Efficacy and safety of obeldesivir in low-risk, non-hospitalised patients with COVID-19 (OAKTREE): a phase 3, randomised, double-blind, placebo-controlled study

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Summary

Background Obeldesivir is an oral nucleoside analogue prodrug antiviral that inhibits SARS-CoV-2 replication. We aimed to assess the efficacy, safety, and tolerability of obeldesivir for the treatment of COVID-19 in non-hospitalised individuals at low risk of progression to severe disease.

Methods OAKTREE was a phase 3, randomised, double-blind, placebo-controlled trial in 107 centres (including research centres, primary care centres, and hospitals) in Japan and the USA. Low-risk, non-hospitalised adults and adolescents with mild-to-moderate COVID-19 were enrolled within 3 days of symptom onset. Eligible participants were randomly assigned 1:1 using permuted block randomisation (block size of four), stratified by historical completion of a primary COVID-19 vaccination series, to receive either oral obeldesivir 350 mg or matched placebo twice daily for 5 days. The primary efficacy endpoint was time to COVID-19 symptom alleviation by day 29, which was assessed in all randomly assigned participants who received one or more doses of study drug, had positive SARS-CoV-2 RT-PCR (per central laboratory testing) at baseline, and had COVID-19 symptom data (full analysis positive set). The primary safety endpoint was the incidence of adverse events and laboratory abnormalities and was assessed in all randomly assigned participants who received one or more doses of study drug. As a secondary endpoint we assessed change from baseline in nasal swab viral RNA copy number at day 5 in all randomly assigned participants who received one or more doses of study drug and had a quantifiable baseline value. This trial is registered with ClinicalTrials.gov, NCT05715528, and is complete.

Findings Between Feb 13, 2023 and Oct 31, 2023, 1955 participants (1155 female and 800 male; 1698 White, 207 Black, 42 Asian, and eight Other) were randomly assigned and received at least one dose of either obeldesivir (n=979) or placebo (n=976). Overall, 1368 (70·0%) participants had completed a primary COVID-19 vaccination series and 1938 (99·6%) were seropositive for SARS-CoV-2 antibodies. There were 884 participants in each group in the full analysis positive set. Among those in the full analysis positive set who completed the symptom questionnaire (ie, who had COVID-19 symptom data; 879 obeldesivir, 882 placebo), median time to COVID-19 symptom alleviation was 5·9 days (95% CI 5·4–6·1) in the obeldesivir group and 6·0 days (5·8–6·3) in the placebo group (hazard ratio 1·099 [95% CI 0·997–1·211], p=0·068). The least-squares mean change from baseline in viral RNA copy number at day 5 was –2·13 log_{10} copies per mL (SE 0·04) and –1·95 log_{10} copies per mL (0·04) for the obeldesivir group (n=637) and placebo group (n=622), respectively, with a least-squares mean difference of –0·18 (95% CI –0·30 to –0·06) log_{10} copies per mL (p=0·0037). The safety profile was comparable between groups. 53 (5·4%) of 979 participants in the obeldesivir group and 56 (5·7%) of 976 participants in the placebo group had one or more treatment-emergent adverse events. 753 (77·5%) participants in the obeldesivir group and 757 (78·5%) participants in the placebo group had one or more graded laboratory abnormalities, most of which were grade 1 or 2.

Interpretation Obeldesivir was generally safe and well tolerated, with greater reduction of SARS-CoV-2 viral RNA copy number versus placebo at day 5. However, obeldesivir did not significantly reduce time to symptom alleviation, possibly reflecting the challenges of assessing efficacy in this population in an era of high rates of vaccine-induced and natural immunity.

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Introduction

COVID-19 remains a public health concern, with new SARS-CoV-2 variants emerging continually.[1,2] Population-level immunity has increased over time, resulting in lower disease severity, particularly for younger and non-immunocompromised individuals.[3]

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Research in context

Evidence before this study

Obeldesivir is an oral prodrug that delivers the same active metabolite as remdesivir. It has been shown to be safe in phase 1 trials in healthy participants and to have antiviral activity against SARS-CoV-2 in preclinical studies. We searched PubMed for articles published in any language from database inception to Feb 8, 2023, using the terms "COVID-19" AND "low risk" AND "antiviral", restricted to "Randomized Controlled Trial". This search produced zero studies including people without any risk factors for progression to severe COVID-19. Since commencing this study, other randomised controlled trials evaluating populations at low risk of progression to severe COVID-19 have been reported. We searched PubMed with these same terms, but included studies published up to Oct 31, 2024. This search produced five results, with no publications related to obeldesivir. We excluded one phase 2/3 study because it focused on an at-risk population. The remaining four results were related phase 2 trials from the omicron era in adults at low risk of developing severe COVID-19; three of these four studies were related to oral antivirals. In the only masked, randomised, placebo-controlled study (conducted from September, 2022 to December, 2022), pomotrelvir did not result in increased virological clearance, nor symptom resolution. In the open-label PLATCOV randomised controlled trial (enrolled between September, 2021 and October, 2022), favipiravir had no effect on the rate of viral clearance. Conversely, in an analysis of participants from the PLATCOV trial recruited in Thailand between June, 2022 and February, 2023, both molnupiravir and nirmatrelvir–ritonavir had faster rates of viral clearance than no study drug, and faster time to symptom resolution (although not clinically significant) than placebo in a secondary endpoint analysis. It is important to note, however, that this study also showed viral rebound in 10% of those treated with nirmatrelvir–ritonavir and found that three of nine individuals with persistent infection developed viral mutations while receiving molnupiravir. A few additional randomised controlled trials in non-hospitalised participants with COVID-19 included participants with and without risk factors for severe disease. The global EPIC-SR study, which randomised outpatients between August, 2021 and July, 2022, showed no significant difference in time to sustained alleviation of all targeted signs and symptoms to day 28 between the nirmatrelvir–ritonavir and placebo groups among the subgroup of participants who had no risk for severe illness and had never been vaccinated or had not been vaccinated within the previous 12 months. In the SCORPIO-SR study (conducted in Japan, Viet Nam, and South Korea from February, 2022 to July, 2022), in which 72% of participants did not have risk factors for severe disease, there were significant reductions in time to resolution of five targeted COVID-19 symptoms and in SARS-CoV-2 RNA level on day 4 in the 125 mg ensitrelvir group compared with the placebo group. The global SCORPIO-HR trial randomly assigned non-hospitalised participants from August, 2022 to December, 2023 and found no significant difference in restricted mean time to sustained symptom resolution between ensitrelvir and placebo in the subgroup of participants without risk factors for progression to severe disease; in this subgroup, there was a greater reduction in SARS-CoV-2 RNA levels in the ensitrelvir group relative to the placebo group. Lastly, a phase 3, multicentre study conducted in China from October, 2022 to January, 2023 (in which hospitalised participants were stratified by vaccine status and the presence of risk factors for severe COVID-19) showed a reduction in time to sustained clinical symptom resolution with VV116 compared with placebo. Although these studies provide valuable insights, there remains a relative paucity of randomised controlled trials specifically focused on non-hospitalised individuals with COVID-19 at low risk of progression to severe disease.

