RAPID C-19 report to CMO 01/09/2022:

Tixagevimab plus cilgavimab (Evusheld, AZD7442; AstraZeneca) in pre-exposure prophylaxis

Senior RAPID C-19 members	• **James Palmer:** National Medical Director Specialised services, NHSE/I • **Helen Knight:** Programme Director, Technology Appraisals and Highly Specialised technologies, NICE • **Daniel McAuley:** Director, NIHR Efficacy and Mechanisms Evaluation Programme • **Krishna Prasad:** Deputy Director, Innovative Medicines, MHRA, Principal Assessor to Commission on Human Medicines • With expert advice from the NIHR COVID-19 Prophylaxis Oversight Group

Context of current and previous reports	• In December 2021, RAPID C-19 advised the CMO of a strong signal of efficacy from the PROVENT trial of tixagevimab plus cilgavimab in pre-exposure prophylaxis (now published; Levin et al. 2022, see appendix 3).
	• RAPID C-19 proposed to prepare for patient access subject to marketing authorisation being granted (this was granted on 17 March 2022; see page 9) and confirmation of neutralising activity against Omicron by the UK Health Security Agency (UKHSA) and/or independent laboratories.
	• In May 2022, RAPID C-19 considered non-clinical data from UKHSA and the University of Oxford (now published in a pre-print; Tuekprakhon et al. May 2022) on the neutralising activity of tixagevimab and cilgavimab against Omicron variants. RAPID C-19 advised the CMO that this new information did not warrant action to progress towards patient access (see appendix 2).
	• Given the current exceptional circumstances (noted below), RAPID C-19 has reviewed real-world evidence because:
	  ○ tixagevimab and cilgavimab has a conditional marketing authorisation for the pre-exposure prophylaxis of COVID-19
	  ○ results from the key trial, PROVENT, are not generalisable to the current UK context (see page 16)
	  ○ there are no ongoing randomised controlled trials
	  ○ there is a significant unmet need in the vulnerable population who would potentially be eligible for this treatment. There is also significant interest from patient groups and clinicians for access to tixagevimab plus cilgavimab prophylaxis.

Information reviewed	The following comparative real-world evidence was considered in detail: • Young-Xu et al. 2022, Tixagevimab/cilgavimab for prevention of COVID-19 during the omicron surge: retrospective analysis of National VA electronic data (pre-print, issued 29 May 2022)

	• Kertes et al. 2022, Association between AZD7442 (tixagevimab-cilgavimab) administration and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hospitalisation and mortality, *Clinical Infectious Diseases* • Jurdi et al. 2022, Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave, brief communication in the *American Journal of Transplantation* • Bertrand et al. 2022, Efficacy of anti-SARS-CoV-2 monoclonal antibody prophylaxis and vaccination on the omicron variant of COVID-19 in kidney transplant recipients, *Kidney International,* letter to the editor • Kaminski et al. 2022, COVID-19 morbidity decreases with tixagevimab-cilgavimab pre-exposure prophylaxis in kidney transplant recipient non-responders or low-vaccine responders, *Kidney International,* letter to the editor • Non-comparative evidence was reviewed (see appendix 1) but was not considered in significant detail as inferences cannot be drawn about the outcomes for people having tixagevimab plus cilgavimab compared with those who did not. • The real-world evidence reviewed was not identified through a systematic review.
Key areas discussed	**Evidence** **Young-Xu et al. 2022, pre-print (issued May 2022)** • A retrospective cohort study in the US of veterans (≥18 years) who had healthcare through the US Department of Veterans Affairs (VA) healthcare system until 30 April, 2022 or until death (whichever occurred earlier). • Tixagevimab plus cilgavimab (300 mg total dose) was first administered in the VA on 13 January 2022. The dose was increased to 600 mg total dose on 24 February 2022 in line with the revision to the Emergency Use Authorization. Patients who had the lower dose were advised to have an additional dose. The analysis includes any patient who had ≥1 dose of tixagevimab plus cilgavimab and identified controls. • VA electronic health records were analysed and compared for a cohort of patients who had tixagevimab plus cilgavimab (n=1,733) to a propensity-matched control cohort (n=6,354) of immunocompromised or high-risk patients who did not have tixagevimab plus cilgavimab over the follow-up period. Immunocompromised status was defined as having an immunosuppressive medication within 30 days before the index date or the presence of an immunocompromising condition within 2 years before the index date. • Patients who were diagnosed with SARS-CoV-2 infection within 3 months of the date of tixagevimab plus cilgavimab administration were excluded.

