The use of Evusheld will allow them a semblance of normality, but it is unlikely such patients will put themselves at a greater risk, they value what health they have too much to do this. We therefore refute these assumptions as simply unlikely in the vast majority of patients. We also know from speaking to lots of group members who have privately paid for Evusheld, that they are not going out partying or mixing in large groups, but actually only doing the simple things that most take for granted like being able to see their families and friends and giving them a hug, and attending indoor settings only when not busy.
3	**Mental Health** We are concerned that there has been little evaluation of the mental health impacts on those in this position, who are now facing a 4th year of shielding. The chance to have some return of even a small amount of normality would be a massive release to those facing this long and drawn out situation. The mental impact and its effect on everyday lives and their physical conditions cannot be understated or played down in any way. The damage being caused to people's lives and their families by having to live in this never ending situation is real, severe and with the effects on their physical and mental health long lasting. For this cohort to be left for another year without any freedoms could have untold damage not just now, but for years to come. The recently published study from UWE Bristol on the impact of shielding on immunocompromised patients highlights the serious mental health impact on patients and should be viewed in relation to this decision.
4	**Inequality** By denying this drug to those in these cohorts, it places those in this position in a massive equality debt of treatment compared to the general population. It is inequitable to explain to a person that simply because they are immunosuppressed that they cannot have access to a drug that will give them the same quality of life as the general population obtains from an alternative drug ie covid vaccines. The decision affects their quality of life and also restricts their freedom to have economic independence by returning to work. This is one of the main economic aims of the health service in this country to allow people's health to be improved to allow them the ability to return to work. This is being denied by this decision. Those that are immunosuppressed are those most likely to need to attend care and hospital settings on a regular basis, yet the danger each visit represents to these cohorts, borne out by the covid infection statistics in care settings, means they are placed at an unacceptable risk, leading to an inequality in treatment and in many cases treatments being delayed or cancelled, simply because they do not have the protection. We also know that the wearing of masks in these settings is now significantly reduced, placing them at even more risk

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5	**Future Evaluation Process** We are very pleased to see that there is a general acceptance that existing systems for evaluating protective MABS and Antivirals for covid 19 are too slow and not effective. We applaud the conclusion that a new system needs to be put in place. It must therefore be a matter of the utmost urgency for NICE to draw up exactly what these new procedures and systems will be, with relevant timescales. However these must be published as a matter of urgency to give a clear and defined process and timeline, so that this can then be applied to the next generation of protective medications which are already in trials. This will allow them to be speedily assessed so that efficacy is maximised. This situation of an inflexible slow process is unfit for the purpose of evaluating Covid drugs in a fast changing pandemic situation and MUST be streamlined quickly. Every day lost in the making of these decision has a real and negative impact on people's lives and their health and unfortunately every delay is simply costing more lives of those in these cohorts
6	**Summary** Evusheld is a drug that has been in use across the globe for over a year and is still showing its effectiveness in the real world, both in the UK and abroad. The view of the JCVI when it comes to vaccines and the immunosuppressed, is that any increase in protection if only by a few percent is better than nothing and should be pursued, yet Evusheld offers the chance of significantly more protection from a severe outcome for patients against many variants still in circulation, but the draft decision is happy to ignore that. We should be giving patients in this exposed position whatever protection we can, not leaving them totally unprotected whilst we await to see what happens. It is proven to have effectiveness against many variants and represents the best option that is currently available for protection of the immunocompromised, if not from neutralisation of all variants, at least from progression to severe outcomes for many. NICE has agreed that there is an unmet need for such protection and there is a large gap in the protection strategy for the most vulnerable that needs plugging. Evusheld is that drug at present that can do this. Whilst other drugs may be in development, at present this represents the ONLY viable option to give protection for the most vulnerable and release from the massive life altering situation they are in. A situation that all members of the UK public have lived through on a much shorter time scale and know how hard it is to live through and adjust from. To not utilise this drug based on a binary decision at one point in time with no flexibility to adapt to changing variant scenarios is wrong and does nothing to fulfil that unmet need By the conclusions of the draft decision Evusheld is below the incremental cost effectiveness ratio (ICER) threshold. That means it is effective and cost effective. A clear demonstration that the use of MABs is a wholly acceptable way to provide protection to what is defined by NICE as nearly 2% of the UK population.

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	The decision is a binary decision and this cannot be the case for a drug that is accepted to work on some variants will some views are harboured regarding its effectiveness on others No threshold of acceptance has been set It is a fixed point decisions offering no ability to allow the decision to be reversed and the drug brought into use at short notice in the future, compounded by the NHS implementation 3 month window The decision compounds the inequality of care for those not in a position to access the drug privately and denies then the ability to return to a more normal life, especially compared to the rest of the general population who have free protection from covid vaccines In light of all the above it is our view that Evusheld should be authorised and it is essential that the new review pathway for future drugs is consulted on with stakeholders as a matter of urgency. We would urge the panel to take on board the points raised and reassess the protection given to patients who are in dire need of protection now. We sadly were relayed this account by the daughters of one of our patients today (8th March 2023) For all we have written, we feel her words sum up the situation more effectively than anything anyone can say on this issue. This is why this drug is so desperately needed in its current form to give some protection and why the fast pathway for the next generation needs to be put in place with extreme urgency. This is not about facts and figures, this is simply about the lives of those affected and their loved ones and for too long they have suffered. “Yesterday my dad, a blood cancer patient, died. I have protected him for the last three years, but he was in hospital as he had cellulitis 7 weeks ago. He caught covid whilst he was in hospital. I can't help thinking if he had been given Evusheld I might still have had my Dad here. Although too late for my wonderful Dad I hope you win this battle and get it for people . Yes Dad caught covid in hospital. I tested positive Sunday, the first time having covid. So they tested dad and he was positive. I pleaded for antivirals for Dad from that moment, but he didn't get connected to antiviral iv until 11pm Monday night. He was sleepy Monday night, but no temperature and his pulse was strong and regular. Strange it was strange he was so bad after iv antivirals, maybe just a coincidence. So it fills me with horror that I may have it given to him. Although the hospital is full of it at the moment and Dad or staff could have given it to me. Maybe best I don't know. For three years we haven't been in supermarkets or anywhere etc. We always still wear ffp2 and 3 masks out. Anything we had to do to protect my Dad. They called us to come to the hospital Tuesday morning and the scene in the room was horrific. They had waited

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	for me to arrive before giving him morphine. Thankfully Dad's breathing was more settled once he had the morphine. But it will haunt me forever what I saw beforehand. Sorry for going on, I think I'm just so shocked. But thank you all so much . God bless you" Every day this drug is denied we will continue to hear more accounts like this, and more people will die. Evusheld For The UK

Insert extra rows as needed

Checklist for submitting comments

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Immunodeficiency UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	It is important for this and future evaluations that NICE define what is considered the effectiveness threshold against COVID-19 variants as the FDA have done. This would add some transparency to the process and help define the scenario by which Evusheld may become a suitable treatment option.
2	
3	
4	
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Care UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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1	It is not reasonable to apply the utility gain only to people fully or partially shielding. There are many people who do not have the option of fully or partially shielding – reasons being retaining employment and therefore income, fulfilling caring or parental duties. These individuals may experience significant distress and anxiety because they know they are exposing themselves to the risk of Covid-19 infection but cannot choose to stay at home. A treatment that offered protection would therefore provide substantial utility benefits in terms of reducing anxiety and distress in this group, and its vital that the model is able to capture this. Failing to capture the benefits for people who cannot choose to shield risks exacerbating inequalities that have been present throughout the Covid-19 pandemic, as ONS data to Jan '23 shows, those with the lowest incomes and education levels, in elementary occupations are the least likely to work from home. The data also showed some slight differences between ethnicities - workers in the "Black or Black British" ethnic group reported the highest levels of travelling to work without the option to work from home (60%) compared with workers in the "White British/Irish" ethnic group (46%).
2	We do not believe it is reasonable to use a cost based on administration in the CDMU, given that we know CDMUs will no longer be in place after April 2023. Local arrangements will be made in each ICB for the delivery of Covid treatments. It may be more appropriate to base costs on the administration of other preventative treatments, such as Hep B vaccination for kidney patients.
3	The draft guidance states that there is uncertainty about how people's behaviour would change after having tix-cil. We suggest that a NICE appraisal of prophylactic Covid-19 treatment is an opportunity to develop guidance that optimises the benefits of a preventative treatment in terms of quality of life and clinical effectiveness, by ensuring people at high risk are offered advice and guidance on appropriate levels of activity/social mixing following preventative treatment (taking a similar approach to that used in the PrEP guidance). This advice would support people to maximise their quality of life as far as possible while avoiding significant increases in their risk of infection. The model should incorporate these assumptions of how people would behave.
4	We do not think it is reasonable to use a hospitalisation rate close to the 2.8% reported by Patel for people with renal disease, given that the OpenSAFELY study found a hospitalisation rate among this group of about 4%. We suggest NICE consider a subgroup analysis of this group, using this more appropriate hospitalisation rate.
5	We very much welcome NICE's announcement of ongoing surveillance of the disease and available evidence and rapid review of Covid treatments as required, but it is vital that problems with the current model are addressed promptly to enable the rapid review and fair, timely access to effective preventative treatment.
6.	There is an unmet (and not fully understood) need in a population which remains at risk from Covid-19 and it is not fair that the burden of protection relies solely on the individual's behaviour. We very much want to work with NICE to understand and develop plans to address a future for living with Covid-19.

Insert extra rows as needed

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1	We are concerned that the process that has been followed for providing this draft guidance cannot be relied upon to give sound and suitable guidance for the NHS. While we have confidence that relevant evidence has been considered, our key issue is that that evidence has been assessed far too slowly. This draft guidance has been published far too late. The guidance itself acknowledges that studies analysed were from earlier in the pandemic when different variants of the Covid-19 virus were circulating. Omicron subvariants BQ.1 and CH.1.1 and XBB lineages were not dominant variants in the summer of 2022. By July 2022, when the NICE's consultation began after licensing was approved in the March, Evusheld had already been procured across 32 other countries. In August 2022, while those at high-risk of Covid could have benefited from the drug, the NICE HTA process was only just being formally referred to NICE by the Department of Health and Social Care – with no end in sight for eight more months. This process was slow to start, unsuitable for assessing a rapidly evolving virus, and has been incredibly protracted. The draft guidance acknowledges these key points throughout its summation. The committee 'considered that SARS-CoV-2 is rapidly evolving and acknowledged that this makes assessing neutralising monoclonal antibodies difficult'. In future, a faster, more adaptive, and flexible process must be considered for assessing the efficacy of new treatments for Covid-19. We welcome the decision to introduce a new mechanism for reviewing new evidence for existing treatments, but this must be extended to future new appraisals.
2	We are concerned that parts of the rationale provided for recommendations would set an unfair precedent that will exacerbate health inequalities. Those shielding face great unmet treatment need. Shielding has taken a significant toll on the physical, emotional, and financial well-being of kidney patients. Addressing the risk of COVID-19 to those who are immunocompromised must be prioritised. As the evidence shows, vaccination can be less effective in transplant recipients. The importance of the vaccination and booster programme is clear, but we must continue to push for more effective strategies and review new data promptly. No utility gain from the technology was considered as arising from the increased confidence of vulnerable people to resume normal activities as the Draft Guidance suggests that it could increase the risk of infection. This is a perverse reading of potential outcomes. There is a significant underestimation of the effect of shielding if it is to be implied that patients "may not realise any quality-of-life benefit from the ability to reduce shielding behaviour". We know from kidney patients that shielding has had a direct impact on social isolation, on input into the economy, on loved ones and carers. We outlined in our previous evidence submission how kidney disease is known to be associated with an increased risk of mental ill-heath, and how the mental health impact of shielding has been shown to have a significant effect on health-related anxieties compared to the rest of the population.
3	The binary recommendation that tixagevimab plus cilgavimab (tix-cil) is considered not clinically effective is too inflexible considering the ever-evolving nature of the Covid-19 virus. The summary

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	of evidence clearly indicates that assessments made of the tix-cil's efficacy was based on the prevalence of particular variants. Given that the prevalence of said variants are ever-changing, it may be unwise to make such a black and white declaration of a medicine's efficacy. Antibody treatments must be assessed against different variants to assess where there is efficacy, and where there is not. As noted by clinical experts, tix–cil may not be clinically effective against many new variants but could still be effective against some of them. It is also possible that tix–cil may regain efficacy against future variants. In the United States, the FDA has decided upon a threshold of effectiveness of antibody treatments. They have decided upon a threshold of efficacy of 10% against circulating variants. It would be prescient for NICE to consider this as an appropriate way forward.
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Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Leukaemia Care**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/a**
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about the committee's inability to make a reliable cost-effectiveness estimate due to the uncertainty in the clinical evidence. Whilst we appreciate the challenge of translating the in vitro data into estimates of efficacy in humans, the treatment does show neutralisation activity against some variants. Additionally, the treatment remains licensed by the MHRA. We therefore ask the committee to consider this treatments' suitability for the Innovative Medicines Fund (IMF). This would grant a period of managed access to patients who want this treatment to be available on the NHS and would enable NICE to gather more real-world evidence for the committee to make a more accurate decision on the treatments' clinical and cost-effectiveness.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	LUPUS UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Evusheld was effective and cost-effective, and therefore likely to have been approved, when previous Omicron variants were more dominant. It is both frustrating and concerning that an opportunity was missed to address an urgent unmet need for people who are at high risk from COVID-19, particularly those who do not have a good response to, or are unable to receive, vaccinations. If Evusheld had been appraised more rapidly, these vulnerable patients may have been able to have some protection from COVID-19 when previous variants were dominant during the second half of 2022. In addition to providing vital protection by reducing risk of severe illness, this treatment could have drastically improved quality of life for a group of people continuing to experience the adverse impact of shielding. We welcome the recommendation to create a new fast-track system for updating recommendations for COVID-19 treatments, particularly in the case of monoclonal antibodies which are most effective against particular variants. However, as we understand it, this process is for *updating* existing recommendations, and not for the evaluation of *new* treatments. This means potential future prophylaxis preventative treatments will not be included. Therefore, the rapid review scheme will not solve the problem of appraising novel treatments in a timely manner. It is essential that new and novel COVID-19 treatments are included in a fast-track system, so that another effective treatment is not wasted due to the appraisal process taking place after the window of opportunity for its effective use is passed.
2	We are concerned that the recommendations imply that NICE requires a threshold of evidence which is too high for medicines such as these to be approved in a timely manner. In section 3.23, the committee recommends that “further data collection through clinical trial would be a more appropriate way to resolve key uncertainties”. Given the long timescales of clinical trials, and the issues of changes in circulating variants, waiting for the outcome of a clinical trial will likely delay appraisal to a point at which the variants have changed and the treatment becomes less effective (as discussed above). The reliance on in-vitro evidence alone is problematic, as this approach makes significant assumptions regarding tissue penetration and mechanism of action of monoclonal antibodies, as research has indicated that in-vitro studies analysing the neutralising effect of monoclonal antibodies on different variants of SARS-Cov-2 do not accurately demonstrate the real-world, clinical efficacy of treatments. In some cases a monoclonal antibody developed for a historic variant could regain activity against the spike protein of a future variant. As such, the recommendations should not be reliant on in-vitro analyses. Uraki et al. (2022) demonstrated that another monoclonal antibody treatment, sotrovimab, can restrict viral replication in the lungs of hamsters infected with Omicron BA.2 in an in-vivo experiment, despite in-vitro experiments suggesting that Omicron BA.2 had resistance to sotrovimab.