Added value of this study

Few randomised controlled trials have evaluated oral antiviral treatments in individuals at low risk of progression to severe COVID-19. The OAKTREE study is the first phase 3 study of obeldesivir to be published. This study analysed results from 1955 low-risk, non-hospitalised individuals from February, 2023 to January, 2024, allowing for robust analyses of time to COVID-19 symptom alleviation and SARS-CoV-2 viral dynamics in both individuals treated with obeldesivir and those treated with placebo during the omicron variant era. In these individuals, obeldesivir was safe and well tolerated and was associated with greater reductions in viral copy number on day 5 compared with placebo but did not significantly reduce time to symptom alleviation or resolution.

Implications of all the available evidence

Obeldesivir has shown safety, no clinically relevant drug–drug interactions, and broad-spectrum in-vitro antiviral activity against all SARS-CoV-2 variants, as well as other RNA viruses (including respiratory syncytial virus, dengue viruses, Ebola virus, and Nipah virus). However, it did not show efficacy in reducing time to COVID-19 symptom alleviation or resolution in non-hospitalised individuals without risk factors for progression to severe disease, possibly reflecting the challenges of assessing efficacy in this population in an era of high rates of vaccine-induced and natural immunity. The safety data from this large phase 3 study could be beneficial to support future development for other indications.

However, SARS-CoV-2 infection still causes morbidity in these populations, with mortality rates for those hospitalised for COVID-19 exceeding those of patients hospitalised for influenza.[4–6] Shortening illness duration and decreasing SARS-CoV-2 transmissibility would benefit even patients at low risk of progression to severe COVID-19, expediting return to usual health, activities, and work. Although several oral antivirals have undergone phase 2 trials to assess their safety and efficacy in low-risk individuals infected with

SARS-CoV-2,[7–9] in most countries no antiviral options are approved for treatment of mild-to-moderate COVID-19 in non-hospitalised individuals without risk factors for progression to severe disease.[10]

Obeldesivir is an oral 1□-cyano-substituted adenosine-like analogue prodrug that delivers the same active metabolite as remdesivir, through a different pharmacometabolic pathway, to inhibit SARS-CoV-2 RNA-dependent RNA polymerase with a low pill burden. Obeldesivir has shown in-vitro activity against SARS-CoV-2 variants, including the recent omicron variants of interest BA2.86 and KP.3. Phase 1 studies conducted in healthy participants revealed an acceptable safety profile and no clinically relevant drug–drug interactions between obeldesivir and substrates or inhibitors of cytochrome P450, as well as drug transporters known to interact with obeldesivir and its metabolites.[11–16] Here, we report the results of a phase 3 trial that aimed to assess the clinical efficacy, antiviral activity, and safety of obeldesivir for COVID-19 treatment in low-risk, non-hospitalised participants.

Methods

Study design

OAKTREE was a phase 3, randomised, double-blind, placebo-controlled study conducted at 107 centres (including research centres, primary care centres, and hospitals) in Japan and the USA. The protocol (appendix) was approved by Advarra IRB or institutional review boards at participating centres, as required (appendix pp 3–5). The study was designed and conducted by Gilead Sciences according to International Council for Harmonisation guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki. This trial is registered with ClinicalTrials.gov, NCT05715528.

Participants

Eligible participants were aged 12–64 years with SARS-CoV-2 infection confirmed by rapid antigen or RT-PCR tests and initial onset of two or more prespecified targeted COVID-19 signs or symptoms at moderate or higher participant-reported severity (ie, stuffy or runny nose, sore throat, shortness of breath [difficulty breathing], cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, and feeling hot or feverish) up to 3 days before randomisation. Participants were ineligible if they had risk factors for progression to severe disease, including specified comorbidities and immunosuppressive conditions and medications; the full list of specified risk factors is provided in the appendix (p 7). Participants were also excluded if they had a COVID-19 diagnosis or received a COVID-19 vaccine within 120 days before randomisation, or if they had an anticipated need for hospitalisation within 48 h after randomisation. Full eligibility criteria are provided in the appendix (pp 6–8). Written informed consent was provided by each participant or by a parent or legal guardian. Participants were recruited through centres using either sponsor-provided adverts or centre-owned materials that were pre-approved by the sponsor.

Randomisation and masking

Computer software-generated permuted block randomisation (block size of 4) was used by the trial sponsor to assign treatment through a centralised interactive response technology system. Eligible participants enrolled by investigators were stratified by historical completion of a primary COVID-19 vaccination series and randoml assigned 1:1 to receive obeldesivir or placebo (appendix p 10).

This was a double-blinded study in which all participants, personnel directly involved in the conduct of the study, and the sponsor were masked to trial group assignments. The full 5-day course of study drug was dispensed by a masked pharmacist. The placebo tablets (provided by Gilead Sciences) were identical in size, shape, colour, and appearance to the obeldesivir tablets (appendix p 8).

Procedures

Obeldesivir 350 mg and placebo were administered orally twice daily during the treatment period (days 1–5; appendix p 10). Extent of exposure was quantified by counting the number of tablets taken by the study participants. Sex at birth, race, and ethnicity data were self-reported on a demographics form completed by participants. Efficacy and safety assessments were performed up to day 90 (appendix pp 14–15). Assessments included physical examinations, laboratory testing of blood and mid-turbinate nasal swabs, and adverse event (AE) reporting (appendix p 9). AEs were coded using the *Medical Dictionary for Regulatory Activities* version 26.1. Severity grades were defined using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1, July, 2017.[17] Mid-turbinate nasal swab samples were collected by study site staff at in-person visits on days 1, 3, 5, 10, 15, 20, and 29, and at the early discontinuation visit, if applicable. Nasal swab samples were used to assess SARS-CoV-2 viral RNA copy number by RT-qPCR (appendix p 8). Serious AEs (SAEs) and AEs related to protocol-required procedures were recorded by investigators on the AE electronic case report form. Patient-reported outcomes were collected through a COVID-19 symptom questionnaire adapted from US Food and Drug Administration guidance, which was completed daily through an electronic diary up to day 29 and on days 60 and 90.[18]

See Online for appendix

Outcomes

The primary efficacy endpoint was time to COVID-19 symptom alleviation by day 29. Symptom alleviation was defined as all targeted symptoms that were scored by participants as moderate or severe at baseline that were scored as mild or none for at least 48 consecutive hours

and all targeted symptoms that were scored as mild or none at baseline that were scored as none for at least 48 consecutive hours; the first day of the 48 consecutive hours was considered the symptom alleviation date. The time to COVID-19 symptom alleviation was the time from the first dose date (origin and start time) to the date of symptom alleviation.