	• The primary outcome was a composite of SARS-COV-2 infection confirmed by RT-PCR or antigen testing, COVID-19 hospitalisation (defined as having both an admission and discharge diagnosis for COVID-19 from a hospital or within 30 days of positive SARS-CoV-2 test), and all-cause mortality. The outcomes were also presented individually. • Sensitivity analysis using a difference in difference methodology and a falsification test (negative control) were performed. • After matching, the average age of the population who had tixagevimab and cilgavimab was 67.4 years and the average age of the control group was 68.1 years. A total of 73% of the treatment group and 74% of the control group had had 3 doses of vaccine, 92% of patients in both groups were considered immunocompromised based on diagnosis or use of immunosuppressants. **Results** **Primary outcome: composite of COVID-19 infection, COVID-19 hospitalisation, and all-cause mortality** 17/1,733 (1.0%) tixagevimab plus cilgavimab vs. 206/6,354 (3.2%) control; hazard ratio (HR) 0.31; 95% confidence interval (CI) 0.18 to 0.53 **Individual outcomes of the primary composite endpoint:** **SARS-CoV-2 infection:** <0.5% tixagevimab plus cilgavimab (numbers not shown in pre-print to protect patient information) vs. 69/6,354 (1%) control; HR 0.34; 95% CI 0.13 to 0.87 Sensitivity analysis incidence rate ratio: 0.32; 95% CI 0.24 to 0.44 **COVID-19 hospitalisation:** <0.5% tixagevimab plus cilgavimab (numbers not shown in pre-print to protect patient information) vs. 38/6,354 (0.5%) control; HR 0.13; 95% CI 0.02 to 0.99 Sensitivity analysis incidence rate ratio: 0.10; 95% CI 0.05 to 0.22 **All-cause mortality:** <0.5% tixagevimab plus cilgavimab (numbers not shown in pre-print to protect patient information) vs. 99/6,354 (2%); HR 0.36; 95% CI 0.18 to 0.73 **Kertes et al. 2022, peer-reviewed paper** • A retrospective study among members of Maccabi HealthCare Services, a large health maintenance organisation in Israel. • Between 23 February 2022 and 2 May 2022, all members aged 12 and over, weighing at least 40 kg, who did not have a positive COVID-19 test in the previous month, were not vaccinated against COVID-19 in the previous 2 weeks, and had evidence of severe immunosuppression

	were invited by SMS or email to have tixagevimab plus cilgavimab (300 mg total dose). • The study population was divided into 2 groups: those who had tixagevimab plus cilgavimab (n=825) and those who did not have the drug over the follow up period (n=4,299). • The primary outcome was the occurrence of SARS-CoV-2 infection, defined as any person with a recorded positive PCR or antigen test result in the follow-up period. • The tixagevimab plus cilgavimab group was followed up between the date of administration and the end of the study period (26 May 2022; median 53 days). The control group was followed up between the date of first SMS or email and the end of the study period (median 73 days). • Data from the Maccabi HealthCare Services database were analysed using logistic regression. Modelling adjusted for a limited set of variables which had univariate significant associations with the outcome variable. • There were statistically significant differences in the baseline characteristics between the 2 groups before adjustment (not presented after adjustment). A higher proportion of patients in the tixagevimab plus cilgavimab group were male (62.1% vs. 53.3%), had cardiovascular disease (32.6% vs. 28.1%), chronic kidney disease (61.9% vs. 49.4%), diabetes (29.2% vs. 25.8%), and had at least 3 doses of COVID-19 vaccine (91.3% vs. 76.3%) than those who did not have tixagevimab plus cilgavimab. **Results** **Primary outcome: SARS-CoV-2 infection** 29/825 (3.5%) tixagevimab plus cilgavimab vs. 308/4,299 (7.2%) control; p<0.001: odds ratio (OR) after adjustment 0.51; 95% CI 0.30 to 0.84; absolute risk reduction: 3.7%; number needed to treat (NNT): 27 **Secondary outcome: severe COVID-19 disease, defined as either COVID-19-related hospitalisation and/or all-cause mortality** **COVID-19-related hospitalisation:** 1/825 (0.1%) tixagevimab plus cilgavimab vs. 27/4,299 (0.6%) control; p=0.05; absolute risk reduction: 0.5%; NNT: 200 **All-cause mortality:** 0/825 tixagevimab plus cilgavimab vs. 40/4,299 (0.9%) control; p=0.005; absolute risk reduction: 0.9%; NNT: 111 **Severe COVID-19 disease:** 0.1% tixagevimab plus cilgavimab vs. 1.5% control; p=0.001 **Jurdi et al. 2022, Bertrand et al. 2022 and Kaminski et al. 2022 studies** • These were retrospective studies in France and the US between December 2021 and May 2022. They were reported in brief communications or letters to the editor,

