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REAEARCH ARTICLE

From Clinical Trials to Communities: an observational study to evaluate the efficacy of Antiviral Therapies for Severe Acute Respiratory Syndrome Coronavirus 2 infections within Wales

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ABSTRACT

Background and Purpose. The COVID-19 pandemic of SARS-CoV-2 poses significant health risks, namely respiratory and immune-related symptoms, which can lead to hospitalisation or death. Several antiviral drugs have undergone clinical trials with mixed results, but ultimately Paxlovid, molnupiravir, and sotrovimab have been approved by the UK's medicines regulatory agency. This study aims to evaluate their effectiveness in the Welsh community, as their efficacy outside of clinical trials remains uncertain.

Experimental approach. Using a retrospective cohort design, this study was conducted in Wales to evaluate the efficacy of antiviral drugs in high-risk (see Appendix A) non-hospitalised COVID-19 patients. These patients were retrospectively monitored for 28 days examining for the primary endpoints of hospitalisation and mortality. Confirmation of antiviral prescription was obtained from the National Antiviral Service Cymru. From this, digital copies of patients' notes were reviewed online for evidence of hospitalisation or death. Ethical approval was not required since no further clinical testing was involved. Data handling was congruous with the Cardiff and Vale University Health Board policies.

Key Results. The primary study included 820 total patients, with a male-to-female ratio of 41:59 and a median age of 60. Overall analysis identified that 6.2% of all patients (N=820) met the criteria for a primary endpoint within the 28-day window. The combined mean primary endpoint rates for all drugs between the primary study (6.2%) and pivotal trials (1.9%) did not differ, $p = 0.24$.

There was no statistical difference between the incidence in the Molnupiravir treatment group (8.2%) and its respective pivotal clinical trial (8.2%), $p = 0.27$. Sotrovimab displayed a significantly higher primary endpoint rate of 2.6% when compared to the pivotal trial result of 1.1%. This decrease in efficacy since market authorisation was statistically significant to $p = 0.04$.

Conclusion. COVID-19 antiviral treatment with Paxlovid, molnupiravir, or sotrovimab reduced the risk of hospitalisation or death in high-risk non-hospitalized patients. However, the efficacy of these drugs in the community setting appears lower than in pivotal clinical trials. The reasoning behind this is not clear, although it may be due to SARS-CoV-2 mutations or the UK vaccination program. Specifically, a higher incidence rate was found within the sotrovimab treatment group than the clinical trial. Further research across a larger UK-wide patient population is needed to confirm the true effect of COVID-19 antiviral drugs in the community.

Introduction

The variation of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a wide range of symptoms, including fever, shortness of breath and acute respiratory distress syndrome (ARDS).[1] The latter has been found to have a 67% fatality event rate in high-risk groups, such as people with immunosuppressive comorbidities.[2] This study uses the high-risk definition as outlined in the Department of Health and Social Care's May 2022 report, see Appendix A.

To mitigate against this potential cost of life, many clinical trials have been heavily funded and researched to produce efficacious antiviral drugs. As clinical guidance has adapted to the recent literature, we have three key drugs available in the UK: Paxlovid, remdesivir and sotrovimab.[3] Following clinical trials, these drugs have all respectively passed the UK's Medicines and Healthcare products Regulatory Agency (MHRA) scrutiny.[4] However, to be truly effective these drugs must have long-term proven results in the community, not just in the controlled clinical trial conditions. The purpose of this study is to evaluate the effect of these drugs on the Welsh community.

For some patients, they may be diagnosed with conditions that cause immunodeficiencies. This puts them at higher risk of developing severe COVID-19 complications, such as ARDS. To support the natural immune system to fight viral infections, several treatments have been developed and are available, including antiviral drugs and monoclonal antibodies. These treatments aim to reduce viral replication and assist the immune response.

