OpenSAFELY Protocol: Effectiveness and safety of sotrovimab and molnupiravir for prevention of severe COVID-19 outcomes

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Background

Several antiviral medicines and neutralising monoclonal antibodies (nMAbs) have recently been approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for use in symptomatic COVID-19 patients in the community to prevent disease progression. On 16th December 2021, COVID-19 Medicine Delivery Units (CMDUs) were launched across England to provide antiviral medicines and nMAbs to treat COVID-19 patients in community settings who are at high risk of severe outcomes.

Among the available pharmacological therapeutic options for these non-hospitalised COVID-19 patients, sotrovimab and molnupiravir have been the two most frequently prescribed medications by CMDUs [1] (though Paxlovid is now being prescribed at a higher rate than molnupiravir). The approval and early routine clinical use of these two medications have been mainly supported by evidence from two phase 3 randomised controlled trials (RCTs) [2,3].

The COMET-ICE trial [2] (abbreviated from COVID-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early) was a phase 3 double-blind RCT that evaluated the use of intravenous sotrovimab in non-hospitalised high-risk adult patients with symptomatic COVID-19. An interim analysis with 583 patients from four countries showed a reduced risk of all-cause hospitalisation or death within 29 days in the sotrovimab group compared with the placebo group (1% vs. 7%, $P = 0.002$) [2]. Similar results were reported for the final sample of 1057 patients from five countries, with the risk estimate of 1% with molnupiravir vs. 6% with placebo (adjusted relative risk = 0.21, 95% CI: 0.09 - 0.50; absolute difference = -4.53%, 95% CI: -6.70% - -2.37%]; $P < 0.001$) [4]. The phase 3 component of MOVe-OUT trial [3] for molnupiravir, an oral antiviral prodrug that inhibits viral replication by mutagenesis, was also a double-blind RCT in non-hospitalised, unvaccinated adults with mild-to-moderate COVID-19 and at least one risk factor for severe illness. The interim results of 755 participants from 15 countries showed that the risk of all-cause hospitalisation or death during a 29 days follow-up was lower with molnupiravir than with placebo (7.3% vs. 14.1%; absolute difference = -6.8%, 95% CI: -11.3% - -2.4%; $P = 0.001$) [3]. However, in the final sample of 1433 participants from 20 countries, a lower efficacy was observed, with the risk estimate of 6.8% in molnupiravir group vs. 9.7% in placebo group (absolute difference = -3.0%, 95% CI: -5.9% - -0.1%; $P = 0.043$) [3].

Findings of these RCTs were limited by relatively small sample size and lack of population generalisability (especially with the strict inclusion/exclusion criteria). There have also been some debates on the robustness of existing evidence and the appropriateness of early regulatory authorisations, especially for molnupiravir given the weak evidence from final trial results of MOVe-OUT in terms of both effect magnitude and statistical significance [5]. Validating the effectiveness of these drugs in preventing adverse prognosis in real-world settings with wider populations is thus crucial to support their large-scale clinical use among COVID-19 patients. For instance, no evidence is yet available for their effectiveness in vaccinated COVID-19 patients or those with severe renal or liver impairment, and there has been preliminary trial results on the lack of efficacy of molnupiravir in seropositive patients at baseline (with prior SARS-CoV-2 infection), diabetes patients and some non-White populations [3].

In addition, although both trials showed comparable risk of adverse events between sotrovimab or molnupiravir treatment group and placebo groups, the sample sizes were likely to be insufficient for a comprehensive safety assessment. Besides several mild or moderate post-treatment symptoms reported during the trials, some uncommon side effects like urticaria and anaphylaxis were observed [6], and a preclinical study of molnupiravir suggested a possibility of bone marrow suppression and thrombocytopenia [7]. Immediate post-marketing surveillance, especially with large-scale electronic health record (EHR) data, is vital for these drugs issued during the pandemic.

More importantly, according to the latest NHS England policy statement [8], sotrovimab was recommended as one of the first-line treatment options for non-hospitalised symptomatic COVID-19 patients while molnupiravir as the third-line option (following another two antivirals: Paxlovid and remdesivir), but no comparative effectiveness study has ever been conducted to support such clinical pathways. Given that sotrovimab is administered by intravenous infusion, molnupiravir as an oral drug has the advantages of convenient and non-invasive administration. Validation research directly comparing the effectiveness and safety profiles of these two drugs is urgently needed to establish the evidence-based clinical management pathway and algorism.

Therefore, following the national CMDU rollout since last December, this study aims to examine and compare the effectiveness of sotrovimab and molnupiravir on preventing severe outcomes in non-hospitalised high-risk adult patients with COVID-19 across England, utilising the near real-time EHR data in the OpenSAFELY platform. We will also explore the drug effectiveness in different patient groups by demographic and clinical factors and evaluate their safety profiles.