Clinical secondary efficacy endpoints included time to COVID-19 symptom resolution by day 29 and proportions of participants with moderate relapse of COVID-19 symptoms, COVID-19-related medically attended visits or all-cause death, and COVID-19-related hospitalisation or all-cause death by day 29. The definitions for these endpoints can be found in the appendix (pp 8–9). Virological secondary endpoints included change from baseline in SARS-CoV-2 nasal swab viral RNA copy number at day 5. Prespecified exploratory endpoints reported in this Article are change from baseline in SARS-CoV-2 nasal swab viral RNA copy number at days 3, 10, 15, 20, and 29; proportion of participants with negative SARS-CoV-2 nasal swab at days 3, 5, 10, 15, 20, and 29; levels of anti-SARS-CoV-2 antibodies at baseline; and proportions of participants with symptoms at days 60 and 90. Median time to COVID-19 symptom alleviation by duration of COVID-19 symptoms before study enrolment was a post-hoc analysis. Other secondary and exploratory endpoints specified in the protocol (pharmacokinetic assessments of obeldesivir and its metabolites; effect on work productivity, activities of daily living, and functionality; viral resistance to obeldesivir; and proportion of participants with post-COVID-19 condition [also known as long COVID] symptoms and outcomes for up to 12 months) will be reported elsewhere.

The primary safety endpoints were the incidence of treatment-emergent AEs and laboratory abnormalities, and the incidence of SAEs and AEs leading to study drug discontinuation. All AEs and clinically significant laboratory abnormalities were followed until resolution or stabilisation, when possible.

Statistical analysis

Assuming a 13-day median time to symptom alleviation in the placebo group,[19,20] and that 90% of participants would be confirmed SARS-CoV-2 positive at baseline by the central laboratory, a sample size of 1900 participants (n=950 per group) would provide approximately 87% power to detect a median difference of 2 days in time to alleviation of targeted symptoms, which would permit detection of a hazard ratio (HR) of 1·18 (assuming an exponential distribution) for comparison of obeldesivir with placebo at a two-sided significance level of 0·05. The full analysis set and safety analysis set consisted of randomly assigned participants who received at least one dose of study drug, except for all (n=32) participants from one site who were excluded due to GCP non-compliance being identified at the site; this exclusion was documented in the statistical analysis plan before breaking the blind. The primary efficacy endpoint was assessed in participants with COVID-19 symptom data in the full analysis positive set, which included all participants in the full analysis set with central laboratory-positive SARS-CoV-2 RT-PCR at baseline. A prespecified subgroup analysis was performed for the primary efficacy endpoint, in which the full analysis positive set was stratified by age, sex, race, ethnicity, region, baseline SARS-CoV-2 viral RNA copy number, and BMI. The virology analysis set included participants in the full analysis set with a quantifiable baseline SARS-CoV-2 viral RNA copy number. Handling of intercurrent events and missing data for each analysis is described in the protocol and statistical analysis plan (appendix pp 92–93).

Demographic data, baseline characteristics, and laboratory abnormalities are summarised with descriptive statistics. Median times to COVID-19 symptom alleviation and resolution and their corresponding 95% CIs with log–log transformation,[21] along with the proportion of participants with COVID-19-related medically attended visits or all-cause death by day 29, were estimated using the Kaplan–Meier product-limit method and compared using a log-rank test (times to COVID-19 symptom alleviation and resolution were stratified by completion of a primary COVID-19 vaccination series). HRs and 95% CIs were estimated using a Cox proportional hazards regression model (with the randomisation stratum as a covariate for times to COVID-19 symptom alleviation and resolution). The proportion of participants with moderate relapse of COVID-19 symptoms by day 29 and proportion of participants with negative SARS-CoV-2 nasal swab at days 3, 5, 10, 15, 20, and 29 were compared between treatment groups using Fisher's exact test. Change from baseline in SARS-CoV-2 nasal swab viral RNA copy number at each visit was compared between treatment groups using a mixed-effects model for repeated measures, with baseline viral RNA copy number and completion of a primary COVID-19 vaccination series as covariates. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

An external multidisciplinary data monitoring committee reviewed the progress of the study and performed interim reviews of the safety and efficacy data in order to protect participant welfare and preserve study integrity. An interim O'Brien–Fleming boundary (at 50% information fraction) with Lan–DeMets modification was applied for futility analysis.

Role of the funding source

The funder directed the study design and conduct of the study; collection, management, analysis, and interpretation of the data; writing, review, and approval of the manuscript; and the decision to submit the manuscript for publication. Data were collected by trial-site investigators in conjunction with the study funder.

Results

Between Feb 8, 2023 and Oct 31, 2023, 2253 participants were screened for eligibility, of whom 1005 were randomly assigned to the obeldesivir group and 1006 were randomly assigned to the placebo group (figure 1). 459 important protocol deviations occurred in 386 (19·2%) participants during the study (appendix p 16). Most of the important protocol deviations (283 [61·7%]) were for participants with missing data related to the primary or secondary efficacy endpoints. Relevant protocol deviations were distributed proportionally between treatment groups (appendix p 16). 26 important protocol deviations occurred in participants from one site, all of whom were excluded