	which made it impossible to assess the robustness of these studies. **Safety** • Adverse events were not reported in the Young-Xu et al. and Kertes et al. studies. • On 8 August 2022 the NIH COVID-19 treatment guidelines were updated to include a warning about the potential risk of cross-hypersensitivity between COVID-19 vaccines and tixagevimab plus cilgavimab. **COVID-19 variants** • The Young-Xu et al. study coincided with the Omicron BA.1 surge across the US. • The Kertes et al. study coincided with Omicron BA.1 predominantly between February and March 2022, and from April 2022 BA.2 was the most prevalent variant. • In vitro data suggest that the neutralising activity of tixagevimab plus cilgavimab varies against the Omicron subvariants (see appendix 2). • A pre-print (Jian et al., issued on 10 August 2022) suggests that tixagevimab plus cilgavimab's neutralising activity is completely compromised against the BA.4.6 variant in vitro. BA.4.6 is a new subvariant of Omicron that has been recently identified in the US, South Africa and Germany.

Recommendation to the CMO	**Evidence critique**
	
	Young-Xu et al. 2022
	• This study was considered the most methodologically robust, with relatively well-matched populations, and sensitivity analyses and a falsification test (negative control) performed. However, there were significant reporting and methodological limitations:
	  ○ It was unclear how the population having tixagevimab plus cilgavimab was identified compared with those who did not have treatment.
	  ○ The study excluded patients who were diagnosed with SARS-CoV-2 within 3 months of the date of tixagevimab plus cilgavimab administration. It is assumed that this refers to patients who were diagnosed with SARS-CoV-2 in the 3 months before tixagevimab plus cilgavimab administration.
	  ○ There was no active comparator and therefore greater potential for confounding.
	  ○ The comparator group was identified using follow-up data after the assigned index date which induces a selection bias.
	  ○ The outcomes may not be optimal: all-cause mortality was measured in a potentially very ill population and COVID-19-related mortality was not recorded, and the definition for COVID-19 hospitalisation was not clear (requiring a COVID infection to be recorded at both admission and discharge; not all individuals will have been discharged).

	○ The 95% confidence intervals for the individual outcomes of the composite endpoint were very large. ○ The exact figures are not reported for the individual outcomes of the composite endpoint in the tixagevimab plus cilgavimab population and therefore absolute risk reduction and number needed to treat could not be calculated. This was to protect patient information. ○ The population was veterans who were mostly male and older and may not be generalisable to the UK population who would be eligible. ○ The analysis occurred when the Omicron BA.1 variant was dominant and may not be generalisable to the current UK context. ○ The study was published as a pre-print in May 2022 and has not yet been peer-reviewed. **Kertes et al. 2022** • The Kertes et al. study was considered relatively well reported, however there were significant methodological limitations: ○ There was no active comparator and therefore greater potential for confounding. ○ There was potential for significant selection bias relating to factors influencing response to the SMS or email invite, such as different healthcare practices between those who presented for treatment and those who refused or lacked the motivation for treatment. It was unknown what proportion of patients in the control group never opened the invite or intended to have treatment but did not complete the process. ○ Selection bias is also likely induced by the fact that the control group was identified based on follow-up information (i.e., that they never went on to receive the study drug). ○ The methods used to identify variables for inclusion in the final multivariable model (i.e., those with independent significant association with the outcome) is not recognised best practice. ○ The length of follow up was longer in the control group than the treatment group and therefore there was more time for events to happen in the control group (which is especially problematic given the use of logistic regression). ○ It was assumed that all patients who were positive for SARS-CoV-2 presented to Maccabi HealthCare Services. However given that the Omicron variant is associated with mild illness and that home testing kits are available, it is likely that not all patients presented to the service. **Conclusion** • Overall, RAPID C-19 considers that the quality of the data is insufficient to warrant action to progress to consideration of an access policy as an interim measure