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	The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, especially due to the rapid changes in circulating variants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities mean they have little response to, or are unable to receive, vaccination. A wider range of evidence needs to be synthesised for rapid and accurate assessment of the efficacy of monoclonal antibody treatments.
3	We are concerned that evidence used by the committee for this recommendation implies that, because (some) people at higher risk from COVID-19 continue to modify their behaviour by shielding, their true risk cannot be fully considered in cost-effectiveness modelling. Section 3.16 of the draft recommendations states that: "…data for the general population [on infection risk] may not be generalisable to those likely to have Evusheld. The committee considered it likely that the risk of infection in those eligible for Evusheld would be lower than the general population. This is because those eligible for Evusheld modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden." The committee then considered that the model should be sensitive to changes or differences in background levels of risk. It is unreasonable to expect people in the eligible group to continue to modify their behaviour to reduce risk of infection. Using this as evidence of a lower level of risk than the general population could mean recommendations require people to continue to shield and does not account for the large number of eligible people unable to do this. The committee may need to review any stereotypes of a person who is shielding. We cannot assume that those at risk can reduce their risk of exposure to the virus by modifying just their own behaviour. Many in the at-risk group do not live alone. It is more likely that someone is in a household with family or friends whose behaviour would also need to be modified. This becomes increasingly unlikely due to the lack of precautionary measures and governmental support such as widespread testing. We must also consider the reduced opportunities for at-risk people to practice shielding. Most people in this group are living with a disease and/or treatment which requires attendance to medical settings for medication administration and/or monitoring. Even if an at-risk person can stay safe traveling to and from appointments, the precautionary measures in medical settings are being increasingly abandoned. It is not reasonable to use lower risk values to model cost-effectiveness for this group, because it is not reasonable to assume that all at-risk people and their households are able to adequately modify their behaviour, nor is it reasonable to expect those that are able to, to continue shielding given the difficulties and well-documented mental and physical health impacts of this (e.g. Sloan et al, 2021; Ryan et al, 2022; Maldonado et al, 2021). This is also a matter of health inequalities. A disproportionate number of those unable to shield are from minority ethnic groups, due to the higher likelihood that they are in employment without remote working options, higher likelihood to work in occupations with higher risk of exposure to COVID-19, and higher likelihood of needing to use public transport to travel to work (POST, 2020). Lupus also disproportionately affects those from African-Caribbean or Asian heritage, who also tend to have more severe disease (e.g. Hasan et al, 2022), and so would likely be a high proportion of those eligible for Evusheld.
4	We are concerned that the committee has underestimated the direct utility gain to shielding patients. The committee suggests that the evidence submitted by patient experts implies a lower direct utility gain due to more limited behaviour change in shielding behaviours than the Company submitted in evidence. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for almost three years, to immediately return to pre-pandemic

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	behaviour, even if a treatment was able to provide 100% protection. Patients in recent research (as referenced in point 3 above) have discussed impacts to their mental and physical health, including a loss of confidence and physical decline. Given these impacts, it is unrealistic to expect these patients to immediately or fully return to pre-pandemic behaviours. Additionally, COVID-19 is not the only viral risk for this group, so many would have been practicing enhanced precautionary measures to reduce risk of exposure to viral and bacterial threats before the pandemic. Therefore, it is likely patients will continue to modify their behaviour in some form due to the very real need to reduce risk from infections of all kinds. Additionally, in the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients, patients were not necessarily requesting a complete return to their pre-pandemic life, but a desire and need to have more of life open to them (even if that still includes some precautions like masking, for example), and that this could make huge improvements to their mental and physical health. When considering direct utility gains related to changes in shielding behaviours, the committee should consider change over time as people re-gain confidence and physical strength, rather than just immediate changes in behaviour. Continuing some shielding or protective behaviours should also not be viewed as a lack of impact, as there can still be a significant impact on mental and physical health if people feel able to do more whilst still masking, for example, and some protective behaviours are likely due to increased risk from other viral or bacterial infection for this group.
5	We are concerned that the recommendations do not include or imply a defined threshold of accepted effectiveness. The landscape of the pandemic has changed dramatically since the clinical trials for Evusheld. We are no longer experiencing a single dominant variant in circulation at one time but instead there are several dominant variants. It is unclear how this could change in the future, but it may not return to a pattern of single variants at a time. Monoclonal antibodies such as Evusheld usually work most effectively against one particular variant. As there will be more than one variant circulating, it is imperative that NICE develops a definition for the threshold of effectiveness to support rapid appraisal and deployment of effective treatments. This must include a threshold related to the estimated prevalence of variants the monoclonal antibody is likely to be effective at neutralising. If a monoclonal antibody is appraised to be effective (and cost-effective) against particular variants (such as is the case with Evusheld), then a threshold must be set for it being appraised as effective and cost-effective in the context of there always being multiple variants in circulation (for example, the FDA have accepted a threshold of using a monoclonal preventative treatment if the variant it works against is estimated to be responsible for greater than 10% of cases; FDA, 2023). Setting a clearly defined threshold will support rapid and transparent appraisal and updating of recommendations as variants change within the UK.
	References: - FDA (26th January 2023). Emergency use update open letter to AstraZeneca. https://www.fda.gov/media/154704/download - Hasan, B., Fike, A., & Hasni, S. (2022). Health disparities in systemic lupus erythematosus – a narrative review. *Clinical Rheumatology, 41(11)*, 3299-3311

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	- Maldonado et al (2021). Association of medication access difficulty and COVID-19-related distress with disease flares in rheumatology patients during the COVID-19 pandemic. *Arthritis Care & Research, 73(8)*, 1162-1170 - POST (2020). Impact of COVID-19 on different ethnic minority groups. Rapid response report. https://post.parliament.uk/impact-of-covid-19-on-different-ethnic-minority-groups - Ryan et al (2022). Exploring the physical, psychological and social well-being of people with rheumatoid arthritis during the coronavirus pandemic: a single-centre, longitudinal, qualitative interview study in the UK. *BMJ Open, 12(7)*, e056555 - Sloan et al (2021). COVID-19 and shielding: experiences of UK patients with lupus and related diseases. *Rheumatology advances in practice, 5(1)*, rkab003 - Uraki, R., Kiso, M., Iida, S., Imai, M., Takashita, E., Kuroda, M., ... & Kawaoka, Y. (2022). Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA. 2. *Nature*, *607*(7917), 119-127.

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	**Has all of the relevant evidence been taken into account?** The Faculty of Pharmaceutical Medicine (FPM) has noted that patient perspectives, in vitro and clinical data were considered by the Committee and particularly welcomed the consideration of the patient perspective from this group of vulnerable individuals. FPM notes that two trials with different antibodies have successfully demonstrated that monoclonal antibodies can prevent infection and illness due to SARS-CoV-2 infection: the BLAZE 2 trial with bamlanivimab (Cohen MS et al. JAMA. 2021 Jul 6;326(1):46-55. doi: 10.1001/jama.2021.8828. PMID: 34081073; PMCID: PMC8176388) and the PROVENT trial with tix-cil (Levin MJ et al N Engl J Med. 2022 Jun 9;386(23):2188-2200. doi: 10.1056/NEJMoa2116620. Epub 2022 Apr 20. PMID: 35443106; PMCID: PMC9069994). These trials documented that clinical activity followed successful demonstration of antiviral effect from in vitro and in vivo animal studies. Antiviral medications that have shown inhibitory activity in vitro and efficacy in animal models can be anticipated to be effective in human diseases. This has been confirmed recently with the clinical use of tecovirimat, which was conditionally approved based on documented efficacy in an animal model of monkeypox, accompanied by human studies documenting the dose required to match exposure in humans to those achieved in the successful animal model. Recent confirmatory clinical evidence has been amassed during the monkey pox outbreak in the UK and elsewhere. If this approach was considered appropriate for COVID-19 antivirals, permitting earlier access by high-risk patients during an outbreak when confirmatory proof of clinical efficacy can be collected from treated patients, then all parties – MHRA, DHSC, UKHSA and NICE – should work together to enable accelerated access. Early human studies should demonstrate that adequate exposure can be achieved with acceptable safety.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** FPM concurs that the product is not anticipated to be efficacious in preventing or treating COVID-19 caused by current circulating variants and should not be approved for use in the NHS.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** As the product being considered is currently not anticipated to be efficacious from the data, the recommendation is sound. FPM would like to note that it has had representations from multiple patient organisations representing some of the >500,000 immunosuppressed patients in the UK, which overwhelmingly confirm the patient perspectives in the report, stating predominantly that shielding has placed patients and their families at great strain, with constant anxiety and reduced mobility. This has interfered with everyday life and has contributed to some carers having to stop work during the

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	ongoing epidemic in order to protect their immunosuppressed relative. The patient perspectives have reflected that for some patients e.g. those being treated for cancer or receiving dialysis, there is a necessity to travel to hospital centres for treatment, which places them at greater risk of infection, given the considerably higher rate of infection in healthcare facilities than in the general community. Patients that have undergone organ transplantation cannot take the NICE recommended Paxlovid treatment for covid infection and those recently transplanted cannot respond to vaccination. This puts them at greater risk of infection and death from disease. Taken in context with the MTA guidance this is problematic for them. Access to passive protection offered by new monoclonal combinations would enable these individuals to live a more normal life free from fear and protect the considerable investment made in giving them a transplant.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** None.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

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Name of commentator person completing form:	Jill Nicholson
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Discrimination and inequality has occurred.
2	NICE's objective and that of our society is to be inclusive. The legislation that Evusheld has undergone means the "bench mark" for this product has been set higher than other vaccinations in circulation. There is no proof that the longevity and efficacy of Evusheld is any worse than our current vaccines which we know give NO protection to the immunosuppressed community.
3	It is of great concern to discover, that if Evusheld was not available two antiviral post exposure treatments have been withdrawn further limiting lifestyle options for the immunocompromised. Many of these people have contra indications against some of the anti virals, but not so for Evusheld.
4	The mental health of the immune compromised (and that of their dependants) would take another back step without Evusheld. (for example I have actually paid out for this vaccine and travelled on the bus for the first time in 3 years. I now visit my elderly in laws with a mask inside, but don`t ask that they wear theirs) Life quality has this improved with Evusheld for all concerned.
5	We are in the same position as that of 3 years ago, but by ourselves – abandoned and without a government/medical plan.
6	There could be problems in the future. Every single person in the CEV community is DEEPLY CONCERNED that in future this long winded process will yet again leave us cast aside. Whilst this is not necessarily connected to Evusheld evaluation in itself we are utterly terrified about the future, even though we are living in a first world country in the 21st century.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Single Technology Appraisal

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Comments on the DG received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

There is no mention of any evidence being sought from the 30+ other countries who have already been administering Evusheld or indeed any evidence as to why these other countries have decided that, unlike the United Kingdom, it is appropriate to administer Evusheld.

The evidence also does not take account of a lack of United Kingdom Government messaging on the severity of COVID. In particular the United Kingdom Government has not highlighted the significant risks relating to potential cardiovascular, blood vessel, lung, brain, immune system and Long COVID disorders associated with COVID infections.

If the United Kingdom Government highlighted the significant risks in each of these areas to the general population there would be a twofold impact. Firstly Immunocompromised non-shielders would potentially change their behavioural patterns and secondly the general population would potentially engage in more mitigations against COVID. The impact of proper COVID messaging is therefore likely to be that some of the Immunocompromised non-shielders would shield as at the moment they are in an "ignorance is bliss" bubble. There would therefore be an increased requirement for a preventative treatment such as Evusheld as more people would be shielding. The other outcome would be a reduction in the spread of COVID as the general population would engage in more mitigations against COVID. This would have the knock on impact that the Immunocompromised population would feel more able to move about as the ongoing COVID levels would drop and especially if they were administered a preventative treatment against COVID . This all assumes proper messaging as to the severity of COVID by the United Kingdom Government in the first place.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Although it is accepted that there is a need for sophisticated cost modelling with regard to Evusheld there is also a need for a "helicopter view" of the costings.

The percentage of Immunocompromised people who are hospitalised by COVID is disproportionately high compared to the percentage of Immunocompromised people in the general population by a significant amount. Immunocompromised people who are hospitalised are, in general, in hospital for longer and therefore the associated cost is significantly higher. A high level exercise should be carried out to compare the cost saved by the non-hospitalisation of a proportion of Immunocompromised people because of protection from a treatment like Evusheld against the cost of administering preventative treatments such as Evusheld. Since the beginning of COVID tens of thousands of Immunocompromised people have been hospitalised. This exercise would show that the hospitalisation costs which would be saved are significantly higher than the cost of administering Evusheld or an equivalent. If a preventative treatment was administered to the Immunocompromised group it would significantly reduce the number of Immunocompromised people hospitalised and would also free up valuable resource within the NHS. Effectively a significant hidden cost would also be removed.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations do not stress enough the need for a speedy approval process for potential future preventative treatments for the Immunocompromised population. It is imperative that future treatments such as Evusheld 2 are approved rapidly to ensure they are administered to the Immunocompromised population when they are effective as has been the case with COVID vaccines to date.

The irony of the current consideration of Evusheld is that a treatment which was created in the United Kingdom was authorised for emergency use in the United States in December 2021 and was administered to patients up until recently. However, in the United Kingdom the review of Evusheld has not been completed close to 15 months after it was approved for use in the United States.

This cannot be allowed to happen for future preventative treatments or else the Immunocompromised population will have to continue to shield indefinitely.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

All Immunocompromised people should be given the right to future preventative treatments not just those at highest risk. If this were not to be the case then there would still be a significant minority of the Immunocompromised population who would feel discriminated against.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This draft guidance discriminates on the grounds of disability – people who have had no/poor response to covid vaccines are not offered any protection against covid, despite being more vulnerable. As such, there should have been more patient experts and the afternoon session should have been held earlier in the day - at least one patient was exhausted - or the session held in the morning, or patient experts allowed to pre-record responses to set questions. Patient engagement must be realistic and respectful of patients' needs to be valid.

- Section 1 – Recommendations, point 1.1 'The limitations in the clinical evidence mean it is not possible to make a reliable cost-effectiveness estimate.'

Given that Evusheld was effective against previous dominant Omicron variants, and probably cost-effective on that basis, it is devastating that an opportunity was missed to address an urgent unmet need for people who are at high risk from COVID-19 - those who have no/inadequate response to, or unable to receive, vaccinations.

If Evusheld had been appraised more rapidly, vulnerable patients, including those like me with severe SLE, may have been able to have some protection from COVID-19 when previous variants were dominant during the second half of 2022. In addition to providing vital protection, reducing risk of severe illness, this treatment could have drastically improved quality of life

for a group of people continuing to experience the adverse impact of shielding.

As it was since getting covid in August I have ongoing lung damage and aside from participating in the Rapid Protection trial where I have had one dose of Evusheld in January 2023, I still can't leave the flat because, apart from the fact that current variants aren't well covered, I'm now too unwell. No one really understands what has happened to my lungs post-Covid, six months on there is no diagnosis or prognosis. I am concerned about what will happen if I get Covid, or any other respiratory illness on top of this damage. My days are dominated by a hideous productive cough that hasn't responded to several courses of antibiotics, and sleeping. I am now on yet another course of antibiotics. I don't have anything like a life.

First I was robbed of the opportunity for protection by the incredible decision to put Evusheld through a lengthy NICE process, then I was led to believe that there would be antivirals. I had the letter, the phone number etc, but due to bureaucratic delays got the wrong antiviral, too late, then got rebound and nobody knew what to do. Like many patients, I feel let down and abandoned at every turn.

While I welcome the recommendation to create a new fast-track system for updating recommendations for Covid treatments, I am concerned to understand if this a process for updating existing recommendations, or the evaluation of new treatments.

It is essential that new and novel COVID-19 treatments are included in a fast-track appraisal system, so as not to waste future treatments and opportunities to protect vulnerable people.

1. When is NICE going to get an appropriate process in place to deal with pandemic-related medications, especially for the vulnerable?
2. Will it be ready when the next Supernova version of Evusheld that covers new and current variants and is expected in the second half of this year?
3. Failing this, what improved antiviral delivery is being arranged for vulnerable people?

- Section 2 – Information about tixagevimab plus cilgavimab

2. I am concerned that the recommendations suggest a required threshold of evidence that is too high for medicines such as these to ever be approved in a timely manner.

In section 3.23, the committee recommends that "further data collection through clinical trial would be a more appropriate way to resolve key uncertainties". Given NHS constraints on clinical trials in general, the length of time it takes to establish and run clinical trials, and the rapidity of variant mutations, this all conspires to bring us to the same point – the moment when a treatment could have been effective will have passed.
The reliance on in-vitro evidence alone is strange, as in this case it does not

seem to accurately demonstrate real-world, clinical efficacy of the treatment. I may have missed it, but I didn't see/hear any references to the use of Evusheld in other countries and their view of efficacy/cost-benefit.
The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high given the rapid changes in circulating variants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities mean they have no/little response to, or are unable to receive, vaccination. A wider range of evidence needs to be synthesised to more rapidly and accurately assess the efficacy of monoclonal antibody treatments.

- Section 3 – Committee discussion

The evidence used by the committee for this recommendation implies that, because (some) people at higher risk from COVID-19 continue to modify their behaviour by shielding, their true risk cannot be fully considered in cost-effectiveness modelling.

Section 3.16 of the draft recommendations states that: "…data for the general population [on infection risk] may not be generalisable to those likely to have tix-cil. The committee considered it likely that the risk of infection in those eligible for tix-cil would be lower than the general population. This is because those eligible for tix-cil modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden." The committee then considered that the model should be sensitive to changes or differences in background levels of risk.
This implies that because (some) are able to take that burden, their true risk (should they not modify their behaviour) is not an accurate measure. Can I suggest that the committee review stereotypes of a shielding person? You cannot assume that those at risk can reduce their risk of exposure to the virus by modifying just their own behaviour, but also that of family, friends, carers. Behaviour modifications aside from shielding are increasingly difficult due to the withdrawal of general precautionary measures and governmental support, including widespread testing.

Also, it is now more difficult for at-risk people to shield. Most people in this group are living with a disease and/or treatment that requires hospital attendance and medical monitoring. Even if an at-risk person can stay safe travelling to and from appointments, the precautionary measures in these settings are being increasingly abandoned. It is not reasonable to use lower risk values to model cost-effectiveness for this group, because it is not reasonable to assume that all at-risk people and their households are able to adequately modify their behaviour, nor is it reasonable to expect those that are able to, to continue shielding given the difficulties and well-documented mental and physical health impacts of this.

- Section 3 – Committee discussion, point 3.2 ‘Patient perspectives’

The committee appears to have underestimated the direct utility gain to shielding patients. The committee suggests that the evidence submitted by patient experts implies a lower direct utility gain due to more limited behaviour change in shielding behaviours than the Company submitted in evidence. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for almost three years, to immediately return to pre-pandemic behaviour, even if a treatment was able to provide 100% protection. Due to decline in mental and physical health, it is unrealistic to expect these patients to immediately or fully return to pre-pandemic behaviours.

Additionally, in the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients, patients were not necessarily requesting a complete return to their pre-pandemic life, but a desire and need to have more of life open to them (even if that still includes some precautions like masking, for example), and that this could make huge improvements to their mental and physical health.

When considering direct utility gains related to changes in shielding behaviours, the committee should consider change over time as people regain confidence and physical strength, rather than just immediate changes in behaviour. Continuing some shielding or protective behaviours should also not be viewed as a lack of impact, as there can still be a significant impact on mental and physical health if people feel able to do more whilst still masking, for example.

