Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19 [ID6136]

Slides for public, redacted

Technology appraisal committee C [24 January 2023]

Chair: Richard Nicholas

Lead team: Iain McGowan, Stella O'Brien, Michael Chambers

External assessment group: School of Health and Related Research (ScHARR), Sheffield

Technical team: Anna Willis, Adam Brooke, Ross Dent

Company: AstraZeneca

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- **Background, patient and clinical perspectives**
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Background on COVID-19

Causes

- COVID-19 is an acute respiratory illness caused by the SARS-CoV-2 virus

Epidemiology

- There have been over 22.2 million recorded COVID-19 cases and over 213,000 deaths due to COVID-19 in the UK[1]

Symptoms and prognosis

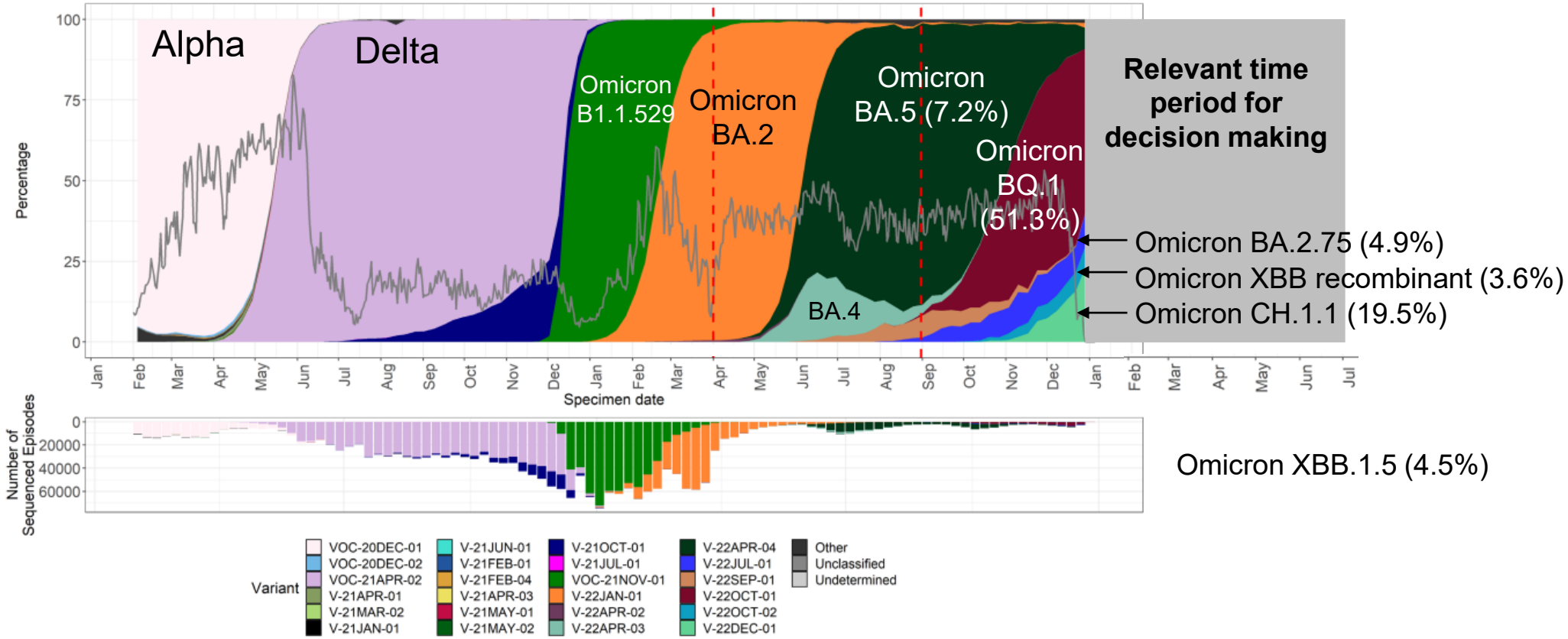
- May start with a cough, fever or breathlessness
- Infections range from mild and self-limiting to severe with a risk of hospitalisation or death
- After the initial COVID-19 infection, people may experience ongoing symptoms (long COVID)

High-risk populations

- There are some people in England who remain at higher risk of serious illness from COVID-19, despite the availability of vaccines[2]
- High-risk populations include those with genetic disorders, cancer, renal or liver disease, transplant recipients and those with immune system disorders[3]

Recap: Changing variants of concern

Figure 4. Variant prevalence (UKHSA designated variant definitions only) of available sequenced cases for England from 1 February 2021 as of 6 January 2023



Abbreviations: UKHSA, UK Health Security Agency.

Tixagevimab–cilgavimab (Evusheld, AstraZeneca)

Marketing authorisation	• Tixagevimab–cilgavimab (tix-cil) received a conditional marketing authorisation from the MHRA on 17 March 2022 • Marketing authorisation wording: "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: - who are unlikely to mount an adequate immune response to COVID-19 vaccination or - for whom COVID-19 vaccination is not recommended"
Mechanism of action	• Tix-cil is a combination of tixagevimab and cilgavimab, two recombinant human IgG1k monoclonal antibodies • Both antibodies can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain of SARS-CoV-2
Administration	• The expected dose of 600mg is administered as 2 x 150 mg vials of tixagevimab, and 2 x 150 mg vials of cilgavimab; given as two separate sequential intramuscular injections at different injection sites in different muscles
Price	• The list price of tix-cil is £1,600 per 600 mg dose • There is a commercial arrangement (simple PAS discount) in place

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency. PAS, patient access scheme.

Patient perspectives

Submissions received from 18 patient organisations:

- Action for Pulmonary Fibrosis
- Anthony Nolan
- Blood Cancer UK
- CLL Support
- Crohn’s and Colitis UK
- Clinically Vulnerable Families
- Evusheld for the UK
- Immunodeficiency UK
- Kidney Care UK
- Kidney Research UK
- Leukaemia Care
- Long COVID SOS
- LUPUS UK
- Lymphoma Action
- MS Trust
- Myeloma UK
- Scleroderma and Raynaud's UK
- Vasculitis UK

Abbreviations: CLL, Chronic Lymphocytic Leukaemia; MS, multiple sclerosis.

Patient perspectives

COVID-19 continues to have a major impact on the lives of people who remain at higher risk

- People with weakened immune systems still cannot live a normal life – many have been shielding since the start of the pandemic
- They feel let down by the government and society, and feel as though the country has moved on and left them behind
- Many avoid going outside in public especially now there are no mitigations against COVID infection
- Some still avoid seeing friends and family, or having children and grandchildren in their house, and have missed out on significant life events

"Infection rates are still high and it does not feel safe to mix with people given my weakened immune system. This is getting increasingly more challenging as most other people have resumed normal activities and are not taking precautions for others."

"My actions are the same as when the strictest restrictions were in force. I meet only my bubble, I shop once a week at the quietest time while wearing a mask - other than that, I remain at home."

"I know…I have no Covid antibodies…I have been told to make informed decisions and carry out the necessary risk assessments as I see them…[because] everyone else is 'living with Covid'."

Patient perspectives

Families and carers are also affected, and there is a significant financial burden

- There is also an impact on the household, with family members not being able to go to work for fear of bringing home COVID
- This has led to the loss of jobs and businesses with many living off savings.
- For family members who have no choice but to work, there is anxiety and guilt
- Working conditions are sometimes dangerous, with inadequate protection against COVID infection
- Children have missed out on school and college

"My daughter didn't go to secondary and we are paying for an online school as we feel we can't risk me going through that and her bringing covid home and my partner will likely have to give up his job that he's been in for 25 years for the same reason as no mitigations have been made in school or work."

"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."

"[When] my husband's colleagues [tell] him a household member…has Covid…the rota [is] changed so he can avoid them."

Patient perspectives

Continued restrictions are detrimental to physical and mental health

- People report reduced fitness and mobility as they are unable to leave the house to exercise
- Some are fearful of attending essential medical appointments due to the risk of getting COVID. For those who need to attend clinics frequently, such as people on dialysis, the risk is very high
- Treatments for underlying conditions often have to be stopped in the case of COVID-19 infection, impacting health
- Restrictions have had a severe impact on people's mental health with many reporting feelings of loneliness, anxiety, worry, fear, depression isolation and hopelessness
- People who are immunosuppressed have been known to act as a reservoir for COVID, enabling the virus to mutate, which impacts the health of the population

"Every time I leave the house, I could catch something that I have been told that my body might not be able to deal with...it could kill me. That is frightening."

"My diagnosis of Mantle Cell Lymphoma means that I have a potential lifespan of 5-10 years, so I would like to spend this time making memories with my family and friends. The fact that I am having to shield means that me and also my family are deprived of this valuable time together, this has a huge psychological impact."

"We live in constant fear of catching COVID-19 and have to isolate from friends and families…[The] need for constant vigilance can cause anxiety and other mental health issues."

Patient perspectives

Current available options such as vaccination and post-exposure antivirals are inadequate for those with a weakened immune system

- Many report a lack of antibody response despite receiving multiple vaccinations, leaving them extremely vulnerable.
- Drugs to treat people's underlying conditions commonly impair vaccine response, therefore doctors may be deterred from prescribing useful treatments
- People report difficulties in accessing post-exposure COVID treatments, such as Paxlovid, through COVID Medicines Delivery Units (CMDUs), leaving them with no safety net
- Paxlovid cannot be used for those taking many types of chemotherapy medication and is contraindicated in those with severe kidney or liver disease
- For those that have had Paxlovid, some report still testing positive for COVID weeks later

"I take immune-suppressants for pulmonary fibrosis linked to my rheumatoid arthritis. I have had all six covid vaccinations but there has been no antibody response."

"I recently tested positive for COVID. Accessing antivirals is proving almost impossible. I keep being told by the COVID-19 Medicines Delivery Unit that I am on the list for a doctor assessment, but it is a very long list and I am not yet near the top."

Patient perspectives

There is an urgent need for a prophylactic therapy to reduce the risk of COVID-19 infection for those at high risk

- People report that having a prophylactic treatment would give them the confidence to start living a more normal life
- It would allow people to meet family indoors, go to the supermarket, return to work, attend medical appointments, use public transport and reconnect with friends
- Advantages would extend to carers and other household members
- Anxiety and fear would be alleviated and physical health would also improve
- There would be reduced pressure on NHS services
- People consider prevention to be better than cure
- Treatment should be offered to those who would benefit most

"Much more needs to be done to support the immune compromised in getting back to normal life and being able to function in society and prophylactic medicines would facilitate us being able to take steps to do this."

"Knowing that I had preventative protection would allow me to freely exercise in gym/pool without worry and allow me to socialise more confidently. I would be happier knowing that my family could be more relaxed going to school/work."

"Since receiving Evusheld, I have started to hold face-to-face professional meetings…and have had many face-to-face gatherings with family and grandchildren."

Patient perspectives

Potential disadvantages of tix-cil

- Patients and carers understood that tix-cil may not be fully effective
- Most agreed that some protection is better than none, some said that they would still continue to take measures to protect themselves
- People should be well informed about level of protection tix-cil can offer
- People were concerned that tix-cil may only be available in hospitals and would like to see it given in a community setting too

"[I would] still continue to take measures to protect myself, such as wearing filtered masks in public places and generally risk assess most situations."

"I think that as Covid 19 evolves [tix-cil] will need to evolve to keep up with the variants we are seeing, I'm not saying I wouldn't have it but how long will it remain effective?"

