Obeldesivir for Treatment of COVID-19 in Adults and Adolescents Without Risk Factors for Progression to Severe Disease: The OAKTREE Study

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Conclusions

- In nonhospitalized adults and adolescents without risk factors for progression to severe disease, obeldesivir 350 mg administered twice daily for 5 days was generally safe and well tolerated but did not significantly reduce time to COVID-19 symptom alleviation or resolution compared to placebo
- Obeldesivir treatment reduced SARS-CoV-2 viral RNA copy number at Days 3 and 5 and resulted in a greater proportion of participants who tested negative for SARS-CoV-2 at Day 5 compared to placebo
- COVID-19 symptom duration was markedly shorter than in earlier trials, consistent with milder disease in a population with high rates of hybrid immunity during the Omicron era
- Obeldesivir remains a promising treatment for COVID-19 and other coronavirus-mediated diseases given its demonstrated antiviral activity and favorable safety profile

Plain Language Summary

- Obeldesivir is an oral medication that stops the replication of SARS-CoV-2, the virus that causes COVID-19
- This study aimed to find out if obeldesivir was safe and effective for treating COVID-19 in people at low risk of becoming severely ill from the disease
- There were no major differences in the time to COVID-19 symptom improvement when people took obeldesivir compared to placebo
- This may have been because most people in the study already had some immunity to the virus and got better quickly, even without treatment
- Obeldesivir was generally safe and well tolerated, and almost all people completed their assigned treatment
- Obeldesivir also lowered the amount of SARS-CoV-2 virus a person had compared to placebo
- Overall, obeldesivir remains a promising treatment for COVID-19 and other similar illnesses

Introduction

- COVID-19 remains a public health priority, with a higher annual mortality than influenza¹⁻³
- There are currently no antiviral treatment options approved in the United States for mild-to-moderate COVID-19 for nonhospitalized individuals without risk factors for progression to severe disease⁴
- Obeldesivir (ODV) is an oral nucleoside analog prodrug that, through a different pharmacometabolic pathway, delivers the same active metabolite as remdesivir that inhibits SARS-CoV-2 RNA-dependent RNA polymerase^{5,6}
- ODV has a low pill burden, no clinically meaningful drug-drug interactions, and in vitro antiviral activity against SARS-CoV-2 variants^{5,7-10}

Objective

• To evaluate the efficacy, safety, and tolerability of ODV for the treatment of COVID-19 in nonhospitalized individuals without risk factors for progression to severe disease

Methods

- OAKTREE (ClinicalTrials.gov Identifier: NCT05715528) was a Phase 3, randomized, double-blind, placebo-controlled study in nonhospitalized participants aged ≥12 to <65 years without specified risk factors for progression to severe COVID-19
- Participants were enrolled (February 13-October 31, 2023) within 3 days of the onset of ≥2 targeted COVID-19 symptoms (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), stratified by completion of a primary COVID-19 vaccine series, and randomized 1:1 to receive ODV 350 mg or placebo twice daily for 5 days
- Primary endpoints were time to COVID-19 symptom alleviation by Day 29, incidence of treatment-emergent adverse events (AEs) and laboratory abnormalities, and incidence of serious AEs and AEs leading to study drug discontinuation
- Symptom alleviation occurred if, for ≥48 consecutive hours, all targeted symptoms scored as moderate or severe at baseline were scored as mild or none and all targeted symptoms scored as mild or none at baseline were scored as none
- Secondary endpoints included time to COVID-19 symptom resolution by Day 29, change from baseline in SARS-CoV-2 nasal swab viral RNA copy number, and COVID-19—related hospitalization or all-cause death by Day 29

Results

Participants

- Overall, 1955 participants (ODV, 979; placebo, 976) were randomized and received ≥1 dose of study drug, of whom 1924 (98%) completed study drug
- Baseline characteristics were generally similar between groups (Table 1)
- Overall, 70% of participants had completed a primary vaccination series, 99% were positive for SARS-CoV-2 anti-spike antibodies, 86% were positive for anti-nucleocapsid antibodies, and the mean baseline SARS-CoV-2 viral RNA copy number was 5.1 log₁₀ copies/mL