In April 2021, the UK government launched a project aimed at looking for UK-based solutions to reduce COVID-19 infections and increase recovery times. This was to protect the National Health Service (NHS) later in the year from winter pressures. They also provided protection against viral infection for patients who may not be fully immunised after vaccination.[5] This could be evident in patients with significant disease-related immunodeficiencies, e.g. leukaemia, or patients taking immunosuppressants, e.g. rituximab.[6-7]

This led to the MHRA granting emergency permissions for the use of the nMAb therapeutics casirivimab/imdevimab and sotrovimab and the antiviral agents remdesivir, molnupiravir and Paxlovid.[4,8-10] These drugs were found to be efficacious within their respective clinical trials however, this data was collected before the UK vaccination rollout, Appendix B.[11-15] Additionally, the clinical trial populations were experiencing an earlier variant of SARS-CoV-2 so it could be a possibility that emerging mutations could be antiviral resistant.

Evidence has since been found supporting this theory as the manufacturer for casirivimab-imdevimab shows a "diminished potency" against the Omicron BA.1 variant, however, it still "retains its activity against" other variants of concern, including Delta and Omicron BA.2,4 and 5. and BA.[16,17] This has been further reflected in the WHO statement that strongly discourages the use of sotrovimab in non-severe COVID-19 cases as its efficacy is reduced against the Omicron BA.1 variant.[18,19]

Aim and Hypothesis

Whilst these antiviral drugs were found to be effective in their pivotal clinical trials, their efficacy in the community is yet to be determined. This study will examine the primary study evidence

from the community to determine whether their use remains justified today.

Specifically, the primary aim is to investigate the efficacy of antiviral drugs in the Welsh population of high-risk patients. The dependent variable for this will be whether patients suffered hospitalisation due to COVID-19 or mortality within 28 days of starting antiviral treatment. During data analysis, hospitalisation and mortality results will be collated together to form a composite primary endpoint. Next, these data points will be compared to the respective drugs' pivotal clinical trials as a comparative control. The hypothesis is that all antiviral drug treatment groups will show a primary endpoint event rate that is less than or equal to the respective pivotal clinical trial data.

Methods

Antiviral Efficacy Study Design and Population

A retrospective cohort study was conducted in Wales to investigate the efficacy of anti-viral drugs in patients with confirmed SARS-CoV-2 infection and belonging to one or more of the high-risk COVID-19 cohorts, as defined by the Department of Health and Social Care (DHSC), see appendix A.[20] Inclusion criteria were limited to patients who had received a prescription for antiviral drugs and had undergone confirmation testing for COVID-19 using either a lateral flow device or polymerase chain reaction test.

The study population consisted of non-hospitalized patients residing in the community, who were monitored retrospectively for a period of 28 days from the index date, which was defined as the start date of anti-viral treatment, see **Figure 1**. The primary endpoints of hospitalisation or mortality were recorded if they occurred during the study period. The composite primary endpoint was calculated as a combination of hospitalisation and mortality. The range of index dates for the study was 67 days, spanning from March 10, 2022, to September 12, 2022

