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BIRCH

# Obeldesivir for the Treatment of COVID-19 in People With Risk Factors for Progression to Severe Disease: The BIRCH Study


Anca Streinu-Cercel[1,2], Antonella Castagna[3], Shan-Chwen Chang[4], Yao-Shen Chen[5], Yiannis Koullias[6], Afsaneh Mozaffarian[6], Robert H Hyland[6], Rita Humeniuk[6], Luzelena Caro[6], Santosh Davies[6], Charlotte Hedskog[6], Shuguang Chen[6], Kim Etchevers[6], Nicole Behenna-Renton[7], Joe Llewellyn[6], Anu Osinusi[6], Frank Duff[6], Alejandro Barrat Hernández[8], Damien McNally[9], Jesus Abraham Simon-Campos[10,11], Fabio Eudes Leal[12,13], Leon F Fouche[14], Juan Maria González Del Castillo[15]

[1]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]National Institute of Infectious Diseases "Prof. Dr. Matei Bals", Bucharest, Romania; [3]Infectious Diseases Clinic, Vita-Salute San Raffaele University, Milan, Italy; [4]National Taiwan University College of Medicine, Taipei, Taiwan; [5]Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [6]Gilead Sciences, Inc., Foster City, CA, USA; [7]Gilead Sciences Europe Ltd, Uxbridge, UK; [8]FAICIC Clinical Research, Veracruz, Mexico; [9]Ormeau Clinical Trials, Belfast, UK; [10]Köhler & Milstein Research, Mérida, Mexico; [11]Universidad Autónoma de Yucatán, Mérida, Mexico; [12]Brazilian National Cancer Institute, Rio de Janeiro, Brazil; [13]Faculdade de Medicina da Universidade Municipal de São Caetano do Sul, São Paulo, Brazil; [14]Limpopo Clinical Research Initiative, Thabazimbi, South Africa; [15]Emergency Department, Hospital Clínico Universitario San Carlos, Madrid, Spain

Anca Streinu-Cercel
anca.streinucercel@gmail.com




## Conclusions

- In the context of a changing COVID-19 landscape with lower-than-expected clinical event rates, obeldesivir treatment did not meet the primary endpoint of COVID-19–related hospitalization or all-cause death by Day 29 in nonhospitalized participants with risk factors for progression to severe COVID-19
- Obeldesivir treatment resulted in greater decreases in SARS-CoV-2 viral RNA copy number and infectious viral titer and a trend in faster time to symptom alleviation compared to placebo and was generally safe and well tolerated
- Obeldesivir remains a promising oral antiviral with the potential to reduce the burden of COVID-19 in the event of waning individual and population immunity or the emergence of more virulent variants

## Plain Language Summary

- Obeldesivir is an oral drug that blocks replication of SARS-CoV-2, the virus that causes COVID-19
- People with certain risk factors, like obesity, older age, and cardiovascular disease, have a higher rate of hospitalization and death following SARS-CoV-2 infection compared to those who do not have them
- This clinical study aimed to find out if obeldesivir was safe and effective in treating COVID-19 in participants at high risk of developing severe disease
- The study was stopped early, with 468 of 2300 people enrolled, because there were fewer deaths and hospitalizations than were expected
  - This may be because most people had antibodies against SARS-CoV-2 and were vaccinated against COVID-19, which means they had some immunity against the virus
- There was no significant difference between the obeldesivir and placebo groups in the proportion of participants who were hospitalized for COVID-19 or died
- However, this study showed that obeldesivir treatment is generally safe, reduces levels of SARS-CoV-2 virus compared to placebo, and may result in a faster time to symptom relief compared to placebo

## Introduction

- The risk of severe COVID-19 increases with age and certain comorbid conditions[1-3]
- Early antiviral therapy in nonhospitalized individuals with COVID-19 has been shown to prevent severe disease progression[4,5]
- Obeldesivir (ODV) is an oral, broad-spectrum, nucleoside analog prodrug inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase with a low pill burden and without clinically meaningful drug-drug interactions[6-10]