Table 1. Demographic and Baseline Characteristics (Safety Analysis Set^a)

Characteristic	ODV (n = 979)	Placebo (n = 976)	Total (n = 1955)
Age, years, median (range)	42 (12-64)	40 (12-64)	41 (12-64)
Sex at birth, n (%)			
Female	583 (60)	572 (59)	1155 (59)
Race, n (%)			
Asian	21 (2)	21 (2)	42 (2)
Black	106 (11)	101 (10)	207 (11)
White	850 (87)	848 (87)	1698 (87)
Otherb	2 (<1)	6 (1)	8 (<1)
Ethnicity, n (%)			
Hispanic or Latino	918 (94)	901 (92)	1819 (93)
Completed primary vaccination series, n (%)			
Yes	687 (70)	681 (70)	1368 (70)
COVID-19 vaccination status, n (%)			
Never	271 (28)	266 (27)	537 (27)
Duration of COVID-19 symptoms prior to first dose of study drug, days, median (Q1, Q3)°	2 (2, 2)	2 (2, 2)	2 (2, 2)
Participants with COVID-19 symptom data available at baseline, n	962	962	1924
Number of targeted COVID-19 symptoms at baseline, median (Q1, Q3)	8 (6, 9)	7 (6, 9)	8 (6, 9)
Serostatus, n (%) ^d			
Overall positive	970 (>99)	968 (99)	1938 (>99)
Overall negative	1 (<1)	7 (1)	8 (<1)
Missing	8	1	9
SARS-CoV-2 anti-spike antibody, ne	884	884	1768
Positive, n (%)	869 (>99)	869 (99)	1738 (99)
Negative, n (%)	3 (<1)	7 (1)	10 (1)
Missing, n	12	8	20
SARS-CoV-2 anti-nucleocapsid antibody, ne	884	884	1768
Positive, n (%)	755 (86)	756 (86)	1511 (86)
Negative, n (%)	125 (14)	121 (14)	246 (14)
Missing, n	4	7	11
SARS-CoV-2 viral RNA copy number, n ^f	913	911	1824
Log ₁₀ copies/mL, mean (SD)	5.1 (1.4)	5.1 (1.5)	5.1 (1.4)

^aSafety analysis set included participants who were randomized and received ≥1 dose of study drug. Participants in the safety analysis set were summarized according to the actual treatment received.
^bFor the race category, "other" includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, other, and "not permitted."
^cDuration of COVID-19 symptoms was defined as the first dosing date minus the COVID-19 symptom onset date (Day 0).

nissing values. Evaluated in the full analysis positive set (participants who were randomized, received ≥1 dose of study drug, and were SARS-CoV-2 positive at baseline as confirmed by RT-PCR at the central laboratory). Percentages do not include those with missing values.