Finally, on a personal note, while an at-risk person living alone might be able to manage to avoid Covid, the toll of the social isolation over the years of the pandemic puts them at very real risk of a collapse of their mental state. They might not have Covid, but they don’t have a life either.
Like most at-risk people who are also at risk of other infectious diseases, I am habituated to avoiding crowds and other aspects of shielding. Nevertheless, when I was given Evusheld as part of the Rapid Protection trial, I did experience a reduction in the sense of abandonment and a greater hopefulness for the future. My days have been very bleak, and I’ve wondered what I’m going through all of this for. If I got nothing else from Evusheld, this was worth it and will hopefully keep me going until the more timely approval of the next Supernova version of Evusheld or another prophylactic treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Re section 4.3
It's my anecdotal experience that a good proportion of these patients are actually very poorly informed of their situation. A significant proportion have never heard of Evusheld and many don't even realise they are not well protected by vaccination. I spoke to a transplant patient recently who has only had 3 vaccines for example, he thought he was well protected and no one told him otherwise. He hadn't had a booster for well over a year. Another whom I discussed the situation with recently had no idea there was anything else out their apart from vaccines, she was shocked when i told her about Evusheld and the fact other countries had protected their transplant communities many months ago.

The communication to these vulnerable groups from government has been exceptionally poor in my opinion. Many people do not seek out information, it has to be put in front of them. It's a mistake to assume that just because someone has a serious medical condition that they all take a deep active interest in their situation. Therefore, an ONS type study would be of limited use. Asking people if they are still shielding when a fair proportion don't actually realise they are still at high risk is meaningless. It's a disgraceful situation in my view and exacerbated with the false and deluded narrative that "it's all over". Vulnerable groups are not immune to this narrative and also suffer a lot of ill-informed peer pressure from "friends" and family.

Re section 3.3
My own situation is similar to the patient experts who appeared at the committee meeting. I have been effectively shielding since the beginning of March 2020,soon to be three years. During that time I have not been in a shop or a restaurant. I have had no one inside my house and have been in no indoor spaces aside from medical facilities. If we need petrol I "pay at pump" while wearing a mask, my medication is delivered and left at the door, likewise my supermarket deliveries. Everything I do is risk assessed. Accessing safe health care is increasingly difficult, I wear an FFP3 mask at all times outside my home.

I have transplant friends who have been abused in the street and even in a pharmacy for wearing a mask and trying to navigate a dystopian world safely. We are discriminated against.

I can't even see my own father in his nursing home, I am restricted to window visits from the car park and an occasional garden visit in PPE in the summer. The staff in the home no longer wear masks, nobody is testing, they have had multiple outbreaks one of which very nearly caused my

father’s demise last year. It's a high risk environment which is not safe for me to enter.

I and my husband are retired, he has shielded with me throughout and hence has not seen his family in Yorkshire since 2019.We have economic spending power but can't use it, we have been effectively excluded from society and the economy by government Covid policy and the lack of preventative drugs. I have looked after my transplant fiercely for many years and will not gamble with my health when i am not adequately protected. We desperately need effective preventative drugs and rapid action on procurement when they are available.

The availability of post infection treatments is absolutely no solace to me. Firstly, the provision is hit and miss, I know a number of people who have had a dreadful battle to access treatment, some failing entirely. Other people have been told "they aren't ill enough " at the time to be given them, absolutely ludicrous.

Even if the system worked properly it's not a risk to be a taken. If I may use the analogy of a car accident it's much better not to have it than get treatment for the damage afterwards.

I have not had Evusheld, I had a virtual private consultation for it around Christmas time at a proposed cost of £1500. It was apparent to me by that time that it was probably approaching the end of its useful life, so I didn't proceed. I will be waiting and shielding until the updated version is available, hopefully on the NHS but privately if not. This protection should be provided by the state, no question of that. We don't have the tools to "live with Covid".

I am a former medical professional in the transplant field and also a transplant patient with multiple comorbidities, perhaps a near unique situation. I believe NICE have made a reasonable decision on Evusheld given the situation on the ground by the time this drug reached the committee. However the fact that this has taken so long is appalling, Evusheld did have proven effectiveness earlier in its life and UK patients have missed out on a years worth of protection sinch MHRA approval.
I am heartened by NICE acknowledging the need for rapid appraisal of preventative Covid drugs such as these. We cannot carry on with the status quo, these drugs have a limited useful life against a moving target, they need rapid rollout as soon as efficacy is proven. The current system means nobody would ever get anything, the drug would be past it's "use by date" or approaching it before it even reaches a decision-making process.

I hope we now have a window for NICE to instigate the rapid evaluation process in time for the updated version of Evusheld which is due for release in the second half of this year.

I think this is a reasonable decision given the current variant mix in the UK. However it does not excuse the lamentable time it has taken to get to this

stage during which these cohorts have missed out on many months worth of protection.
I am however heartened by the committees acknowledgment of the urgent clinical need and the wish to act much faster with similar future preventative drugs.

- Has all of the relevant evidence been taken into account?

Given so much evidence around current efficacy of Evusheld is anecdotal then the NICE decision is understandable.
It is however a great shame that it has taken so long to get to this stage.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I believe NICE has made a fair appraisal of the situation given the current situation on the ground in terms of variant mix etc.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I believe so, I am heartened by the recommendation for a rapid assessment committee and the acceptance of the urgent clinical need for Covid preventative drugs.

I am less convinced by the stated need for an ONS type survey of the highly vulnerable cohorts. It's my opinion that too many do not understand they are still at high risk and would act differently if they were properly informed.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I don't believe the NICE decision in isolation is discriminatory in any way, it is fair and balanced.

However, these groups are most certainly being discriminated against or even persecuted in day-to-day life in a way which is not acceptable in a modern Western nation. They have been constructively excluded from society because of their medical vulnerabilities.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No. There are problems with the studies used in evidence and the arguments used in justification of preventing access to this treatment. There was a lack of evidence as to the effectiveness of covid vaccination when first given and for new variants, but mass vaccination was provided. We know the risk to immunocompromised and those groups not able to access vaccination. We know the impact on lives although underestimated. In reality many people are impacted other than the person shielding or vulnerable. QUALYs are hugely impacted for those who are in need of this health care provision. To prevent it is discriminatory when available and is prevention of basic healthcare need. There is a need to look at alternative treatments such as infusions for those who need Covid treatment after catching it who are immunocompromised - further immunity impact for 3 months - hardly appropriate against the use of Evusheld. To prevent this preventative is unethical. It is a choice to leave people at risk of death when this is preventable. It is discriminatory as due to our health care needs, we are placed at higher risk and this choice to prevent lowering risk is a choice against the most vulnerable in certain groups of society based on certain characteristics.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. The cost to health and social care of failure to give this treatment is outweighed massively by vulnerable people who are immunocompromised if they should contract COVID. A transplant patient may lose their transplant. The ongoing costs of this are huge and would massively outweigh treatment with prevention. The treatment of covid once contracted are more likely to need more intensive costs for the population groups being discussed. The summaries detract from the ethical reality which is that most vulnerable people are not able to shield in reality as they cannot remove themselves from risk if they live with family or are cared/carers for/by someone else and are having contact with medical services, food from shops, mail, parcels and all other sources of possible sources of infection. To say that people who take responsibility for their healthcare and do everything to minimise their risk would take more risk if access to prevention is given is both insulting and naïve. For many it would be lowering risk in everyday life circumstances within their home or work which they cannot do anything about whilst doing everything possible to mitigate these risks. They took vaccination and still shielded. They fought to keep the 8-week gap between vaccinations as recommended in little green vaccination book for

immunocompromised despite the government deciding against advice on a 12-week gap for all members of society. The arguments do not stack up in reality. To treat certain groups as unvalued members of society not provided with equality of protection is a failure of the government to keep its citizens safe and protected. If our risk is heightened by measures to relax lock down for other members of society, then we need other measures to protect us due to our health characteristics.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. It holds the same negligence and disregarding attitude when decisions were taken to start discharging people from hospital back to nursing homes without a known COVID status at the start of the pandemic. Same as not ensuring vulnerable were vaccinated according to guidance at 8-week internals due to lack of immune response and antibody death after this period. We know the risk, we know how we could prevent harm and vulnerable people are put at additional preventable risk of severe illness, harm and even death as a result of a decision to continue to fail to protect. It is an unethical decision against a vulnerable at-risk group. It is as though society would rather reduce their burden of the vulnerable rather than the vulnerable's burden of risk. It is discriminatory and not sound or suitable to recommend as guidance to the NHS if we are a modern moral society measured by how we take care of our most vulnerable.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

prevention of access to equitable healthcare is an issue and this is discriminatory to those with long term health conditions and or disabilities for which this treatment has been developed. Groups affected should have been contacted and views given as part of equality impact assessment. In itself the wording in the impact assessment acknowledges the groups likely to be affected most but personally I find the wording offensive...it might as well say but it only affects...the less contributing members of society. Personally, the document appears as skewed towards declining this treatment for the most vulnerable and leaving them at the mercy of living in society with no protection or interest in protecting them against Covid. The whole decision is appalling and unethical. Cost effective decision - well it may ultimately reduce benefits and pensions budgets, and free up hospital and social care places if the risk is left high for vulnerable groups to succumb to COVID? What is the political motivation to provide this protection? morals? well vulnerable were all given priority in vaccination roll out weren't we? or were we the first guinea pigs subjected to a vaccination program that was hailed a success but in reality did very little for the protection of the most vulnerable immunocompromised groups as the 8

week interval was not carried out as clinically advised by JVCI to be effective...civilised moral society? I do wonder.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No, real life data was not taken into account and the effect of delay on the human beings involved.
These are real people and the delay has seriously affected peoples quality of life!

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, real life data was not included and the whole process was unfair!

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, it was based on insufficient holistic data, a lot of valuable time has been lost and the questions asked on the 24th of January should have been asked months ago!

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity

Yes, you were aware that Evusheld had some effect against covid in the early stages, yet you still took this length of time to make a decision, the government and NICE discriminated against immunosuppressed patients compared to the general population and you have already disabled them by your inaction!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Cardiothoracic Transplant Patient Group at NHSBT
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

The Cardiothoracic Transplant Patient Group appreciates that the clinical evidence suggests that tix-cil is unlikely to be effective against the current relevant Covid 19 variants.

The Cardiothoracic Transplant Patient Group believe that the extreme length of the assessment process has directly led to a missed opportunity of tix-cil's window of effectiveness. The Medicines and Healthcare products Regulatory Agency approved tix-cil on 17 March 2022. At this time Omicron BA.2 was the dominant UK variant and remained so until approximately June 2022. Omicron BA.5 then succeeded in becoming the dominant variant until approximately Nov 2022.

The In Vitro Advisory Group report demonstrated tix-cil had neutralising activity against Omicron BA.2 and to a lesser extent Omicron BA.5 which were the dominant strains for the 8 months preceding the drug's authorisation. Additionally, the observational study Young-Xu et al was conducted when Omicron BA.2 was one of the dominant variants.

If approval and delivery of tix-cil had been given as close as possible to 17 March 2022, then the Cardiothoracic Transplant Patient Group believe that some of its patient population could have gained a material benefit.

As a direct consequence of the length of assessment process some patients who have received a heart and / or lung transplant will have experienced avoidable morbidity and mortality.

Whilst the preliminary recommendations have not been discriminatory, the speed at which they have been produced has discriminated against people whose life is sustained by either a donated heart or lung.

The Cardiothoracic Transplant Patient Group appreciate further organisations in addition to NICE were involved during the whole decision process for tix-cil. These include commissioners and the Medicines and Healthcare products Regulatory Agency.

The Cardiothoracic Transplant Patient Group would encourage all relevant bodies to work collaboratively in the future to ensure appraisals and approvals of any treatments to prevent Covid 19 in high-risk groups are conducted rapidly.

The Cardiothoracic Transplant Patient Group is concerned that the committee may have not received all relevant evidence related to

cardiothoracic transplant recipients due to the lack of professional inclusion and engagement from the cardiothoracic transplant clinical community. The Cardiothoracic Transplant Patient Group are extremely concerned that the list of professional groups does not include The British Transplantation Society, or any cardiac related group such as The British Society for Heart Failure.

The Cardiothoracic Transplant Patient Group is further concerned by the relative lack of stakeholder engagement from cardiac related patient / carer groups. Other relevant groups could include, British Heart Foundation, Somerville Heart Foundation, Pumping Marvellous and Pulmonary Hypertension Association UK.

The Cardiothoracic Transplant Patient Group consider that the NICE appraisal process should place patients at the centre of their decision making. To achieve this patient engagement could be enhanced. Representative patients from NHS formally appointed bodies should be considered preferential to those from other organisations. The Cardiothoracic Transplant Patient Group (part of NHSBT) would be a good example of such a body. The Group has formal processes to ensure that the views it gives are representative of a whole patient population rather than that of an individual patient.

- Has all of the relevant evidence been taken into account?

No - please see comments made within the relevant document sections.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes at a higher level, but insufficient analysis at a defined patient group analysis.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, but the speed of the process has deficiencies which are acknowledged in the recommendations.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes, please see relevant comments within the relevant body of the document.

- Section 3 – Committee discussion, point 3.17 ‘Hospitalisation risk (without tix-cil)

The Cardiothoracic Transplant Patient Group recognise the challenges the NICE Appraisal Committee have with estimating Covid-19 hospitalisation risk. The Group, however, considers that the Appraisal Committee need to improve engagement with stakeholder groups to facilitate this process.

Whilst NICE acknowledge that the benefit gain will vary within the selected eligible population the only defined sub patient group which has a hospitalisation rate tested by NICE is that within Shield et al. (2022). More proactive engagement with stakeholder groups on this specific matter may yield further useful information.

The Cardiothoracic Transplant Patient Group wish to highlight several pieces of additional information, all of which indicate that NICE may have underestimated hospitalisation risk in certain high-risk patient groups, with some specific references to risk within solid organ transplant recipients and cardiothoracic transplant recipients.

1) Callaghan et al (2023) (Vaccine Effectiveness Against the SARS-CoV-2 B.1.1.529 Omicr... : Transplantation (lww.com)) measured vaccine effectiveness against the Covid 19 Omicron B.1.1.529 variant in solid organ or islet transplant recipients. This revealed an overall hospitalisation or death risk of 5.8% in this patient population. Further interrogation of the information provided, showed a Covid 19 mortality rate of 6.2% and 12.0% for heart and lung recipients respectively in the whole study period (Dec 20 – March 22 - which is post UK vaccine deployment). Every solid organ transplant study demonstrates heart and particularly lungs transplant recipients to be at higher risk of severe Covid 19 than the whole transplant population. It is thus reasonable to assume that the risk of hospitalisation or death risk to heart and lung transplant recipients was much higher than 5.8% in the Covid 19 Omicron B.1.1.529 variant era.

2) The first results of the MELODY study have been published, Pearce et al (2023) (Antibody prevalence after 3 or more COVID-19 vaccine doses in 23,000 immunosuppressed individuals: a cross-sectional study from MELODY | medRxiv).

This investigated the prevalence of spike-protein antibodies following at least 3 Covid 19 vaccinations in immunocompromised individuals. Three patient groups were included, solid organ transplants, rare autoimmune rheumatic diseases, and lymphoid malignancies. The headline results revealed that solid organ transplant recipients had the highest levels (23.3%) of no detectable IgG spike protein antibodies in the three patient cohorts.

Further interrogation of the data reveals that heart (25.7%) and lung (35.4%) have the highest percentage of undetectable antibodies of the solid organ transplant cohort.

3) Evans et al (2023) (Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study | medRxiv) undertook a retrospective study on high risk patients in Wales eligible for out of hospital Covid 19 therapies. This study revealed an all-cause hospitalisation or death risk within 28 days of 10.9% of those who had not received any treatment.

4) Radcliffe et al (2022) (Real-world experience with available, outpatient COVID-19 therapies in solid organ transplant recipients during the omicron surge - American Journal of Transplantation (amjtransplant.org)) conducted a single centre retrospective study on the effectiveness of out of hospital Covid therapies on reducing the risk of hospitalisation. This showed that of the patient cohort which did not receive any treatment, 27% were hospitalised within 30 days of Covid 19 diagnosis. It should be noted that the study group did not contain any lung transplant recipients and 18% were heart transplant recipients.

5) The latest Covid 19 mortality figures published by NHS Blood and Transplant (monthly-report-on-covid-19-nhsbt-16-march-2022.pdf (windows.net)), reveals mortality rates of 15.5% and 7.5% for lung and heart transplant recipients respectively.

In summary The Cardiothoracic Transplant Patient Group believe that future NICE appraisals must, where information is available, analyse benefit at a defined patient cohort level. This is especially relevant where the patient cohort is congruent with a single identifiable protected characteristic such as individuals with donated heart or lungs.

The Cardiothoracic Transplant Patient Group is concerned that the focus on hospitalisation risk underestimates the risk of severe Covid 19. Data provided by Callaghan et al (2023) revealed that in solid organ or islet transplant recipients 0.71% of patients died within 28 days of a positive Covid 19 test who were not admitted to hospital for a noninjury. As such The Cardiothoracic Transplant Patient Group believe that in future calculations of severe Covid 19 NICE should utilise hospitalisation and mortality statistics. Alternatively, a multiplier on hospitalisation risk could be used to estimate the additional patient cohort – based on Callaghan et all, for solid organ or islet transplants this would be 1.14.

- Section 3 – Committee discussion, point 3.23 ‘Recommendation’

The Cardiothoracic Transplant Patient Group commend the NICE Evaluation Committee for recognising the urgent need for an effective prophylactic treatment for people who do not have an adequate response to vaccination. The Cardiothoracic Transplant Patient Group believe that the NHS need to commit to all members of the public receiving an equitable opportunity for protection from Covid 19 regardless of their disability.