	before NICE technology appraisal (see proposed actions). There is uncertainty that tixagevimab plus cilgavimab would prevent symptomatic COVID-19 caused by the current Omicron variants in the vulnerable population who would potentially be eligible for this treatment. There is insufficient evidence to proceed to patient access in the current pandemic context. **Proposed actions** • It is recommended that further research is considered to determine the clinical effectiveness and safety of tixagevimab plus cilgavimab in the current UK population, together with pharmacokinetic analysis to establish the optimal dosage and in vitro-in vivo correlation. This analysis would support future decision making on the clinical effectiveness of neutralising monoclonal antibodies with the evolving nature of the SARS-CoV-2 virus. • RAPID C-19 will continue to monitor for results from randomised controlled trials. • To note: the NICE technology appraisal of tixagevimab and cilgavimab for preventing COVID-19 is in development. The expected publication date for draft guidance is April 2023 and for final guidance is 31 May 2023.
Abbreviations: CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; OR: odds ratio; RT-PCR: reverse transcription polymerase chain reaction	

Appendix 1. Non-comparative real-world evidence reviewed

- Nguyen et al. 2022, Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients, Research note in *Clinical Microbiology and Infection*
- Ordaya et al. 2022, Characterization of early-onset severe acute respiratory syndrome coronavirus 2 infection in immunocompromised patients who received tixagevimab-cilgavimab prophylaxis, *Open Forum Infectious Diseases*
- Benotmane et al. 2022, Breakthrough COVID-19 cases despite prophylaxis with 150 mg of tixagevimab and 150 mg of cilgavimab in kidney transplant recipients, Brief communication in *American Journal of Transplantation*
- Goulenok et al. 2022, Pre-exposure anti-SARS-CoV-2 monoclonal antibodies in severely immunocompromised patients with immune-mediated inflammatory diseases, Comment in *The Lancet Rheumatology*
- Benotmane et al. 2022, Pre-exposure prophylaxis with Evusheld™ elicits limited neutralizing activity against the omicron variant in kidney transplant patients, Research letter pre-print
- Bruel et al. 2022, Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies, *Nature Medicine*

Appendix 2.

RAPID C-19 report to CMO 30/05/2022:

Tixagevimab plus cilgavimab (Evusheld, AZD7442; AstraZeneca) in pre-exposure prophylaxis

Senior RAPID C-19 members	• [redacted] on behalf of **James Palmer:** National Medical Director Specialised services, NHSE/I • [redacted] on behalf of **Helen Knight:** Programme Director, Technology Appraisals and Highly Specialised technologies, NICE • **Daniel McAuley:** Director, NIHR Efficacy and Mechanisms Evaluation Programme • **Krishna Prasad:** Deputy Director, Innovative Medicines, MHRA, Principal Assessor to Commission on Human Medicines • With expert advice from the NIHR COVID-19 Prophylaxis Oversight Group
Context of current and previous reports	• In December 2021, RAPID C-19 advised the CMO of a strong signal of efficacy from the PROVENT trial of tixagevimab plus cilgavimab in pre-exposure prophylaxis (now published; Levin et al. 2022, see page 4). • RAPID C-19 proposed to prepare for patient access subject to marketing authorisation being granted (this was granted on 17 March 2022) and confirmation of neutralising activity against Omicron by the UK Health Security Agency (UKHSA) and/or independent laboratories.
Information reviewed	• In vitro analysis of neutralising activity against Omicron variants from UKHSA and Oxford University, provided in confidence • Expert advice from the NIHR COVID-19 Prophylaxis Oversight Group, including commentary from [redacted] on behalf of the group
Key areas discussed	**Evidence considerations** [redacted] UKHSA data from live virus neutralisation assays suggests that tixagevimab plus cilgavimab [redacted] • Results from the Oxford University assessment suggest that tixagevimab plus cilgavimab retains neutralising activity against Omicron BA.2 but has reduced