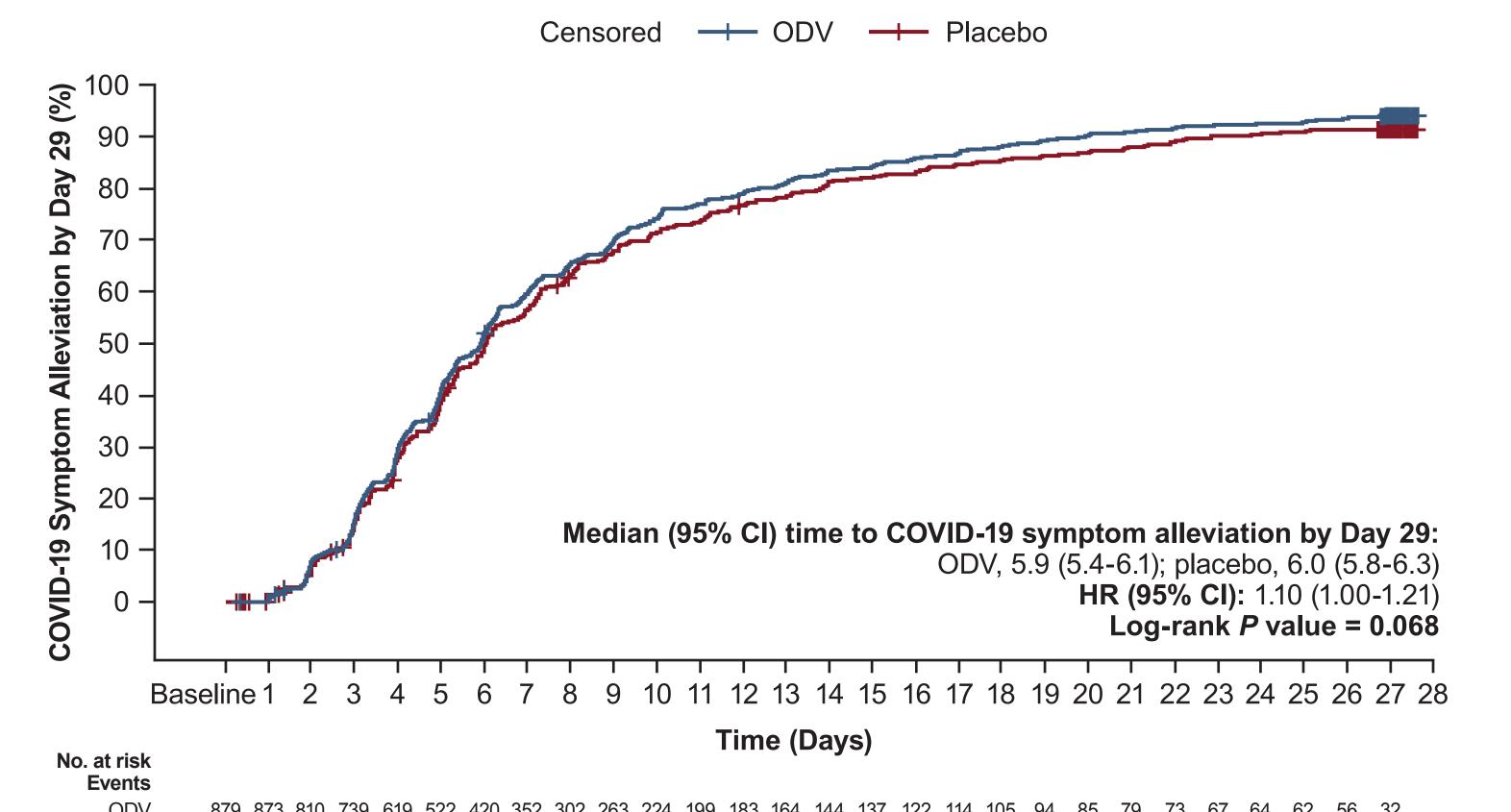
Result of "No SARS-CoV-2 detected" was imputed as 746.5 copies/mL (2.87 log₁₀ copies/mL); "<2228 copies/mL" was imputed as 1114 copies/mL (3.05 log₁₀ copies/mL).

ODV. obeldesivir: RT-PCR, reverse transcriptase—polymerase chain reaction.

Clinical Efficacy

- Of the 1955 participants who were randomized and received ≥1 dose of study drug, 1768 (90%) participants (884 per group) had reverse transcriptase—polymerase chain reaction—confirmed SARS-CoV-2 infection at baseline
- Among those with COVID-19 symptom data, the Kaplan-Meier estimate of median time to symptom alleviation was 5.9 (95% CI, 5.4-6.1) days in the ODV group and 6.0 (95% CI, 5.8-6.3) days in the placebo group (*P* = 0.068; **Figure 1**)

Figure 1. Kaplan-Meier Estimate of Time to COVID-19 Symptom Alleviation (Full Analysis Positive Set^a)



Placebo 882 872 821 744 629 535 442 379 319 279 247 230 199 187 163 154 145 133 126 117 112 103 94 85 82 75 74 48

0 2 52 128 242 336 428 491 549 589 621 638 668 680 704 713 722 734 741 750 755 764 773 782 785 792 793 794 794