Clinical perspectives

Submissions received from UK CLL forum and UK Renal Pharmacy Group

- Many patients are on systemic immunosuppression which attenuates vaccine response
- Antivirals are available for the treatment of COVID-19 but these may be unsuitable due to comorbidities and drug interactions
- Tix-cil may alleviate pressure on CMDUs, and reduce hospital admissions and mortality
- Antibody response could be used to stratify immunocompromised patients and identify those eligible for tix-cil. At present, antibody levels are not tested routinely
- Many patients continue to shield and avoid mixing. Tix-cil is likely to improve this for patients but this must be weighed up against future variants and the potential for being less cautious or changing behaviour

"Careful observation of real world data and neutralisation data would be needed – participants need to be aware that it is unlikely to prevent COVID-19 infection"

Abbreviations: CLL, chronic lymphocytic leukaemia; CMDU, COVID Medicines Delivery Unit.

Clinical perspectives

Clinical expert and NHS England perspectives

Clinical expert:
"Less than 40% accessed treatment [in CMDUs] in a timely manner"

Clinical expert:
"[treatment] would…allow patients on active therapy to continue [their] therapy on schedule"

Clinical expert:
"[Many] US, EU and UK studies [show] patients below a certain antibody threshold have increased risk of hospitalisation and death"

Clinical expert:
"[in some BMT and CART patients]…viral persistence has created the risk of viral mutation in vivo with patients still positive weeks after infection. This jeopardises their treatments and is a risk to all other patients and their carers"

NHS England:
"Many immunocompromised people are taking extra precautions to protect themselves from SARS-CoV-2 infection. There is therefore a potential that these people may be reassured by tix-cil treatment, but not protected and remove these precautions, resulting in a higher risk of poor COVID-19 outcomes"

Abbreviations: BMT, bone marrow transplant; CART chimeric antigen receptor T-cell therapy; CMDU, COVID Medicines Delivery Unit.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- **Cost-effectiveness results and key issues**
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Company and EAG base case results – WITH PAS DISCOUNT

Company deterministic incremental base case results, with PAS discount

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]			
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	£5,004

EAG deterministic incremental base case results, with PAS discount

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]			
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	£18,646

NICE

Note: ICERs generated by NICE technical team. **Abbreviations:** EAG; External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Company and EAG base case results

EAG caveats:

EAG notes that several areas of uncertainty raised in the EAG report have not been addressed by the company and are not explored in the scenario analyses.

These include:

- heterogeneity in the characteristics of patients in the target population
- uncertainty regarding the efficacy of tix-cil against current and future variants
- the lack of evidence on the safety and efficacy of repeat doses of tix-cil
- the assumption of a constant treatment effect for 6 months after each dose
- uncertainty about future risk of COVID-19 in the population eligible for tix-cil.

Abbreviations: EAG; External Assessment Group.

Key issues

No.	Issue	ICER impact
Decision problem		
1	Eligible population and heterogeneity	Unknown
Clinical effectiveness		
2	Efficacy against current COVID-19 variants	Large
3	Repeated dosing of tix-cil	Unknown
Cost effectiveness		
4	Risk of COVID-19 infection (without tix-cil)	Large
5	Risk of hospitalisation for COVID-19 (without tix-cil)	Large
6	Direct utility gain for people receiving tix-cil	Large
7	Cost of administering tix-cil	Medium
8	Long COVID – risk, duration, utility decrement, cost	Medium

Abbreviations: ICER, incremental cost-effectiveness ratio.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- **Decision problem**
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Decision problem (1/2)

	Final scope	Company	EAG comments
Population	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: • **who are unlikely to mount an adequate immune response to COVID-19 vaccination or** • for whom COVID-19 vaccination is not recommended	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: • **who are at the highest risk of an adverse COVID-19 outcome, namely hospitalisation and death, or** • for whom COVID-19 vaccination is not recommended	Company are positioning tix-cil for those with the highest risk of adverse clinical outcomes – the EAG's clinical advisors consider this appropriate but noted that the McInnes report[1] commissioned by the Department of Health and Social Care should be used to identify these groups
Intervention	Tix-cil	As per scope	None

Source: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. **Abbreviations:** EAG; External Assessment Group.

Decision problem (2/2)

	Final scope	Company	EAG comments
Comparators	No prophylaxis	As per scope	None
Outcomes	• Incidence of symptomatic COVID-19 • Mortality • Requirement for respiratory support • Hospitalisation • Symptoms of long COVID • Anxiety and depression • Time to return to normal activities • Adverse effects of treatment • Health-related quality of life	As per scope	• None of the studies included in the company submission report health-related quality of life, anxiety or depression in those receiving tix-cil • The TACKLE study reports time to return to usual health, but this study investigated treatment with tix-cil, not prophylaxis

Abbreviations: EAG; External Assessment Group.

Key issue 1: Eligible population and heterogeneity (1/5)

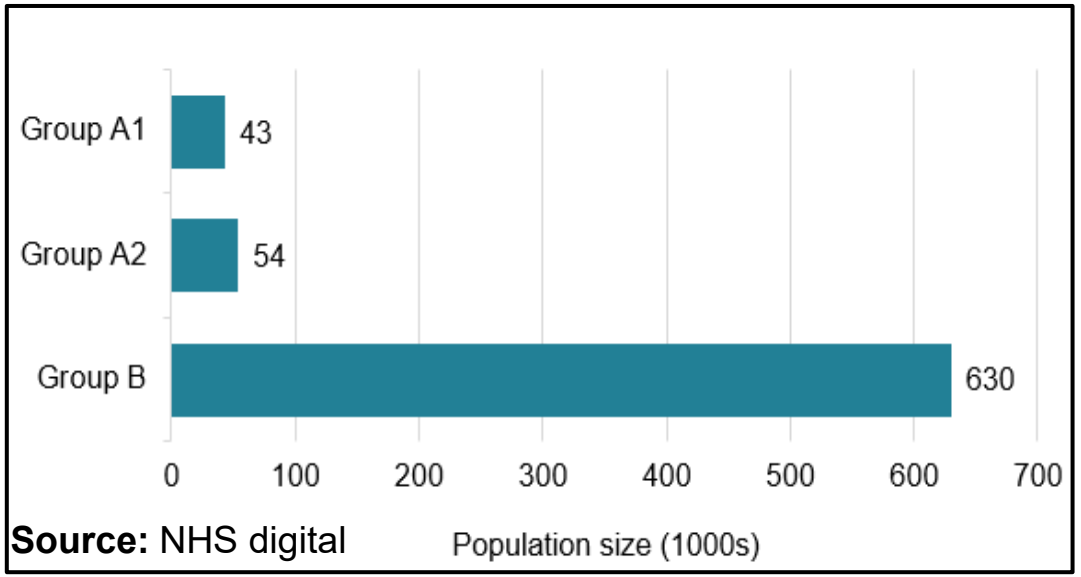
Independent Advisory Group (IAG) report

Background

- An Independent Advisory Group (IAG) was set up by the Department of Health and Social Care to identify patient cohorts that are deemed to be at the very highest risk of an adverse COVID outcome, for the purposes of treatment with antivirals and monoclonal antibodies (IAG/McInnes report)

- A similar report has been produced for prophylaxis by IAG/McInnes and stratified cohorts in order of risk, into the following groups:
  - Group A1 – Known failure of vaccination
  - Group A2 – Anticipated failure of vaccination
  - Group B – Anticipated sub-optimal vaccination response: physician discretion advised
  - *Group C – Anticipated good vaccination response (therefore not eligible for tix-cil according to the marketing authorisation)*

Figure: Anticipated size of each IAG cohort



Source: NHS digital

Key issue 1: Eligible population and heterogeneity (2/5)

Independent Advisory Group (IAG) report – Group A1, A2

Group	Description
Group A1 – Known failure of vaccination	• Person in any risk group unable to complete vaccination schedule according to contemporaneous recommendations[1] • Person in any risk group with one or more admissions due to moderate or severe COVID-19 despite completing recommended vaccinations
Group A2 – Anticipated failure of vaccination	• Any person with primary immunodeficiencies with impairment of antibody production[2] • Any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Any person receiving anti-CD20 monoclonal antibodies or other B cell depleting therapy (including ATG and alemtuzumab) within the last 12 months • Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or with active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases) • Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases) • Any person receiving CAR-T cell therapy in the last 24 months • Any person with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or AL amyloidosis or myelodysplastic syndrome (MDS), or chronic myelomonocytic leukaemia (CMML) or myelofibrosis, who do not fit the criteria above • Solid organ transplant recipients

Group A1: People who have not been vaccinated or have been admitted to hospital for moderate or severe COVID-19 despite vaccination

Group A2: Primary or secondary immunodeficiency, B-cell depleting therapy, HSCT in last 12 months, CAR-T, specific haematological malignancies or solid organ transplant

Abbreviations: CAR-T, Chimeric antigen receptor T-cell therapy. HSCT, haematopoietic stem cell transplant.

Key issue 1: Eligible population and heterogeneity (3/5)

Independent Advisory Group (IAG) report – Group B, C

Group B – Anticipated sub-optimal vaccination response: physician discretion advised	• Any person with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months, not already covered in A2. • Metastatic or locally advanced inoperable cancer • Lung cancer (at any stage) • People receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy[3] within 12 months • People who have had cancer resected [4]within 3 months and who received no adjuvant chemotherapy or radiotherapy • People with immune mediated inflammatory diseases (IMIDs) on biologics[5] or small molecule JAK-inhibitors (except anti-CD20 depleting monoclonal antibodies) or who have received these therapies within the last 6 months • People with IMIDs who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR • People with IMIDs who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver, *intestinal* and/or interstitial lung disease), methotrexate (for interstitial lung disease or inflammatory bowel diseases) and/or ciclosporin
Group B – Anticipated sub-optimal vaccination response: physician discretion advised	• People with IMIDs who exhibit at least one of: (a) uncontrolled/clinically active disease (i.e. required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) major organ involvement such as significant kidney, liver or lung inflammation or significantly impaired renal, liver and/or lung function. • People who are on corticosteroids (equivalent to ≥ 10 mg/day of prednisolone) for at least the 28 days prior to positive PCR • People with CKD 4 or 5 • People with Liver cirrhosis (Childs Pugh A, B and C cirrhosis) • Allogeneic or autologous stem cell transplant recipients beyond 12 months and without active GVHD • People with HIV infection with CD4 < 350 cells/mm3 OR not on treatment OR evidence of failure of treatment • People with Down's syndrome or other chromosomal disorders known to affect immune competence
Group C – Anticipated good vaccination response: unlikely to require prophylaxis	• People with sickle cell disease, thalassaemia or other inherited anaemia • People with rare neurological conditions (e.g. motor neuron disease, multiple sclerosis, myasthenia gravis or Huntington's chorea), unless on immunosuppression as defined in other groups • People who have had cancer resected within 3-12 months and receiving no adjuvant chemotherapy or radiotherapy. • People living with HIV stable on treatment (suppressed viral load) with CD4 >350 cells/mm3

Group B: Most other cancers, chemotherapy, biologics, immunosuppressants, kidney or liver disease, HSCT beyond last 12 months, HIV (CD4 < 350), Down's syndrome

Group C: Inherited anaemia, rare neurological conditions, cancer (resected within 3-12 months, no adjuvant therapy), HIV (CD4 > 350)

Abbreviations: HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplant.