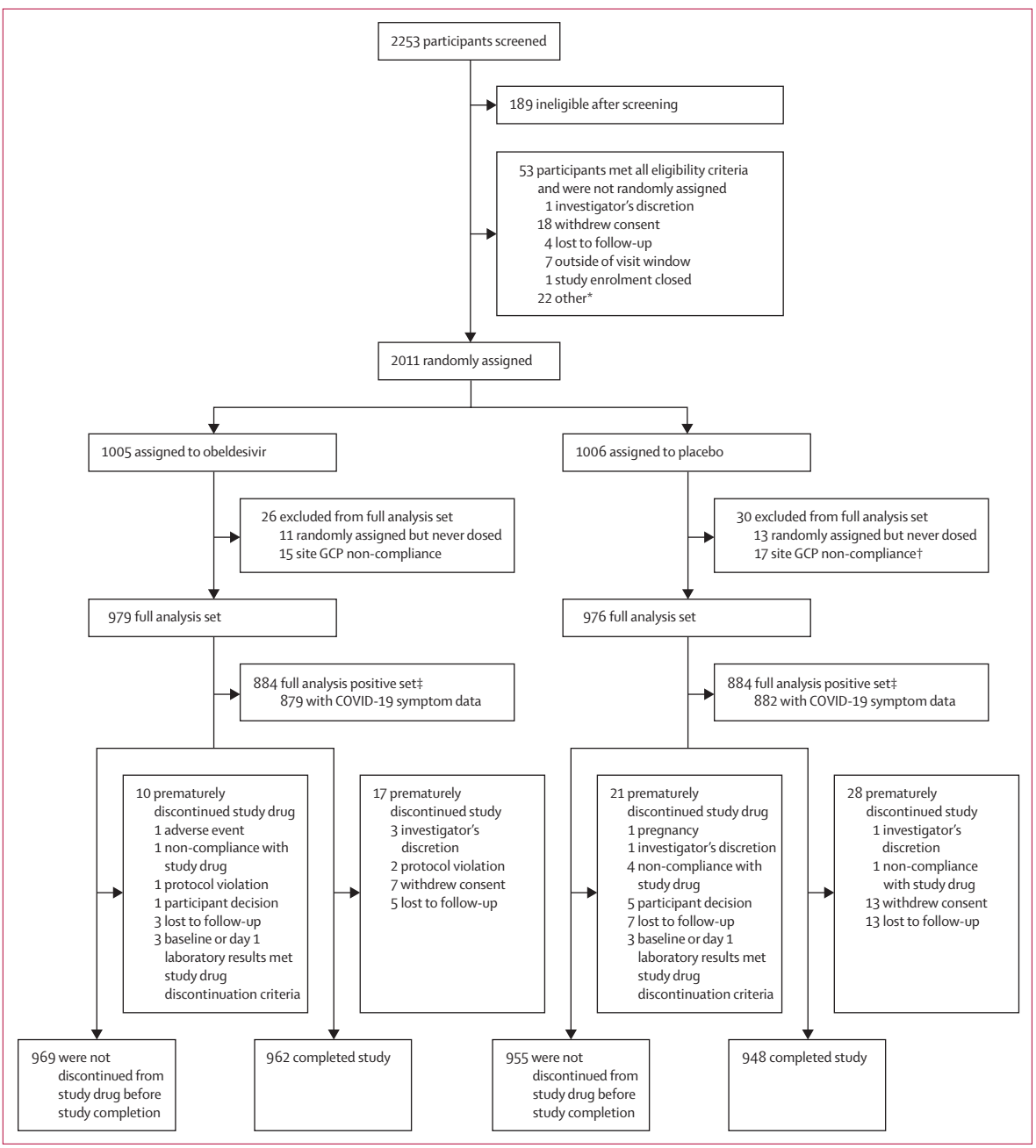

Figure 1: **Trial profile**

GCP=Good Clinical Practice. *Other=insufficient investigational product available at the study site (n=15), participant was out of window for randomisation (n=3), participant decided not to participate (n=2), duplicate participant record (n=1), and conflict of interest (n=1). †All randomly assigned participants from a single site were dosed but excluded from analysis due to site GCP non-compliance; this exclusion was performed in a masked manner. ‡The full analysis positive set included all participants in the full analysis set with positive SARS-CoV-2 RT-PCR (per central laboratory testing) at baseline.

	Obeldesivir (n=979)	Placebo (n=976)
Age, years	42 (31–53)	40 (31–52)
Age category, years		
≥12 to <18	8 (0·8%)	6 (0·6%)
≥18 to <65	971 (99·2%)	970 (99·4%)
Sex at birth		
Female	583 (59·6%)	572 (58·6%)
Male	396 (40·4%)	404 (41·4%)
Race*		
Asian	21 (2·1%)	21 (2·2%)
Black	106 (10·8%)	101 (10·3%)
White	850 (86·8%)	848 (86·9%)
Other	2 (0·2%)	6 (0·6%)
Ethnicity		
Hispanic or Latino	918 (93·8%)	901 (92·3%)
Not Hispanic or Latino	61 (6·2%)	75 (7·7%)
BMI, kg/m²	27·1 (24·8–28·7)	27·4 (24·9–28·8)
Completed primary vaccination series†		
Yes	687 (70·2%)	681 (69·8%)
No	292 (29·8%)	295 (30·2%)
COVID-19 vaccination status‡		
Ever	708 (72·3%)	710 (72·7%)
Never	271 (27·7%)	266 (27·3%)
Duration of COVID-19 symptoms prior to first dose of study drug, days†	2 (2–2)	2 (2–2)
Number of targeted COVID-19 symptoms at baseline		
N	962	962
Median (IQR)	8 (6–9)	7 (6–9)
Total of targeted COVID-19 symptom scores§		
N	962	962
Median (IQR)	13 (10–16)	13 (10–16)
Serostatus¶		
Overall positive	970 (99·9%)	968 (99·3%)
Overall negative	1 (0·1%)	7 (0·7%)
Missing	8	1
SARS-CoV-2 anti-spike antibody‖		
N	884	884
Positive	869 (99·7%)	869 (99·2%)
Negative	3 (0·3%)	7 (0·8%)
Missing	12	8
SARS-CoV-2 anti-nucleocapsid antibody‖		
N	884	884
Positive	755 (85·8%)	756 (86·2%)
Negative	125 (14·2%)	121 (13·8%)
Missing	4	7
SARS-CoV-2 viral RNA copy number**		
N	913	911
Mean (SD) log_{10} copies per mL	5·08 (1·416)	5·09 (1·479)

(Table 1 continues in next column)

(Continued from previous column)

Data are median (IQR) or n (%), unless otherwise stated. The safety analysis set consisted of randomised participants who received at least one dose of study drug, except for all (n=32) participants from one site who were excluded due to Good Clinical Practice non-compliance being identified at the site; this exclusion was documented in the statistical analysis plan before breaking the blind. *For the race category, "Other" includes Native American or Alaska Native, Native Hawaiian or Pacific Islander, other (a free-text field), and not permitted (for participants from whom such information was not permitted to be collected by local regulators). †Duration of COVID-19 symptoms was defined as the first dosing date minus the COVID-19 symptom onset date (day 0). ‡Randomisation was stratified by completion of a primary vaccination series. §Total of targeted COVID-19 symptom scores was defined as the total scores of nine targeted COVID-19 symptoms with score 0=none, 1=mild, 2=moderate, and 3=severe. ¶Serostatus was defined as positive when either anti-spike antibody or anti-nucleocapsid antibody was positive, and negative when both were negative; serostatus percentages do not include those with missing values. ‖Anti-SARS-CoV-2 antibodies were evaluated in the full analysis positive set using independent assays; results from each assay should be interpreted individually. Percentages do not include those with missing values. **The lower limit of detection and lower limit of quantitation for SARS-CoV-2 viral RNA were 1493 and 2228 copies per mL, respectively. The result of "no SARS-CoV-2 detected" was imputed as half the lower limit of detection (746·5 copies per mL; 2·87 log_{10} copies per mL); the result of "<2228 copies per mL" was imputed as half the lower limit of quantitation (1114 copies per mL; 3·05 log_{10} copies per mL).