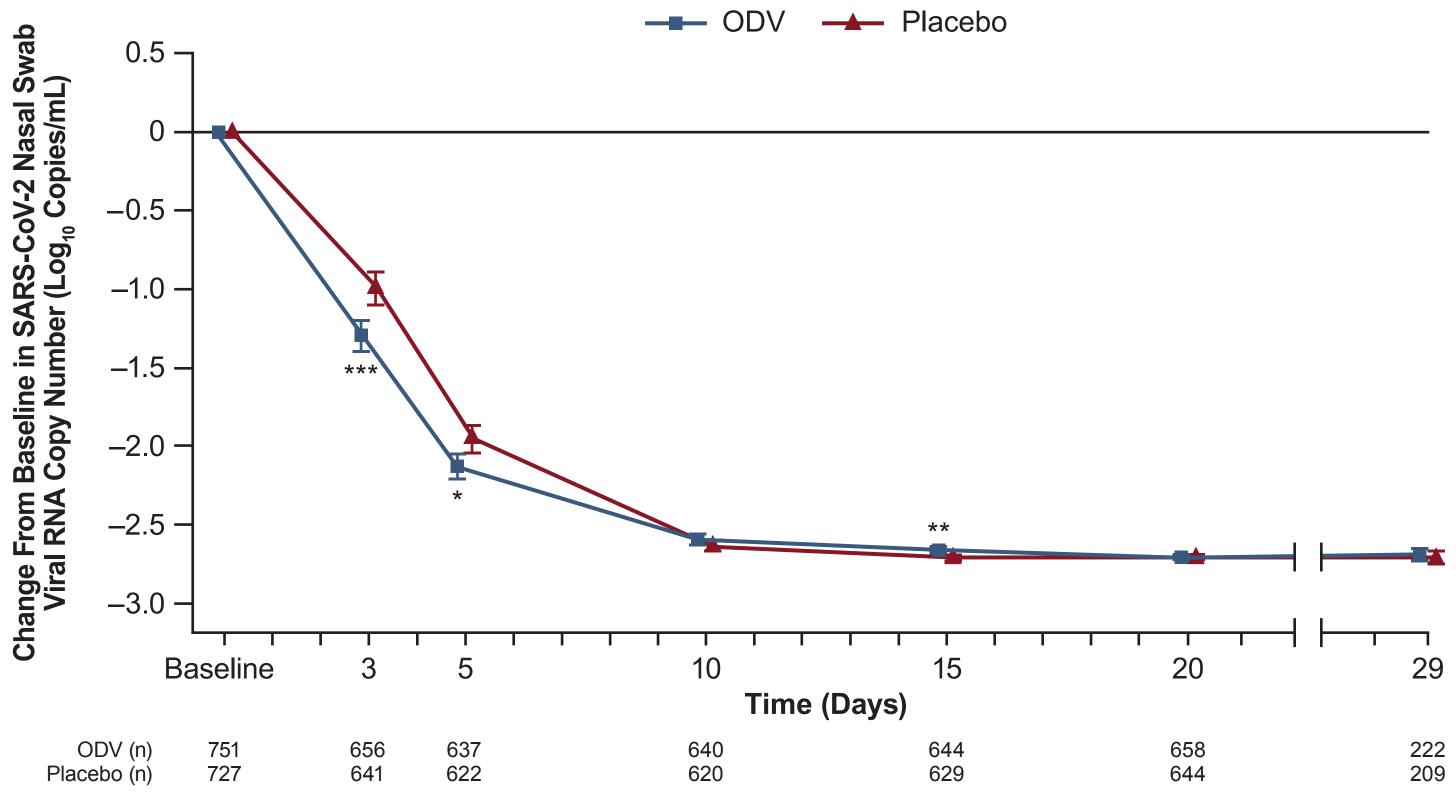
at-reported outcomes were collected through a COVID-19 symptom questionnaire adapted from US Food and Drug Administration guidance that participants completed daily through Day 29 and on 60 and 90. Participants who prematurely discontinued the study prior to Day 29 or whose alleviation status was missing were censored at the last date/time at which the symptom was assessed or Day 28, ever occurred first. HR and 2-sided 95% CI for HR were estimated using the Cox regression with the randomization stratification factor as a covariate. P value was calculated from stratified log-rank test