Key issue 1: Eligible population and heterogeneity (4/5)

Company

- Positioning tix-cil in a narrower population than that specified in the marketing authorisation, for people who are at the highest risk of an adverse COVID-19 outcome

EAG / NICE technical team comments

- It is unclear how the population eligible for tix-cil should be defined
- Many model parameters have been selected to reflect particular groups and may not represent the eligible population as a whole, or heterogeneity within the eligible population. These include:
  - Baseline characteristics (which impact life expectancy and quality of life)
  - Risk of COVID-19 infection (without tix-cil)
  - Risk of hospitalisation for COVID-19 (without tix-cil)
  - Direct utility gain for people receiving tix-cil
- The company has also excluded potentially useful efficacy data for high-risk subgroups such as those receiving solid organ transplant
- Effectiveness and cost-effectiveness estimates may vary for different subgroups – this has not been assessed in the company's modelling.
- Scenarios assessing the impact of varying each of the above parameters **separately** are presented

Key issue 1: Eligible population and heterogeneity (5/5)

Model parameter	Company's source	Population	IAG cohorts
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
Risk of COVID-19 infection (without tix-cil)	UK government	General population of England between August 2021 and August 2022	Mostly uncategorised
Risk of hospitalisation for COVID-19 (without tix-cil)	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 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
Direct utility gain for people receiving tix-cil	Gallop et al. (2022), commissioned by company	Immunocompromised: [redacted]	Majority A2

How should the population who are unlikely to mount an adequate immune response to COVID-19 vaccination be defined?

Abbreviations: CMDU, COVID Medicines Delivery Unit; IAG, Independent Advisory Group; SCT, stem cell transplant.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- **Clinical effectiveness**
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

PROVENT
Pivotal phase 3 trial of tix-cil pre-exposure prophylaxis

	PROVENT (Levin et al. 2022)
Design	Phase 3, randomised, double-blind, placebo-controlled trial
Population	Adults at increased risk of inadequate response to vaccination or at increased risk of SARS-CoV-2 infection, **unvaccinated**, negative serology test at screening (n=5197, n = 198, **[3.8%] immunocompromised**)
Intervention	Tix-cil **300mg, single dose** (n=3460)
Comparator	Placebo (n=1737)
Primary outcome	SARS-CoV-2 infection, adverse events
Date	Recruitment between November 2020 and March 2021 (median follow up 83 days [primary analysis] 196 days [extended follow-up])
Circulating variant/s	**Alpha and Delta**
Locations	87 sites across 5 countries including UK
Used in model?	Baseline characteristics, efficacy data used as a scenario analysis only

EAG comments

The PROVENT trial was conducted when Alpha and Delta variants were dominant, in an unvaccinated population at a lower (single) dose of 300mg, all participants were required to have a negative point of care COVID test, which is not expected in clinical practice

PROVENT results

Tix-cil was associated with a statistically significant reduction in incidence of COVID-19 compared to placebo, with a relative risk reduction of 76.7%

	Tix-cil (n=3,441)	Placebo (n=1,731)	Relative risk reduction % (95% CI)	P-value	Absolute risk reduction (%)	Number needed to treat
Primary analysis (data cut-off May 2021, median follow up 83 days)						
First case of COVID-19*	8 (0.2%)	17 (1.0%)	76.7 (46.0, 90.0)	<0.001	0.8	133
Extended follow-up (data cut-off August 2021, median follow up 196 days)						
First case of COVID-19*	11 (0.3%)	31 (1.8%)	82.8 (65.8, 91.4)	N/A**	1.5	68

EAG comments

- The extended follow-up analysis was not pre-specified in the study protocol
- Participants were unblinded at the point of vaccination, it is unclear how this might affect results

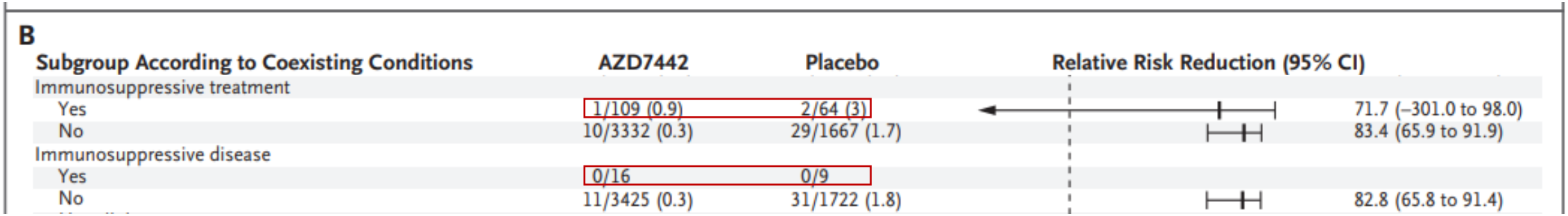
Notes: *RT-PCR-positive symptomatic illness with data censored at unblinding or receipt of COVID-19 vaccine. **Analysis not prespecified, P-value not calculated. **Abbreviations:** CI, confidence interval; RT-PCR, reverse transcription polymerase chain reaction.

PROVENT results

Efficacy was explored across subgroups, but sample sizes were small

Background

Figure: PROVENT subgroup results for those receiving immunosuppressive treatment or with immunosuppressive disease, Levin et al. (2022)



B

Subgroup According to Coexisting Conditions	AZD7442	Placebo	Relative Risk Reduction (95% CI)
Immunosuppressive treatment			
Yes	1/109 (0.9)	2/64 (3)	71.7 (−301.0 to 98.0)
No	10/3332 (0.3)	29/1667 (1.7)	83.4 (65.9 to 91.9)
Immunosuppressive disease			
Yes	0/16	0/9	
No	11/3425 (0.3)	31/1722 (1.8)	82.8 (65.8 to 91.4)

EAG comments

- Based on Levin et al. (2022), Only 3.8% of trial population had immunosuppressive disease or were having immunosuppressive therapy – it is unclear how these groups align with company's target population
- The study authors of the PROVENT trial note that "*The limitations of our trial include the low number of events in smaller but important subgroups, including immunocompromised persons, so that efficacy in these groups could not be estimated*"
- The company assume a larger proportion of PROVENT would be eligible for treatment ([redacted]) – they report that results for this subgroup were aligned with the overall population

Abbreviations: AZD7442, tix-cil; CI, confidence interval; EAG, External Assessment Group.

Real-world evidence

	Young Xu et al. 2022	Kertes et al. 2022
Design	Retrospective cohort study	Retrospective cohort study
Population	Veterans, immunocompromised (92%) or otherwise at high risk for COVID-19 (8%), majority vaccinated (n=8,087)	Immunocompromised individuals considered at high risk for SARS-CoV-2 infection and complication, majority vaccinated (n=5,124)
Intervention	Tix-cil 300 mg (17%) and 600 mg (83%), **single dose** (n=1,733)	Tix-cil **300mg**, **single dose** (n=825)
Comparator	Propensity matched controls, no tix-cil (n=6,354)	Unmatched controls, no tix-cil (n=4,299)
Primary outcome	Composite SARS-CoV-2 infection, COVID-19-related hospitalisation, all-cause mortality	SARS-CoV-2 infection
Date	Recruitment between Jan 2022 and Apr 2022. Max follow-up ~3.5 months	Recruitment between Feb 2022 and May 2022. Median follow-up: tix-cil; 53 days, no prophylaxis; 73 days
Circulating variant/s	**Omicron BA.1, BA.2 and BA.2.12.1**	**Omicron BA.1 and BA.2**
Locations	Multiple sites across the US	Multiple sites across Israel
Used in model?	Model base case	Scenario analysis only

Young Xu et al. 2022 results

Compared to propensity-matched controls, treated patients had a lower incidence of infection, hospitalisation and all-cause mortality

	Matched controls (n=6,354), number of events (%)	Tix-cil recipients (n=1,733), number of events (%)	Propensity-score analysis hazard ratio (95% CI)
Individual component outcomes (overall cohort)			
SARS-CoV-2 infection	69 (1%)	(<0.5%)*	0.34 (0.13, 0.87)
COVID-19-related hospitalisation	38 (0.5%)	(<0.5%)*	0.13 (0.02, 0.99)
All-cause mortality	99 (2%)	(<0.5%)*	0.36 (0.18, 0.73)

EAG comments

- Considers the propensity matching approach to be reasonable, however there is the potential for residual confounding despite matching
- Highlights wide confidence intervals for individual outcomes
- Study may lack generalisability to current UK context:
  - Conducted in a unique population (mostly male and elderly)
  - Coincided with Omicron BA.1 surge
- Investigated single 600mg dose of tix-cil – does not provide evidence on repeat dosing

Notes: *Numbers not shown to protect patient information. **Abbreviations:** CI, confidence interval. EAG, External Assessment Group.

Kertes et al. 2022 results

Patients receiving tix-cil had around half the odds of SARS-CoV-2 infection

Table: Factors associated with SARS-CoV-2 infection among selected immunocompromised individuals, logistic regression model

Characteristic	Category	Infections	Total N	OR	95% CI
Tix-cil	Not administered	308	4299	-	
	Administered	29	825	0.51	0.30, 0.84

EAG comments

- Highlights potential for selection bias, limiting generalisability to the UK context
- Length of follow up was shorter in the tix-cil administered group than the non-administered group, therefore there was more time for events to occur in the non-administered group
- Adjustment for only a limited number of baseline characteristics means there is potential for residual confounding (for example, vaccination rates were lower in non-administered group)
- Study coincided with coincided with Omicron BA.1 surge – generalisability to current UK context unclear
- Investigated single 300mg dose of tix-cil and does not provide evidence on repeat dosing
- **The EAG considers Young-Xu et al. to be the more methodologically robust RWE source**

NICE

Abbreviations: CI, confidence interval. EAG, External Assessment Group; OR, odds ratio; RWE, real-world evidence.

In vitro data

In vitro data that will be considered by the committee:

Lead	Title	Date	Tix-cil neutralisation versus…		
			BQ.1	BQ.1.1	XBB
Planas 2022	Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies	Nov 22			
Arora 2023	Omicron sublineage BQ.1.1 resistance to monoclonal antibodies	Nov 22			
Wang 2022	Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants	Dec 22			
Cao 2022	Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution	Dec 22			
Imai 2023	Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB	Jan 23			

Not evaluated

No neutralisation

Abbreviations: RBD, receptor-binding domain.

Adverse events

Treatment-related adverse events were similar across groups based on TACKLE

- Adverse events were based on the TACKLE trial, which investigated the 600mg dose of tix-cil for the treatment of COVID-19
- TACKLE did not investigate repeated dosing with tix-cil
- Results are available for a median follow-up of 84 days. The study is ongoing.

Table: Adverse events based on TACKLE trial

Participants with an adverse event (median follow-up 84 days)	Tix-cil 600mg (n=452), n (%)	Placebo (n=451), n (%)
Any adverse event	132 (29%)	163 (36%)
Total deaths	6 (1%)	6 (1%)
Any serious adverse event including death	33 (7%)	54 (12%)
Any treatment-related adverse event	**23 (5%)**	**21 (5%)**
Any adverse event leading to study withdrawal	5 (1%)	7 (2%)
Common adverse events:		
COVID-19 pneumonia	26 (6%)	49 (11%)
Headache	5 (1%)	2 (<1%)
Any adverse event of special interest	15 (3%)	15 (3%)

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- **Clinical effectiveness key issues**
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Key issues

No.	Issue	ICER impact
Decision problem		
1	Eligible population and heterogeneity	Unknown
Clinical effectiveness		
2	Efficacy against current COVID-19 variants	Large
3	Repeated dosing of tix-cil	Unknown
Cost effectiveness		
4	Risk of COVID-19 infection (without tix-cil)	Large
5	Risk of hospitalisation for COVID-19 (without tix-cil)	Large
6	Direct utility gain for people receiving tix-cil	Large
7	Cost of administering tix-cil	Medium
8	Long COVID – risk, duration, utility decrement, cost	Medium

Abbreviations: ICER, incremental cost-effectiveness ratio.