## Objective

- To evaluate the efficacy of ODV in reducing the rate of COVID-19–related hospitalization or all-cause death in nonhospitalized adults with risk factors for progression to severe COVID-19

## Methods

- BIRCH (ClinicalTrials.gov Identifier: NCT05603143) was a Phase 3, randomized, double-blind, placebo-controlled study
  - Participants were adults aged ≥18 years who were not currently hospitalized or requiring hospitalization with risk factors for developing severe COVID-19
  - The first participant was screened on November 5, 2022, and the last participant visit was on November 7, 2023
- Eligible participants were randomized 1:1 to ODV 350 mg or placebo twice daily for 5 days
  - Randomization was stratified by duration of symptoms at enrollment and vaccination status
- The primary endpoint was the proportion of COVID-19–related hospitalization or all-cause death by Day 29
- Other efficacy endpoints included time to symptom alleviation by Day 15, change in SARS-CoV-2 nasal swab viral RNA copy number, and change in SARS-CoV-2 nasal swab infectious viral titer
- Safety endpoints included incidences of treatment-emergent adverse events (AEs), laboratory abnormalities, serious AEs, and AEs leading to study drug discontinuation

## Results

### Participants

- Study enrollment was stopped early, reflecting the evolving COVID-19 landscape with low rates of clinical events
- Overall, 465 participants were randomized, received ≥1 dose of study drug, and were included in the safety analysis set
- Demographic and baseline characteristics were generally similar between groups (**Table 1**)
  - Overall, the median age of participants was 56 years, 135 (29%) were ≥65 years of age, 262 (56%) were assigned female at birth, 343 (74%) were White, 78 (17%) were Hispanic or Latino, and the median body mass index was 28.2 kg/m$^2$
  - Most participants (352 [76%]) had a duration of symptoms ≤3 days prior to the first dose of study drug, and 196 (42%) had never received a COVID-19 vaccination prior to enrollment
  - 426 (92%) participants were seropositive for SARS-CoV-2 anti-spike or anti-nucleocapsid antibodies
- The most common risk factors among participants were body mass index ≥25 kg/m$^2$ (395 [85%]), age ≥50 years (324 [70%]), cardiovascular disease (205 [44%]), diabetes mellitus (73 [16%]), and chronic lung disease (40 [9%])

**Table 1. Demographic and Baseline Characteristics (Safety Analysis Set[a])**

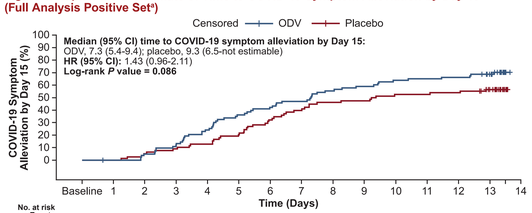
| Characteristic | ODV (n = 234) | Placebo (n = 231) | Total (n = 465) |
|---|---|---|---|
| Age, years, median (range) | 57 (20-89) | 55 (18-88) | 56 (18-89) |
| Age category, years, n (%) | | | |
| ≥18 to <65 | 160 (68) | 170 (74) | 330 (71) |
| ≥65 to <75 | 49 (21) | 38 (16) | 87 (19) |
| ≥75 to <85 | 22 (9) | 20 (9) | 42 (9) |
| ≥85 | 3 (1) | 3 (1) | 6 (1) |
| Sex at birth, n (%) | | | |
| Female | 147 (63) | 115 (50) | 262 (56) |
| Race, n (%) | | | |
| American Indian or Alaska Native | 21 (9) | 19 (8) | 40 (9) |
| Asian | 24 (10) | 32 (14) | 56 (12) |
| Black | 9 (4) | 10 (4) | 19 (4) |
| Native Hawaiian or Pacific Islander | 0 | 2 (1) | 2 (<1) |
| White | 179 (76) | 164 (71) | 343 (74) |
| Other | 1 (<1) | 4 (2) | 5 (1) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 36 (15) | 42 (18) | 78 (17) |
| Body mass index, kg/m$^2$, median (Q1, Q3) | 28 (26, 32) | 28 (26, 32) | 28 (26, 32) |
| Duration of COVID-19 symptoms, days[b] | | | |
| ≤3, n (%) | 177 (76) | 175 (76) | 352 (76) |
| Median (Q1, Q3) | 2 (2, 3) | 2 (2, 3) | 2 (2, 3) |
| Vaccination status, n (%) | | | |
| Ever | 136 (58) | 133 (58) | 269 (58) |
| Duration from first positive SARS-CoV-2 diagnostic test to first dose of study drug, days, median (Q1, Q3)[c] | 0 (0, 1) | 1 (0, 1) | 0 (0, 1) |
| Number of baseline risk factors, mean (SD)[d] | 3 (1.1) | 2 (1.0) | 3 (1.1) |
| Serostatus, n (%)[e] | | | |
| Overall positive | 214 (91) | 212 (92) | 426 (92) |
| Missing | 0 | 1 | 1 |
| SARS-CoV-2 viral RNA copy number, n[f] | 218 | 215 | 433 |
| $Log_{10}$ copies/mL, mean (SD) | 6.2 (1.6) | 6.2 (1.6) | 6.2 (1.6) |