Table 1: **Baseline characteristics (safety analysis set)**

from the full analysis set (appendix p 9). Overall, 979 participants received at least one dose of obeldesivir and 976 received at least one dose of placebo and were included in the full analysis and safety analysis sets, of whom 969 (99·0%) and 955 (97·8%) were not discontinued from study drug before study completion, respectively. The number of tablets taken by treatment group is summarised in the appendix (p 17). 45 (2·3%) participants prematurely discontinued the study, primarily due to withdrawal of consent (seven [0·7%] participants in the obeldesivir group and 13 [1·3%] in the placebo group) and loss to follow-up (five [0·5%] participants in the obeldesivir group and 13 [1·3%] in the placebo group).

Table 1 shows demographic and baseline characteristics of the safety analysis set. The median age was 41 years (IQR 31–52), and of the 1955 participants in the safety analysis set, 1155 (59·1%) were female, 1698 (86·9%) were White, and 1819 (93·0%) were Hispanic or Latino. The median duration of COVID-19 symptoms before the first dose of study drug was 2 days (IQR 2–2) for both treatment groups. The mean baseline SARS-CoV-2 viral RNA copy number was 5·08 log_{10} copies per mL (SD 1·416) for the obeldesivir group and 5·09 log_{10} copies per mL (1·479) for the placebo group. Most participants had completed a primary COVID-19 vaccination series (1368 [70·0%]; appendix p 18) and were seropositive for antispike or antinucleocapsid antibodies (1938 [99·6%]). In the full analysis positive set at baseline, 1738 (99·4%) of 1748 participants with available data were positive for SARS-CoV-2 spike and 1511 (86·0%) of 1757 participants with available data were positive for nucleocapsid protein antibodies (appendix pp 19–20).

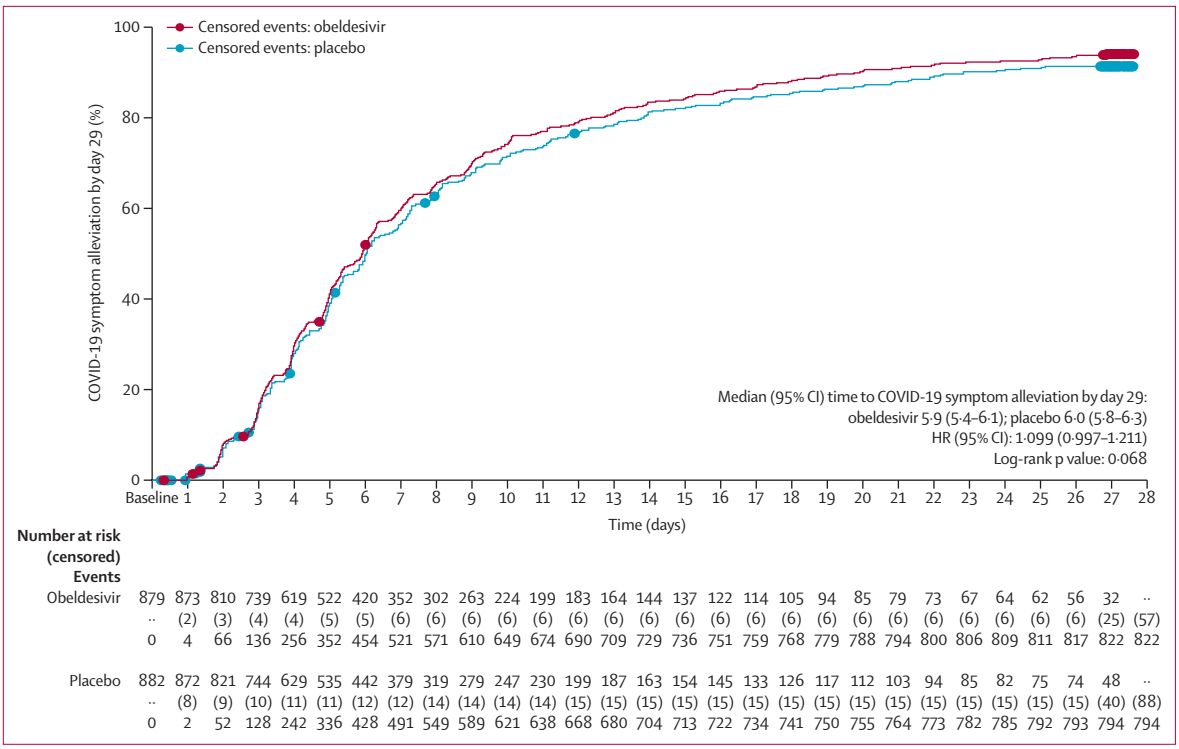

Figure 2: **Kaplan–Meier estimate of time to COVID-19 symptom alleviation (full analysis positive set)**
Only includes participants with COVID-19 symptom data. The full analysis positive set included all participants in the full analysis set (all randomly assigned participants who received ≥1 dose of study drug, except for those from the single Good Clinical Practice-non-compliant site) with positive SARS-CoV-2 RT-PCR (per central laboratory testing) at baseline. HR and two-sided 95% CI were estimated using a Cox proportional hazards regression model with the randomisation stratification factor as a covariate. p value calculated from stratified log-rank test with the randomisation stratification factor as the stratum. Participants who prematurely discontinued the study before day 29 or whose alleviation status was missing were censored at the last date or time at which the symptom was assessed or day 28, whichever occurred first. HR=hazard ratio.