	neutralising activity against the emerging Omicron variants BA.3, BA.4 and BA.5. • The UKHSA data is difficult to interpret, and there are no accompanying pharmacokinetic and pharmacodynamic data to understand whether the medicine reaches the required concentrations in patients to neutralise the virus. • [redacted] Although the UKHSA data suggest that [redacted] • Using a treatment in which 1 component is not effective against the BA.2 variant of Omicron could potentially give rise to escape variants, antibody-dependent enhancement, or viral resistance. • Using cilgavimab as a monotherapy has not been tested. • When the UKHSA data are considered with all the currently available in vitro and animal studies, the results are broadly consistent. However, an inconsistent approach to the in vitro neutralisation studies makes the overall data picture difficult to interpret, particularly when there is no pharmacokinetic and pharmacodynamic data to aid further understanding. Because of this, it is not anticipated that more in vitro assessments would resolve the issue. • After considering the UKHSA and Oxford University data plus the expert interpretation of the overall non-clinical data by members of the Prophylaxis Oversight Group, RAPID C-19 cannot be confident that tixagevimab plus cilgavimab (300 mg dose) is clinically effective against the Omicron variant and subvariants. • The Group considered that a high level of confidence was needed in the clinical effectiveness of this prophylactic treatment because the potential eligible patient population is vulnerable. The risk of deployment leading to behaviour change that increases the risk of exposure to the virus is too great when evidence of its clinical benefit is not sufficiently robust. **Regulatory** • Tixagevimab plus cilgavimab (Evusheld) has a conditional marketing authorisation in the UK for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and: o who are unlikely to mount an adequate immune response to COVID-19 vaccination or o for whom COVID-19 vaccination is not recommended. • Further evidence is awaited, and new information will be reviewed at least every year.

	The summary of product characteristics notes that: • A higher dose, 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1) based on in vitro neutralisation susceptibility data which show reduced susceptibility for tixagevimab plus cilgavimab. • Tixagevimab plus cilgavimab retained full to nearly full neutralisation activity against pseudovirus and/or live virus SARS-CoV-2 variant strains harbouring all spike substitutions identified in Alpha, Beta, Gamma, Delta and Omicron (BA.2) variants of concern. • Evaluation of neutralisation susceptibility of variants identified through global surveillance and in participants who had tixagevimab plus cilgavimab is ongoing. • It is not known how pseudotyped virus-like particles (VLP) or authentic SARS-CoV-2 neutralisation susceptibility data correlate with clinical outcome. Data collection is ongoing to better understand how reductions in activity seen in authentic SARS-CoV-2 or pseudotyped VLP assays may correlate with clinical outcomes.
Recommendation to the CMO	• RAPID C-19 considers that the results from the PROVENT clinical trial are robust, but there were some limitations (including a low number of events, see page 16 for details). However, the emergence of Omicron BA.2 as the dominant variant in the UK means that the results from the PROVENT clinical trial are not directly relevant to the current situation. • RAPID C-19 does not consider that the available non-clinical data supports the clinical effectiveness of the treatment against Omicron. This is because of the difficulties in interpreting the available non-clinical data, making it impossible to extrapolate to conclusions about clinical effectiveness. • It is also recognised that it is not feasible to obtain clinical effectiveness data in the current pandemic context of low event rates. There is a need to understand how non-clinical trial data could be used to support decision making on clinical effectiveness for neutralising monoclonal antibodies with the evolving nature of the SARS-CoV-2 virus. • It is recognised that this is likely to be an ongoing issue for neutralising monoclonal antibodies (with potential use in prophylaxis or treatment or both) that are currently available and in the pipeline. • Because of the difficulties in extrapolating non-clinical data to conclusions about clinical effectiveness, there is no certainty that tixagevimab plus cilgavimab would prevent symptomatic COVID-19 caused by the Omicron variants in the vulnerable population who would potentially be eligible for this treatment. So, the risks of proceeding to patient access are considered to outweigh the risks of not providing this treatment in the current pandemic context.

	• Overall, RAPID C-19 considers that this new information does not warrant action to progress towards patient access. **Proposed actions** • RAPID C-19 will continue to monitor for results from ongoing clinical trials. • RAPID C-19 will contribute as needed to system-wide work to consider what evidence is required to be confident that neutralising monoclonal antibodies work against emerging SARS-CoV-2 variants. The Antivirals and Therapeutics Taskforce will be taking this work forward.

Appendix 3.