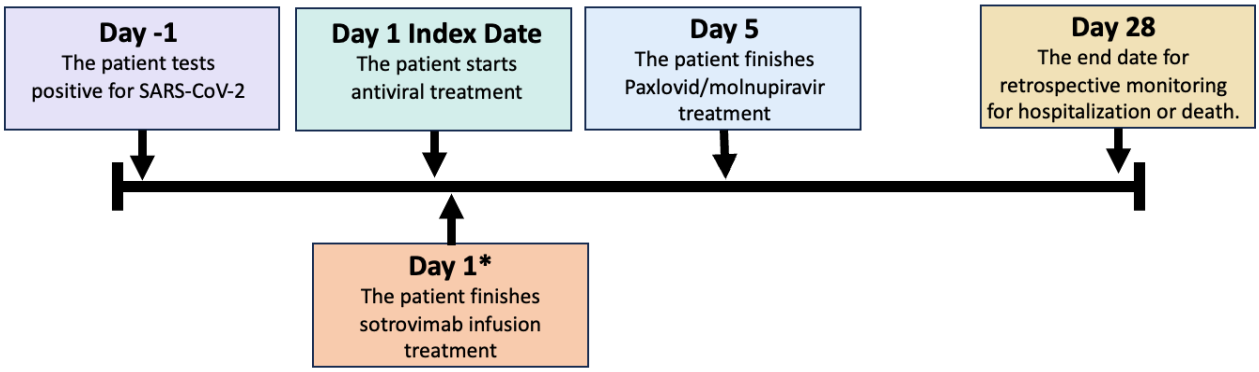

Figure 1: A timeline of the methodology for the primary study on the efficacy of antiviral drugs.

Day -1 is the day before the index date when the patient tests positive for severe acute respiratory syndrome coronavirus 2, SARS-CoV-2. Paxlovid and molnupiravir are prescribed in a 5-day dose regimen that starts on the index date (Day 1) and finishes on Day 5. Sotrovimab is administered via a single intra-venous infusion, this is carried out on the index date. The 28-day period for retrospective monitoring for hospitalisation or death begins on the index date and is completed on day 28.

Patient Search Methodology

The study utilized a patient database provided by the National Antiviral Service Cymru (NAVS). This listed all patients who were prescribed antiviral treatment within Wales. Unique patient identifiers, such as NHS number and date of birth, were used to search the Welsh Clinical Portal (WCP). This is a digital platform for healthcare professionals across Wales to access patient health records.

For each patient, a chronological systematic review of their notes was conducted starting from their index date and extending to the next 28 days. The primary objective of this review was to identify any evidence of COVID-19-related hospitalisation or mortality as the study's primary endpoint.

Hospitalisation

Hospitalisation due to COVID-19 was identified through a systematic examination of clinical notes available on the WCP. For the study, hospitalisation was defined as a hospital admission due to symptoms associated with COVID-19, supported by evidence. Examples of evidence include discharge summaries, GP referral letters or emergency department triage reports. However, hospitalisation due to sotrovimab infusion was excluded as a primary endpoint for hospitalisation.

If a patient's WCP record was found to be empty without any entries, it was assumed that they had not been hospitalized for COVID-19. Similarly, if a patient was hospitalized without any evidence of COVID-19-related symptoms, no primary endpoint completion was recorded.

Mortality

The WCP system did not consistently provide access to death certificates or reasons for death. To ensure standardisation, the date of death was recorded from the patient's demographics page and compared to the index date. This was done to determine if it occurred within the 28-day window. If so, it was considered a primary endpoint completion. If no date of death was recorded on the WCP, the patient was assumed to be alive, and no primary endpoint completion was recorded.

Data Coding Procedure

Within the specified 28-day window, patients were coded with either a 1 or a 2 based on the occurrence of primary endpoints, namely hospitalisation due to COVID-19 and mortality.

A code of 1 was assigned to patients who met the primary endpoint, with clinical evidence to support this. Examples include a recorded date of death within the 28-day window or a clinical letter showing hospital admission for COVID-19 symptoms. A code of 2 was given to those patients for whom hospitalisation reasons were unclear, for example when the cause of respiratory impairment could not be precisely ascertained. Given the subjective nature of this coding method, codes 1 and 2 were merged during the final analysis.

Statistical Analysis

All data collection and statistical analysis were conducted using Microsoft Excel (Version 16.72, Office 365 License). The primary endpoint event frequencies were assessed for independence using Chi-Squared analysis. The level of significance was established by the p-value, which was set to less than 0.05. The demographic characteristics of age are described as a median ± interquartile range.

Within the primary study, the endpoints of hospitalisation and death were combined to

form a composite primary endpoint. This methodology increases the statistical power and reduces the chance of type II statistical error.