- The Kaplan-Meier estimates of median time to symptom resolution were also similar between treatment groups (ODV, 9.2 [95% CI, 8.9-10.0] days; placebo, 9.3 [95% CI, 8.9-10.1] days; nominal *P* = 0.556)
- No COVID-19—related hospitalizations or deaths were reported by Day 29 in either group
- No meaningful differences were seen between groups for symptoms at Day 90

Virologic Efficacy

- In the 1478 participants (ODV, 751; placebo, 727) in the virology analysis set, viral RNA copy number
 decreased rapidly from baseline to Day 5 in both groups (Figure 2)
- Compared to the placebo group, there were greater reductions in least squares mean viral RNA copy number from baseline to Day 3 (treatment difference [95% CI], -0.31 [-0.46 to -0.16] \log_{10} copies/mL; nominal P < 0.0001) and to Day 5 (treatment difference [95% CI], -0.18 [-0.30 to -0.06] \log_{10} copies/mL; nominal P = 0.004) in the ODV group

Figure 2. Least Squares Mean (95% CI) Change From Baseline in SARS-CoV-2 Nasal Swab Viral RNA Copy Number (Log₁₀ Copies/mL) Using MMRM (Virology Analysis Set^a)



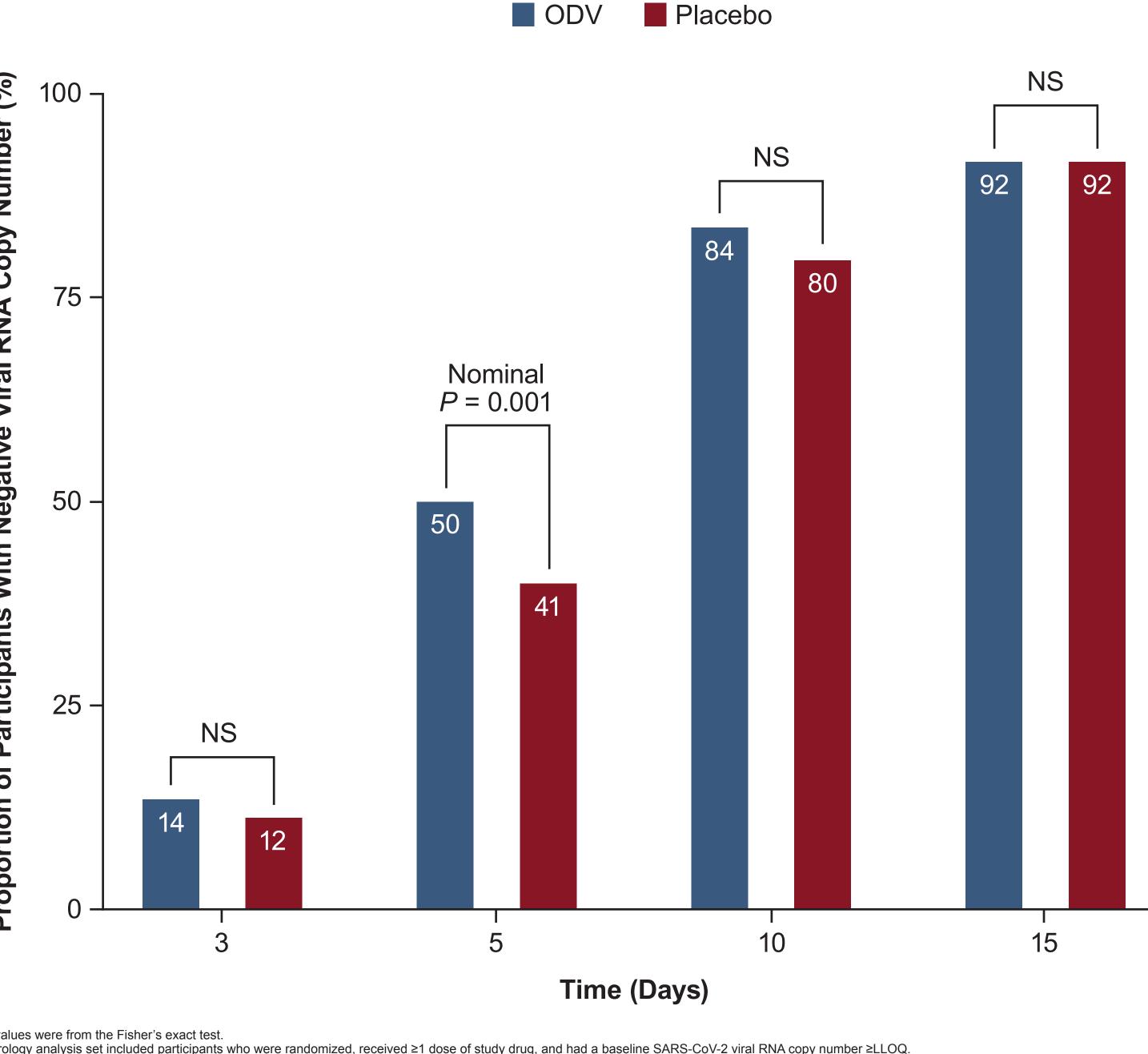
Placebo (n) 727 641 622 620 629 629 644 209