- Section 4 – Recommendations for research, point 4.1

The Cardiothoracic Transplant Patient Group welcome the NICE Evaluation Committee acknowledging the need for tix-cil to be evaluated quickly against all new variants.

The Cardiothoracic Transplant Patient Group would also encourage the company to enter tix-cil into the suggested ongoing platform trials.

- Section 4 – Recommendations for research, point 4.2

The Cardiothoracic Transplant Patient Group supports the recommendation outlined in 4.2.

In the stakeholder meeting of 15 February 2023, a potential quicker assessment timeframe of 90 days was suggested. The Cardiothoracic Transplant Patient Group does not consider this aim to be sufficiently ambitious. Covid variant evolution is rapid and variant domination can easily pass within such a time duration.

As such the Cardiothoracic Transplant Patient Group would recommend a pre-emptive approval and delivery model. Such a model could establish pre agreed in vitro efficacy achievement levels at which the required cost effectiveness estimates are delivered. This could grant automatic (or very rapid authorisation) and trigger pre planned delivery methods. The model and delivery could be tailored at patient group levels, with different authorisation points depending on benefit gained by each group.

The Cardiothoracic Transplant Patient Group, post-transplant patients, would be an excellent example of a known defined, very high-risk patient group.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I believe that there a two main issues with respect to relevant evidence. The first issue is the disparity with which prophylactic protection for the disabled immunocompromised (Evusheld) was forced down a different process than that of the prophylactic protection for the immunocompetent (vaccines). This caused a vastly elongated timescale, 15 months longer than in other countries such as the USA, in which Covid-19 naturally mutated many times, to the point where Evusheld naturally became less

effective against current variants. Hence, the immunocompromised in the UK missing out on at least 15 months of protection that many other countries took advantage of.

The second issue is the fact that NICE took too little notice of the real world clinical data, that proved Evusheld was effective in many countries, and put too much of an emphasis on in vitro studies that have been proven by medical experts to have little or no bearing on the clinical effectiveness of a medicine. Whilst the experts do say that where there is no reaction at all of the medicine on the Covid-19 variant, it is safe to say that the medicine will not be effective, they go on to say that where there is some effect of the medicine at whatever level on the Covid-19 variant, that there will be some clinical effectiveness, however there is no collation of the percentage effectiveness from in vitro to real world effectiveness. In fact low in vitro percentages have been proven not to be an indicator in the real world, where higher effectiveness has been demonstrated.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe the summaries of the clinical or cost effectiveness reasonably interpret the evidence.
For example, in the clinical effectiveness it is stated that Evusheld is not effective against the current variants nor those likely in the next 6 months. The effectiveness against the current variants is largely based on the flawed conclusions drawn from the in vitro studies, as outlined above in question 1. The exact knowledge of the variants that will be prevalent in 6 months' time can be little more than guess work, given the evidence of how Covid-19 has mutated over the last 3 years. Therefore, the conclusion that Evusheld will not be clinically effective on the variants that will be prevalent in 6 months' time, is clearly flawed. A much better approach would have been to approve Evusheld or similar medicines against future variant, but to hold the distribution until it is probable that they would be more clinically effective against the imminently future variants, similar to what the USA has done.
On cost effectiveness I believe the interpretations of the evidence were fundamentally flawed on a number of accounts. For example, a large amount of the cost/ benefit analysis was weighted on the number of people shielding, and to base the number of people shielding on a Gallop survey of 48 people was fundamentally and statistically flawed.
In addition, the utility study was based on the total population estimates of those shielding, which are heavily based on the estimates of those people who are immunocompromised. There is strong evidence that the numbers shielding does not only include those who are immunocompromised, but also the family members that they live with. This would greatly increase the utility population numbers, and the associated impact. Also, on this impact, I do not believe the cost effectiveness has truly factored in the full economic cost of making so many immunocompromised and their loved ones economically inactive. For example, in my own case I have had to give up my business, not only losing my income, but my employees also losing their income. In itself this has cost the UK economy not only in lost employment,

lost corporate tax, lost income and NI tax, but also lost VAT as there is a reduced spending power, and a reduced spending opportunity for myself and my wife. This tax cost alone is more than a dozen times the cost of Evusheld per annum. In addition, my wife had to give up her profession as a nurse, at a much-needed time for nurses. In terms of ongoing costs, we have been living off our retirement savings, and at some point, these will run out and then we will have to turn to the State for support, which we would not have had to do if we could have carried on working. My wife and I are not alone in the community of the unprotected shielding immunocompromised, where the relatively low cost of Evusheld would be more than made up for in direct tax income to the economy.
Also none of the lost income to the economy of forcing the immunocompromised to continue shielding seems to take notice of the multiplier effect that those lost jobs, income and expenditure that has been lost to our economy through shielding. For example, in my business I worked many companies delivering value to them, and spent much more than I can whilst shielding with UK businesses, on holidays, eating out, etc. All the above cost benefit to the economy have been lost and needs to be factored in the cost effectiveness calculation.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

For the above reasons in the answers to question 1 and 2, the recommendations for guidance to the NHS, and indeed to the British economy, are not sound. The evaluation process used is not fit for purpose to use in a case like Covid-19, and the clinical and cost effectiveness interpretations of the narrow field of evidence are neither medically nor economically sound or complete. As a result, the recommendation to the NHS are not sound.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The population that Covid-19 impacts the greatest are the CEV disabled immunocompromised. For this group the effectiveness of the prophylactic vaccines that were rolled out through a fit for purpose rapid evaluation process is close to no existence, due to the fact that vaccines need a working immune system to produce the antibodies.

When medical science caught up and AZ developed an effective prophylactic for the immunocompromised, Evusheld, that was delivered to people in the USA and 30+ other countries from December 2021, it was at this point or before that the same rapid evaluation process used for the immunocompetent vaccines should have been used for the disabled immunocompromised on Evusheld. This did not happen in the UK and the immunocompromised prophylactic, Evusheld, was forced by our

government to go down a different, elongated, and not fit for purpose evaluation process. As a result, the disabled immunocompromised, and their loved ones, have been forced to shield for an additional 15 months plus more than others. I believe this to have been unlawful discrimination against a disabled group of people.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I do not believe that the devastating impact on patients and their close family has been taken into account sufficiently. It is well past the point that the permanent damage done to shielders and their loved ones needs to be fully recognised and action taken immediately to release us from purgatory.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

What cost can be put on releasing us from a life sentence in solitary confinement, which prevents us from being able to live rather than exist? I have paid several hundred thousand in taxes but now when we don't have access to funds. we are cast aside, the computer says NO. Tell my beautiful granddaughter that she doesn't matter. That we don't matter after 3 years in solitary confinement for no crime other than my partner having leukaemia.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I really don't know.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

For people like my partner and I, we will never have a post Covid era. We, like millions of others, are stuck in permanent exclusion from life. A life sentence in solitary with no prospect of a release date. It is not just the extremely clinically vulnerable who stay shut away from real life, it is all of their friends and family. [redacted] oldest daughter has a beautiful daughter, born on [redacted], who we have only seen in photos or video calls.

She lives in the South West of England, but we can't smell her hair, hold her hand, throw her up and catch her in fits of giggles. Knowing what you are prevented from doing because our governments have decided that we and our granddaughter just don't matter, is absolute torture. We were shut up, locked away and they have lost the key and have no interest in buying a key to release us from this existing Hell, for it can't be called a living Hell.

Could any one of the politicians look that beautiful little girl in the face and say "You don't matter, your need to know where you come from, who your grandparents are, doesn't matter. For her and her parents' privacy I can't share her photo, but I can tell you that every person who has seen the sheer joy in that little girl's eyes will tell you, she is a girl who deserves everything the world can provide. The politicians all stood up and justified lock down as protecting the NHS and protecting the vulnerable. Both in Westminster and Holyrood, they got their hours of faked concern in front of the world's cameras, when we all know it was fake. Meanwhile they ruined lives not then begun without a second of consideration. How has their plan worked out? The NHS is, across all parts of the UK, broken beyond repair. The vulnerable are forgotten, left to rot in torture with their nearest if not always dearest, amputated from life as they knew it.

I am neurodiverse and heartbroken, I live with the searing heartachingly sad knowledge that my man, the person I love more than anyone I have ever known, is in decline, his spirit is broken, he has given up any hope of being alive. He exists. He committed no crime but together with myself, his daughters and his beautiful granddaughter, we are all serving a life sentence in solitary from each other, never mind all the other things we could be doing. Were he a criminal it would be a breach of law in every country in the world to be treated this way. I doubt even North Korea would imprison a man's spirit in this way. We cannot and will not remain silent any longer. This is abuse of the worst kind.

I returned home from a work trip, having worn a mask, sanitised throughout, just 2 weeks ago, desperate to see [redacted], hug and kiss him. But I couldn't, I left the train, walked to the car, wearing a mask, he was wearing his mask, exhausted from a drive of 20 minutes, we passed each other with barely a look. drove home with the windows down on a chilly late evening in February. Little was said. Why, because hugs, kisses and excited sharing has to wait until I know it is safe. It became clear the following day that I had contracted a very nasty virus, most likely Influenza A. So my quarantine continues, I am still very unwell, with no GP able to tell me when it will be safe to escape from my bedroom. As I type this, the evening before his birthday, [redacted] has just put a flask of tea and a chocolate biscuit outside the door, although I only asked for tea, he showed his love for me in the only way he can until my quarantine is over, a chocolate biscuit.
If anyone thinks that what I have shared is acceptable, please ask them to contact me and explain why they think it is fine for us to "just wait, be patient". We have had enough, it is cruel beyond measure to expect anyone to live like this, when you have in your hands the means to release us all. It

may not be perfect but 32 other countries have enabled their citizens to have the opportunity to live. I fail to see why this cannot be provided for us.

Tixagevimab–cilgavimab for preventing COVID-19: A Single Technology Appraisal

3rd ADDENDUM

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Date completed 27/03/2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135698.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

1 Introduction

In February 2023, NICE published draft guidance for consultation.[1] The company submitted a consultation response in March 2023,[2] and this addendum provides a critique of the additional evidence provided by the company in their response to the appraisal consultation document (ACD).

This EAG addendum is structured around the key issues discussed in the company's ACD response. Section 2 summarises the additional evidence submitted and also includes the EAG's critique of the new data and/or assumptions. The key areas of additional evidence are: a recent in press article reporting utility values in patients receiving Evusheld (see Section 2.3), some studies reporting hospitalisation risks in specific subpopulations (see Section 2.5), and a set of updated cost-effectiveness analyses (see Section 3.1). The ACD response also provides an updated definition of the company's preferred target population (see Section 2.1) and some additional discussion of the relevance of various model parameters to the target population (see Section 2.2). The EAG also provides comment on areas of the ACD response that impact the cost-effectiveness analysis including: assumed dosing regimen (Section 2.8), administration costs (Section 2.9), setting for administration (Section 2.10), relevance of carer disutility (Section 2.4), potential for Evusheld to provide clinical benefit in the absence of *in vitro* neutralisation (Section 2.6) and evidence cited to support the company's proposed *in vitro* neutralisation threshold (Section 2.7). The methods of the company's updated economic analysis are described in Section 3.1 along with the EAG's critique of these analyses, whilst Section 3.2 describes the methods for the EAG's additional analyses. Results of the company's updated analysis and the EAG's additional analyses are provided in Section 4.1 and 4.2 respectively, followed by conclusions in Section 5.

The company's response to the ACD also made comments on what the company considers to be most appropriate process going forward for the evaluation of prophylactic treatments for COVID-19.[2] The EAG believes that is not appropriate for it to comment on process issues and therefore the company's comments on these matters are not considered here. Similarly matters related to the committee's conclusions are not commented on here except where these may be impacted by any additional evidence or justifications provided by the company.

2 Summary of the company's response to the ACD and EAG critique

2.1 Target population for Evusheld

In the original company submission (CS), the company described the target population as being a subset of the licensed indication representing those at highest risk of an adverse COVID-19 outcome. The CS acknowledged that this 'highest-risk' group would be a subgroup of the marketing authorisation which was more broadly specified as those who are unlikely to mount an adequate immune response to

COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended. The company stated that this highest-risk subgroup should be aligned with the population identified in a report by an Independent Advisory Group (IAG), chaired by McInnes, which defined the highest-risk clinical subgroups when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs for the treatment of COVID-19 (referred to in the EAG report as McInnes *et al*).[3]

Between the receipt of the CS and the first appraisal committee meeting, a second report was produced by the same IAG which defined the highest-risk groups when considering COVID-19 prophylaxis with antibodies (document 8 of the committee papers; referred to as the 'IAG report' in the committee slides at ACM1).[4] This report defines priority cohorts as follows:

A1 – Known failure of vaccination

A2 – Anticipated failure of vaccination

B – Anticipated suboptimal vaccination response

C – Anticipated good vaccination response

In the first committee meeting (ACM1), the committee considered how the marketing authorisation of Evusheld relates to the risk groups defined in this IAG report. The committee concluded that the marketing authorisation for Evusheld would include groups A1, A2 and B.

In its ACD response[2], the company provided further clarification on its preferred target population for Evusheld which it described as follows:

- Adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to a person infected with SARS-CoV-2 and:
    - are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, with high-risk reflecting groups A1, A2 and a subset of group B (patients who do not have serological response to vaccination) from the IAG report[4], or
    - for whom COVID-19 vaccination is not recommended
    - where Evusheld displays neutralisation activity against a threshold of circulating variants

The company's ACD response is therefore focused on presenting the clinical and cost-effectiveness evidence relevant to groups A1, A2 and the subgroup of patients in group B who do not have serological response to vaccination. In the ACD the committee concluded that it would have preferred to see an analysis that included the whole population covered by the marketing authorisation (A1, A2 and B), in addition to a subgroup analysis in those with the highest risk (A1 and A2).[1]

EAG critique

The EAG notes that the company's proposed target population is still a subset of the marketing authorisation and therefore the company's ACD response dose not fully address the committee's preferences expressed in the ACD. In fact, the company's preferred target population is now more narrowly defined than at the time of the original CS because it restricts group B to those with a demonstrated lack of serological response to vaccination.

The company also does not define how serological response to vaccination should be defined and does not include any costs in their economic analysis to reflect the need to identify those without a serological response from within IAG group B. The IAG report offers a provisional recommendation for serology testing stating that an appropriately timed measurement of BAU/ml on the Roche assay (or equivalent on an alternative platform) could be used and states that it would be most useful in group B.[4] The EAG considers that if the only reason to conduct serology testing is to determine the individual's eligibility for prophylaxis with Evusheld, then the cost of serology testing for group B should be included in the modelling. The costing analysis should take into account the number of serological tests that are likely to be needed in group B to identify one eligible patient. The EAG notes that group B was reported in the committee slides as being anticipated to include 630,000 people and therefore the total cost of serology testing in this population could be high.

The MELODY study has recently reported the prevalence of spike-protein antibodies following at least three COVID-19 vaccine doses in immunocompromised individuals.[5] This study included patients with rare autoimmune rheumatic diseases (RAIRD) and the prevalence of antibodies was examined according to the immunosuppressive treatment received. Overall, 14% of RAIRD patients had no detectable spike-protein antibodies, with this being more common (50%) in those treated with an anti-CD20 therapy who would fall in IAG group A2. In the patients receiving an immunosuppressive treatment that would place them in IAG group B, the risk ranged from 7.6% in those receiving methotrexate to 13.5% in those receiving cyclophosphamide. This suggests that approximately 10 serological tests would need to be conducted in RAIRD patients falling in IAG group B to identify one patient eligible for Evusheld under the company's proposed approach. However, the EAG note that this ratio could be significantly different in the other specific patient populations falling within IAG group B who were not examined in the MELODY study. The EAG considers that the expected cost for serological testing to identify the company's proposed target population from within IAG group B is an area of considerable uncertainty that is not adequately addressed by the company's ACD response.

2.2 Relevance of the data sources applied in the model to the target population for Evusheld

The committee slides for the first meeting included a table presenting how some of the data sources related to the different risk cohorts defined in the IAG report (slide 26). In the company's ACD response it provides a narrative justification for each of these data sources. The EAG has reproduced this as Table 1 below and has provided additional comments where relevant. It has also included information provided by the company in Appendix 2 of its ACD response on the relevance of the various parameter sources to the target population and included critique of these where appropriate.

EAG critique

Overall, the EAG still considers that many of the parameter inputs to the model are either not specific to the target population, or they are specific to one subgroup within the target population and therefore they do not reflect the potential heterogeneity within the target population. As stated previously in its description of Issue 3 and Issue 15 in the main EAG report, the EAG would have preferred the company to have provided cost-effectiveness analysis for specific subgroups of interest within the target population. Although the EAG acknowledges that because the key driver for benefits in the model is the direct utility gain from patients feeling protected and reducing shielding behaviours, capturing potential heterogeneity in this parameter would be more important than reflecting heterogeneity in other parameters which have a smaller impact on cost-effectiveness. In addition, the interaction between perceived efficacy, reduced shielding behaviours and risk of infection is complex and difficult to predict and may be very dependent on the individual's circumstances and their particular reason for being considered high risk. The EAG considers that this complex interaction is likely to contribute significantly to heterogeneity in the benefits of Evusheld achieved in clinical practice.