The full analysis positive set had 1768 participants (884 per group; appendix pp 19–20), with 879 participants in the obeldesivir group and 882 participants in the placebo group with COVID-19 symptom data. The median time to COVID-19 symptom alleviation by day 29 was similar for those receiving obeldesivir (5·9 days [95% CI 5·4–6·1]) versus placebo (6·0 days [5·8–6·3], p=0·068), with an HR of 1·099 (0·997–1·211; figure 2). In subgroup analyses, time to COVID-19 symptom alleviation was generally similar between treatment groups regardless of sex, race, ethnicity, region, baseline SARS-CoV-2 viral RNA copy number, or BMI (appendix p 12). In participants aged 12–17 years, median time to symptom alleviation by day 29 was longer for those receiving obeldesivir (13·6 days) than for those receiving placebo (2·5 days, HR 0·119 [95% CI 0·023–0·630]), although the sample sizes were low for this subgroup (obeldesivir=8, placebo=6). In a post-hoc subgroup analysis, the Kaplan–Meier estimate for median time to COVID-19 symptom alleviation in those enrolled within 1 day of symptom onset was shorter with obeldesivir (6·1 days [95% CI 5·4–7·0]) than placebo (7·2 days [6·2–8·0], HR 1·333 [1·081–1·644], nominal p=0·0081) but was similar between groups in those enrolled 2 days after symptom onset (HR 1·123 [0·989–1·276], nominal p=0·082) and in those enrolled 3 days or 4 days after symptom onset (HR 0·805 [0·643–1·007], nominal p=0·077; appendix p 22).

Median time to symptom resolution by day 29 was 9·2 days (8·9–10·0) for the obeldesivir group compared with 9·3 days (8·9–10·1) for the placebo group (HR 1·036 [0·935–1·147], p=0·56; appendix p 11). Of participants who had at least 2 days during which targeted COVID-19 symptoms were absent (obeldesivir=760, placebo=743), moderate relapse of COVID-19 symptoms by day 29 occurred in 63 participants (8·3%, 95% CI 6·4–10·5) in the obeldesivir group and 67 (9·0%, 7·1–11·3) in the placebo group (p=0·65). COVID-19-related medically attended visits by day 29 were reported in one (0·1%) participant in the obeldesivir group and two (0·2%) participants in the placebo group (HR 0·495, 95% CI 0·045–5·464, p=0·56), with no deaths in either group. No COVID-19-related hospitalisations occurred by day 29 in either group. The proportions of participants with COVID-19 symptoms at days 60 and 90 were similar between groups (appendix p 21).

The virology analysis set included 751 participants in the obeldesivir group and 727 participants in the placebo group. Nasal swab viral RNA copy number decreased

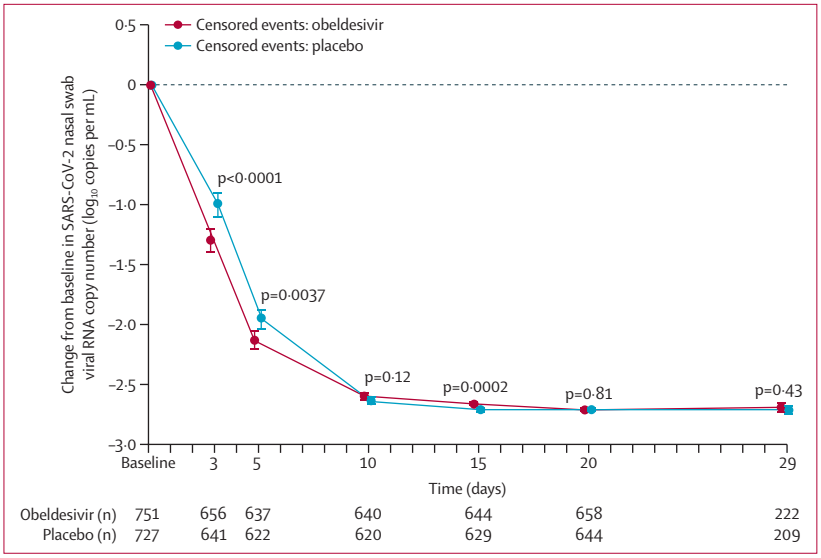

Figure 3: **Least-squares mean (95% CI) change from baseline in SARS-CoV-2 nasal swab viral RNA copy number using MMRM model (virology analysis set)**

The virology analysis set included participants in the full analysis set (all randomised participants who received ≥1 dose of study drug, except for those from the single Good Clinical Practice-non-compliant site) with a quantifiable baseline SARS-CoV-2 viral RNA copy number. The LLOD and LLOQ for SARS-CoV-2 viral RNA were 1493 copies per mL and 2228 copies per mL, respectively. The result of "no SARS-CoV-2 detected" was imputed as half the LLOD (746·5 copies per mL; 2·87 log_{10} copies per mL); the result of "<2228 copies per mL" was imputed as half the LLOQ (1114 copies per mL; 3·05 log_{10} copies per mL). LLOD=lower limit of detection. LLOQ=lower limit of quantitation. MMRM=mixed-effects model repeated measures. n=number of participants included in model.

	Obeldesivir (n=979)	Placebo (n=976)	Total (N=1955)
Any adverse event	53 (5·4%)	56 (5·7%)	109 (5·6%)
Grade ≥3 adverse event	2 (0·2%)	3 (0·3%)	5 (0·3%)
Adverse event related to study drug	5 (0·5%)	13 (1·3%)	18 (0·9%)
Grade ≥3 adverse event related to study drug	0	1 (0·1%)	1 (<0·1%)
Serious adverse event	2 (0·2%)	4 (0·4%)	6 (0·3%)
Serious adverse event related to study drug	0	1 (0·1%)	1 (<0·1%)
Adverse event leading to premature discontinuation of study drug	1 (0·1%)	0	1 (<0·1%)
Deaths	0	0	0
Adverse event by Preferred Term			
Diarrhoea	7 (0·7%)	4 (0·4%)	11 (0·6%)
Headache	6 (0·6%)	2 (0·2%)	8 (0·4%)
Dizziness	3 (0·3%)	4 (0·4%)	7 (0·4%)
Cough	2 (0·2%)	3 (0·3%)	5 (0·3%)
Dysgeusia	0	5 (0·5%)	5 (0·3%)
Nausea	4 (0·4%)	1 (0·1%)	5 (0·3%)
Back pain	2 (0·2%)	2 (0·2%)	4 (0·2%)
Hyposmia	2 (0·2%)	2 (0·2%)	4 (0·2%)
Pyrexia	1 (0·1%)	3 (0·3%)	4 (0·2%)
Vomiting	3 (0·3%)	1 (0·1%)	4 (0·2%)

Data are n (%). The safety analysis set consisted of participants randomly assigned to receive at least one dose of study drug, except for all (n=32) participants from one site who were excluded due to Good Clinical Practice non-compliance being identified at the site; this exclusion was documented in the statistical analysis plan before breaking the blind. Preferred Terms are shown for treatment-emergent adverse events that occurred in four participants or more.