Key issue 2: Efficacy against current COVID variants

Background

- SARS-CoV-2 is rapidly evolving, with variants of concern changing over time
- Currently, the most prevalent variant BQ.1 comprises 51.3% of new COVID infections
- Studies of tix-cil were conducted when Alpha, Delta and Omicron variants BA.1 or BA.2 were circulating

Work done by NICE

- To establish how the committee should consider in vitro evidence NICE set up the “In Vitro Data Expert Advisory Group” (IVAG)
- The aim of the group was to develop a framework to link in vitro neutralisation data to clinical outcomes and use this to assess the in vitro evidence
- Five studies were identified, which investigated the in vitro neutralisation of tix-cil against a range of COVID variants (see Appendix)
- The studies reported resistance of Omicron subvariants BA.2.75.2, BA.4.6, BQ.1, BQ.1.1, BJ.1 and XBB to neutralisation by tix-cil
- Exploratory scenarios showing the impact on the ICER of a 50% reduction in efficacy are presented

Are the results of the company’s studies generalisable to the current situation?
Based on the in vitro data presented and the conclusions of IVAG, is tix-cil expected to be clinically effective against current variants? Could further research could address the uncertainties?

Abbreviations: ICER, incremental cost effectiveness ratio; IVAG, in vitro assessment group.

Key issue 3: Repeated dosing

Background

- The Summary of Product Characteristics for tix-cil states: *"[tix-cil] may be effective for pre-exposure prophylaxis for six months post administration"* and *"[tix-cil] has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing."*

Company

- The company's economic analysis assumes one year of tix-cil treatment consisting of an initial 600mg dose, followed 6 months later by a second 600mg dose
- The second dose was assumed to have same efficacy as the first dose

EAG comments

- Company's economic analysis is not aligned with the Summary of Product Characteristics
- There are currently no data on the efficacy of repeat dosing, however, there are ongoing studies investigating repeat dosing (PROVENT sub-study, ENDURE)
- **Note:** The EAG's model was not adjusted to take into account a single dose, however a scenario analysis provided by the company showed a small impact on the ICER.

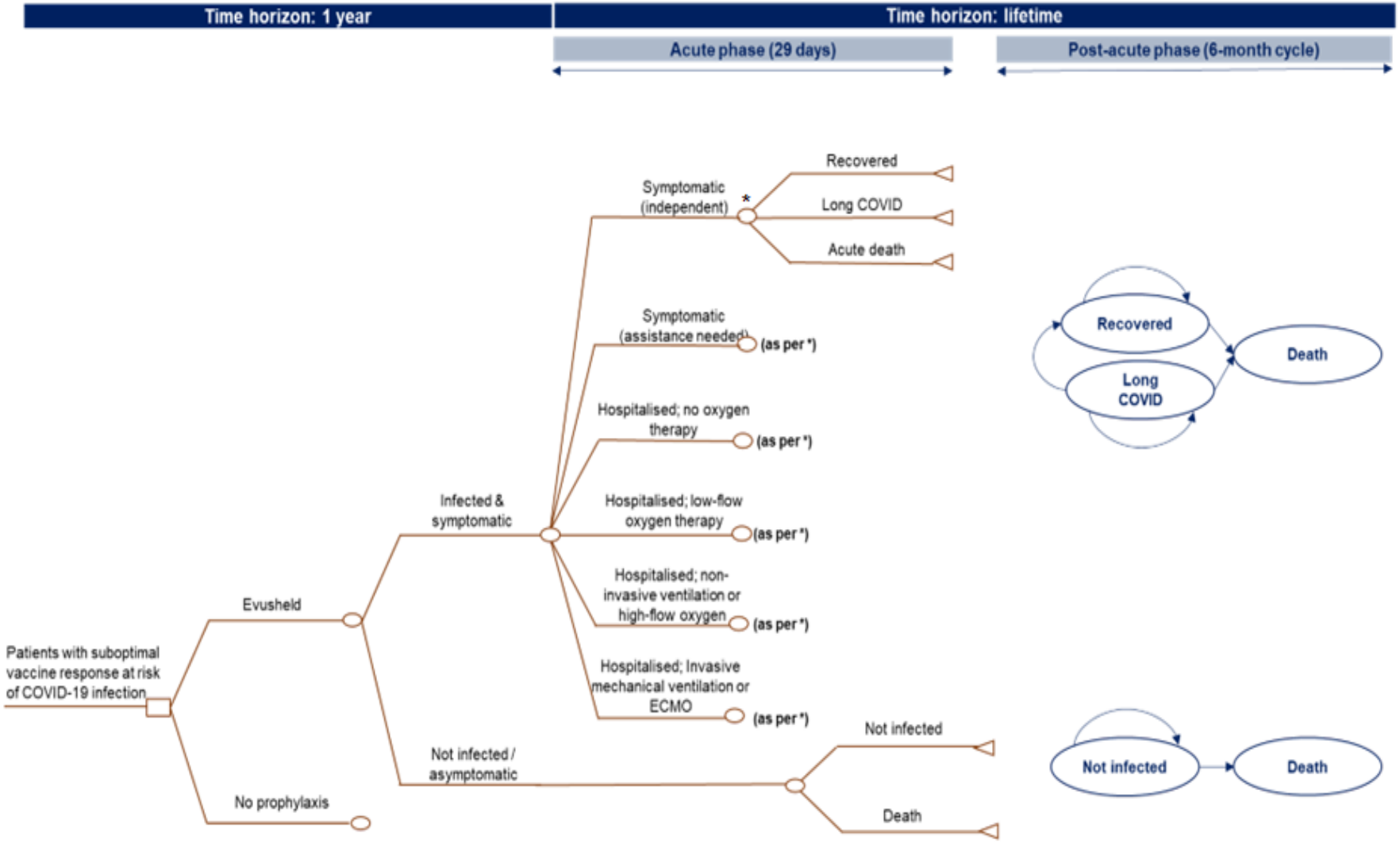
Comment from MHRA: *Use of the product for repeat dosing is outside of the current authorisation in the SmPC and would be regarded as off-label use. It is not for the MHRA to recommend such use, but comes under the responsibility of the prescribing doctor, as for all off-label use of medicines.*

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MHRA, Medicines and Healthcare products Regulatory Agency; SmPC, Summary of Product Characteristics.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- **Cost effectiveness**
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Company's model overview



Model structure	Decision tree (acute phase) followed by a Markov model (post-acute)
Perspective	NHS and PSS
Time horizon	Lifetime
Cycle length	Decision tree – 1 year and 29 days, Markov model – 6 months
Discounting (costs, health outcomes)	3.5% annually

EAG comments

- The EAG considered the model structure to be appropriate with the exception of the company's handling of cases of COVID-19 occurring after the first year. (**Note:** This is unresolvable with the current clinical evidence)

Impact of the technology

How the technology affects **costs**:

- Additional costs for drug acquisition and administration
- Reduced costs for acute hospital management and monitoring in the period of treatment
- Reduced cost for managing long COVID

How the technology affects **QALYs**:

- Direct utility gain from feeling protected from COVID
- Utility gain through avoided infections in the period of treatment
- Utility gain due to lower proportion of cases resulting in hospitalisation or death in the period of treatment
- Prevention of excess deaths in the years after hospital discharge for some patients, by reducing number of patients with severe infection
- Prevention of long COVID by preventing cases of COVID-19 in the period of treatment

Abbreviations: QALY, quality-adjusted life year.

How company incorporated evidence into model (1/2)

Input		No prophylaxis	Tix-cil
Baseline characteristics		53.5 years, 53.9% male; PROVENT	
Efficacy	**Risk of infection**	22.58% annually, general population England, Aug 21-22	66% reduction based on Young Xu et al. 2022
	Risk of hospitalisation	15.9% of infections (Shields et al. 2022)	62% reduction, given infection with COVID (i.e. applied to 15.9%). Overall hospitalisation rate = 0.46% Calculated based on Young Xu et al. 2022
	Level of hospital ventilation	Same distribution for both arms (Cusinato et al. 2022)	
Adverse events		TACKLE trial (Montgomery et al. 2022)	
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	
	Acute	Based on Ohsfeldt et al. 2022 and ICNARC data	
	Post-discharge	33% increased risk of mortality for 5 years following discharge from critical care (high flow oxygen or any form of ventilation), based on Lone et al. 2016	

Abbreviations: ICNARC, Intensive Care National Audit and Research Centre.

How company incorporated evidence into model (2/2)

Input		No prophylaxis	Tix-cil
Utility	**Utility in target population**	Disutility of 0.116 taken from Rafia et al. 2022, for people with heart conditions	
	Direct utility gain due to tix-cil treatment	N/A	Utility gain of [redacted] for 100% patients based on company's utility study
Long COVID	**Proportion**	Hospitalised patients 100% (assumed) Non-hospitalised patients: 34.8% (Augustin et al. 2022)	
	Cost	Annual cost of £2500, ScHARR COVID-19 MTA exploratory analysis	
	Disutility	Based on PHOSP-COVID cohort, Evans et al. 2021 and 2022, range 0.1542-0.3597 depending on acute hospitalisation requirements	
	Duration	Log normal curve based on ScHARR COVID MTA, calibrated using PHOSP-COVID cohort data	
Costs	**Acquisition**	N/A	Company's list price £1,600 per 600 mg dose.
	Administration	N/A	£41 – 1 hour, band 5 hospital nurse time

Notes: Only key utilities and costs are included on this slide. Standard age-specific population values for utility are used (Ara 2010). **Abbreviations:** MTA, Multiple Technology Appraisal; ScHARR, School of Health and Related Research.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- **Cost effectiveness key issues**
- Summary of base case assumptions
- Results: base case and scenario analysis
- Other considerations

Key issues

No.	Issue	ICER impact
Decision problem		
1	Eligible population and heterogeneity	Unknown
Clinical effectiveness		
2	Efficacy against current COVID-19 variants	Large
3	Repeated dosing of tix-cil	Unknown
Cost effectiveness		
4	Risk of COVID-19 infection (without tix-cil)	Large
5	Risk of hospitalisation for COVID-19 (without tix-cil)	Large
6	Direct utility gain for people receiving tix-cil	Large
7	Cost of administering tix-cil	Medium
8	Long COVID – risk, duration, utility decrement, cost	Medium

Abbreviations: ICER, incremental cost-effectiveness ratio.

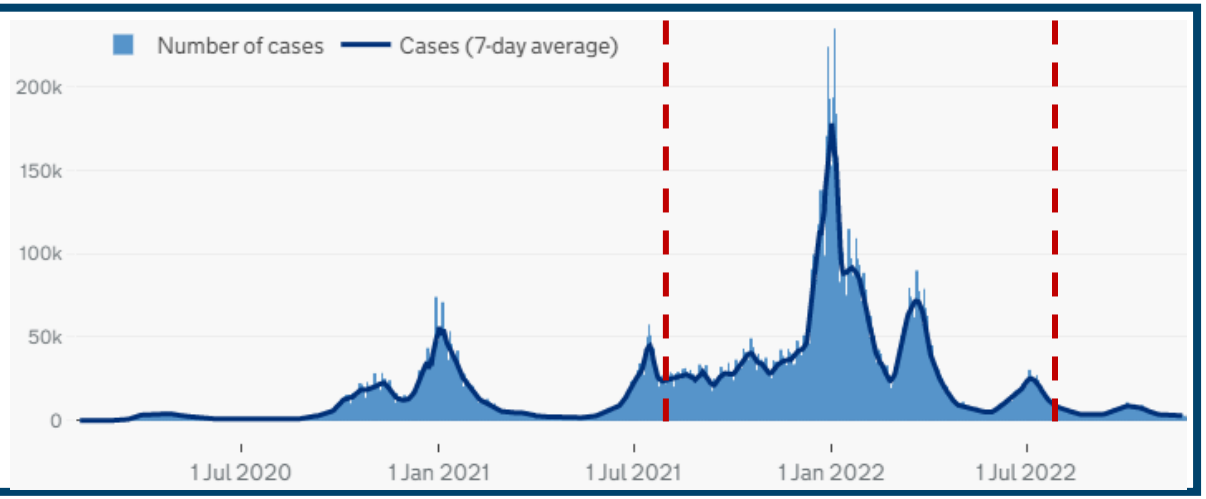
Key issue 4: Risk of COVID-19 infection (without tix-cil)

Background

- To generate estimates of comparative effectiveness, COVID-19 risk for those not receiving prophylaxis must be determined

Company

- Assumed the risk of symptomatic COVID-19 for those not receiving prophylaxis is 22.58% annually
- This was based on the average 7-day risk of reporting a positive test for SARS-CoV-2 in the general population of England between August 2021 and August 2022 (red dashed lines)



EAG comments

- Historical risks for COVID-19 may not reflect the risk in the year after guidance on tix-cil is published
- Risk may be overestimated as not all patients reporting a positive test will have been symptomatic
- Risk may be underestimated during period when access to testing was restricted (from April 2022)
- Data represents risk for general population as a whole, not the group likely to be offered tix-cil
- Future risk is uncertain as this depends on circulating variant, protection offered by vaccines, measures to prevent transmission and infection avoidance behaviours in the target population
- Scenarios are presented where the risk is reduced to 10% to reflect uncertainty in this parameter

What is the risk of contracting COVID-19 infection (without tix-cil) for the target population?