This statistical analysis evaluated the differences in primary endpoint frequencies between observed and expected values. The p-value determined the level of significance for these differences, with values below 0.05 considered statistically significant. These results were presented in tabular format to allow for data interpretation.

Ethical Considerations

Ethical approval was not required for this study as it was a retrospective evaluation of an existing clinical service. The data was processed following the Cardiff and Vale University Health Board (UHB) data protection policy. Only anonymised patient data was collated and presented. This anonymisation process was self-conducted and occurred prior to the analysis of data to reduce unconscious bias.

Results

A total of 828 patients were identified as potential candidates for the study. However, due to duplicates (n=2) or missing demographic information (n=6), 820 patients completed the study (Appendix C). All patients received only one type of antiviral medication within the date range of March 10, 2022, to September 12, 2022. All genders and ages were included in the study, with a male-female percentage ratio of 41:59. The median age was 60.

The treatment group sizes were as follows: Paxlovid, 461 (56%); molnupiravir, 189 (21%); and sotrovimab, 170 (23%), Appendix C.

Overall, 51 (6.2%) of the total of 820 patients met the criteria for a primary endpoint within the 28-day window. The event rates for each treatment group were: 6.9% (32/461) for Paxlovid, 7.4% (14/189) for molnupiravir and 2.9% (5/170) for sotrovimab. When combining all treatment groups, the use of antiviral drugs did not differ between patients who experienced and those who did not experience a primary endpoint, p = 0.11 .

The analysis of the Paxlovid treatment group shows that a total of 29 patients met the criteria for a primary endpoint: 27 hospitalisations and 2 deaths. There was a primary endpoint event rate of 7% from a total of 409 patients. There was no difference between patients who experienced and those who did not experience a primary endpoint, p=0.47.

Table 1 – A comparison between the primary endpoint rates in this study and the respective antiviral drugs' pivotal clinical trials.

Following Chi-Squared testing, no difference was found between the primary study data and pivotal clinical trials, p = 0.24.

Antiviral Drug (Author. Publication date)	The frequency of patients met the criteria for a primary endpoint (number of participants/total participants)	
	Primary Study	Pivotal Clinical Trial
Paxlovid [13] (Hammond et al. 2022)	0.07 (32/461)	0.01 (5/687)
Molnupiravir [12] (Jayk Bernal et al. 2022)	0.08 (14/170)	0.07 (28/385)
Sotrovimab [11] (Gupta et al. 2022)	0.03 (5/189)	0.01 (6/528)

The analysis of the molnupiravir treatment group shows that 14 patients met the criteria for a primary endpoint: 8 hospitalisations and 6 deaths. When collated together, the primary endpoint event rate was 8% of a total of 170 patients. This was the largest of each of the drugs, thus suggesting it is the least efficacious within the community. When comparing this percentage against the total patients who did not meet the criteria for a primary endpoint, there was no statistical difference, $p = 0.27$. However, of all the antiviral treatments, when compared to the pivotal clinical trial (Table 1), molnupiravir shows the closest frequency of primary endpoint events.

From the patients prescribed sotrovimab, a total of 5 patients met the criteria for a primary endpoint, 4 hospitalisations and 1 death. For this group, the primary event point rate was 3% from 189 patients. This was the only antiviral drug that was found to have a significantly different, $p = 0.04$, primary endpoint event rate to the pivotal clinical trial (1%, 6/528).

Discussion

The study examined the efficacy of antivirals by measuring the primary endpoint rate in high-risk patients with COVID-19. The data shows that within a 28-day window from prescription, 6.2% of all the participants in the study met the criteria for a primary endpoint of hospitalisation or death. This was consistent with the pivotal clinical trials.

Within each of the treatment groups, sotrovimab was the only antiviral found to cause a significant difference between the patients that did and did not experience a primary endpoint. However, since market authorisation by the MHRA, of the antiviral drugs featured in this study, it is the only drug to be seriously discouraged in non-severe COVID-19 cases.[18,19]

This contradiction highlights the need for future investigations to determine if sotrovimab should remain a viable antiviral treatment option. For example, research into a possible complementary drug to prescribe alongside sotrovimab to mitigate the adverse drug reactions.