Table 1 Model inputs and eligible populations [adapted from Table 1 and Table 5 of the company's response to the ACD[2]]

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
Baseline characteristics (Used to estimate mortality and utility)	PROVENT trial[6]	Adults at increased risk of inadequate response to vaccination or at increased risk of SARS-CoV-2 infection	A1, A2, B, C and uncategorised	The baseline characteristics, sourced from the PROVENT trial, included individuals that were immunocompromised or had an inadequate immune response to a COVID-19 vaccine. Baseline characteristics used in the model only include age, percentage of males and weight. These characteristics are not specifically linked to defining the IAG cohorts however these would be expected to have minimal impact if the population used by the model were broader than the scoped population. Results of the deterministic sensitivity analysis in both the Company and EAG base cases showed that when age, percentage male and weight were varied using the standard error, there was not a substantial impact on the ICER.	The EAG notes that the EAG's base case ICER at the time of ACM1 was not particularly sensitive to the patient's baseline characteristics as the majority of the QALY gain (64%) was derived from the direct utility gain attributable to patients feeling protected by pre-exposure prophylaxis which was not dependent on patient characteristics in the model. However, the EAG believes that there is likely to be considerable heterogeneity in the direct utility gain experienced within the target population as the amount to which an individual patient's health-related quality of life (HRQoL) is improved by pre-exposure prophylaxis will depend on the degree to which they are currently shielding, the extent to which their behaviour is likely to change and their perception of the protection provided. These in turn could be highly variable across individuals and could depend on their overall general health, their comorbidities and their susceptibility to infections other than SARS-CoV-2.
Risk of COVID-19 infection (without Evusheld)	UK government[7]	General population of England between August 2021 and August 2022	Mostly uncategorised	The risk of infection was taken from the general population risk of COVID-19 without Evusheld. This risk was used in the economic model for the cohort that had not received Evusheld. Since this risk was taken from a mostly uncategorised risk, it can be assumed that in practice, the risk of COVID-19 to cohorts IAG A1, A2 and	The committee concluded in the ACD that it considered it likely that the risk of infection in those eligible for Evusheld would be lower than the risk in the general population because immunocompromised groups are likely to modify their behaviour to avoid infection.[1] However, it was uncertain how risk may vary across different

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
				seronegative B patients, would be higher. Therefore, the company would like to highlight that this is a conservative estimate of the risk of COVID-19 in the target population. Furthermore, scenario analysis has been run including varying the infection risk by ± 20% and showed limited impact on the ICER (See Table 3 of the company's response to the ACD).[2]	risk-based groups and wanted to see different risk levels explored in sensitivity analyses. The EAG notes that the company has not presented any additional evidence on the risk in different groups within their ACD response, although it provides scenario analyses to explore different levels of risk as requested by the committee (± 20 of baseline risk). The EAG notes that this is a small variation in the absolute risk (9.6% to 14.4% versus 12.0% in the base case) and may not capture the true uncertainty in the future infection risk or the potential variability between groups. The EAG also notes that the period used by the company to estimate the risk in the general population (August 2021 to August 2022) included the large peak at the end of 2021 and start of 2022 and restricting the data to the 3 months up to August 2022 would reduce the annual incidence from 22% to 8%. Whilst this does not predict the incidence going forwards it does demonstrate how variable the risk is over time.
Efficacy of Evusheld in preventing infection	66% reduction based on RWE study by Young-Xu *et al.* 2022.[8]	US veterans (aged ≥18 years), immunocompromised or otherwise at high-risk for COVID-19.	Not stated by company	The company has not provided any justification in Table 5 of their ACD response[2] of whether the efficacy evidence from the RWE study by Young *et al.* is reflective of the expected outcomes in the target population.	As discussed in Issue 3 of the EAG report (see also Section 4.3.4.3), Young-Xu *et al.* report consistent results between their overall cohort who they describe as being immunocompromised and the severely immunocompromised subgroup. However, the company explicitly excluded other studies in specific populations from their clinical effectiveness review (see Section 3.2 of the EAG report). The EAG would prefer to see the model populated for specific

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
					subgroups, such as those having solid organ transplant, as previously stated in Issue 3 of the EAG report.
Risk of hospitalisation for COVID-19 (without pre-exposure prophylaxis)	Shields *et al.* 2022[9]	Patients with primary and secondary immunodeficiency* in the UK, during Omicron wave (up to April 2022). Subgroup that was not treated in COVID-19 Medicine Delivery Units (CMDUs). *Receiving immunoglobulin replacement therapy or had a serum IgG concentration less than 4g/L and were receiving regular antibiotic prophylaxis to prevent infections.	A2	The risk of hospitalisation is based on Shields *et al.* (2022) which assess the hospitalisation and mortality risk for immunodeficient individuals (IAG group 2). This population is deemed appropriate since the study was conducted on individuals with primary or secondary immunodeficiency, and would therefore, not mount a sufficient response to vaccination. Whilst the company acknowledges that this population contains individuals with both more severe and less severe immunodeficiency, this source was deemed most appropriate to capture the target population. This source is also most representative of the optimised population in which AstraZeneca seeks reimbursement in i.e., those in A1, A2 and seronegative B patients. These patients represent the highest risk of the high-risk population.	The EAG notes that the company has not provided any additional evidence on this point. Although they state that the population in Shields *et al.*[9] are reflective of IAG group A2, the EAG notes that patients with primary and secondary immunodeficiencies are only two of the eight populations specified in group A2. The relevance of the estimated risk of hospitalisation from Patel *et al.*,[10] which the committee preferred at the time of the first meeting,[1] is further discussed in Section 2.5 of this addendum.
Direct utility gain for people receiving Evusheld	Gallop *et al.* 2022,[11] commissioned by company	Immunocompromised individuals	Majority A2	A study by Gallop *et al.* 2022[11] (commissioned by AstraZeneca) determined the direct utility gain for individuals receiving Evusheld. The study was conducted in a population that were largely categorised into the IAG cohort A2. The utility gain could be even greater if it were to include the estimates of QOL impact for the more vulnerable A1 population, who would likely exhibit shielding behaviours. The utility gain, of 0.098, has only been applied to 82% of the model population to	The EAG notes that the company has not provided any evidence to support their statement that the group in A1 are '*more vulnerable*' and more likely to exhibit shielding behaviour. This group includes those unable to complete vaccination and people in any risk group who have had one or more admissions due to moderate to severe COVID-19 despite vaccination. These groups could potentially include a large number of people who may not currently be shielding because they were not in the cohort originally advised to shield.

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
				reflect the proportion of patients who are either fully or partially shielding according to the ONS survey.[12] Based on the evidence collected in the general population, this utility gain may be considered conservative since: • An EQ-5D utility gain of 0.324 was reported between the post-treatment and shielding health states in the general population, and • An EQ-5D utility gain of 0.156 was reported between the post-treatment and modified behavior health states in the general population[11]	Therefore, the direct utility gain estimated by the company may not be realised in patients falling in group A1 unless they also have a condition that would place them in groups A2 or B.
Level of hospital care required	Cusinato, 2022[13]	Cusinato *et al.*2022 utilised a UK based population to derive hospital ventilation levels.	Not stated by company but considered by the EAG to be mostly uncategorised	The company acknowledges that the population of Cusinato *et al.* is not specific to immunocompromised patients and thus may underestimate the true severity of hospitalisation associated with COVID-19 infection in the high-risk cohort, however it was the only UK based study identified at the time and the data captured reflected the model structure chosen for the evaluation.	The EAG consider that the proportion of patients requiring invasive mechanical ventilation (IMV) should reflect recent data to capture the shift in practice across the NHS to using non-invasive ventilation (NIV) between the first and second waves as well as the potential impact of vaccination and the Omicron variant on COVID-19 severity (see EAG report section 4.3.4.8). The EAG estimated a risk of 2.51% based on routine data from the general population in the 3 months up to Oct 2022.[14] However, the EAG used the higher risk of 4.92% in its base case which the company had estimated over a longer period (Oct 2021 to Oct 2022)[14] because it acknowledged that the risk of hospitalisation may be higher in the target cohort who are immune compromised.

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
					The company has not provided any additional data or rationale in its ACD response that changes the EAG's preferred approach.
Adverse events	TACKLE trial, Montgomery *et al.*, 2022[15]	Immunocompetent outpatients	Not stated by company but considered by the EAG to be mostly uncategorised	The TACKLE trial utilises the higher dose of 600mg and was therefore used to assess the safety profile of 600mg Evusheld. The TACKLE trial was conducted in immunocompetent outpatient individuals with COVID-19. Since the population was immunocompetent, it may be considered a conservative estimate of adverse events for Evusheld.	The EAG notes that at least 60% of randomised patients in TACKLE were required to meet the definition of high-risk for severe COVID-19, and 90% had one or more risk factor, but these risk factors were different to those defined in the IAG report. Only 5% were categorised as being in the immunocompromised state. It is unclear to the EAG how this would impact on the expected incidence of adverse events, but these were not a significant driver of cost-effectiveness.
All-cause mortality	Odnoletkova *et al.*, 2018[16]	All-cause mortality in the general population taken from UK life tables with standardised mortality ratio of 1.7 applied for common variable immunodeficiency disorders (CVID), based on Odnoletkova *et al.* 2018	A1 and A2	Odnoletkova *et al.* 2018 derived a standardised mortality ratio for patients with CVID. CVID is a primary immunodeficiency typically characterised by significantly decreased levels of IgG, in combination with decreased IgA and/or IgM, poor vaccine response, and increased susceptibility to bacterial infections. This population largely aligns with IAG cohort A1 and A2, with reduced vaccine response.	The EAG considers that this cohort aligns with a subgroup of A2. However, it may not reflect all-cause mortality across all the different populations included in IAG group A2 and is unlikely to reflect the whole target population as discussed in section 4.3.4.3 of the original EAG report. The EAG considers that all-cause mortality may vary significantly across the groups covered within IAG groups A1, A2 and B and the company's modelling dose not explore this heterogeneity.
Acute mortality	Based on Ohsfeldt *et al.* 2022[17] and ICNARC data[18]	Mortality from the COV-BARRIER study for patients nor requiring oxygen and routine data from ICNARC for all other groups.	Not stated by company but considered by the EAG to be mostly uncategorised	Ohsfeldt *et al.* 2022 did not require eligible population to be immunocompromised. Whilst this data was deemed most appropriate for the economic evaluation, it could be a conservative estimate when applied to the immunocompromised population.	The EAG had some difficultly verifying these data from the stated sources (see 4.3.4.11 of the EAG report). However, the EAG concluded that the overall mortality rate of 2.5% appeared to be similar to the infection fatality rate in the Shields *et al.*[9] cohort during the Omicron wave. Therefore, these data were considered to have external validity for IAG group A2. The EAG does

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
					not believe that the company has made a case to support these estimates being conservative across the whole target population.
Utility in the target population	Rafia *et al.*, 2022[19] which cites Ara and Brazier.[20]	A baseline disutility of 0.1160 is applied to all patients to reflect baseline comorbidities in line with the utility value applied in Rafia *et al.* 2022, for people with heart conditions (sourced from Ara *et al.*).	Not stated by company but considered by the EAG to be mostly uncategorised	The company acknowledges that the utility decrement is not directly from the IAG cohorts A1 or A2, however, this data was not available. This disutility was used to reflect the comorbidities of patients hospitalised with COVID-19 at study entry and is based on UK tariff EQ-5D-3L data. Furthermore, since the A1 and A2 populations are considered "the highest risk of the high-risk population", this is likely to be a conservative estimate.	As previously stated in Section 4.3.4.3 of the EAG report, the EAG is unclear how this utility decrement relates to the target population. The company has not presented any new information in the ACD response to justify why it considers the utility decrement for people with heart conditions (other than hypertension) to be smaller than the HRQoL decrement for the various groups that make up the target population. It considers that there is likely to be significant heterogeneity in baseline HRQoL within the IAG groups A1, A2 and B.
Risk of long COVID in hospitalised patients	Augustin 2021[21]	General population	Not stated by company but considered by the EAG to be mostly uncategorised	In the model the proportion of non-hospitalised patients who suffer with long-COVID is 34.8%, based on a study by Augustin *et al.* (2021). At the time of the study, patients were unvaccinated. Given the target population are known, anticipated to fail vaccination or expect a weak immune response, the company believe this study to be a good approximation of the long COVID rate in non-hospitalised patients and can be assumed to be equivalent to those who are unable to mount a vaccine response (IAG cohort A1, A2 and a proportion of B).	The EAG prefers to take the risk of long COVID (12.7%) from a study by Ballering *et al.*[22] which accounted for the prevalence of long COVID symptoms in those not reporting a SARS-CoV-2 infection (see EAG report section 4.3.4.13). Although the company argues that the data from Augustin *et al.* would be more reflective of the target population because the cohort in Augustin *et al.* was unvaccinated, the EAG notes that only 9.8% of the cohort reported by Ballering *et al.* was vaccinated.
Risk of long COVID in hospitalised patients	100% assumed for hospitalised	Based on assumption	Not applicable	It was assumed all of the hospitalised patients develop long COVID. A study Evans *et al.*[23] found that only 20-30% of the general population in most severe health states had recovered at 6 months. The target populations are expected to have a	The company has not provided any evidence to support its statement that the target population would be expected to have worse outcomes than the general population.

Model parameter	Company's source	Population	IAG cohorts	Company justification	EAG comments
				significantly worse outcomes and therefore a slower recovery.	
Disutility of long COVID	PHOS-COVID cohort (Evans 2021 and Evans 2022)[23, 24]	Patients admitted for COVID-19	Not stated by company but considered by the EAG to be mostly uncategorised	In the absence of available disutility data specific to long COVID patients, long-term post discharge disutility values were calculated from Evans *et al.* 2021. Since Evans used a largely immunocompetent population, this disutility value could be considered a conservative estimate when applied to the IAG cohort IA1, IA2 and part of B.	As discussed previously in Section 4.3.4.15 of the EAG report, the company has applied the long COVID disutility reported in a cohort admitted for COVID-19 who did not require oxygen to COVID-19 cases in the model that did not require hospitalisation. The EAG is not satisfied that the symptoms of long COVID will be similar in those who did and did not require admission for COVID-19. The company has not provided any evidence to support its statement that the disutility from Evans *et al.* is expected to be conservative which implies that the target population would be expected to have worse outcomes than the general population.

2.3 Estimation of the direct utility gain attributable to Evusheld

The company restates that the utility study by Gallop *et al.*,[11] which informed both the company's base case analysis and the EAG's preferred base case analysis at the time of ACM1, is the best available evidence to quantify the direct utility gain associated with pre-exposure prophylaxis. The company has provided an additional new study by Follows *et al.* as supporting evidence.[25]

The study by Follows *et al.* was an online questionnaire which used 35 questions drawn from the EQ-5D-3L, DSM5 agoraphobia score, Duke's Social Support Index (DSSI) and Hospital Anxiety and Depression Score (HADS).[25] Questionnaires were sent to [redacted] patients who had received self-funded Evusheld treatment at a non-NHS UK clinic. All patients who received Evusheld had a diagnosis of blood cancer but not all had received systemic anti-cancer therapy (SACT). Questionnaires were also sent to [redacted] control patients, who were blood cancer patients, recruited from the same non-NHS clinic, who had not received Evusheld but who had received SACT within the preceding 6 months. Control patients received an additional 3 questions regarding their reasons for not receiving Evusheld. For the patients receiving Evusheld, scores were compared for the 3-weeks pre and 3-weeks post Evusheld treatment. It is unclear if this was based on a single questionnaire asking about two different time periods or questionnaires administered at different time points. Differences were analysed statically using chi-squared and paired t-tests. Responses were available for [redacted] of the [redacted] Evusheld patients and [redacted] of the [redacted] control patients. Follows *et al.* report that the proportion reporting some problems on the EQ-5D usual activities domain [redacted] pre-Evusheld to [redacted] post-Evusheld [redacted] whereas the proportion was [redacted] in the control group. For the anxiety/depression EQ-5D domain, the proportion reporting some problems [redacted] whereas the proportion was [redacted] in the control group [redacted] no statistical comparison is reported versus controls). The authors report that Evusheld [redacted] other EQ-5D domains (mobility, self-care, pain/discomfort). The authors report that the EQ-5D 'mean measure of global health' [redacted] following Evusheld with the latter being [redacted] the value in controls [redacted] The EAG is not sure whether this measure refers to a utility value generated from the EQ-5D or the EQ-5D visual analogue scale (VAS) score, but it assumes that it refers to the EQ-5D VAS because no reference is provided for the valuation algorithm applied to estimate utility values from EQ-5D domain scores.