Table 2: **Incidence of treatment-emergent adverse events and serious adverse events (safety analysis set)**

rapidly from baseline to day 5 in both groups (figure 3). At day 3, the least-squares mean change from baseline in viral RNA copy number was –1·30 log_{10} copies per mL (SE 0·05) for the obeldesivir group and –0·99 log_{10} copies per mL (0·05) for the placebo group, with a least-squares mean difference of –0·31 log_{10} copies per mL (95% CI –0·46 to –0·16, p<0·0001). At day 5, the least-squares mean change from baseline in viral RNA copy number was –2·13 log_{10} copies per mL (0·04) for obeldesivir and –1·95 log_{10} copies per mL (0·04) for placebo, with a least-squares mean difference of –0·18 log_{10} copies per mL (95% CI –0·30 to –0·06, p=0·0037). At day 5, the proportion of participants with negative SARS-CoV-2 nasal swab was 50·0% (330 of 660) in the obeldesivir group and 40·8% (258 of 633) in the placebo group (difference 9·2% [95% CI 3·5–14·6], nominal p=0·0010; appendix p 13).

53 (5·4%) of 979 participants (safety analysis set) in the obeldesivir group and 56 (5·7%) of 976 in the placebo group had one or more treatment-emergent AEs (table 2). Grade 3 AEs were reported in two (0·2%) participants in the obeldesivir group and three (0·3%) in the placebo group (appendix p 23). No grade 4 or 5 AEs were reported. AEs related to study drug were reported in five (0·5%) participants in the obeldesivir group (none of which were grade 3 or higher) and 13 (1·3%) in the placebo group (one [0·1%] of which was grade 3), with SAEs reported in two (0·2%) and four (0·4%) participants in the obeldesivir and placebo groups, respectively (table 2). No SAEs related to study drug were reported in the obeldesivir group, but one (0·1%) was reported in the placebo group (transient ischaemic attack). One (0·1%) participant had an AE leading to premature study drug discontinuation (grade 1 diarrhoea in the obeldesivir group). The most common treatment-emergent AEs were diarrhoea (seven [0·7%]), headache (six [0·6%]), and nausea (four [0·4%]) in the obeldesivir group, and dysgeusia (five [0·5%]), diarrhoea (four [0·4%]), and dizziness (four [0·4%]) in the placebo group.

Similar proportions of participants had one or more graded laboratory abnormalies (obeldesivir 753 [77·5%] of 972, placebo 757 [78·5%] of 964); most were grade 1 or 2 (appendix p 24). The frequency of laboratory abnormalities of grade 3 or higher was also similar in both groups (obeldesivir 59 [6·1%] of 972, placebo 82 [8·5%] of 964). There were no clinically relevant changes from baseline for haematology, chemistry, or coagulation parameters.

Discussion

In this study of non-hospitalised adolescents and adults without risk factors for progression to severe COVID-19, obeldesivir did not significantly reduce time to

COVID-19 symptom alleviation or resolution by day 29. The reduction in SARS-CoV-2 nasal swab viral RNA copy numbers was greater in the obeldesivir group at days 3 and 5 but did not differ between groups by day 10. In a post-hoc analysis of participants enrolled within 1 day after symptom onset, but not those enrolled more than 1 day after, median time to symptom alleviation was non-significantly shorter with obeldesivir versus placebo, consistent with studies showing clinical benefits with early treatment of other respiratory viruses.[22] There were no differences between proportions of participants in the obeldesivir or placebo groups with moderate relapse of COVID-19 symptoms or with COVID-19-related medically attended visits or all-cause death by day 29. Obeldesivir was generally safe and well tolerated, with similar rates of AEs, SAEs, and graded laboratory abnormalities as placebo. These findings, along with other studies showing minimal drug–drug interactions,[15] highlight the favourable safety profile of obeldesivir.

The findings of OAKTREE should be interpreted in the context of the study population and era in which the study was done, taking into account COVID-19 epidemiological factors and virus–host interactions.

Clinical benefits of early intervention with obeldesivir in a population at low risk of progression to severe disease have not yet been shown. High rates of previous vaccination and infection resulted in improved host immunity to SARS-CoV-2 infection during this omicron-dominated study period[23] and relatively mild symptoms, particularly in those without risk factors for severe disease.[3] The SARS-CoV-2 lineages circulating at the time of this study were primarily descendants of omicron variants XBB and JN.1.[24] At enrolment, more than 99% of the study population were positive for SARS-CoV-2 spike protein and 86% for nucleocapsid protein antibodies, which can reduce symptomatic infections.[25] Accordingly, COVID-19 symptom duration in the placebo group was shorter than in previous trials and the timeframe assumed in the power calculation for this study; similarly, rates of COVID-19-related hospitalisation and death were lower than in earlier trials.[20,26–29] Ultimately, the mild clinical course and rapid recovery seen in this study, which is representative of the current COVID-19 landscape in non-hospitalised adults without risk factors for progression to severe disease,[7–9] might have impeded demonstration of a significant and clinically meaningful treatment benefit with regard to time to symptom alleviation or resolution. The finding of a non-significantly shorter time to COVID-19 symptom alleviation in participants who received obeldesivir in a post-hoc analysis of those enrolled within 1 day after symptom onset leaves an open question as to whether very early obeldesivir treatment might be efficacious in a low-risk population. However, this result should be interpreted with caution given the small sample size, post-hoc nature of the analysis, and practical difficulty in delivering medical treatments on the day of symptom onset. Overall, these findings suggest that population characteristics, particularly regarding risk factors for severe COVID-19, could influence early antiviral treatment benefits.

SARS-CoV-2 viral load dynamics in non-hospitalised participants, especially in those without risk factors, have changed over the course of the pandemic, with a more rapid decline of viral RNA copy number observed in the OAKTREE study compared with earlier trials.[27,29–31] Despite the more rapid decline, and the lower baseline nasal swab viral RNA copy number observed in OAKTREE compared with earlier trials, obeldesivir showed antiviral activity, with greater reductions in mid-turbinate nasal swab viral RNA copy number in the obeldesivir group versus the placebo group on days 3 and 5. A faster rate of viral clearance with obeldesivir could be beneficial for reducing transmission of SARS-CoV-2 in the overall population.[32] Furthermore, research suggests that a slower rate of viral RNA clearance within the first 28 days of COVID-19 could be linked to the presence of certain long COVID symptoms.[33] Ultimately, additional studies are needed to establish whether obeldesivir treatment can reduce transmission of SARS-CoV-2, the incidence of long COVID, or both. Additionally, given the antiviral activity and favourable safety profile of obeldesivir, its utility for treating coronavirus-mediated diseases in higher-risk populations remains promising.[34]

In addition to activity against SARS-CoV-2, obeldesivir has shown broad-spectrum antiviral activity and success in protecting against other RNA viruses in non-human primates.[14,35] In a recent study conducted in cynomolgus macaques, obeldesivir treatment initiated 24 h after exposure to Sudan virus resulted in 100% protection against lethal infection.[14] In another study, obeldesivir treatment initiated 24 h after exposure to Marburg virus led to 80% protection against lethal infection in cynomolgus macaques.[35] Additionally, intravenous administration of remdesivir, which generates the same active nucleoside triphosphate (GS-443902) as obeldesivir, has shown potent antiviral activity against respiratory syncytial virus in African green monkeys.[36] Given this evidence, obeldesivir has the potential to be a valuable tool in preventing future epidemics and pandemics driven by RNA viruses.