Key issue 5: Risk of hospitalisation for COVID-19 (without tix-cil)

Company and EAG

- Risk of hospitalisation due to COVID-19 was based on Shields et al. (2022) which assessed impact of vaccination on hospitalisation and mortality for people with immunodeficiency in the UK (IAG group A2)
- Hospitalisation rate up to April 2022 for the Omicron wave was 9.9%
- However, this includes people who were treated in COVID Medicines Delivery Units (CMDUs) with monoclonal antibodies and antivirals
- The hospitalisation risk was higher in those not receiving COVID-19 therapeutics (15.9% vs 4.3%).
- As COVID-19 therapeutics are not in routine commissioning, hospitalisation risk should be based on patients treated during the Omicron wave who were not treated in CMDUs (15.9%)

NICE technical team

- The proportion requiring hospitalisation (without tix-cil) assumed by the company and the EAG is higher than the proportion preferred by the committee in the COVID-19 MTA (without treatment)
- The MTA uses a lower proportion based on Patel et al. (2022) – a retrospective cohort study of high-risk patients with COVID-19 between December 2021 and May 2022
- Based on Patel et al., 2.8% of untreated patients were hospitalised with COVID-19 as the primary diagnosis (study included those eligible for treatment under McInnes report criteria) – this is included as a scenario analysis

What is the risk of hospitalisation for COVID-19 in the target population?

NICE

Abbreviations: EAG, External Assessment Group; IAG, Independent Advisory Group; MTA, Multiple Technology Appraisal.

Key issue 6: Direct utility gain for people receiving tix-cil (1/2)

Company

- Submitted evidence from a commissioned utility study (Gallop et al. 2022) investigating the impact of the pandemic on people who are immunocompromised
- Of the whole cohort [redacted] were fully shielding, [redacted] were partially shielding and [redacted] were not shielding or modifying their behaviour
- The study provides EQ-5D scores for immunocompromised patients' current health state and for a vignette that describes a treated patient
- The treated vignette included the statement: *"You now have a level of protection from COVID-19 which is similar to that given by vaccination in individuals who have a healthy immune system"*

Table: Patient valuations of health states, mean EQ-5D (95% confidence interval)

	Current	Treated - vignette	Difference
Whole cohort [redacted]	[redacted]	[redacted]	[redacted]
Partially shielding [redacted]	[redacted]	[redacted]	[redacted]
Shielding [redacted]	[redacted]	[redacted]	[redacted]

Note: No subgroup results are provided for the subgroup who are no longer shielding or modifying their behaviour.
Abbreviations: EQ-5D; EuroQol 5 Dimensions

Key issue 6: Direct utility gain for people receiving tix-cil (2/2)

Company continued…

- To estimate the utility gain, the company weighted utility estimates for shielding and partially shielding, according to the corresponding proportions (13% and 69%) from an Office for National Statistics (ONS) survey
- A final utility increment of [redacted] was applied to 100% of patients receiving tix-cil – assuming that all those who desire prophylaxis would be modifying their behaviour
- The utility increment is applied for the duration of tix-cil treatment (1 year), with the duration halved in those infected while on tix-cil

EAG / NICE technical team comments

- Not all people eligible will be modifying their behaviour and would therefore not benefit from the utility gain
- EAG base case applies the utility increment of [redacted] to the 82% who are fully or partially shielding according to the ONS survey
- This aspect of the economic analysis is subject to considerable uncertainty, as it is uncertain how patients' behaviour would change following tix-cil administration – this depends on perceived efficacy
- The company's evidence suggests that [redacted] patients would return to their pre-treatment behaviour if there is a new variant that the treatment was not effective against
- Therefore EAG has explored scenarios assuming the utility of [redacted] would apply to only [redacted] of patients
- As this parameter is related to efficacy, a scenario also explored the impact on the ICER if efficacy and direct utility gain are both reduced

NICE

Should a direct utility gain for tix-cil be applied? If so, what size utility gain is most appropriate and what proportion of people should this apply to?

Key issue 7: Cost of administering tix-cil

Background

- The recommended dose is 600mg tix-cil, administered as 300mg of tixagevimab, and 300mg of cilgavimab; given as two separate sequential injections
- Summary of Product Characteristics: *"Individuals should be observed for at least 1 hour after injection."*

Company

- Tix-cil can be offered as part of patients' routine outpatient appointments or via secondary care led community services
- Assumed a cost of £41 per administration of tix-cil, based on 1 hour of band 5 hospital nurse time

EAG comments

- Believes that the cost of delivering tix-cil is unlikely to be properly accounted for by the company
- It is not clear if all eligible patients would be receiving routine appointments sufficiently regularly to provide timely administration of tix-cil
- Prefers to assume tix-cil would be administered within COVID-19 Medicines Delivery Units (CMDUs)
- The CMDU unit cost of £410 per administration (of an oral antiviral) is considered to better reflect cost for administering tix-cil (ScHARR COVID-19 MTA)
- The company's assumed cost is explored as a scenario

How is tix-cil likely to be administered in practice and what is the expected cost?

NICE

Abbreviations: MTA, Multiple Technology Appraisal; ScHARR, School of Health and Related Research.

Key issue 8: Long COVID risk, duration, utility decrement, cost

Company and EAG assumptions and data sources

Parameter	Company	EAG
Risk of long COVID (not hospitalised)	34.8% - Augustin et al. 2022	12.7% - Ballering et al. 2022
Long COVID duration	Lognormal curve from ScHARR MTA – ONS May 2022, with adjustment to account for lower proportion recovering between 5 months and 1 year in the PHOSP-COVID cohort (Evans et al. 2022)	Lognormal curve from ScHARR MTA – ONS October 2022, without Evans et al. adjustment – company's extrapolations counterintuitive and result in longer duration of long COVID than would be expected based on latest ONS data
Long COVID cost	£2,500 - ScHARR COVID-19 MTA exploratory scenario	£2,267 - chronic fatigue syndrome (Hunter et al. 2017)
Long COVID utility decrement	Based on Evans et al. 2022 (not recovered) Utility decrement assumed constant over duration of long COVID	Based on Evans et al. 2022 (not recovered and unsure) Assumed linear improvement over duration of long COVID (50% utility decrement at y5)

Scenarios are presented for all long COVID parameters

Abbreviations: EAG, External Assessment Group; MTA, Multiple Technology Appraisal; ONS, Office for National Statistics; ScHARR, School of Health and Related Research.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- **Summary of base case assumptions**
- Results: base case and scenario analysis
- Other considerations

Summary of company and EAG base case assumptions (1/2)

Assumption	Company	EAG
Risk of COVID-19 infection (without tix-cil)	22.58% - UK government data for general population of England between August 2021 and August 2022	
Risk of hospitalisation for COVID-19 (without tix-cil)	15.9% - Shields et al. 2022	
Relative risk reduction tix-cil, COVID-19 infection	66% - real-world evidence (Young Xu et al. 2022)	
Relative risk reduction tix-cil, hospitalisation given COVID-19	62% - calculated based on real-world evidence (Young Xu et al. 2022)	
Proportion hospitalised patients requiring invasive mechanical ventilation	15.4%	4.92%
Repeated dosing	Yes (2 doses of tix-cil, 6 months apart)	
Adverse events	TACKLE – incidence doubled to reflect 2 doses of tix-cil	
Direct utility gain for people receiving tix-cil	[redacted] for 100% of target population	[redacted] for 82% of target population
Tix-cil administration cost	£41 - 1 hour, band 5 hospital nurse time	£410 - CMDU cost for administering COVID-19 therapeutics

Abbreviations: CMDU, COVID Medicines Delivery Units; EAG, External Assessment Group

Summary of company and EAG base case assumptions (2/2)

Assumption	Company	EAG
Mortality (acute)	Based on Ohsfeldt et al. 2022 and ICNARC data: - No oxygen therapy: 4.6% - Low-flow oxygen therapy: 7.6% - Non-invasive ventilation or high flow oxygen: 13.9% - Invasive mechanical ventilation: 47.0%	
Mortality (long-term)	UK life tables, with SMR of 1.7 applied to reflect target population. Odnoletkova et al. 2018 – common variable immunodeficiency disorders 33% increased risk of mortality post-discharge from critical care Lone et al. 2016	
Long COVID risk (not hospitalised)	34.8% - Augustin et al. 2022	12.7% - Ballering et al. 2022
Long COVID duration	Lognormal curve from ScHARR MTA – ONS May 2022, with Evans et al. adjustment	Lognormal curve from ScHARR MTA – ONS October 2022, without Evans et al. adjustment
Long COVID cost	£2,500 - ScHARR COVID-19 MTA exploratory scenario	£2,267 - chronic fatigue syndrome (Hunter et al. 2017)
Long COVID utility decrement	Based on Evans et al. 2022 (not recovered) Utility loss assumed constant over duration of long COVID	Based on Evans et al. 2022 (not recovered and unsure) Assumed linear improvement over duration of long COVID

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- **Results: base case and scenario analysis**
- Other considerations

Company and EAG base case results, list price and PAS price

Company deterministic incremental base case results

	List price					PAS price
Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]				
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,004

EAG deterministic incremental base case results

	List price					PAS price
Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)
No prophylaxis	[redacted]	[redacted]				
Tix-cil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,646

Note: EAG's probabilistic ICER, list price = [redacted]

NICE

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Company and EAG base case results – LIST PRICE

Individual impact of EAG changes on the ICER

Change	ICER (£) versus no prophylaxis
Company base case	[redacted]
Direct utility gain due to receiving tix-cil – applied to 82% patients only	[redacted]
Long COVID, proportion of those not hospitalised – 12.7%	[redacted]
CMDU administration cost for tix-cil – £410	[redacted]
Long COVID duration – Office for National Statistics, October 2022, not calibrated	[redacted]
Long COVID duration – Evans adjustment for hospitalised cohort removed	[redacted]
Long COVID cost – EAG's original cost of £1,128	[redacted]
Long COVID disutility – post-hospitalisation disutilities recalculated by EAG	[redacted]
Long COVID disutility – linear improvement over duration of long COVID	[redacted]
Distribution, acute hospitalisation – 4.92% requiring IMV or ECMO	[redacted]
Long COVID cost – EAG's updated cost of £2,267	[redacted]

Notes: ICERs generated by NICE technical team. **Abbreviations:** EAG, External Assessment Group; ECMO, extracorporeal membrane oxygenation; ICER, incremental cost-effectiveness ratio; IMV, invasive mechanical ventilation.