A confounding factor within this study could be the mutation in SARS-CoV-2 variants. During our study period from March to September 2022, the UK key variant of concern was Omicron.[21] For each of the multinational pivotal clinical trials, the global variant of concern from March to December 2021 was Delta and its respective mutated forms.[22] As the virus mutated to the Omicron variant, it developed to be more infectious. This is due to mutations causing the S-proteins present on Omicron to have a higher binding affinity for the ACE2 receptors, thus increasing the likelihood of host cell infection.[23] This change is due to specific mutations, such as N501Y, altering the receptor binding domain which strengthens the linkage between the receptor and S-protein.[24]

When comparing the population groups, the eligibility criteria for the high-risk cohort varied between our studies. Within our study, the inclusion criteria were defined by the high-risk patient groups outlined by the National Antiviral Service Cymru, which were determined by the UK Department of Health and Social Care.[20] Whereas, within clinical trials, due to them being run by a private company they were able to set their own criteria. For example, within the sotrovimab trial patients ≥55 years old and >60 in the molnupiravir trial were deemed high-risk and therefore included.[11,13] Despite

this, the median ages for the Paxlovid, molnupiravir and sotrovimab studies were 45.0, 42.0 and 53.0, respectively.[11-13]

When compared to the primary study's median age of 60, the pivotal clinical trials reviewed a younger population. Across multiple studies, there is found to be a correlation between older patients experiencing more severe symptoms of COVID-19, leading to an increased risk of mortality.[25,26] Therefore, the younger population could offer an alternate explanation for the increased efficacy.

When the clinical trial population is examining a high-risk population, there is an underlying risk that the mortalities or hospitalisation could be unrelated to the antiviral. Within this study, it was anecdotally recognised that during the search of the patient notes some cancer patients were deemed as palliative. In these cases, antiviral drugs may have been used alongside opioid medication to ease the symptoms.[27] However, despite easing the symptoms, for many of these patients' mortality is still inevitable. This may have had a greater impact on our study as all patients were included, however within clinical trials this is likely to be included within the screening/exclusion factors.

Conclusion

The findings of this study suggest that antiviral treatment with Paxlovid, molnupiravir and sotrovimab may be effective in reducing the risk of hospitalisation or death in non-hospitalised high-risk patients. This study was conducted retrospectively within Wales using data supplied by the National Antiviral Service Cymru.

When compared to the respective pivotal clinical trial data, these drugs were found to be less efficacious within the community. The reasoning to why this occurred is unclear however it could be due to changes in SARS-CoV-2's viral strain or the UK vaccination rollout. To improve the strength of these conclusions, this study should be repeated using a larger quantity of patient data from across the UK to determine the true effect of antiviral drugs in the community setting.

Conflict of Interest Statement:

None

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None

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None

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ABBREIVIATION	DEFINITION
$3CL^{pro}$	Chymotrypsin-like protease
ACE2	Angiotensin-converting enzyme 2
ARDS	Acute Respiratory Distress Syndrome
CCL2	Chemokine ligand 2
COVID-19	Coronavirus disease 2019
CYP3A4	Cytochrome P450 3A4
DHSC	Department of Health and Social Care
DNA	Deoxyribonucleic acid
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FP	Fusion Peptides
IFN	Type-I Interferon
LFD	Lateral Flow Device
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare products regulatory agency
M^{pro}	Main protease enzyme
mRNA	Messenger ribonucleic acid
MTP	Molnupiravir triphosphate
NAVS	National Antiviral Service Cymru
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nMAb	Neutralising monoclonal antibody
PAMPs	Pathogen-associated molecular pattern
PCR	Polymerase Chain Reaction
RBD	Receptor binding domain
RdRp	RNA-dependent RNA polymerase
S	Spike Glycoproteins
S1, S2	Subunit 1, Subunit 2
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
TMPRSS2	Transmembrane protease, serine 2
UHB	Cardiff and Vale University Health Board
WCP	Welsh Clinical Portal
WHO	World Health Organisation