[a]Safety analysis set included participants who were randomized and received ≥1 dose of study drug.
[b]Duration of COVID-19 symptoms was defined as the first dosing date minus the COVID-19 symptom onset date (Day 0).
[c]Duration from first positive SARS-CoV-2 diagnostic test to first dose of study drug was defined as the first dosing date minus the first positive SARS-CoV-2 test date (Day 0).
[d]Risk factors were defined in the inclusion criteria of the protocol.
[e]Serostatus was defined as positive when anti-spike or anti-nucleocapsid antibody was positive and was defined as negative when both were negative. Serostatus percentages do not include those with missing values.
[f]Result of "No SARS-CoV-2 detected" was imputed as 746.5 copies/mL (2.87 $log_{10}$ copies/mL); "<2228 copies/mL" was imputed as 1114 copies/mL (3.05 $log_{10}$ copies/mL).
ODV, obeldesivir.

### Clinical Efficacy

- 418 participants (ODV, 211; placebo, 207) who were randomized, received ≥1 dose of study drug, and were SARS-CoV-2 positive at baseline by central laboratory polymerase chain reaction were included in the full analysis positive set for efficacy analyses
- COVID-19–related hospitalization or all-cause death through Day 29 was reported in 0/211 (0%) participants in the ODV group and 1/207 (0.5%) participants in the placebo group ($P$ = 0.316)
- Among the 162 participants who completed the Symptoms of Infection with Coronavirus-19 questionnaire, there was a 2-day improvement in median time to symptom alleviation by Day 15 in the ODV group compared to the placebo group (ODV, 7.3 days; placebo, 9.3 days; nominal $P$ = 0.086; **Figure 1**)

**Figure 1. Kaplan-Meier Estimate of Time to COVID-19 Symptom Alleviation by Day 15 (Full Analysis Positive Set[a])**

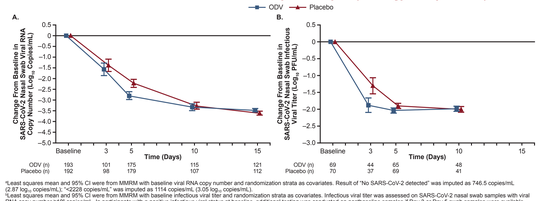



Participants who prematurely discontinued the study prior to Day 15 or whose alleviation status was missing were censored at the last date/time at which the symptom was assessed or Day 14, whichever occurred first. Symptom alleviation was evaluated via the SIC questionnaire, which was only collected for participants enrolled under the original protocol. HR and 2-sided 95% CI for HR were estimated using the Cox proportional hazards model with the randomization stratification factors as covariates. $P$ value was calculated from stratified log-rank test with the randomization stratification factors as the strata. The last known symptom alleviation occurred at Day 14.
[a]Full analysis positive set included 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.
HR, hazard ratio; ODV, obeldesivir; RT-PCR, reverse transcriptase–polymerase chain reaction; SIC, Symptoms of Infection with Coronavirus-19.