EAG deterministic scenario analysis (1/2) – LIST PRICE

Key issue	Scenario (applied to EAG base case)	Incremental costs (£)	Incremental QALYs	ICER (£)
0	**EAG base case**	[redacted]	[redacted]	[redacted]
#1	Baseline characteristics from the immunocompromised subpopulation of PROVENT	[redacted]	[redacted]	[redacted]
#6, 1	Applying the direct utility gain to [redacted] of patients	[redacted]	[redacted]	[redacted]
#2, 1	Reducing efficacy (risk of infection) of tix-cil by 50%	[redacted]	[redacted]	[redacted]
#2, 6, 1	Reducing efficacy of tix-cil (risk of infection) of tix-cil by 50% + applying the direct utility gain to [redacted] of patients	[redacted]	[redacted]	[redacted]
#4, 1	Reducing risk of COVID-19 infection without tix-cil to 10% - exploratory scenario	[redacted]	[redacted]	[redacted]
#5, 1	Reducing risk of hospitalisation for COVID-19 (without tix-cil) to 2.8% - Patel et al. (2022)	[redacted]	[redacted]	[redacted]
#7	Using the company's preferred estimate of the administration cost - £41	[redacted]	[redacted]	[redacted]

Notes: Scenarios exploring 6 month duration of tix cil (key issue #3) are not available. *ICERs requested by committee lead team to understand impact of key uncertainties and generated by NICE technical team. **Abbreviations:** EAG, External Assessment Group, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

EAG deterministic scenario analysis (2/2) – LIST PRICE

Key issue	Scenario (applied to EAG base case)	Incremental costs (£)	Incremental QALYs	ICER (£)
0	**EAG base case**	[redacted]	[redacted]	[redacted]
#8	Using the company's preferred estimate of the duration of long COVID	[redacted]	[redacted]	[redacted]
#8	Assuming 4.2% of the non-hospitalised cohort would develop long COVID (ONS data)	[redacted]	[redacted]	[redacted]
#8	Assuming 34.8% of the non-hospitalised cohort would develop long COVID (company's approach)	[redacted]	[redacted]	[redacted]
#8	Using company's preferred estimate for long COVID cost (£2,500)	[redacted]	[redacted]	[redacted]
#8	Using company's preferred approach for long COVID disutility	[redacted]	[redacted]	[redacted]
N/A	Reducing proportion of hospitalised patients requiring invasive mechanical ventilation to 2.51%	[redacted]	[redacted]	[redacted]

NICE

Note: *ICERs generated by NICE technical team. **Abbreviations:** EAG, External Assessment Group, ICER, incremental cost-effectiveness ratio; ONS, Office for National Statistics; QALY, quality-adjusted life year.

Tixagevimab–cilgavimab (tix-cil) for preventing COVID-19

- Background, patient and clinical perspectives
- Cost-effectiveness results and key issues
- Decision problem
- Clinical effectiveness
- Clinical effectiveness key issues
- Cost effectiveness
- Cost effectiveness key issues
- Summary of base case assumptions
- Results: base case and scenario analysis
- **Other considerations**

Other considerations

Potential equality issues raised

- Most of the population are protected through vaccination, people with immunosuppression are still leading restricted lives and are disadvantaged in the workplace, educationally and socially
- People eligible for tix-cil are more likely to be covered under the protected characteristics of the Equality Act due to long-term health problems and disabilities
    - Those eligible are also more likely to experience mobility difficulties or be homed in health and social care settings. Travel to treatment centres may be an additional barrier
    - Black, Asian and minority ethnic groups are less likely to receive vaccination or post-exposure treatments, and have health conditions that put them at greater risk of severe COVID-19
- Many other countries have approved tix-cil, people in the UK feel disadvantaged compared to people in these countries
- Tix-cil is now available privately, there is disparity between those who can afford it and those who cannot

Is there potential that any recommendations could have a different impact on people protected by the equality legislation than on the wider population?

Other considerations

Disease severity

- The company has not made a case for the severity modifier

Key issues

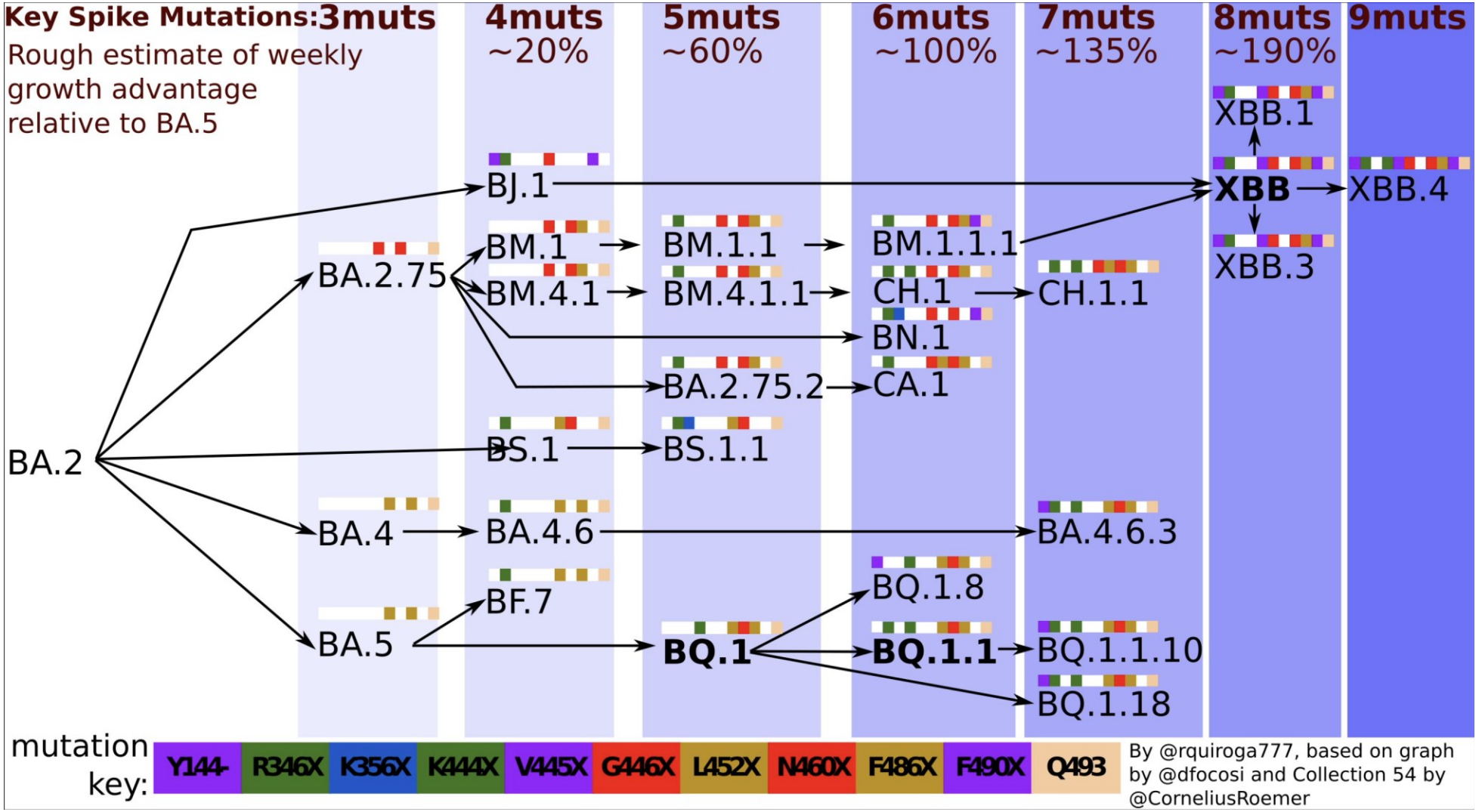
No.	Issue	ICER impact
Decision problem		
1	Eligible population and heterogeneity	Unknown
Clinical effectiveness		
2	Efficacy against current COVID-19 variants	Large
3	Repeated dosing of tix-cil	Unknown
Cost effectiveness		
4	Risk of COVID-19 infection (without tix-cil)	Large
5	Risk of hospitalisation for COVID-19 (without tix-cil)	Large
6	Direct utility gain for people receiving tix-cil	Large
7	Cost of administering tix-cil	Medium
8	Long COVID – risk, duration, utility decrement, cost	Medium

Abbreviations: ICER, incremental cost-effectiveness ratio.

NICE National Institute for Health and Care Excellence

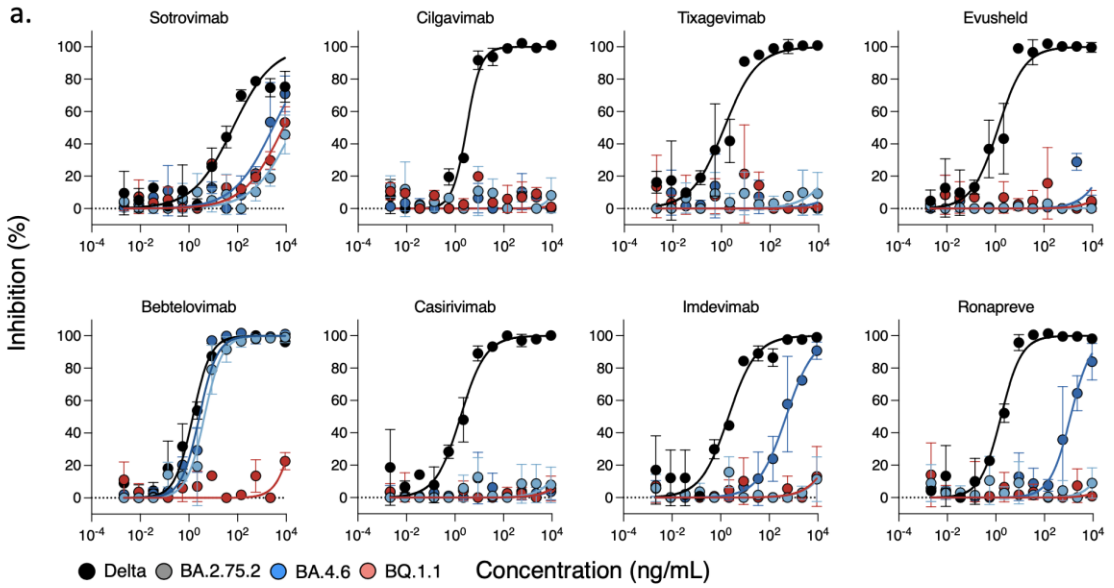
Appendix

Evolution of SARS-CoV-2 Omicron variants



1/5 Planas. Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies

a.



b.