Appendix

Appendix A – A table to outline the specific definitions for each of the high-risk patient cohorts. This was produced by the Department of Health and Social Care. [20] This table forms the basis of the eligibility criteria used by the National Antiviral Service Cymru when prescribing antiviral treatment with paxlovid, molnupiravir and sotrovimab.

Cohort	Description
Down's syndrome and other genetic disorders	All patients with Down's syndrome Patients with chromosomal disorders known to affect immune competence[1]
Patients with a solid cancer	Active metastatic cancer and active solid cancers (at any stage) Locally advanced inoperable cancer Lung cancer (at any stage) All patients receiving any chemotherapy within the last 12 months (including antibody-drug conjugates and PI3K inhibitors) Patients receiving radiotherapy within the last 12 months Cancer resection within the previous 12 months, who received no adjuvant chemotherapy or radiotherapy
Patients with a haematological disease and stem cell transplant recipients	Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs 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) Individuals with haematological malignancies who have received chimeric antigen receptor (CAR)-T cell therapy in the last 24 months, or radiotherapy in the last 12 months Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months All patients who do not fit the criteria above, who are diagnosed with: myeloma (excluding MGUS) AL amyloidosis chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) myelodysplastic syndrome (MDS) chronic myelomonocytic leukaemia (CMML) myelofibrosis All patients with sickle cell disease Thalassaemia or rare inherited anaemia with any of the following: Severe cardiac iron overload (T2* < 10ms)[2] Severe to moderate iron overload (T2* ≥ 10ms) PLUS an additional co-morbidity of concern (e.g. diabetes, chronic liver disease or severe hepatic iron load on MRI)

Patients with a haematological disease and stem cell transplant recipients	Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g. anti-CD20, anti-thymocyte globulin [ATG] and alemtuzumab) within the last 12 months
Patients with renal disease	All renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who: o Received B-cell depleting therapy within the past 12 months (including alemtuzumab, rituximab, ocrelizumab, ofatumab, obinutuzumab [anti-CD20], anti-thymocyte globulin) o Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals o Not been vaccinated prior to transplantation Non-transplant patients who have received a comparable level of immunosuppression Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 mL/min/1.73m2) without immunosuppression
Patients with liver disease	Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease) All liver transplant recipients Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Patients with immune-mediated inflammatory disorders (IMID)	IMID treated with rituximab or other B-cell depleting therapy3 in the last 12 months Currently treated with/have been treated within the past 6 months with: Cyclophosphamide (IV or oral) Biologics or small molecule JAK-inhibitors4 Current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine/mercaptopurine (for major organ involvement such as kidney, liver and/or interstitial lung disease), methotrexate (for interstitial lung disease only) and/or ciclosporin Taking equivalent or greater than prednisolone 10mg per day (including budesonide) for at least 28 days prior to positive test IMID patients with active/unstable5 disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Immune deficiencies	Common variable immunodeficiency (CVID) Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) Hyper-IgM syndromes Good's syndrome (thymoma plus B-cell deficiency) Severe Combined Immunodeficiency (SCID)

Immune deficiencies (Continued)	Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) Primary immunodeficiency associated with impaired type I interferon signalling X-linked agammaglobulinae
HIV/AIDS	Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis On treatment for HIV with CD4 350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Rare neurological conditions	Multiple sclerosis Motor neurone disease Myasthenia gravis Huntington's disease

[1] Examples of chromosomal disorders know to affect immune competence: DiGeorge syndrome (22q11.2 deletion), CHARGE syndrome (CHD7 mutation), Corneal de Lange syndrome, Chromosome 8 or 18 abnormalities, Primary immunodeficiency syndromes, including: X-linked agammaglobinaemia, X-linked lymphoproliferative syndrome