### Virologic Efficacy

- 385 participants (ODV, 193; placebo, 192) who were randomized and received ≥1 dose of study drug had a baseline SARS-CoV-2 viral RNA copy number greater than or equal to the lower limit of quantitation and were included in the virology analysis set
- There were greater reductions in least squares mean viral RNA copy number from baseline to Day 5 in the ODV group compared to the placebo group (treatment difference [95% CI], –0.58 [–0.83 to –0.33] $log_{10}$ copies/mL; nominal $P$ <0.001; **Figure 2A**)
- In the subset of participants with a SARS-CoV-2 nasal swab infectious viral titer ≥200 plaque-forming units (PFU)/mL at baseline and tested on Day 3 or Day 5, there was a treatment difference in SARS-CoV-2 nasal swab infectious viral titer least squares mean (95% CI) for ODV compared to placebo at Day 3 of –0.58 (–0.90 to –0.26) $log_{10}$ PFU/mL (nominal $P$ <0.001) and at Day 5 of –0.13 (–0.22 to –0.05) $log_{10}$ PFU/mL (nominal $P$ = 0.002; **Figure 2B**)

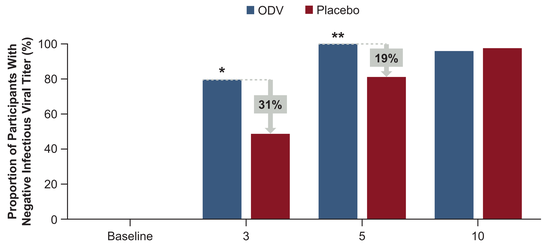
**Figure 2. (A) Least Squares Mean (95% CI) Change From Baseline in SARS-CoV-2 Nasal Swab Viral RNA Copy Number Using MMRM[a] and (B) Least Squares Mean (95% CI) Change From Baseline in SARS-CoV-2 Nasal Swab Infectious Viral Titer Using MMRM in Participants With Value ≥200 PFU/mL at Baseline and Tested on Day 3 or Day 5[b] (Virology Analysis Set[c])**




[a]Least squares mean and 95% CI were from MMRM with baseline viral RNA copy number and randomization strata as covariates. Result of "No SARS-CoV-2 detected" was imputed as 746.5 copies/mL (2.87 $log_{10}$ copies/mL); "<2228 copies/mL" was imputed as 1114 copies/mL (3.05 $log_{10}$ copies/mL).
[b]Least squares mean and 95% CI were from MMRM with baseline infectious viral titer and randomization strata as covariates. Infectious viral titer was assessed on SARS-CoV-2 nasal swab samples with viral RNA copy number ≥10$^5$ copies/mL. In participants with a positive infectious viral titer at baseline, additional testing was conducted on postbaseline samples if Day 3 or Day 5 swab samples were available, independent of viral RNA copy number value. If Day 3 or Day 5 samples were available, Day 10 sample was also tested, if available. A value of 100 PFU/mL (half of the limit of quantitation [200 PFU/mL]) was used to calculate descriptive statistics if the datum was reported as "<200 PFU/mL" and the corresponding qualitative result was "Positive." A value of 50 PFU/mL (1/4 of the limit of quantitation [200 PFU/mL]) was used to calculate descriptive statistics if the datum was reported as "<200 PFU/mL" and the corresponding qualitative result was "Negative."
[c]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.
LLOQ, lower limit of quantitation; MMRM, mixed-effects model repeated measures; ODV, obeldesivir; PFU, plaque-forming unit.