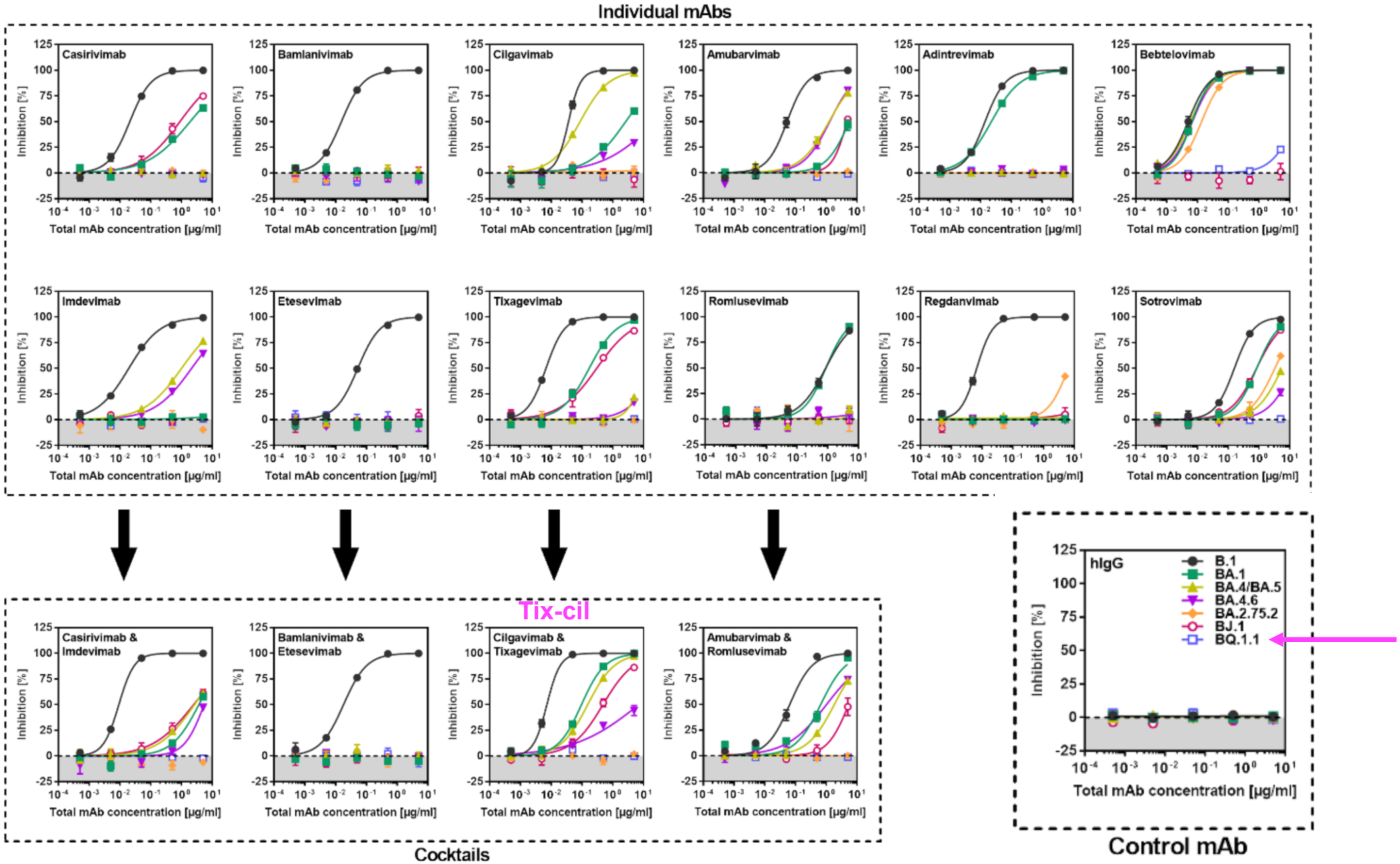
mAb	D614G	BA.2*	BA.5*	BA.2.75.2	BQ.1.1	BA.4.6
Bebtelovimab	1.4	4.5	2	4,3	-	2,7
Sotrovimab	65	11,519	1,088	19,391	764	2,874
Cilgavimab	2.9	6.1	11	-	-	-
Tixagevimab	1.3	-	-	-	-	-
Evusheld	1,3	24.7	22.6	-	-	-
Casirivimab	1.7	-	-	-	-	-
Imdevimab	2.1	1,12	208	-	-	493
Ronapreve	1.6	1,985	700	-	-	1,181

IC50 (ng/mL)

Figure 3. Neutralization activity of therapeutic monoclonal antibodies against BQ.1.1, BA.2.75.2 and BA.4.6. a. Neutralization curves of monoclonal antibodies. Dose–response analysis of the neutralization by the indicated antibodies or their clinical combinations. Evusheld: Cilgavimab and Tixagevimab. Ronapreve: Casirivimab and Imdevimab. Data are mean ± s.d. of 2 independent experiments. **b.** IC50 values in ng/ mL for each antibody against the indicated viral strains. *ED50 against BA.2 and BA.5 are from [47].

NICE

2/5 Arora. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies

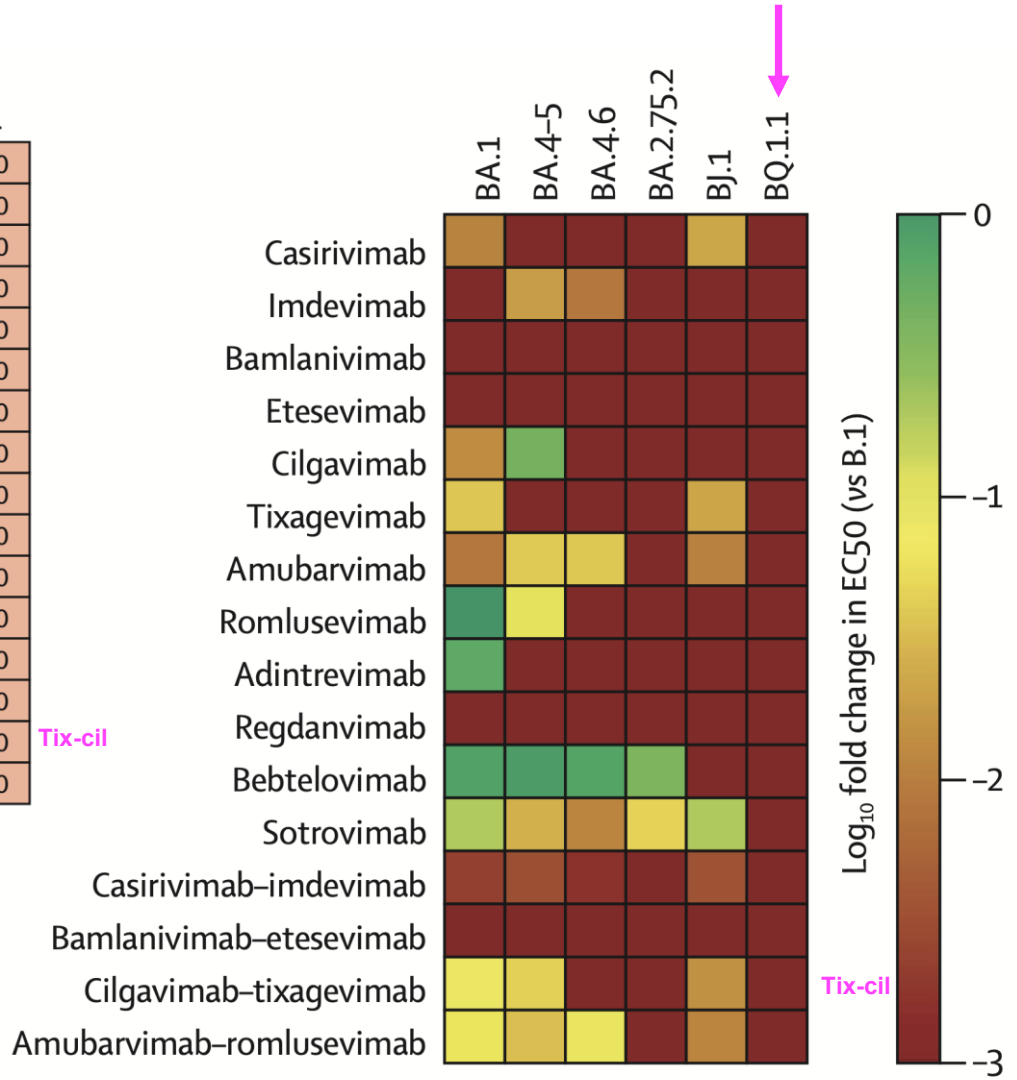


2/5 Arora. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies

		B.1	BA.1	BA.4–5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
	Sotrovimab	157	833	5554	13000	3239	825	>50000
Cocktails of mAbs	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

EC50 (ng/ml)

Tix-cil



3/5 Wang. Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants

IC50 (μg/ml)	NTD	NTD-SD2	SD1	RBD Class 1				RBD Class 2			Tixagev	RBD Class 3										Cilgav	RBD Class 4	Tix-cil
	C1520	C1717	S3H3	S2K146	Omi-3	Omi-18	BD-515	XGv051	XGv347	ZCB11	COV2-2196	LY-CoV1404	XGv289	XGv264	S309	P2G3	SP1-77	BD55-5840	XGv282	BD-804	35B5	COV2-2130	10-40	Evusheld
D614G	0.002	0.125	0.022	0.004	0.004	0.012	0.010	0.001	0.002	0.002	0.002	0.002	0.002	0.001	0.023	0.001	0.003	0.002	0.001	0.011	0.014	0.007	0.049	0.003
BA.4/5	0.001	0.209	0.014	0.090	0.023	0.013	0.010	0.050	3.450	4.868	>10	0.001	0.038	0.002	0.514	0.002	0.005	0.009	0.001	0.019	>10	0.021	2.414	0.035
BQ.1	0.001	0.666	0.019	0.585	0.860	0.131	0.343	0.159	2.830	>10	>10	>10	0.425	0.494	0.600	1.608	>10	0.034	0.020	>10	>10	>10	>10	>10
BQ.1.1	0.003	1.117	0.025	0.527	0.804	0.170	0.377	0.191	3.311	>10	>10	>10	1.013	>10	2.140	>10	>10	>10	0.098	>10	>10	>10	>10	>10
BA.4/5-R346T	0.002	0.141	0.020	0.081	0.019	0.009	0.006	0.042	2.166	2.560	>10	0.001	0.045	0.003	1.726	0.041	>10	1.447	0.001	>10	>10	>10	5.069	>10
BA.4/5-K444T	0.002	0.116	0.009	0.104	0.016	0.010	0.006	0.040	4.766	3.731	>10	>10	0.161	0.273	0.552	1.245	4.007	0.038	0.006	>10	>10	>10	6.976	>10
BA.4/5-N460K	0.002	1.166	0.016	0.542	1.279	0.186	0.431	0.152	3.046	>10	>10	0.002	0.353	0.003	0.934	0.003	0.009	0.012	0.002	0.122	>10	0.030	>10	0.063
BA.2	0.002	0.561	0.016	0.028	0.015	0.005	0.012	0.001	0.003	0.012	1.924	0.001	0.067	0.003	0.833	0.002	0.006	0.014	0.001	0.038	0.827	0.009	8.770	0.019
XBB	>10	0.836	0.016	0.223	1.181	0.468	0.555	>10	>10	>10	>10	>10	>10	>10	0.343	>10	>10	>10	>10	>10	>10	>10	>10	>10
XBB.1	>10	0.693	0.019	0.190	1.705	0.605	0.803	>10	>10	>10	>10	>10	>10	>10	0.405	>10	>10	>10	>10	>10	>10	>10	>10	>10
BA.2-V83A	0.001	0.354	0.015	0.036	0.019	0.007	0.015	0.002	0.003	0.013	3.039	0.001	0.070	0.002	0.641	0.002	0.007	0.019	0.001	0.045	1.274	0.011	>10	0.025
BA.2-Del144	0.002	0.501	0.011	0.026	0.016	0.004	0.011	0.002	0.002	0.008	4.134	0.001	0.063	0.002	0.455	0.002	0.005	0.014	0.001	0.031	0.341	0.010	8.766	0.021
BA.2-H146Q	0.001	0.356	0.011	0.032	0.011	0.004	0.009	0.002	0.002	0.010	2.924	0.002	0.055	0.002	0.641	0.003	0.007	0.019	0.001	0.044	1.107	0.009	9.106	0.019
BA.2-Q183E	0.322	0.307	0.019	0.034	0.018	0.006	0.014	0.002	0.003	0.013	3.098	0.001	0.067	0.003	0.649	0.002	0.008	0.020	0.002	0.028	1.019	0.011	9.251	0.022
BA.2-V213E	0.002	0.406	0.013	0.030	0.014	0.004	0.010	0.002	0.002	0.006	2.177	0.001	0.047	0.003	0.720	0.002	0.006	0.014	0.001	0.026	1.247	0.009	8.198	0.018
BA.2-G252V	0.001	0.577	0.013	0.030	0.012	0.004	0.008	0.002	0.003	0.008	2.258	0.001	0.048	0.002	0.564	0.002	0.005	0.012	0.001	0.032	0.939	0.011	>10	0.026
BA.2-G339H	0.001	0.485	0.017	0.034	0.020	0.006	0.012	0.002	0.002	0.010	3.876	0.002	0.114	0.002	0.302	0.002	0.007	0.040	0.002	0.050	0.661	0.012	8.575	0.023
BA.2-R346T	0.003	0.372	0.012	0.017	0.010	0.003	0.007	0.001	0.002	0.007	2.109	0.002	0.048	0.004	1.433	0.007	>10	1.442	0.001	0.112	>10	>10	7.767	1.486
BA.2-L368I	0.003	0.453	0.019	0.027	0.010	0.004	0.010	0.002	0.001	0.006	2.603	0.001	0.030	0.002	0.605	0.002	0.005	0.021	0.001	0.026	0.324	0.008	3.202	0.018
BA.2-V445P	0.001	0.433	0.019	0.026	0.009	0.004	0.009	0.002	0.002	0.008	2.313	>10	>10	1.141	0.428	>10	0.007	0.144	>10	1.582	0.486	>10	6.311	3.135
BA.2-G446S	0.002	0.367	0.012	0.021	0.009	0.004	0.009	0.001	0.003	0.008	2.614	0.002	0.026	0.004	0.686	0.002	0.004	0.014	0.022	0.026	0.965	0.017	5.774	0.029
BA.2-N460K	0.002	1.323	0.012	0.132	0.784	0.013	0.358	0.007	0.004	0.073	1.756	0.001	0.355	0.003	0.878	0.002	0.011	0.017	0.001	0.058	1.957	0.013	>10	0.025
BA.2-F486S	0.002	0.677	0.008	>10	0.583	0.011	0.017	>10	>10	>10	>10	0.001	0.049	0.003	0.581	0.002	0.006	0.009	0.002	0.060	2.264	0.011	>10	0.023
BA.2-F490S	0.001	0.428	0.014	0.022	0.033	0.004	0.008	0.001	0.004	0.012	1.105	0.001	0.030	0.002	0.564	0.002	0.006	0.011	>10	0.048	>10	0.013	5.337	0.016
BA.2-R493Q	0.003	0.338	0.024	0.005	0.006	0.006	0.006	0.001	0.001	0.002	0.034	0.001	0.045	0.002	1.109	0.002	0.007	0.022	0.000	0.010	1.175	0.010	3.419	0.008