Objectives

Primary Objectives

To compare the risk of COVID-19 related hospitalisation or death in non-hospitalised high-risk COVID-19 patients receiving sotrovimab vs. molnupiravir within 29 days from treatment, as well as risks of other outcomes (e.g., all-cause hospitalisation or death, 2-month and 3-month COVID-19 related hospitalisation or death).

Secondary Objectives

To compare risks of the severe outcomes in non-hospitalised high-risk COVID-19 patients receiving sotrovimab or molnupiravir vs. those who were eligible but did not receive any antiviral or nMAbs treatment from CMDUs.

Exploratory Objectives

To explore the effectiveness of sotrovimab and molnupiravir in different high-risk cohorts defined by NHS England, and subgroups according to COVID-19 vaccination status, body mass

index (BMI), presence of diabetes or other comorbidities, age group, sex, ethnicity, time period and variants.

To explore the safety outcomes of sotrovimab and molnupiravir treatment, including allergic reactions (e.g., anaphylaxis and urticaria), infusion-related reactions for sotrovimab, and post-treatment platelet count and thrombocytopenia for molnupiravir.

Methods

Data Source

Primary care records managed by the GP software provider, TPP were linked to the Office for National Statistics (ONS) death data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). OpenSAFELY provides a secure software interface allowing the analysis of pseudonymised primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymised patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. Similarly pseudonymised datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. Further details on our information governance can be found on information governance and ethics.

The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystmOne software. It includes pseudonymised data such as coded diagnoses, medications and physiological parameters. Patient-level vaccination status is available in the GP records directly via the National Immunisation Management System (NIMS). No free text data are included. The following linked data were also used for this study: accident and emergency (A&E) attendance and in-patient hospital spell records via NHS Digital's Hospital Episode Statistics (HES); national coronavirus testing records via the Second Generation Surveillance System (SGSS); and the "COVID-19 therapeutics dataset", a patient-level dataset on antiviral and nMAbs treatments, newly sourced from NHS England, derived from Blueteq software that CMDUs use to notify NHS England of COVID-19 treatments.

Data Sharing

All data were linked, stored and analysed securely within the OpenSAFELY platform https://opensafely.org/. All code is shared openly for review and re-use under MIT open license. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without prior funding to deliver timely analyses on urgent research questions in the context of the global Covid-19 health emergency: now that the platform is established we are developing a formal process for external users to request access in collaboration with NHS England; details of this process will be published shortly on OpenSAFELY.org.

Information Governance

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant; patient data have been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is through a virtual private network (VPN) connection; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; and only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts. The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure. Together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Study Design and Population

We will conduct a population-based cohort study with all adults (≥ 18 years old) within OpenSAFELY who tested positive with SARS-CoV-2 infection (PCR or lateral flow test) and had treatment records of either sotrovimab or molnupiravir or were eligible for such treatments from CMDUs since 16th December 2021.

Patients were required to be non-hospitalised for COVID-19 (as recorded in COVID-19 therapeutics dataset) and registered in GP surgeries before treatment initiation. Patients were excluded if they had treatment records of any other antivirals or nMAbs for COVID-19 before receiving sotrovimab or molnupiravir. Patients with treatment records of both sotrovimab and molnupiravir after the infection were censored at the start date of the second treatment.

To generate a no-treatment control group for the secondary objectives, we operationalised the official eligibility criteria for COVID-19 antiviral or nMAb treatment in the community [8] (by NHS England) in OpenSAFELY to define potentially eligible population: tested positive for SARS-CoV-2 and being a member of a high-risk cohort, including patients with Down's syndrome, a solid cancer, a haematological disease and stem cell transplant recipients, renal disease, liver disease, immune-mediated inflammatory disorders, primary immune deficiencies, HIV/AIDS, solid organ transplant recipients, or rare neurological conditions.

Study Measures

Exposure

The exposure of interest is treatment with sotrovimab or molnupiravir administered by CMDUs. Exposure status and date of each patient will be ascertained from the COVID-19 therapeutics dataset.

Outcome

The primary outcome is COVID-19 related hospital admission or death within 29 days of follow-up.

Secondary outcomes include 29-day all-cause hospital admission or death, 2-month and 3-month COVID-19 related hospital admission or death.

Safety outcomes include allergic reactions (e.g., anaphylaxis and urticaria) for both medications, infusion-related reactions for sotrovimab, and haematological parameters (e.g., post-treatment platelet count) and thrombocytopenia for molnupiravir. We will also explore the incidence of non-COVID-19 related death and other rare adverse outcomes like PML.