RAPID C-19 report to CMO 23/12/2021:

Tixagevimab plus cilgavimab (Evusheld, AZD7442; AstraZeneca) in pre-exposure prophylaxis

Senior RAPID C-19 members	• **James Palmer:** National Medical Director Specialised services, NHSE/I • **Helen Knight:** Programme Director, Technology Appraisals and Highly Specialised technologies, NICE • **Daniel McAuley:** Director, NIHR Efficacy and Mechanisms Evaluation Programme • **Krishna Prasad:** Deputy Director (Interim) Licensing Division, MHRA, Principal Assessor to Commission on Human Medicines • With expert advice from the NIHR COVID-19 Prophylaxis Oversight Group
Information reviewed	• Pre-publication manuscript provided in confidence by the company with results from the PROVENT trial
Key areas discussed	**Evidence** • Tixagevimab and cilgavimab are neutralising monoclonal antibodies directed against the SARS-CoV-2 spike protein. They simultaneously bind to distinct, non-overlapping epitopes of the SARS-CoV-2 spike protein. They are long-acting antibodies, with preliminary data suggesting an extended half-life of approximately 90 days. Sufficient antibody levels are detectable in serum and nasal mucosa for up to 9 months after a single 300 mg intramuscular dose, and predictions are that this dose could provide protection against COVID-19 for up to 12 months. • PROVENT is an ongoing, randomised, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of tixagevimab plus cilgavimab in preventing symptomatic SARS-CoV-2 infection among adults (aged 18 years and above). The eligible population were at increased risk for either inadequate response to COVID-19 vaccination, or increased risk of SARS-CoV-2 infection owing to location or circumstance. All participants had a negative SARS-CoV-2 serology test result at screening. Participants who had a history of SARS-CoV-2 infection, a positive SARS-CoV-2 result, or prior vaccine or biologic indicated for prevention of SARS-CoV-2 or COVID-19 were excluded. • The trial was conducted at 87 sites in the UK, Belgium, France, Spain, and the US. • Participants (n=5,197) were randomised 2:1 to receive treatment (300 mg single dose) or placebo between 21 November 2020 and 22 March 2021. • The mean age of the population was 53.5 years, approximately 43% were 60 years old or above, 4% were 75 years old or above, 46% were female, 73% identified

	as white and 17% identified as black, and 15% identified as Hispanic or Latinx. • 73.3% of participants were considered to be at risk of inadequate response to vaccination (including, but not limited to, ≥60 years old, BMI ≥30 kg/m^2, immunocompromised, COPD and CKD), 52.5% at increased risk of exposure to SARS-CoV-2 (including, but not limited to, healthcare workers, military personnel and students living in dormitory accommodation) and 77.5% were at high risk for severe COVID-19 disease (baseline comorbidities and other characteristics that are associated with an increased risk for severe COVID-19, including those with immunosuppressive disease or taking immunosuppressive medications, diabetes, severe obesity or cardiac disease, COPD, CKD and chronic liver disease). • The primary efficacy endpoint was the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing and before day 183. Participants met the primary endpoint if they presented with qualifying symptoms (including, but not limited to, fever or shortness of breath with no minimum duration, or cough or loss of smell and taste for at least 2 days) and had a positive RT-PCR result between 5 days before and up to 10 days after symptom onset. • The data cut-off for the primary analysis occurred on 5 May 2021. An additional extended follow-up data cut-off for the primary endpoint occurred on August 29, 2021; this analysis was not prespecified, therefore p values were not computed. • Participants were allowed to unblind if they wished to consider COVID-19 vaccination, and results for these patients censored in the primary endpoint analysis. • Participants will continue to be followed for 15 months. The estimated study completion date is 29 June 2022. **<u>Primary efficacy outcome: first case of any SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose before day 183</u>** • **Primary analysis (median follow up 83 days)** o 8/3,441 (0.2%) tixagevimab plus cilgavimab vs. 17/1,737 (1.0%) placebo o relative risk reduction: 76.7% o 95% CI 46% to 90% o p<0.001 o absolute risk reduction: 0.8% corresponding to NNT=125 • **Extended follow up (median follow up 196 days)** o 11/3,441 (0.3%) tixagevimab plus cilgavimab vs. 31/1,731 (1.8%) placebo o relative risk reduction: 82.8% o 95% CI 65.8% to 91.4%