<u>EAG critique</u>

The EAG notes that the study by Follow *et al.* provided by the company is currently unpublished and appears to be a pre-peer review version. The paper provides insufficient information for the EAG to properly assess any risk of bias. In addition, the EAG has the following concerns regarding the study

based on the information that is provided. Firstly, the authors do not explicitly state whether the pre-treatment scores were collected prospectively or based on post-treatment recall. However, the fact that there was no reporting of loss to follow-up or response rates at the two different time points and the fact that the methods refer to a single questionnaire suggests that the data were collected at single time point which would result in the potential for recall bias. There are no baseline characteristics reported for either group and therefore it is not possible to assess if the controls were similar to the treated group, but it is known that all controls had received SACT whereas not all treated patients had received SACT. It is also unclear how representative these patients might be of the broader group likely to receive Evusheld in clinical practice. The patients are described as having 'blood cancer', which is too vague to assess which IAG group the patients would be categorised under. For example, some haematological malignancies are covered in IAG group A2, with others covered in group B but only if they received SACT in the past 12 months, which was not the case for all those in the study who received Evusheld. Also, the patients were all receiving treatment in a private clinic making them a selective subset of the population eligible for treatment in the NHS. There was the potential for significant bias due to non-response rates of [redacted] in the Evusheld group and [redacted] in the control group, with no information provided in the paper on whether those who responded to the questionnaire were similar or different to those who did not respond. The authors acknowledge that the group suffering the greatest psychological burden from fear of COVID-19 are both the group most likely to self-fund Evusheld and the group most likely to report benefit. This is reflected in the fact that [redacted]. The EAG agrees with the author's conclusion that, *"these data need to be validated in a larger patient cohort without potential biases introduced by the 'self-funding' nature of Evusheld treatment in this study"*. Although the company states in their submission that the study was conducted during a period where several variants which Evusheld did not neutralise were emerging, the EAG was unable to confirm the time period of the study from the paper itself, other than the fact that it likely occurred after Evusheld became available in the private sector in October 2022. The FDA's warning on the reduced efficacy against certain variants was not added to the FDA fact sheet for Evusheld until October 2022 and the temporary suspension of Evusheld's FDA authorisation did not occur until January 2023. Therefore, it is unclear whether the patients who received Evusheld in the study were aware of its reduced neutralising capacity against emerging variants at the time of the questionnaire and whether any changes in shielding behaviour that occurred in response to receiving Evusheld will have been maintained since studies reporting the limited neutralising capacity of Evusheld against some variants have become more widely reported. It is also interesting [redacted] Overall, the EAG does not have much confidence that the

findings of this study are generalisable to the proposed use of Evusheld in the NHS across the target population defined by the company. The company's proposal that Evusheld would be offered in the NHS when it displays neutralisation activity against only a proportion of circulating variants further adds to the uncertainty regarding whether the HRQoL outcomes reported by Follows *et al.* would be realised in clinical practice.

The company's response to the ACD acknowledges that up to 50% of patients would return to their pre-treatment behaviour if there was a new treatment which Evusheld was not effective against, and the company provides a scenario in which the direct treatment utility gain is reduced by 50% accordingly.[2] The EAG now believes that this is a more realistic scenario given the data on *in vitro* neutralisation presented at the committee meeting and the decision by the FDA in late January 2023 to temporarily suspend the authorisation for Evusheld.[26] This decision by the FDA was made on the basis that the authorisation for Evusheld is now limited to periods when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90% (i.e., 10% or more are susceptible to neutralisation by Evusheld).[26] An assumption that patients will re-engage with at least some infection avoidance behaviours in situations where Evusheld is known to neutralise a small proportion of circulating variants is also consistent with the company's claim that Evusheld will not increase the risk of infection because this population of individuals who live with chronic immunosuppression are experienced at modifying their behaviours to reduce their overall risk of infection in their day-to-day lives.

2.4 Relevance of carer disutility

The CS argues that carer disutility would be relevant in this case and should be included in the economic model. However, the company has not provided any estimates of carer disutility for inclusion in the model.

EAG critique

As discussed in Addendum 1 of the EAG report, the protocol for the vignette study by Gallop *et al.* stated that the inclusion of caregiver health state vignettes will be considered if patients report in the interviews that their being at high risk of COVID-19 infection has an impact on their informal caregiver.[27] However, any discussion of results related to caregivers were omitted from the study report.[11] In the absence of the company providing any evidence on the presence and size of a caregiver disutility in the target population for Evusheld, the EAG would not support its inclusion in the model and does not consider that the company's base case analysis should be considered conservative because of the exclusion of caregiver disutility.

2.5 Risk of hospitalisation in the target population

The committee concluded in the ACD[1] that the risk of hospitalisation following COVID-19 of 15.9% based on data from Shields *et al.*[9] was likely to be "*unfeasibly high*" and preferred the estimate of 2.8% from Patel *et al.*[10] The company argues in its response to the ACD that the population in Patel *et al.* is more closely matched to those eligible to receive COVID-19 therapeutics based on the McInnes criteria and that this is a broader and lower risk group than the target population for Evusheld as now defined by the company.[2] The company also claims that a '*surprisingly large proportion*' of the patients (between 39.2% and 45.7%) included by Patel *et al.* had no evidence of having the highest risk conditions when using data from Systematized Nomenclature of Medicine (SNOMED) and International Classification of Disease version 10 (ICD-10) codes from patients' history.[2]

The company also argues that the hospitalisation risk is likely to be higher in its newly defined target population (see Section 2.1) and cites studies with hospitalisation risks ranging from 7.7% to 31.9% across five papers reporting hospitalisation following SARS-CoV-2 infection in five specific cohorts (chronic lymphocytic leukaemia,[28] haematological malignancy,[29] immunosuppressed kidney transplant recipients,[30] lung transplant patients[31] and solid organ transplant recipients[32]). All five papers report data from a single centre with three[28-30] being in the UK and two[31, 32] in the US and all have attempted to identify a cohort infected after Omicron variants emerged in December 2021 (see **Table *2***). The cohort reported by Bradwell *et al.*[29] included patients infected from October 2021 before Omicron became the dominant variant in the UK, but Bradwell *et al.* report that within the 40% of patients (n=21) in whom variant type was known, 86% of the patients were infected with an Omicron variant.

The company also states that there is an association between vaccine response and infection severity in cancer patients with an odds ratio for hospitalisation of 6.48 (95% CI, 3.31-12.67; P < .001) for individuals without an antibody response compared to those with an antibody response, based on a study by Lee *et al.*[33] In addition, Lee *et al.* report an association between COVID-19 hospitalisation and the level of antibody response across different types of cancer with lymphoma and leukaemia patients having both the highest risk of COVID-19 hospitalisation and the lowest level of antibody response.[33] The company states that this demonstrates that these groups have a higher risk when compared to other types of cancer.

Table 2 Hospitalisation risk after SARS-CoV2 infection for specific subgroups in studies reporting outcomes after Omicron variants emerged

First author, year, country	Population	Time frame	Vaccine status [a]	COVID-19 therapeutics	N_1 hospitalised / N_2 infected (N_1/N_2)
Parry, 2022[28], UK	Chronic lymphocytic leukaemia	Dec 2021 to Feb 2022	100%	36%	3/39 (7.7%)
Gleeson, 2022[30], UK	Kidney transplant recipients	Dec 2021 to Mar 2022	100%	No [b]	10/48 (20.8%)
Bradwell, 2022[29], UK	Haematological malignancy	Oct 2021 to Jan 2022	95%[c] 'vaccinated'	Yes but % not reported	14 /53 (26.4%)
Trindade, 2022[31], USA	Lung transplant recipients	Dec 2021 to Mar 2022	95% 'vaccinated'	73% nMAB 20% other	10/56 (17.9%)
Anjan, 2022[32], USA	Solid organ transplant recipients	Dec 2021 to Jan 2022	73.6% [d]	67.4%	53/166 (31.9%)

EAG critique

The EAG notes that the untreated group in the study by Patel *et al.*[10] was selected on the basis of meeting the McInnes criteria and therefore was an exact match for the group described as the target population in the original CS. The company has only provided a narrower definition since ACM1 (see Section 2.1). The patients who did not receive a COVID-19 therapeutic in the study by Patel *et al.* were recruited solely on the basis of the SNOMED and ICD -10 codes identifying one of the conditions specified by McInnes *et al.*[3] as defining the '*highest-risk*' group for adverse outcomes upon infection and it is this untreated group in which the 2.8% risk of COVID-19 related hospitalisation in patients having SARS-CoV-2 infection was estimated.[10] The figures of 39.2% to 45.7% cited by the company as the proportions having no evidence of having the highest-risk conditions, based on SNOMED and ICD-10 codes, relate to patients recruited on the basis of receiving COVID-19 therapeutics.[10] These cohorts are separate from the untreated cohort in which the estimate of 2.8% was reported. This information is therefore not relevant to whether the estimate of 2.8% is representative of the hospitalisation risk for those considered to be at the highest risk after infection with COVID-19.

The EAG also notes that Patel *et al.* conclude that in the untreated cohort there was some evidence of higher rates of hospitalisation in the pre-specified subgroup of patients with advanced kidney disease, where the incidence was 4.4%.[10] The EAG considers that this estimate and the data from the five single centre studies (see Table 2) suggest that specific patient groups within the target population may have a higher risk than the average higher-risk patient. The risk of hospitalisation applied by the EAG at the time of ACM1 was 15.9% but it should be noted that this was estimated from a study by Shields *et al.*[9] in patients with primary or secondary immunodeficiency and the figure of 15.9% relates specifically to patients who were infected after COVID-19 therapeutics became available but who did not receive COVID-19 therapeutics. The EAG agrees with the company's claim that there will be variability in the risk of hospitalisation across the various groups included in the target population. However, the EAG believes that unless the company is able to provide an economic model for each specific subgroup, the best approach is to use the average risk reported across the target population and this is provided by the 2.8% reported by Patel *et al.*

The EAG agrees with the committee's preference to use the data from Patel *et al.*[1] as the untreated group reported by Patel *et al.* is more representative of the broader group likely to receive Evusheld than the data from the specific population of primary or secondary immunodeficiency patients (Shields *et al.*[9]) applied by the EAG at the time of ACM1. In its exploratory analyses described in section 3.2, the EAG uses the 2.8% figure[10] in its base case but explores a higher figure of 31.9% from Anjan *et al.*[32] in a scenario analysis to reflect the potential higher risk in some specific groups. However, it notes that this estimate of hospitalisation risk is also uncertain as it was based on a small single-centre study in the US of patients having solid organ transplants and it may not be representative of the risk within the UK NHS for this or the other specific populations that fall within the broader target population.

2.6 Immunomodulatory function of Evusheld beyond neutralisation

The company states that monoclonal antibodies may have a range of additional functions not directly measured by in-vitro neutralisation assays and says that if real-world evidence (RWE) data emerge in the future demonstrating a clinical effect in the absence of neutralisation, then these data should be factored into decision making. It further notes that no such benefits have been incorporated in the updated economic modelling and therefore the case put forward by the company could be considered conservative.

EAG critique

The EAG notes that the company has not provided any evidence to support a clinical benefit for Evusheld in the absence of *in vitro* neutralisation in its ACD response. Therefore, the EAG does not consider the economic modelling to be conservative on the basis that these benefits have not been included.

2.7 Clinical evidence supporting efficacy against later variants.

The company proposes that an IC50 of <10,000 ng/mL is used by NICE as a threshold to determine whether Evusheld would have clinical efficacy against a particular variant. It claims that an IC50 of <10,000 ng/mL is a widely accepted threshold for neutralisation, citing Wu *et al.*,[34] and that values below this threshold would infer a clinical effect, citing Wu *et al.*[35] The company states that its proposed threshold is supported by a systematic review by Suribhatla *et al.*[36] which, *"included studies which were conducted in variants which reflected neutralisation across a range of neutralization values, and these studies also reported Evusheld treatment has led to statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 and hospitalisation. Therefore, it is appropriate to conclude that an IC50 of <10,000 ng/ml infers clinical effect"*. In addition, a brief description is provided of five of the RWE studies[8, 37-40] included by Suribhatla *et al.* which reported comparative data including information on infection risk (the 11 other non-comparative RWE studies included in the review are not described in the company's ACD response). The dominant variants across these five studies are reported by the company to include BA.1, BA.2, BA1.1, BA1.1.529, BA2.12, BA2.12.1, and BA.5.

EAG critique

It is outside of the EAG's remit to determine whether the company's proposed neutralisation threshold of an IC50 of <10,000ng/ml is an appropriate threshold to infer the clinical effectiveness of Evusheld against future variants. However, the EAG was not able to understand how the company's threshold of an IC50 of <10,000ng/ml is supported by either of the cited papers, given that neither paper mentions a threshold expressed in units of ng/mL.[34, 35]

The EAG notes that only a subset of the five RWE studies discussed in the ACD response were included in the systematic literature review in the original CS (Kertes *et al.*,[40] Young-Xu *et al.*[8]) with the others explicitly excluded (Al Jurdi *et al.*,[37] Kaminski *et al.*,[39] Chen *et al.*[38]) from the original CS. The company therefore has not presented any assessment of the potential risk of bias in some of these five studies. The EAG notes in particular that the committee had concerns about the potential for bias in the Young-Xu *et al.* and Kertes *et al.* studies, due to the likely differences between people who sought Evusheld treatment and those in the control group who did not seek treatment.[1] The EAG notes that this potential for bias would also apply to the other three RWE studies which were non-randomised. The company has also not summarised the efficacy information from these studies in their ACD response or provided any analysis exploring the potential relationship between the efficacy estimates reported by these studies and the dominating variants at the time the studies were conducted. Furthermore, not all of the RWE studies included in the review identified statistically significant and clinically important differences between treated patients and controls.[36] The paper with the lowest efficacy estimate, Chen *et al.*,[38] was also the only study that included BA.1.1 as one of the dominating variants and this variant had the most

uncertain and potentially the highest IC50 range of all the variants described as being dominating across the 5 studies (BA.1: 147-715 ng/mL; BA.2: 8.2-42 ng/mL; BA.1.1: 4.7-8090 ng/mL; BA.2.12: 18 ng/mL; BA.5: 140-586 ng/mL).[2] The company appears to be basing their conclusion regarding the efficacy of Evusheld in these RWEs studies on the meta-analyses estimates across all studies included in the review by Suribhatla *et al.*[36] However, the EAG notes that the PROVENT study[6] was included in the meta-analysis that informed the conclusions of the review by Suribhatla *et al.*[36] and therefore it is not correct to characterise the findings of this review as being based only on the five RWE studies conducted in more recent variants. Suribhatla *et al.* also state that these studies *"report on current real-world effectiveness against current SARS-CoV-2 variants and cannot forecast clinical effectiveness against future SARS-CoV-2 variants."*[36] The EAG also notes that none of the RWE studies included by Suribhatla *et al.* were conducted in populations where the dominant variant was XBB.1.5, CH.1.1. or BQ.1 which were the three variants with the highest prevalence at the time this addendum was prepared.[41]

The company also claims that *"there is evidence to suggest that even if there were a decrease in neutralisation for a new variant in relation to older variants, the loss of efficacy would not be diminished in cases of severe COVID-19.*" However, the paper cited relates to the efficacy of vaccines rather than nMABs as prophylaxis and it states that, *"the estimated neutralization level for protection from severe infection is approximately sixfold lower than the level required to protect from any symptomatic infection".*[42] The EAG notes that a sixfold change in neutralisation is small compared to fold-changes for Evusheld reported by Wang *et al.* for the BQ.1, BQ.1.1, XBB and XBB.1 variants compared with either BA.4/5 or BA.2.[43]

The EAG considers that it is outside of its remit to comment on the linkage between *in vitro* studies of drug neutralisation for different historical SARS-CoV-2 variants and expected clinical outcomes for current or future circulating variants. However, the EAG notes that the company has not presented any additional evidence on this issue that was not available at the time of ACM1 and the evidence they have presented is not directly appliable to the question of whether Evusheld maintains neutralisation against the current dominant variants (XBB.1.5, CH.1.1. or BQ.1) or those identified as rapidly increasing in the UK (XBB.1.9.1 and XBB1.9.2) at the time this addendum was prepared.[41]

2.8 Dosing regimen

The company states that the summary of product characteristics (SmPC) for Evusheld does not specifically prohibit a second dose, but has aligned its updated economic analysis with the committee's preference for the cost-effectiveness modelling to be based on a single 600mg dose (See Section 3.1) of Evusheld (as 300 mg of tixagevimab and 300 mg of cilgavimab).[1]

ERG critique

The EAG is satisfied that the company's single dose approach is in line with the committee's preferences and the implementation of this in the economic model is further discussed in Section 3.1.

2.9 Administration cost for Evusheld

The company argues that the cost of administration should be based on the figure on £216 used in the revised budget impact test. The company also argues that Evusheld should be prescribed upon specialist advice, and is therefore expected to be administered as part of routine specialist care in a hospital, or via secondary care led community services. It states that the target population for Evusheld would be expected to attend hospital regularly to manage their underlying health condition and therefore Evusheld could be administered in secondary care during patients' routine outpatient appointments.

EAG critique

The company previously requested that the EAG use the administration cost from the budget impact assessment instead of the CMDU cost and the EAG's response at the time was, *"NICE has informed the EAG that the budget impact assessment and cost-effectiveness assessments are separate processes and the technology appraisal team has not received any further information from NHS England about administration costs. Therefore, no changes are needed in the EAG's addendum."* In the absence of any additional evidence from the company on how the £216 cost has been estimated or any instruction from NICE to use the figure from the budget impact assessment, the EAG has maintained its preference for using the CMDU cost (£410) for administering COVID-19 therapeutics, as a proxy for the likely cost of using Evusheld as a pre-exposure prophylaxis. This is in keeping with the committee's preferences expressed in the ACD.[1] However, the EAG provides a scenario analysis exploring a lower cost of £216 as the ACD acknowledges that there is uncertainty about how Evusheld would be delivered.

The EAG also notes that the points made previously in Section 4.3.4.2 of the original EAG report are still relevant. For example, although the company has provided a narrower definition for the eligible population, the eligible population may be still be large given the uncertainty regarding the proportion of IAG group B who would be eligible due to a lack of serological response to vaccination and the potential size of IAG group A1 (if the EAG is correct in their interpretation that group A1 includes any patient with admission for COVID-19 after vaccination regardless of whether they also fall within group A2 or B). The EAG previously raised concerns regarding whether all eligible patients are currently being seen regularly enough in secondary care to incorporate timely administration of Evusheld within their existing outpatient follow-up schedule. This may be a particular issue for patients in group A1 who

have experienced hospital admission for COVID-19 infection after vaccination but who may not have any particular health conditions requiring ongoing management in secondary care unless they also fall within groups A2 or B. It is also unclear if it would be feasible to administer Evusheld within existing routine secondary care appointment schedules given the need for patients to be monitored for an hour after administration in an environment that does not place them at additional risk of exposure to nosocomial infections.