[2] T2* is referring to the MRI T2 weighted image to make the diagnosis. If this information is not available, the patient may be asked questions such as whether they have haemochromatosis (a disease of increased iron storage) or any condition requiring recurrent blood or iron transfusions

[3] Local additional information: B-cell depleting therapies used in the treatment of immune-mediated inflammatory disorders include: alemtuzumab, belimumab, natalizumab, ocrelizumab, ofatumumab, rituximab, obinutuzumab.

[4] Examples of small molecule JAK-inhibitors may include: abrocitinib, baricitinib, fedratinib, filgotinib, peficitinib, ruxolitinib, tofacitinib, upadacitinib.

[5] Definition of active/uncontrolled IMID: people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is 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)

Appendix B – A table to outline the data from the interim analysis of pivotal clinical trials for each of the antiviral drugs.

The term 'total primary endpoint' refers to the addition of all cases of hospitalisation due to COVID-19 and mortality within the respective study's 28-day window.
EPIC-HR, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients. MOVe-OUT, Molnupiravir Outpatient. COMET-ICE, COVID-19 Monoclonal antibody Efficacy Trial-Intent to Care Early.

Antiviral treatment (Author. Publication date)	Clinical Trial Name	Total Primary Endpoint (Total Patients)	Primary Endpoint Rate % (Statistical significance)
Paxlovid (Hammond et al. 2022)	Phase 2/3 EPIC-HR	5 (687)	0.7 ($p < 0.001$)
Molnupiravir (Jayk Bernal et al. 2022)	Phase 3 MOVe-OUT	28 (385)	7.3 ($p < 0.001$)
Sotrovimab (Gupta et al. 2022)	Phase 2/3 COMET-ICE	6 (528)	1.1 ($p < 0.001$)

Appendix C – A table to outline the baseline demographic and disease characteristics of study participants.

SACT, systemic anti-cancer therapy. Haem., Haematological. IMID, Immune-Mediated Inflammatory Diseases. IMS, Immunoglobulin-M Syndrome. BCD, Beta Cell Depleting. Other ISD, Other immunosuppressive drugs. N = 820

Baseline Characteristic	Paxlovid		Molnupiravir		Sotrovimab		Total Population	
	n	%	*n*	%	*n*	%	*n*	%
Gender								
Female	299	65	90	48	91	46	480	41
Male	162	35	99	52	79	53	340	59
Age								
Median	59	-	64	-	59	-	60	-
[Range]	[19-93]	-	[24-95]	-	[15-92]	-	[15-95]	
Interquartile Range	19	-	22	-	23	-	20	-
Clinical Indication								
Attended for SACT	9	2	6	4	6	3	23	3
Chemotherapy	2	<1	0	0	0	0	2	<1
Down's Syndrome	7	2	1	<1	1	<1	9	1
Haem. Cancer	33	8	18	11	15	8	81	10
IMID	211	52	53	31	51	27	332	41
IMS	4	<1	0	0	3	2	9	1
Liver Cirrhosis	1	<1	20	12	13	7	34	4
Immunodeficiency	18	4	4	2	4	2	28	3
Radiotherapy	12	3	1	<1	3	2	19	2
Rare Neuro Disease	38	9	11	6	10	5	63	8
Recent Cancer	2	<1	2	1	0	0	4	1
Renal Disease	2	<1	17	10	31	16	53	7
Sickle Cell Disease	1	<1	0	0	0	0	1	<1
Solid Cancer	65	16	19	11	29	15	117	14
Organ Transplant	3	<1	17	10	22	12	42	5
Other	1	<1	0	0	0	0	1	<1
Immunosuppressants								
BCD Drug	12	12	5	21	3	14	20	2
Other ISD	87	88	19	79	18	86	130	16