	○ absolute risk reduction: 1.5% corresponding to NNT=67 Tixagevimab plus cilgavimab efficacy was consistent across subgroups (baseline demographics and comorbidities) where evaluable, with all point estimates of relative risk reduction in incidence of symptomatic illness for tixagevimab plus cilgavimab versus placebo being >44%. **Secondary efficacy outcomes** **i) Post-dosing SARS-CoV-2 nucleocapsid antibody positive** **Primary analysis** ○ 21/3,123 (0.7%) in the tixagevimab plus cilgavimab group vs. 21/1,564 (1.3%) in the placebo group ○ Relative risk reduction 51.1% ○ 95% CI 10.6% to 73.2% ○ p=0.02 **Extended follow up** ○ 38/3,121 (1.2%) in the tixagevimab plus cilgavimab group vs. 42/1,564 (2.7%) in the placebo group ○ Relative risk reduction 57.7% ○ 95% CI 34.7% to 72.7% **ii) Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post dose** **Primary analysis** ○ 0 events in the tixagevimab plus cilgavimab group vs. 1 event (0.1%) in the placebo group **Extended follow up** ○ An additional 4 events in the placebo group **iii) Incidence of COVID-19-related emergency room visits occurring post dose** **Primary analysis** ○ 6 events in the tixagevimab plus cilgavimab group vs. 0 in the placebo group; these participants were not hospitalised and 3/6 subsequently tested positive for COVID-19. **Primary safety endpoint: adverse events (AEs), serious AEs, medically attended AEs, and AEs of special interest** • **Primary analysis** ○ All events occurred at similar rates in the treatment and placebo groups: ○ **AEs:** 1,221/3,461 (35.3%) tixagevimab plus cilgavimab vs. 593/1,736 (34.2%) placebo. Most events were of mild or moderate severity.

	○ **Serious AEs:** 50/3,461 (1.4%) tixagevimab plus cilgavimab vs. 23/1,736 (1.3%) placebo ○ **Medically attended AEs:** 360/3,461 (10.4%) tixagevimab plus cilgavimab vs. 157/1,736 (9.0%) placebo ○ **AEs of special interest:** 93/3,461 (2.7%) tixagevimab plus cilgavimab vs. 37/1,736 (2.1%) placebo ○ 8 deaths occurred, 4 in each arm. 2 were COVID-19 related, both in the placebo group. All deaths were unrelated to study drug. • **Extended follow up** ○ No additional AEs of special interest and no unexpected longer-term safety signals were identified. ○ 16 deaths occurred (9 in the treatment group and 7 in the placebo group); none were intervention related. There were no additional COVID-19-related deaths. **COVID-19 variants** • In vitro evidence suggests that tixagevimab plus cilgavimab is active against the Alpha, Beta, Gamma and Delta variants. There is currently limited data to assess its activity against the Omicron variant, although early indications are that it may retain activity. • The PROVENT trial was ongoing when the Alpha variant was predominant in participating countries, with the primary data cut-off occurring as the Delta variant began to spread. Genotypic data were available for some participants who developed symptomatic COVID-19 in the trial (7/11 in the treatment group and 13/31 in the placebo group). With regards to variants of concern, 1 participant in the treatment group was infected with the Beta variant, 5 participants in the placebo group were infected with the Alpha variant, and 5 participants in the placebo group were infected with the Delta variant. **Regulatory** [redacted]Tixagevimab plus cilgavimab is currently unlicensed. A marketing authorisation decision is expected by the end of Q1 2022 for pre-exposure prophylaxis of COVID-19 in adults. [redacted] **Use in clinical practice** • In the PROVENT prophylaxis trial, participants received a 300 mg dose of the combination treatment, with each antibody administered individually (1.5 ml injection of each) to separate gluteal regions. Participants were monitored for safety for 1 to 4 hours after dosing.

Recommendation to the CMO	**Evidence critique** • PROVENT is the only trial of tixagevimab plus cilgavimab in pre-exposure prophylaxis. The results available in a pre-publication manuscript are sufficiently robust to suggest that tixagevimab plus cilgavimab is beneficial in preventing symptomatic COVID-19 infection in adults at increased risk of inadequate response to COVID-19 vaccination or infection. • Tixagevimab plus cilgavimab is the first medicine to show robust benefit in pre-exposure prophylaxis. • No safety concerns have been identified. • The intramuscular route of administration and long-acting nature of the treatment are also positive attributes of this product. • There are some limitations to the data to note: o There were relatively low numbers of events in small but important participant subgroups, such as immunosuppressed people, meaning efficacy and potential for emergence of variants in these groups could not be estimated. o Allowing unblinding for COVID-19 vaccination reduced the number of participants available for long-term double-blind follow up. o It is unclear whether the pre-publication manuscript has yet been peer-reviewed, but this process is not expected to materially change the main findings. • There remain some unanswered questions about the generalisability of these results to the current UK context, specifically: o There is no evidence for the effectiveness of this medicine in a vaccinated patient population. o There is no evidence at present for the effectiveness of this medicine in a patient population in which the Omicron variant is dominant. The NIHR COVID-19 Prophylaxis Oversight Group noted that there is a risk associated with introducing a partially or minimally effective therapy and do not currently recommend routine use of this treatment until more data on efficacy against Omicron are available. o There is no evidence at present for the effectiveness of this medicine in children or pregnant women, and limited evidence for people 75 years and over. • Overall, RAPID C-19 consider these results to represent a strong signal of efficacy that warrants action to prepare for patient access subject to: o marketing authorisation being granted, and o confirmation of continued activity against Omicron by UKHSA and/or independent laboratories. **Proposed actions**