Strengths of this study include a large sample size of non-hospitalised participants recruited during the omicron period, with enrolment of under-represented groups. There was also robust virological sampling, allowing for thorough evaluation of viral kinetics. Limitations include the milder disease course and resultant low frequency of clinical events in a low-risk population that presented challenges for the study design, including assessment of the secondary composite endpoints of COVID-19-related hospitalisations or death, which did not occur. Additionally, the difficulty of developing a patient-reported outcome tool for assessing

COVID-19 symptoms in the context of the changing clinical profile of the disease might have led to inconsistent measurements of time to symptom alleviation or resolution. Furthermore, period-specific HRs, such as those used for the primary endpoint analysis, have a built-in selection bias that could result in HRs that vary over the study period.[37] Although median time to symptom alleviation among adolescent participants was non-significantly shorter with placebo, the result was unreliable due to the low numbers of adolescent participants in each group. Finally, although the primary endpoint was analysed by race and ethnicity, analyses by ethnoracial status were not conducted; thus, potential disparities between different racial subgroups within ethnic groups and vice versa could not be identified.

Overall, in adolescents and adults without risk factors for severe disease progression, obeldesivir treatment was generally safe and well tolerated, reduced SARS-CoV-2 viral RNA copy number, and resulted in a greater proportion of participants testing negative for SARS-CoV-2 compared with placebo. However, obeldesivir did not reduce time to COVID-19 symptom alleviation or resolution in this low-risk population, possibly reflecting the challenges of assessing efficacy in this population in an era of high rates of vaccine-induced and natural immunity. Obeldesivir might enhance population preparedness for SARS-CoV-2 variants that are more virulent or with immune escape, should they arise, and for epidemics and pandemics of other RNA viruses.

Contributors

OO and ALi had direct access to and verified the underlying data. OO, JDG, RLG, US, ALi, AM, YK, RHH, JL, AO, FD, RH, LC, SD, LR, CH, SC, PN, and AK contributed to the conceptualisation of the study. ALi, AM, YK, SD, SC, KE, and PN contributed to the data curation. ALi, AM, YK, RHH, JL, AO, FD, RH, LC, SD, LR, CH, SC, and KE contributed to the formal analysis. MS, GA, DNF, EG, ALu, RH, LC, LR, CH, and AK contributed to the investigation. RLG, ALi, AM, YK, RHH, JL, RH, LC, SD, LR, CH, SC, KE, and PN contributed to the methodology. AO and FD contributed to the supervision. SC and KE contributed to the visualisation. All authors contributed to data analysis and interpretation and vouch for the accuracy and completeness of the data and for fidelity of the trial to the protocol, contributed to review and editing of the manuscript, had access to the study data, and accept responsibility to submit for publication.

Declaration of interests

OO served on advisory boards for Gilead Sciences, Moderna, and ViiV Healthcare/GSK. JDG consulted for Gilead Sciences, GSK, Invivyd, and Merck; received research support or grants from Gilead Sciences, Merck Sharp & Dohme (Biomedical Advanced Research and Development Authority), and Regeneron; and received non-financial support from Adaptive Biotechnologies, Labcorp, and Monogram Biosciences (outside of this study). RLG served as a consultant for AbbVie, AstraZeneca, Eli Lilly, Gilead Sciences, GSK, Invivyd, Johnson & Johnson, Roche Pharmaceuticals, and Roivant Sciences; served as a national coordinating primary investigator for Johnson & Johnson; served on an academic steering committee for Roivant Sciences; received from Gilead Sciences a gift in kind to Baylor Scott & White Research Institute to facilitate NCT03383419; owns de minimis stock in AbCellera Biologics; and served as a speaker for Pfizer, outside the scope of COVID-19. US served on an advisory board for Gilead Sciences and Regeneron; and received research support or grants from Pfizer. MS received research funding to conduct clinical trials from AstraZeneca, Fujifilm Corporation, Genova, Gilead Sciences, GSK, Guerbet, Insmed, Kyorin Pharmaceutical Co, Sanofi, and Shionogi & Co; and received lecture fees from AstraZeneca, GSK, Kyorin Pharmaceutical Co, and Sanofi. DNF served on a Gilead Sciences advisory board, outside the scope of COVID-19; served as a site primary investigator for clinical trials with Gilead Sciences, MetroBiotech, and Regeneron; and received investigator-initiated research support from Gilead Sciences. EG has business relationships with AstraZeneca, DBV, Genentech, Novartis, and Regeneron as a clinical research investigator. PK received institutional grants from Gilead Sciences, Merck, Theratechnologies, and ViiV Healthcare/GSK; received consulting fees from, and served on an advisory board for, Gilead Sciences, Merck, and ViiV Healthcare/GSK; and owns stocks or bonds in Gilead Sciences, Johnson & Johnson, Merck, Moderna, Pfizer, and ViiV Healthcare/GSK. ALu received research grant support to the University of California San Francisco (CA, USA) from Cepheid, Gilead Sciences, GSK, and Merck; and received laboratory support from Cepheid and Hologic. ALi, AM, YK, RHH, AO, FD, LC, SD, LR, CH, SC, KE, and PN are current employees of, and may own stock or stock options in, Gilead Sciences. JL and RH are former employees of, and may own stock or stock options in, Gilead Sciences. AK served on advisory boards for Gilead Sciences and Madrigal Pharmaceuticals; served as a national coordinating principal investigator for Regeneron; and is a speaker for Madrigal Pharmaceuticals, outside the scope of COVID-19. GA declares no competing interests.

Data sharing

The complete de-identified participant dataset will be made available upon request to qualified external researchers, based on submitted curriculum vitae and reflecting non-conflict of interest, immediately upon publication. The request proposal must also include a statistician. Email requests to datarequest@gilead.com. Approval of requests for data is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. For further details please review the policy on the GileadClinicalTrials.com website under Commitment to PhRMA/EFPIA. If Gilead Sciences agrees to the release of clinical data for research purposes, the requestor will be required to sign a data sharing agreement in order to ensure protection of patient confidentiality before the release of any data. Upon execution of the data sharing agreement, Gilead Sciences will provide access to a patient-level clinical trial analysis dataset in a secured analysis environment. The full study protocol is published in the study appendix (p 26).

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