2.10 Impact of care setting for administration on patient access scheme implementation

The ACD expresses the committee's concern that the confidential patient access scheme (PAS) will not be realised in clinical practice given the commissioning expert's preference for Evusheld to be administered in primary care.[1] The company states that it expects Evusheld to be administered in secondary care settings or in secondary care led community services and it would be more appropriate to restrict prescribing of Evusheld to these settings.

ERG critique

The EAG cannot comment on whether the PAS will be realised in clinical practice but notes that the economic analysis assumes that the PAS is implemented fully in all cases when Evusheld is administered, which is consistent with the company's assumption that it will be administered in secondary care in all cases.

3 Additional economic analyses provided by the company and EAG

This section summarises the economic analyses presented by the company in its additional evidence document and the results of the additional analyses conducted by the EAG in response to the additional evidence. In addition to providing an updated company's base case cost-effectiveness analysis, the company response to the ACD also reports cost-effectiveness analysis results for what they call the '*updated EAG base case*'. The EAG notes that this does not in fact represent the EAG's preferred scenario as it is a mixture of data and assumptions preferred by the EAG and those preferred by the company. The EAG refers to this below as '*the company's updated EAG base case*'. For reference, the two scenarios presented by the company and the EAG's preferred updated scenario are summarised in Table 3 in terms of how they differ from the EAG's base case at the time of ACM1 (as reported in Table 7 of the first addendum to the EAG report and slide 57 at ACM1). The remainder of this section focuses on describing the company's updated base case and additional analyses conducted by the EAG, including the EAG's preferred updated scenario. No further comment is made on '*the company's updated EAG base case*' as this was submitted as a separate Microsoft Excel file and the EAG did not have time to validate two separate version of the model and so prioritised the file that generated the company's updated base case.

Table 3: Summary of areas of agreement or disagreement with EAG's base case analysis at the time of ACM1 (Yes indicates agreement) for the two scenarios presented by the company in their additional evidence and the EAG's updated base case

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's 'updated EAG base case' [a]	Company's updated base case [b]	Revised EAG's base case
EAG corrections to the company's base case - partially amended in response to the FAC	Yes	Yes	Yes
EA1: Varying size of direct utility gain or size of group it is applied for to 13%	Yes – now aligned to include utility gain to 0.098 for 82% of target population	Yes – now aligned to include utility gain to 0.098 for 82% of target population	No - utility gain of 0.098 but updated to assume 50% of patients experience direct treatment disutility (scenario assuming reduced to 10%)
EA2 Halving the duration of direct utility gain for those infected while on Evusheld	Yes	Yes	Yes
EA3: Assuming 12.7% of the non-hospitalised cohort would develop long COVID	Yes	No – 34.8% as per company's original base case	Yes
EA4: Assuming cost of administration for Evusheld of £410 based on CMDU costing exercise	No - Amended to £216 per administration from CMDU cost of £410	No - Amended to £216 per administration from CMDU cost of £410	Yes – CMDU cost of £410 maintained (but cost of £216 explored in scenario analysis)
EA5: Using the October 2022 update of the ONS data to estimate the duration for long COVID without the Evans 2022 adjustment	Yes	No, maintained company's original preferred approach using original calibrated lognormal from ScHARR MTA	Yes
EA6: Using the long COVID annual costs of £2267 assuming chronic fatigue as proxy	Yes	Yes	Yes
EA7: Recalculating disutility values due to long COVID and	Yes	Yes	Yes

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's 'updated EAG base case' [a]	Company's updated base case [b]	Revised EAG's base case
assuming linear HRQoL improvement by time for 5 years			
EA8: Using 15.9% as the risk estimate of hospitalisation for infected patients - amended from 9.9% in response to FAC	Yes	Yes	Amended to use risk of 2.8% from Patel *et al.*[10] (but explored higher risk of 31.9%[32] in scenario analysis)
EA9: Updating hospitalisation reference costs associated with acute admissions	Yes	Yes	Yes
EA10: Reducing proportion of hospitalised patients requiring invasive mechanical ventilation (IMV)	Yes	No – original company base case value retained using average data across first and second waves	Yes
EA11: Applying long COVID to new infections after 1 year - partially amended in response to the FAC	Yes	Yes	Yes
Additional changes introduced post ACM1			
Dosing of Evusheld (previously included repeat dose at 6 months)	Single dose with no repeat dose at 6 months	Single dose with no repeat dose at 6 months	Single dose with no repeat dose at 6 months
Proportion of circulation variants against which Evusheld is assumed to have efficacy (previously 100%)	10% with values up to 30% explored - applied only to RRR for COVID-19	10% with values up to 30% explored - applied only to RRR for COVID-19	10% with values up to 30% explored - applied to both RRR for COVID-19 and RRR for hospitalisation

Abbreviations: CMDU, COVID-19 Medicines Delivery Unit; FAC, factual accuracy check; HRQol, health-related quality of life; IMV, invasive mechanical ventilation; ONS, Office for National Statistics

3.1 Company's updated base case

The various model assumptions in the different scenarios are summarised in Table 3 for reference. The key changes made to the company base case since the time of ACM1 are as follows:

- A single dose of 600mg is assumed instead of two 600mg doses 6 months apart
- Direct utility gain of 0.098 from the vignette study is applied to 82% of the population instead of 100%
- Administration cost of £216 from the budget impact analysis is applied instead of the company's previous administration cost of £41
- Cost of long-COVID is updated to £2,267 per annum from £2,500
- Smaller impact of long COVID on long-term utility including a linear decline to 50% of the starting disutility over 5 years
- Reduced efficacy to reflect scenarios in which Evusheld only maintains neutralising activity against a proportion of circulating variants (10% in base case with values up to 30% explored)

In order to model the reduced efficacy expected when Evusheld maintains neutralising activity against a specific proportion of circulating variants, the company assumed that the relative risk reduction (RRR) for Evusheld for the outcome of symptomatic SARS-CoV-2 infection (i.e. COVID-19) is multiplied by the proportion of circulating variants Evusheld is able to neutralise. Therefore, the RRR of 66% for incidence of COVID-19 applied in the company's base case at the time of ACM1 is reduced to 6.6% when assuming a threshold of 10% for the proportion of variants against which Evusheld maintains neutralisation. This increases to a RRR of 46.2% when assuming Evusheld maintains neutralising activity against 30% of circulating variants. The company's base case maintains the same RRR (62%) for risk of hospitalisation in patients with COVID-19. Therefore, the reduction in efficacy due to loss of neutralising activity against a specific proportion of circulating variants is applied only to the efficacy of Evusheld in preventing COVID-19 and not to its effect on COVID-19 severity.

In addition, the company states that it has explored the uncertainty in the risk of infection without Evusheld in scenario analyses and this has been done by increasing and decreasing the risk of COVID-19 in those not receiving Evusheld by 20%. The company also explores scenarios in which 50% of the population do not experience any direct utility gain to reflect the possible impact of patients maintaining or returning to previous shielding behaviours when a high proportion of the circulating variants are known not to be neutralised by Evusheld.

<u>EAG critique</u>

The EAG notes that the company has maintained its original approach for estimating risk of long-COVID and duration of long-COVID despite the committee describing a preference in the ACD for the

EAG's approach on these two issues.[1] The company has also maintained its preference for using the data from Shields *et al.*[9] to estimate the risk of hospitalisation in patients experiencing COVID-19. This is contrary to the committee's stated preference for using data from Patel *et al.*[1, 10] In addition, the company preferred a different source to the EAG on the risk of needing invasive mechanical ventilation (IMV), see Table 3, but the ACD does not provide the committee's preferences on this issue.[1]

The company's approach to adapting the model to incorporate a single dose included two changes which were previously incorporated in their single dose scenario analysis at the time of the ACM1. These were reducing the risk of infection to represent a 6-month period of risk instead of a 12-month period of risk (12.01% vs 22.58%) and reducing the risk of adverse events to half the risk observed in the TACKLE study. The EAG noted that in the company's updated analysis a more appropriate method was used to calculate the 6-month risk from the annual risk than the previous approach at the time of ACM1 which was assuming it was simply half the annual risk. Also, the EAG noted that it was unclear if the 12-month adverse event risk reported in TACKLE should be halved given that the evidence from TACKLE related to adverse events following a single dose (the incidence had not been previously doubled as incorrectly stated in Table 24 of the original EAG report) and the incidence of adverse events may be more closely related to the number of doses than the duration of follow-up for one-off interventions such as this. However, the EAG considered the likely impact on the ICER of correcting this error to be small and therefore the EAG did not adjust the adverse event rates.

In addition to these adjustments made previously for the single-dose scenario, in the updated model the company has also reduced the duration of the direct utility gain from one year to 6 months in patients not experiencing COVID-19 in the 6 months after receiving Evusheld, and from 6 months to 3 months in patients experiencing COVID-19. The EAG considered this to be more realistic than assuming a year of direct utility benefit from a single dose given that the company previously assumed 6 months of treatment effect per dose.

The EAG notes that the company's approach to estimating cases of COVID-19 occurring after the period in which Evusheld was assumed to be efficacious (referred to in the original EAG report as 'post year one cases of COVID-19') was not updated so that reinfections and new cases in patients not previously infected could occur from 6 months instead of from a year. However, the EAG considered it unlikely that amending this to account for the single-dose assumption and a 6-month period of treatment efficacy would have a significant impact on the ICER.

The EAG notes that the company's amendments to the model to reflect a loss of neutralisation against a proportion of circulating variants does not update the proportion of the population experiencing a direct utility gain from being reassured that their risk of infection with SARS-CoV-2 has been reduced by treatment with Evusheld. The EAG believes that these two issues are interlinked and any scenario assuming reduced efficacy should also include reduced direct utility gain. The EAG's base case assumes

a 50% reduction in line with the data from the vignette study by Gallop *et al.*, [11] however, it notes that the vignette study described a situation where there was a *"new variant that the treatment was not effective against"* and did not specify how common this variant was or the specific situation where there could be no efficacy against variants making up 90% of circulating virus. The EAG considers it plausible that if Evusheld was offered when it is known to neutralise only 10% of circulating variants, then this would not provide sufficient reassurance and the majority of patients would return to full shielding. The EAG has therefore provided a scenario assuming that only 10% of patients experience a direct utility gain.

The absolute risk of COVID-19 with and without hospitalisation are shown in Table 4 for the scenario at the time of ACM1, in which Evusheld is assumed to maintain efficacy against 100% of circulating variants, and for the company's update base case where it is assumed that it maintains efficacy against only 10% of circulating variants. It can be seen that the company's approach, which applies a 10% multiplier only to the RRR for COVID-19 and not to the RRR for severe COVID-19 requiring hospitalisation in patients with COVID-19, has the unexpected effect of increasing the absolute proportion experiencing COVID-19 without hospitalisation (see Table 4). The EAG would prefer to assume that both the risk of COVID-19 and the risk of hospitalisation due to COVID-19 are affected when modelling scenarios in which Evusheld only has neutralising activity against a specific proportion of circulating variants. The justification for this is that if the definition for 'loss of neutralising activity' is chosen at the point where Evusheld is not expected to have any clinical effect against a specific variant, then this would mean no expected benefit for either infection risk or severity of infection. The EAG's preferred approach applies a 10% multiplier to both the RRR of COVID-19 and the RRR of severe COVID-19 requiring hospitalisation in patients with COVID-19. It can be seen from Table 4 that this fixes this issue with the company's approach such that the absolute proportion experiencing COVID-19 both with and without hospitalisation reduces with Evusheld, but to a degree that is smaller than when applying the full efficacy data as per the analysis at the time of ACM1.

Whilst the company has argued that the risk of hospitalisation may be higher within subgroups of patients with specific conditions, for example patients who have had solid organ transplantation (see Section 2.5), the company has not provided any cost-effectiveness analysis for these specific groups.

Table 4 Impact on absolute risks of clinical outcomes for the company's and the EAG's preferred approaches to adjusting the efficacy to account for Evusheld having reduced neutralisation activity*

Clinical outcome	Clinical outcomes without Evusheld	Clinical outcomes with Evusheld		
		assuming full efficacy against all variants (as per base case at ACM1)	applying company's approach for 10% neutralisation threshold [a]	applying EAG's approach for 10% neutralisation threshold [b]
No COVID-19	88.0%	95.9%	88.8%	88.8%
Any COVID-19	12.0%	4.1%	11.2%	11.2%
COVID-19 without hospitalisation	10.1%	3.8%	10.5%	9.6%
COVID-19 with hospitalisation	1.9%	0.3%	0.7%	1.7%

[a] reducing RRR for COVID-19 to 10% of the value assumed at ACM1; [b] as per company's approach plus reducing RRR for hospitalisation in patients with COVID-19 to 10% of value assumed at ACM1

*all scenarios presented in this table apply a 15.9% risk of hospitalisation without Evusheld to allow outcomes under the two approaches to be compared without other parameters differing but different hospitalisation risks are applied in the EAG's preferred bae case (see Section 3.2)

3.2 Additional analyses conducted by the EAG

The EAG's preferred base case following consultation on the ACD includes all the EAG's preferences at the time of ACM1 with the addition of the hospitalisation risk of 2.8% from Patel *et al.*[10] and the company's assumptions to implement a single dose. In addition, the EAG assumes that Evusheld is only effective against 10% of circulating variants, as per the company's base case analysis. As this reflects a significant reduction in efficacy, the EAG also includes a reduction from 82% to 50% in the proportion experiencing a direct utility gain in line with the findings from the vignette study (Gallop *et al.*)[11] in which half of patients stated that they would return to their pre-treatment behaviour if there was a new variant that the treatment was not effective against.

The EAG has explored a scenario in which Evusheld is assumed to maintain neutralisation against 30% of circulating variants instead of 10% as this was the upper range explored by the company. It has also explored a scenario in which the direct utility gain is restricted to 10% of patients when assuming that

Evusheld only maintains neutralisation against 10% of variants. In an attempt to address the question of whether variability in hospitalisation risk within the eligible cohort would lead to variation in the cost-effectiveness estimates, the EAG has explored the impact of applying a higher figure for hospitalisation of 31.9% from Anjan *et al.*,[32] which was the highest value from the 5 RWE studies in specific populations provided in the company response to the ACD. The EAG has also explored the impact of lower administration costs (£216) as these were considered uncertain by the committee.[1] The EAG has also explored the impact on the ICER of assuming a lower or higher risk of COVID-19. Whilst the company explored scenarios increasing and decreasing the risk by 20%, the EAG did not consider this range to be sufficient to cover the broad uncertainty regarding the future risk of COVID-19. In particular, the EAG noted that the period used by the company to estimate the risk of COVID-19 in the general population, August 2021 to August 2022, included the large peak in cases in late 2021 and early 2022. Restricting the period used to estimate the risk to the last 3 months of data provided by the company (5th May to 5th August 2022) provides an annual risk of 8% compared to 24% using the company's approach (equivalent to 6-month risks of 4% and 12% respectively). Alternatively restricting the period to 4th December 2021 to 4th March 2022 to capture a period of peak infections would give an annual risk of 40%, equivalent to a 6-month risk of 23%. Although past risks cannot be used to predict future risks with certainty, this demonstrates the potential variability in COVID-19 risk over time and therefore the potential uncertainty associated with this parameter. The EAG therefore explored the impact of halving and doubling the risk assumed in the company's base case (i.e. a 6-month risk varying from 6% to 24%).

In addition to the one-way scenarios presented, the EAG has explored a combined scenario in which the risk of infection is halved and the proportion experiencing a direct utility gain is reduced to 10% when assuming that Evusheld maintains neutralisation against 10% of variants. This is considered plausible if the majority of patients return to their previous shielding behaviour in a situation where Evusheld is known to neutralise only 10% of circulating variants. In addition, the EAG has explored a scenario in which Evusheld is assumed to maintain naturalisation against 30% of variants, and it is offered only to a population with a high risk of hospitalisation (31.9%).

4 Cost-effectiveness results

All results are presented using the PAS price for Evusheld and using the deterministic model. The EAG has not run the PSA for its preferred updated base case because it is unsure if the adjustments made to account for Evusheld being assumed to have naturalisation activity against a specified proportion of circulating variants will be appropriate within the context of the PSA. Also the EAG considers that the uncertainty in the precision of the parameters informing the analysis is likely to be smaller than the

uncertainty that arises from uncertainty regarding the appropriate midpoint for various parameters such as the risk of COVID-19 in the 6-months after Evusheld would be made available.

4.1 Summary of key results from the company's updated analysis

Table ***5*** presents the results for the company's updated base case when varying the threshold for the proportion of circulating variants that Evusheld has demonstrated neutralisation activity against. It can be seen that the ICER decreases from £15,201 to £12,911 when increasing the proportion from 10% to 30%. However, the EAG notes that these analyses do not assume any impact on direct utility gain. The EAG has also included ICERs in

Table ***5*** for the company's scenario assuming a 50% reduction in direct utility gain, and these vary from £16,763 to £20,143. The EAG notes that the company's other scenario analysis demonstrated that the ICERs increase further when combining this 50% reduction in direct utility gain with a 20% reduction in infection risk, giving ICERs ranging from £19,760 to £23,110.