	• NHSE/I to consider preparing a clinical commissioning policy for tixagevimab plus cilgavimab in pre-exposure prophylaxis (for implementation upon marketing authorisation and confirmation of activity against Omicron at 300 mg dose by UKHSA and/or independent laboratories). The NHSE/I National Expert Working Group for neutralising monoclonal antibodies will take this forward. • NHSE/I to consider the options for identifying the potentially eligible patients who might benefit from this medicine, in relation to vaccination response and risk of severe disease, and the potential scenarios for deployment. • Ongoing monitoring for viral escape by UKHSA is recommended and activity against the Omicron and other variants as they emerge will be included as part of implementation arrangements. • RAPID C-19 will continue to monitor for the peer-reviewed publication of this study, as well as results from other ongoing trials. • It is recommended Therapeutics Taskforce consider taking forward procurement of sufficient volumes of product.
Abbreviations: BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; NNT: number needed to treat; RT-PCR: reverse transcription polymerase chain reaction	

Summary of key ongoing trials being monitored

Treatment
TACKLE / NCT04723394 (*AstraZeneca sponsored RCT)* • Actual enrolment: 910 • Location: **UK,** US, South America, Japan, Europe • Setting/population: Adult outpatients with laboratory-confirmed SARS-CoV-2 and mild to moderate symptoms • Primary outcomes: severe COVID-19 or death, and safety • Actual PCD: 21/08/2021. *Active, not recruiting. Top-line results announced in the press suggest benefit in reducing the risk of severe COVID-19 or death in outpatients.*
ACTIV-2/ NCT04518410 (*National Institute of Allergy and Infectious Diseases sponsored RCT)* • Actual enrolment for all interventions: 4,044 • Location: US, South America, South Africa • Setting/population: Adult outpatients with laboratory-confirmed SARS-CoV-2 and symptoms • Primary outcomes: COVID-19 symptom duration, death or hospitalisation, viral load and safety • Actual PCD: 1 March 2022. *Active, not recruiting.*
ACTIV-3/ NCT04501978 (*University of Minnesota sponsored RCT)* • Estimated enrolment for all interventions: 10,000 • Location: **UK**, US, Argentina, Europe, India, Nigeria, Singapore • Setting/population: Hospitalised adults with symptomatic COVID-19

• Primary outcomes: time to sustained recovery • Estimated PCD: July 2022. *Active, not recruiting.*
DisCoVeRy/ NCT04315948 (*Institut National de la Santé Et de la Recherche Médicale, France sponsored RCT)* • Estimated enrolment for all interventions: 2,416, n=620 for tixagevimab plus cilgavimab • Location: Austria, Belgium, Luxembourg, Norway and Portugal • Setting/population: Hospitalised adults with COVID-19 and presence of pulmonary rales/crackles, SpO2 ≤ 94% on room air or requirement of supplementary oxygen including high flow oxygen devices or non-invasive ventilation • Primary outcomes: severity rating on 7-point ordinal scale (includes hospitalisation, oxygen requirement and death) • Estimated PCD: March 2023. *Recruiting.*
Prevention
STORM CHASER / NCT04625972 (*AstraZeneca sponsored RCT, NIHR-prioritised)* • Actual enrolment: 1,121 • Location: **UK**, US • Setting/population: Adults without COVID-19 but with potential exposure to SARS-COV-2 (post-exposure prophylaxis) • Primary outcomes: Incidence of symptomatic SARS-CoV-2, safety and tolerability • Actual PCD: 07/04/2021. *Active, not recruiting. Top line results announced in the press suggest no benefit in reducing the risk of developing symptomatic COVID-19 in unvaccinated adults recently exposed to a person with COVID-19.*
Abbreviation: PCD: primary completion date