Covariates

The following potential confounding factors or moderators available in OpenSAFELY will be extracted at baseline, including age, sex, NHS region of their registered GP practice (STP), ethnicity (grouped into five broad categories: White, Black or Black British, Asian or Asian British, Mixed, Other), Index of Multiple Deprivation (IMD, as quintiles derived from the patient's postcode at lower super output area level), calendar time (to account for secular trend of prescription and COVID-19 outcomes), SGTF indicator, COVID-19 vaccination status (unvaccinated, one vaccination, two vaccinations, or three or more), BMI (most recent record), high-risk cohort categories as mentioned above (allowing multiple categories per patient), and other comorbidities (e.g., diabetes, hypertension, chronic heart diseases, chronic respiratory diseases, haematological cancer, autism, dementia, learning disability, serious mental illness).

Individuals with missing sex, ethnicity, region, IMD, SGTF or BMI were included as "Unknown" category.

Statistical Analysis

For the comparative effectiveness analysis, distributions of baseline characteristics will firstly be compared between patients treated with sotrovimab vs. molnupiravir. Follow-up time of individual patient will be calculated from the date of the treatment initiation record, until the date of outcome event, 29 days since treatment initiation, death, patient de-registration date, or the study end date (to be determined), whichever occurred first.

Risks of COVID-19 related hospital admission/death will be compared between the two groups using the Cox proportional hazards model, with follow-up period as the time scale. To account

for confounding bias, we will use the propensity score weighting (PSW) method to balance the distributions of relevant covariates between groups. The propensity score for each patient is defined as the conditional probability of being treated with sotrovimab, estimated with a binary logistic regression of the actual treatment on relevant baseline covariates. The average treatment effect (ATE) weighting scheme will then be applied to the Cox model based on the estimated propensity scores. Balance check of baseline covariates after weighting will be conducted using standardised mean differences between groups. Robust variance estimators will be used in the weighted Cox model. Similar approach will be used for comparing risks of secondary outcomes.

Further exploratory analyses will be conducted by different subgroups (given sufficient sample size), including each high-risk cohort, COVID-19 vaccination status, presumably detected BA.1 vs BA.2 variants (SGTF indicator), BMI categories, presence of diabetes or other comorbidities, time since test positive (<3 vs 3-5 days), age group, sex and ethnicity. Propensity score weighting procedure will be repeated within each subgroup.

Several sensitivity analyses will be conducted to assess the robustness of main findings, including (1) using stratified Cox models by STP sites and weeks to account for geo-temporal heterogeneity in baseline hazards, with conventional adjustment for other covariates instead of PSW method; (2) using Multiple Imputation by Chained Equations when generating propensity score (given the assumption of MAR or MCAR) instead of treating missing values as a separate category; (3) excluding patients with treatment records of both sotrovimab and molnupiravir, or any other treatments (i.e., casirivimab, Paxlovid, or remdesivir); (4) excluding patients who were identified to be pregnant at treatment initiation; and (5) excluding patients initiating treatment after 5 days since positive SARS-CoV-2 test. Time-varying effect will also be explored.

For safety outcomes, we will describe the incidence rates following treatment and then apply similar analytical approaches as the comparative effectiveness analyses (Cox regressions with PSW). An alternative approach we will consider is self-controlled case series (SCCS) method, firstly for each of the two medicines separately and then comparing the risks of adverse events between them. Only those who received the treatment and experienced the adverse outcome under investigation will be included, of whom the follow-up time period will be divided into an exposure risk period followed by a baseline period. Conditional poisson regression will be conducted to estimate the IRR comparing the safety risks in exposure vs. baseline periods.

For the exploratory effectiveness analyses against the eligible no-treatment group, we will firstly explore the feasibility and appropriateness of applying Cox regressions with PSW by assessing the performance of the propensity score generating model (how well we can predict treatment vs. no treatment based on baseline covariates). Otherwise we will consider conventional adjustment for covariates, or using STP site (stratified by calendar date) as an instrumental variable (proxy) for treatment.

The follow-up period of no-treatment group will be defined from the date of positive SARS-CoV-2 test or plus the mean time gap between positive test and treatment initiation in the treatment

group (e.g., creating ~2 days lag to be consistent with the initial follow-up date of treatment group). Another option will be defining positive test date as the beginning of follow-up for both treatment and no-treatment groups, and using time-varying Cox regression dividing the follow-up period of treatment group into exposure period (after treatment initiation) and unexposed period (between positive test and treatment initiation).

Software and Reproducibility

Data management will be performed using Python, with analysis carried out using Stata 16.1. Code for data management and analysis as well as codelists archived online.

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