Table 5: Cost-effectiveness results for the updated company base case when making different assumptions regarding the proportion of circulating variants against which Evusheld is assumed to have neutralisation activity (deterministic)

Threshold for circulating variants with neutralisation activity	Base case			ICER for scenarios	
	Incr. QALYs	Incr. Costs	ICER	assuming 50% reduction in direct utility gain	assuming 20% lower infection risk and 50% reduction in direct utility gain
10%	[redacted]	[redacted]	£15,201	£20,143	£23,110
15%	[redacted]	[redacted]	£14,597	£19,237	£22,217
20%	[redacted]	[redacted]	£14,014	£18,374	£21,363
25%	[redacted]	[redacted]	£13,452	£17,550	£20,545
30%	[redacted]	[redacted]	£12,911	£16,763	£19,760

4.2 Results of the EAG's additional analyses

The results for the EAG's additional analyses are provided in

Table **6**. It can be seen from examining EAG exploratory analyses 1 to 5 that each of the individual changes made in the EAG's preferred base case has a moderate impact on the ICER increasing it from under to over £20,000, with the exception of the EAG's approach to incorporating the 10% threshold for neutralising activity in which the ICER is £33,319. However, when each of these changes are combined in the EAG's preferred base case the ICER increases substantially to £54,668. (NB: Table 7

showing step-by-step changes between the company's updated base case and the EAG's updated preferred base case is provided in Appendix 1 for reference.)

The ICER for the EAG's preferred base case is most sensitive to changes in the proportion of patients experiencing a direct utility gain from feeling protected from COVID-19, as 97% of the QALY gains in the EAG's base case are attributable to this direct utility gain. This is because the EAG's has assumed that in the context of Evusheld being assumed to maintain neutralisation against 10% of circulating variants, the direct utility gain applies to 50% of patients. Therefore, QALYs related to the utility gain are reduced less by the loss of neutralisation than QALYs gained from preventing COVID-19 and severe COVID-19. When assuming only 10% of patients experience a direct utility gain, the ICER increases from £54,669 to £242,097, but the direct utility gain still accounts for 86% of the QALY gain in this scenario.

The EAG scenario analyses which maintain the neutralisation threshold of 10% and the direct utility gain in 50% of patients have ICERs ranging from £43,212 to £56,083, suggesting that the cost-effectiveness is not particularly sensitive to the other factors explored. The lowest ICER was estimated when assuming both a higher risk of hospitalisation (31.9%[32]) and that Evusheld maintains neutralising activity against 30% of variants. This scenario suggests that the ICER is unlikely to fall below £30,000 even in groups with a high risk of hospitalisation unless Evusheld maintains neutralisation against at least 30% of circulating variants.

Table 6: Cost-effectiveness results for the EAG's additional analyses including the PAS

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
EAG's preferred scenario at the time of ACM1							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 18,644
EAG exploratory analysis 1: EAG's preferences at the time of ACM1 but including single dose assumption							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 17,465
EAG exploratory analysis 2: EAG's preferences at the time of ACM1 but including Patel *et al.* for risk of hospitalisation							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,941
EAG exploratory analysis 3: EAG's preferences at the time of ACM1 but assuming 10% threshold for variant neutralisation using the company's preferred approach							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 23,256
EAG exploratory analysis 4: EAG's preferences at the time of ACM1 but assuming 10% threshold for variant neutralisation using the EAG's preferred approach							
No prophylaxis	[redacted]	[redacted]	[redacted]				

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 33,319
EAG exploratory analysis 5: EAG's preferences at the time of ACM1 but assuming only 50% of patients experience direct utility gain							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 24,905
EAG's updated base case: Includes 1, 2, 4 & 5.							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 54,668
EAG scenario 1: EAG updated base case maintaining threshold of 10% for neutralisation but assuming only 10% experience direct utility gain instead of 50%							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 242,097
EAG scenario 2: EAG updated base case but assuming 30% threshold for variant neutralisation instead of 10% (maintaining 50% experiencing direct utility gain)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 50,716
EAG scenario 3: EAG updated base case maintaining threshold of 10% for neutralisation plus higher risk of hospitalisation (31.9%)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 43,212
EAG scenario 4: EAG updated base case maintaining threshold of 10% for neutralisation plus lower administration cost (£216)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 46,514
EAG scenario 5: EAG updated base case maintaining threshold of 10% for neutralisation plus infection risk halved in the no pre-exposure prophylaxis arm (6% in 6 months instead of 12% in 6 months)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 54,083
EAG scenario 6: EAG updated base case maintaining threshold of 10% for neutralisation plus infection risk doubled in the no pre-exposure prophylaxis arm (24% in 6 months instead of 12% in 6 months)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 56,083
EAG scenario 7: EAG scenario 1 combined with EAG scenario 5 (EAG updated base case including 10% threshold for neutralisation plus infection risk of 6% plus proportion experiencing direct utility gain of 10%)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 253,085
EAG scenario 8: EAG scenario 2 combined with EAG scenario 3 (EAG updated base case with 30% threshold for neutralisation plus 31.9% hospitalisation risk)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,796

5 Conclusions

The company has narrowed their preferred target population to the highest risk categories (as defined in the IAG report[4]) of A1, A2 and those within group B without serological response to vaccination.

However, the company's economic analysis does not incorporate the cost of serological testing to identify the patients without a serological response from within group B. This could have a potentially large impact on the cost-effectiveness given that IAG group B was estimated at the first committee meeting to include 630,000 individuals and the proportion not having a serological response is currently unknown. Any requirement for widespread serological testing would further increase the uncertainty regarding the costs of administration for Evusheld.

Although the company argues that many of the model inputs are conservative because they do not relate specifically to their preferred target population, the company has not provided any cost-effectiveness analyses that explore the cost-effective of Evusheld in specific subgroups within the eligible population. The EAG's exploratory analyses suggest that even in groups with the highest risk of hospitalisation, Evusheld would have an ICER under £30,000 only if it maintained neutralising activity against at least 30% of circulating variants. The hospitalisation risk assumed in this analysis (31.9%) is also uncertain as it was based on a small single-centre study in the US of patients having solid organ transplants.[32] This estimate has only been used to explore what the cost-effectiveness could be in subgroups with high hospitalisation risk. It should not be considered to represent the expected ICER in the specific subgroup of solid organ transplant recipients as the company has not provided a fully populated subgroup analysis for this specific population including, for example, relevant subgroup specific efficacy estimates.

The main driver of uncertainty in the cost-effectiveness analysis is the proportion of patients experiencing a direct utility gain from feeling protected by Evusheld. This parameter is even more important when assuming that Evusheld only maintains neutralising activity against a small proportion of circulating variants (10% to 30%), because this limits the ability of Evusheld to gain QALYs and achieve cost savings through reduced infections and hospitalisations. However, the EAG notes that the direct utility gain is likely to be reduced when patients are aware that Evusheld is not protective against the majority of circulating variants because patients will probably no longer feel as protected and will likely return to previous shielding behaviours. There is also considerable uncertainty regarding the risk of COVID-19 in the target population with the only data provided by the company to inform this estimate being historical data in the general population. The future risk of COVID-19 in the target population is likely to be dependent on many factors which are difficult to predict including the rates of infection in the general population and the degree to which patients in the target population continue infection avoidance measures. Overall, the EAG considers that the ICER is highly uncertain but is likely to be above £30,000 when assuming that Evusheld only maintains neutralising activity against 10% to 30% of circulating variants, largely because the EAG expects this to reduce the direct utility gain patients are assumed to experience from feeling protected.

6 References

1. National Institute for Health and Care Excellence (NICE). *Tixagevimab plus cilgavimab for preventing COVID-19: Draft guidance for consultation*. London, UK: National Institute for Health and Care Excellence (NICE),; 2023.
2. AstraZeneca. *Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]: Company response to draft guidance*. London, UK: National Institute for Health and Clinical Excellence (NICE),; 2023.
3. Government UK. *Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs: independent advisory group report*.
4. McInnes I, on behalf of the IAG. *Independent advisory group report (IAG) concerning the use of COVID-19 directed antibodies in the prophylaxis setting in the highest risk clinical subgroups*. London, UK: National Insititute for Health and Care Excellence, ; 2022.
5. Pearce FA, Lim SH, Bythell M, Lanyon P, Hogg R, al. e. Antibody prevalence after 3 or more COVID-19 vaccine doses in 23,000 immunosuppressed individuals: a cross-sectional study from MELODY. *medRXiv* 2023.
6. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, *et al.* Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19. *New England Journal of Medicine* 2022;**386**:2188-200. https://doi.org/10.1056/NEJMoa2116620
7. Government UK. *Cases in England | Coronavirus in the UK*. URL: https://coronavirus.data.gov.uk/details/cases?areaType=nation&areaName=England (accessed).
8. Young-Xu Y, Epstein L, Marconi V. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data. *medRxiv* 2022.
9. Shields AM, Tadros S, Al-Hakim A, Nell JM, Lin MMN, Chan M, *et al.* Impact of vaccination on hospitalization and mortality from COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. *Front Immunol* 2022;**13**:984376. https://doi.org/10.3389/fimmu.2022.984376
10. Patel V, Yarwood MJ, Levick B, Gibbons DC, Drysdale M, Kerr W, *et al.* Characteristics and outcomes of patients with COVID-19 at high-risk of disease progression receiving sotrovimab, oral antivirals or no treatment in England *medRxiv* 2022; https://doi.org/10.1101/2022.11.28.22282808. https://doi.org/https://doi.org/10.1101/2022.11.28.22282808
11. Gallop K, Hall R, Lloyd A. *Estimating the quality of life benefit for immunocompromised patients treated with Evusheld: Study Report*. London. UK: Acaster Lloyd Consulting Ltd; 2022.
12. Office for National Statistics. *Coronavirus and clinically extremely vulnerable (CEV) people in England - Office for National Statistics*. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronavirusandclinicallyextremelyvulnerablepeopleinengland/latest (accessed 22/12/2022).
13. Cusinato M, Gates J, Jajbhay D, Planche T. Increased risk of death in COVID-19 hospital admissions during the second wave as compared to the first epidemic wave: a prospective, single-centre cohort study in London, UK. *Infection* 2021;**50**:457-65.
14. gov.uk. *Coronavirus (COVID-19) in the UK*. gov.uk. URL: https://coronavirus.data.gov.uk/details/healthcare?areaType=nation&areaName=England (accessed).
15. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, *et al.* Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. *The Lancet Respiratory Medicine* 2022;**0**. https://doi.org/10.1016/S2213-2600(22)00180-1
16. Odnoletkova I, Kindle G, Quinti I, Grimbacher B, Knerr V, Gathmann B, *et al.* The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society

for Immunodeficiency (ESID) registry data. *Orphanet J Rare Dis* 2018;**13**:201. https://doi.org/10.1186/s13023-018-0941-0
17. Ohsfeldt R, Kelton K, Klein T, Belger M, Mc Collam PL, Spiro T, *et al.* Cost-Effectiveness of Baricitinib Compared With Standard of Care: A Modeling Study in Hospitalized Patients With COVID-19 in the United States. *Clin Ther* 2021;**43**:1877-93 e4. https://doi.org/10.1016/j.clinthera.2021.09.016

10.1016/j.clinthera.2021.09.016. Epub 2021 Oct 4.</p>
18. Intensive Care National Audit Research Centre. *ICNARC report on COVID-19 in critical care: England, Wales and Northern Ireland*; 2022.
19. Rafia R, Martyn-St James M, Harnan S, Metry A, Hamilton J, Wong R, *et al. Remdesivir for the treatment of COVID-19: Report by the Decision Support Unit*. Sheffield, UK: University of Sheffield 2021.
20. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;**14**:539-45. https://doi.org/10.1016/j.jval.2010.10.029
21. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, *et al. Recovered not restored: Long-term health consequences after mild COVID-19 in non-hospitalized patients*. preprint: Infectious Diseases (except HIV/AIDS); 2021.
22. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM, Lifelines Corona Research I. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022;**400**:452-61. https://doi.org/10.1016/S0140-6736(22)01214-4
23. Evans RA, McAuley H, Harrison EM, Shikotra A. Physical, cognitive and mental health impacts of COVID-19 following hospitalisation: a multi-centre prospective cohort study. *The Lancet Respiratory Medicine* 2021.
24. Evans RA, Leavy OC, Richardson M, Elneima O. Clinical characteristics with inflammation profiling of Long-COVID and association with one-year recovery following hospitalisation in the UK: a prospective observational study. *medRxiv* 2022.
25. Follows AM, Clark C, Dye C, King L, Skillings G, Byrne G, *et al.* Evusheld prophylaxis improves social interactions, anxiety, depres-sion, agoraphobia, and quality of life in blood cancer patients *COVID* 2023.
26. U.S. Food and Drug Administration. *FDA announces Evusheld is not currently authorized for emergency use in the U.S.* U.S.A,: U.S. Food and Drug Administration,; 2023. URL: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us (accessed 25/03/2023, 2023).
27. Gallop K, Hall R, Lloyd A. *Estimating the quality of life benefit for immunocompromised patients if they were to receive prophylactic treatment for COVID-19: Study Protocol*. London, UK: Acaster Lloyd Consulting Ltd; 2022.
28. Parry H, Bruton R, Roberts T, McIlroy G, Damery S, Sylla P, *et al.* COVID-19 vaccines elicit robust cellular immunity and clinical protection in chronic lymphocytic leukemia. *Cancer Cell* 2022;**40**:584-6. https://doi.org/10.1016/j.ccell.2022.05.001
29. Bradwell S, Hone L, Thorneycroft K, Lambourne J, Aries JA, Davies JK, *et al.* 2022 update on the clinical outcome of coronavirus disease 2019 in haemato-oncology patients. *Leuk Res* 2022;**119**:106908. https://doi.org/10.1016/j.leukres.2022.106908
30. Gleeson S, al. e. Kidney Transplant Recipients and Omicron: Outcomes, effect of vaccines and the efficacy and safety of novel treatments. *medRxiv*; : https://doi.org/10.1101/2022.05.03.22274524. https://doi.org/: https://doi.org/10.1101/2022.05.03.22274524
31. Trindade AJ, Chapin KC, Gannon WD, Hoy H, Demarest CT, Lambright ES, *et al.* Clinical course of SARS-CoV-2 infection and recovery in lung transplant recipients. *Transpl Infect Dis* 2022;**24**:e13967. https://doi.org/10.1111/tid.13967
32. Anjan S, Khatri A, Viotti JB, Cheung T, Garcia LAC, Simkins J, *et al.* Is the Omicron variant truly less virulent in solid organ transplant recipients? *Transpl Infect Dis* 2022;**24**:e13923. https://doi.org/10.1111/tid.13923

33. Lee LYW, Tilby M, Starkey T, Ionescu MC, Burnett A, Hattersley R, *et al.* Association of SARS-CoV-2 Spike Protein Antibody Vaccine Response With Infection Severity in Patients With Cancer: A National COVID Cancer Cross-sectional Evaluation. *JAMA Oncol* 2023;**9**:188-96. https://doi.org/10.1001/jamaoncol.2022.5974
34. Wu MY, Carr EJ, Harvey R, Mears HV, Kjaer S, Townsley H, *et al.* WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. *Lancet* 2022; 10.1016/s0140-6736(22)01938-9. https://doi.org/10.1016/s0140-6736(22)01938-9
35. Wu M, Wall EC, Carr EJ, Harvey R, Townsley H, Mears HV, *et al.* Three-dose vaccination elicits neutralising antibodies against omicron. *Lancet* 2022;**399**:715-7. https://doi.org/10.1016/S0140-6736(22)00092-7
36. Suribhatla R, Starkey T, Ionescu MC, Pagliuca A, Richter A, Lee LY. Systematic review of the clinical effectiveness of Tixagevimab/Cilgavimab for prophylaxis of COVID-19 in immunocompromised patients. *MedRxiv* 2022.
37. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave. *American Journal of Transplantation*;**n/a**. https://doi.org/https://doi.org/10.1111/ajt.17128
38. Chen B, Haste N, Binkin N, Law N, Horton E, Yam N, *et al.* Real World Effectiveness of Tixagevimab/cilgavimab (Evusheld) in the Omicron Era. . *medRxiv* 2022;**2022.09.16.22280034**.
39. Kaminski H, Gigan M, Vermorel A, Charrier M, Guirle L, Jambon F, *et al.* COVID-19 morbidity decreases with tixagevimab–cilgavimab preexposure prophylaxis in kidney transplant recipient nonresponders or low-vaccine responders. *Kidney International* 2022;**0**. https://doi.org/10.1016/j.kint.2022.07.008
40. Kertes J, David SSB, Engel-Zohar N. Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality. *Clinical Infectious Diseases* 2022;**ciac625**.
41. UK Health Security Agency. *SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 51*. 2023. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1141754/variant-technical-briefing-51-10-march-2023.pdf (accessed 10/13/2023, 2023).
42. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, *et al.* Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;**27**:1205-11. https://doi.org/10.1038/s41591-021-01377-8
43. Wang Q, Iketani S, Li Z, Liu L, Guo Y, Huang Y, *et al.* Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. *Cell* 2023;**186**:279-86 e8. https://doi.org/10.1016/j.cell.2022.12.018

Appendix 1

Table 7: Analysis showing incremental steps between the company's updated preferred base case and the EAG's updated preferred baes case (both assume Evusheld maintain neutralisation against 10% of circulating variants)

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company's updated preferred base case							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 15,201
Step 1: Apply changes included in the 'company's updated EAG base case' (see Table 3)							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 18,047
Step 2: Step 1 + Apply CMDU costs as proxy for administration costs							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 21,668
Step 3: Step 2 + Apply hospitalisation risk from Patel *et al.*							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 31,337
Step 3: Step 3 + Apply direct utility gain to 50% of patients							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 49,041
EAG's updated preferred base case: Step 3 + Apply 10% multiplier to RRR for hospitalisation in patients experiencing COVID-19							
No prophylaxis	[redacted]	[redacted]	[redacted]				
Evusheld	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 54,668