>10	1-10	0.1-1	0.01-0.1	<0.01

Figure S2. Pseudovirus neutralization IC_{50} values for mAbs against BQ and XBB subvariants and point mutants, related to Figure 3

Pseudovirus neutralization IC_{50} values for mAbs against D614G, Omicron subvariants, and point mutants of BQ.1, BQ.1.1, XBB, and XBB.1 in the background of BA.4/5 or BA.2.

NICE

4/5 Cao. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution

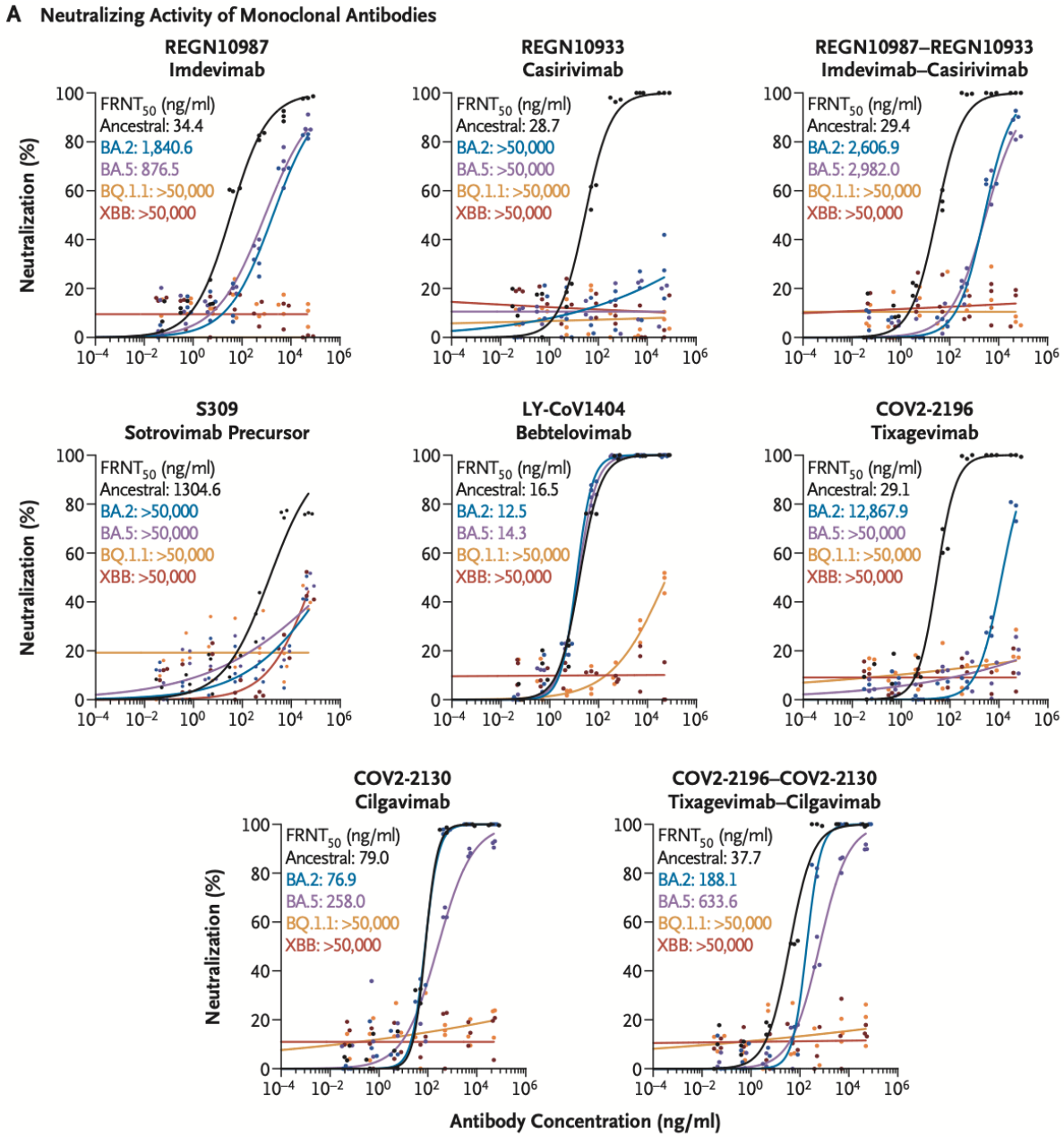
				Tixagev	Cilgav	Tix-cil										
Pango lineages	REGN 10933	REGN 10987	REGN10933 +10987	COV2-2196	COV2-2130	COV2-2196+2130	BRII-196	BRII-198	BRII-196+198	S309	DXP-604	LY-CoV 1404	SA58	SA55	SA55+ SA58	Additional RBD mutations
BA.2	*	590	821	4312	6.3	8.2	8530	8990	8610	852	219	0.9	5.1	7.2	7.8	
BA.2.3.20	121	*	199	15	*	26	14	*	24	897	181	9.7	20	4.6	7.8	K444R+N450D+L452M +N460K+R493Q
BA.2.10.4	*	*	*	*	289	501	2109	7990	3984	706	6348	1.3	4.3	4.9	5.0	G446S+F486P+R493Q +S494P
BJ.1	*	*	*	3076	*	5985	7609	*	*	709	166	*	8163	3.7	8.6	D339H+R346T+L368I+ V445P+G446S+V483A +F490V
XBB	*	*	*	*	*	*	*	*	*	963	*	*	8805	5.3	9.8	D339H+R346T+L368I+ V445P+G446S+N460K +F486S+F490S+R493Q
BA.2.75	278	*	410	119	352	121	1730	6622	3861	672	5920	2.2	246	4.3	9.6	
BL.1	260	*	511	93	*	174	1251	*	3075	508	7193	2.8	7975	6.3	10	R346T
BR.1	319	*	679	117	*	170	1992	*	3160	564	6689	*	1616	5.9	9.7	L452R+K444M
BN.2.1	390	*	701	59	303	109	4101	*	8444	6979	8901	1.7	4960	5.7	9.4	K356T+F490S
BN.1	344	*	599	70	*	166	3683	*	7791	*	6012	3.3	8295	4.9	9.0	R346T+K356T+F490S
BA.2.75.2	*	*	*	*	*	*	*	*	*	852	*	3.0	6922	5.9	9.7	R346T+F486S
BM.1.1	*	*	*	*	*	*	*	*	*	879	*	2.3	8823	5.2	8.9	R346T+F486S
BM.1.1.1	*	*	*	*	*	*	*	*	*	956	*	1.9	8082	4.8	10.5	R346T+F486S+F490S
BR.2	*	*	*	*	*	*	*	*	*	921	*	2.6	7263	4.7	10.5	R346T+L452R+F486I
CA.1	*	*	*	*	*	*	*	*	*	897	*	3.2	6927	6.0	11.5	R346T+L452R+F486S
BA.4/5	*	520	709	*	23	40	7124	*	*	1055	6264	0.8	3.9	5.0	4.5	
BA.4.6.1	*	2338	5402	*	*	*	4763	*	7809	4456	4634	1.2	50	4.8	9.9	R346T
BA.5.6.2	*	*	*	*	*	*	4636	*	7883	1408	5892	1662	58	5.1	8.9	K444T
BQ.1	*	*	*	*	*	*	*	*	*	1709	*	1905	44	6.6	9.2	K444T+N460K
BU.1	*	*	*	*	*	*	*	*	*	1082	*	26	56	5.3	10.5	K444M+N460K
BQ.1.1	*	*	*	*	*	*	*	*	*	5581	*	*	900	5.9	10.3	R346T+K444T+N460K

Pseudovirus IC50 (ng/mL)

<100	100~1,000	>1,000	* >10,000

NICE

5/5 Imai. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB



Company and EAG base case results – LIST PRICE

Cumulative impact of EAG changes on the ICER

Change	ICER (£) versus no prophylaxis
Company base case	[redacted]
Direct utility gain due to receiving tix-cil – applied to 82% patients only	[redacted]
Long COVID, proportion of those not hospitalised – 12.7%	[redacted]
CMDU administration cost for tix-cil – £410	[redacted]
Long COVID duration – Office for National Statistics, October 2022, not calibrated	[redacted]
Long COVID duration – Evans adjustment for hospitalised cohort removed	[redacted]
Long COVID cost – EAG's original cost of £1,128	[redacted]
Long COVID disutility – post-hospitalisation disutilities recalculated by EAG	[redacted]
Long COVID disutility – linear improvement over duration of long COVID	[redacted]
Distribution, acute hospitalisation – 4.92% requiring IMV or ECMO	[redacted]
Long COVID cost – EAG's updated cost of £2,267	[redacted]
Long COVID disutility – correction of application error	[redacted]

Notes: ICERs generated by NICE technical team. **Abbreviations:** EAG, External Assessment Group; ECMO, extracorporeal membrane oxygenation; ICER, incremental cost-effectiveness ratio; IMV, invasive mechanical ventilation.