- Additionally, among those participants with a baseline infectious viral titer ≥200 PFU/mL and tested on Day 3 or Day 5, a greater proportion in the ODV group versus the placebo group had negative SARS-CoV-2 nasal swab infectious viral titer at Day 3 and Day 5 (**Figure 3**)

**Figure 3. Proportion of Participants With Negative SARS-CoV-2 Nasal Swab Infectious Viral Titer With Value ≥200 PFU/mL at Baseline and Tested on Day 3 or Day 5 (Virology Analysis Set[a])**




| Participants With Negative Infectious Viral Titer, n (%) | ODV (n = 69) | Placebo (n = 70) | Nominal $P$ Value |
|---|---|---|---|
| Baseline | 0/69 | 0/70 | N/A |
| Day 3 | 35/44 (80) | 18/37 (49) | 0.005 |
| Day 5 | 67/67 (100) | 56/69 (81) | <0.001 |
| Day 10 | 47/49 (96) | 40/41 (98) | 1.000 |

$P$ values were from the Fisher's exact test. * indicates significant difference from placebo with $P$ <0.01. ** indicates significant difference from placebo with $P$ <0.001. Baseline was the last available value recorded on or prior to the first dosing date of study drug. Infectious viral titer was assessed on SARS-CoV-2 nasal swab samples with viral RNA copy number ≥10$^5$ copies/mL. In participants with a positive infectious viral status at baseline, additional testing was conducted on postbaseline samples if Day 3 or Day 5 swab samples were available, independent of viral RNA copy number value. If Day 3 or Day 5 samples were available, Day 10 sample was also tested, if available.
[a]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 above the LLOQ.
LLOQ, lower limit of quantitation; N/A, not applicable; ODV, obeldesivir.

### Safety

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

**Table 2. Incidence of Treatment-emergent AEs and Most Common (≥5 Participants) Treatment-emergent AEs by Preferred Term (Safety Analysis Set[a])**

| n (%) | ODV (n = 234) | Placebo (n = 231) | Total (n = 465) |
|---|---|---|---|
| Any AE | 52 (22) | 48 (21) | 100 (22) |
| Grade ≥3 AE | 7 (3) | 3 (1) | 10 (2) |
| AE related to study drug | 14 (6) | 11 (5) | 25 (5) |
| Grade ≥3 AE related to study drug | 1 (<1) | 1 (<1) | 2 (<1) |
| Serious AE | 2 (1) | 2 (1) | 4 (1) |
| Serious AE related to study drug | 1 (<1) | 1 (<1) | 2 (<1) |
| AE leading to premature discontinuation of study drug | 4 (2) | 2 (1) | 6 (1) |
| Death | 0 | 1 (<1) | 1 (<1) |
| AEs by preferred term | | | |
| Diarrhea | 10 (4) | 5 (2) | 15 (3) |
| Nausea | 5 (2) | 5 (2) | 10 (2) |
| Headache | 2 (1) | 7 (3) | 9 (2) |
| Fatigue | 2 (1) | 4 (2) | 6 (1) |
| Cough | 2 (1) | 3 (1) | 5 (1) |

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).
[a]Safety analysis set included participants who were randomized and received ≥1 dose of study drug.
AE, adverse event; ODV, obeldesivir.


**References:** **1.** Dessie ZG, Zewotir T. *BMC Infect Dis.* 2021;21:855. **2.** Centers for Disease Control and Prevention. Underlying conditions and the higher risk for severe COVID-19. Accessed July 30, 2024. https://www.cdc.gov/covid/hcp/clinical-care/underlying-conditions.html. **3.** Kompaniyets L, et al. *Prev Chronic Dis.* 2021;18:E66. **4.** Gottlieb RL, et al. *N Engl J Med.* 2022;386:305-15. **5.** Hammond J, et al. *N Engl J Med.* 2022;386:1397-408. **6.** Mackman RL, et al. *J Med Chem.* 2023;66:11701-17. **7.** Anoshchenko O, et al. *Clin Pharmacol Ther.* Published online June 28, 2024. doi:10.1002/cpt.3337. **8.** Rodriguez L, et al. Presented at: IDWeek; October 11-15, 2023; Boston, MA, USA. Poster 545. **9.** Amini E, et al. *Open Forum Infect Dis.* 2023;10:ofad500.574. **10.** Peng CC, et al. Presented at: 34th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 27-30, 2024; Barcelona, Spain. Poster 03881.



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