Mean (SE), 95% CI, and P value were from MMRM with baseline viral RNA copy number and the randomization stratum as covariates. * indicates nominal P <0.01 versus placebo. *** indicates nominal P <0.001 versus placebo. *** indicates nominal P <0.001 versus placebo. The LLOD and LLOQ for SARS-CoV-2 viral RNA were 1493 and 2228 copies/mL, respectively. The result of "No SARS-CoV-2 detected" was imputed as half of the LLOD (746.5 copies/mL; 2.87 log₁₀ copies/mL); the result of "<2228 copies/mL" was imputed as half of the LLOQ (1114 copies/mL; 3.05 log₁₀ copies/mL).

*Virology analysis set included participants who were randomized, received ≥1 dose of study drug, and had a baseline SARS-CoV-2 viral RNA copy number ≥LLOQ.

At Day 5, a greater proportion of participants in the ODV group had negative SARS-CoV-2 nasal swab compared to the placebo group (nominal P = 0.001; Figure 3)

Figure 3. Proportion of Participants With Negative SARS-CoV-2 Nasal Swab Viral RNA Copy Number (Virology Analysis Set^a)



aVirology analysis set included participants who were randomized, received ≥1 dose of study drug, and had a baseline SARS-CoV-2 viral RNA copy number ≥LLOQ. LLOQ, lower limit of quantitation; NS, not significant; ODV, obeldesivir.

Safety

• The safety profiles of ODV and placebo were comparable, with similar rates of AEs, treatment-related AEs, serious AEs, and AEs leading to study drug discontinuation (Table 2)

Table 2. Incidence of Treatment-emergent AEs and Treatment-emergent Serious AEs (Safety Analysis Set^a)

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า (%)	ODV (n = 979)	Placebo (n = 976)	Total (n = 1955)	
Any AE	53 (5)	56 (6)	109 (6)	
Grade ≥3 AE	2 (<1)	3 (<1)	5 (<1)	
AE related to study drug	5 (1)	13 (1)	18 (1)	
Grade ≥3 AE related to study drug	0	1 (<1)	1 (<1)	
Serious AE	2 (<1)	4 (<1)	6 (<1)	
Serious AE related to study drug	0	1 (<1)	1 (<1)	
AE leading to premature discontinuation of study drug	1 (<1)	0	1 (<1)	
Death	0	0	0	

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).¹¹
^aSafety analysis set included participants who were randomized and received ≥1 dose of study drug. Participants in the safety analysis set were summarized according to the actual treatment received.

- There was a similar proportion of participants with ≥1 graded laboratory abnormality in the ODV (753/972 [77%]) and placebo (757/964 [79%]) groups; most (71%) laboratory abnormalities were Grade 1 or 2
- Grade ≥3 laboratory abnormalities were reported in a similar proportion of participants across treatment groups (ODV, 59/972 [6%]; placebo, 82/964 [9%])

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