



Safety and Efficacy of Vidofludimus Calcium in Patients Hospitalized with COVID-19: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Trial

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ABSTRACT

Introduction: Vidofludimus calcium has shown anti-inflammatory effects in clinical trials of autoimmune diseases and recently demonstrated antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We performed a double-blind, randomized, placebo-controlled, phase 2 trial to evaluate the safety and efficacy of vidofludimus calcium in patients hospitalized for coronavirus disease 2019 (COVID-19) in Europe and the USA.

Methods: Patients aged 18 years or older who positive for COVID-19 were randomized (1:1) to receive placebo or 45 mg vidofludimus calcium for 14 days with both groups receiving

standard-of-care treatment. The primary endpoint was the need for invasive ventilation after 28 days (ClinicalTrials.gov NCT04379271; EudraCT 2020-001264-28).

Results: Between June 12, 2020 and December 10, 2020, a total of 223 were randomized to receive either placebo ($n = 112$) or vidofludimus calcium ($n = 111$); three patients withdrew consent and were not treated. Eight (9%) patients in the placebo group and 12 (11%) patients in the vidofludimus calcium group needed invasive ventilation during the 28-day study period, which was lower than the assumed rate of 40%. Time to clinical improvement was shorter by approximately 1 day in the vidofludimus calcium group (15.0 days [90% CI 14.8–15.9]) compared to the placebo group (15.9 days [90% CI 14.9–19.9]). This effect was greatest in patients who initiated therapy within 9 days of symptom onset (3.8 days shorter in the vidofludimus calcium group).

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Higher trough concentrations of vidofludimus calcium were associated with quicker time to clinical recovery. The rate and timing of appearance of anti-SARS-CoV-2 antibodies were not different between groups. Serious adverse events occurred in 4 (4%) patients in the placebo group and 2 (2%) patients in the vidofludimus calcium group; treatment-emergent adverse events of increased severity related to COVID-19 occurred in 13 (12%) patients in the placebo group and 8 (7%) patients in the vidofludimus calcium group. Overall mortality was low (2%).

Conclusions: These findings support vidofludimus calcium being safe and well tolerated in patients with COVID-19.

Keywords: COVID-19; Dihydroorotate dehydrogenase inhibitor; Vidofludimus calcium

Key Summary Points

Why carry out this study?

Novel antiviral therapies are needed to reduce morbidity associated with COVID-19.

This study was the first to investigate the safety and efficacy of a dihydroorotate dehydrogenase (DHODH) inhibitor in patients hospitalized for COVID-19.

What was learned from the study?

Vidofludimus calcium was safe and showed clinical antiviral activity while preserving SARS-CoV-2 humoral response in patients hospitalized for COVID-19.

Further studies, especially during the early viral replication cycle, are warranted to assess clinical efficacy of vidofludimus calcium to treat COVID-19.

INTRODUCTION

Drugs targeting viral entry/replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or that target the immune system to treat coronavirus disease 2019 (COVID-19) have been studied in large randomized trials [1–6]. Targeting antiviral replication in combination with immunomodulation has been speculated as more efficacious to treat COVID-19 than either approach alone [7–9].

Vidofludimus calcium is a highly selective inhibitor of dihydroorotate dehydrogenase (DHODH), an enzyme involved in the rate-limiting step of de novo pyrimidine biosynthesis that is expressed in highly active cells (e.g., metabolically activated lymphocytes) to satisfy their elevated need for pyrimidines. Viruses likewise utilize host DHODH to meet their ribonucleic acid (RNA) demands during replication since the pyrimidine pool cannot be met by DHODH-independent salvage pathway(s) alone, making DHODH a promising therapeutic target against viral infection including SARS-CoV-2 [10–14]. This is supported by in vitro data showing vidofludimus calcium exhibited low micromolar potency against SARS-CoV-2 activity in vitro [14]. Targeting a viral-independent target may have the additional benefit of maintaining efficacy against SARS-CoV-2 variants, which has become an increasingly important therapeutic need given the emergence of highly virulent variants such as delta and omicron. DHODH inhibition also has innate and adaptive immunomodulatory effects by upregulating interferon-inducible antiviral genes [15, 16]. Vidofludimus calcium reduces T cell proliferation and cytokine production in models of autoimmunity, suggesting that hyperinflammation often linked to moderate-to-severe COVID-19 could be diminished through blockade of

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DHODH [17, 18]. The efficacy of vidofludimus calcium to treat autoimmune disease from the phase 2 EMPHASIS trial in patients with multiple sclerosis is consistent with this hypothesis. The clinical safety of vidofludimus calcium has been studied in over 800 healthy volunteers or patients with immune-related conditions to date with a safety and tolerability profile generally similar to placebo [19–22].

Here we report the results from a phase 2, multicenter, double-blind, randomized, placebo-controlled trial (CALVID-1) that investigated the safety and efficacy of vidofludimus calcium plus standard-of-care compared to placebo plus standard-of-care in patients hospitalized with COVID-19.

METHODS

Study Design and Participants

The CALVID-1 trial was a multicenter, double-blind, randomized, placebo-controlled trial conducted in Bulgaria, Germany, Greece, Hungary, Moldova, North Macedonia, Romania, Ukraine, and the USA. Participants were enrolled from June 12, 2020 to December 10, 2020. The study consisted of two parts: a phase 2 study (part 1) with the option to continue enrollment into a confirmatory phase 3 study (part 2). The data presented here describe part 1.

Participants aged 18 years or older who were positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) within 4 days of randomization and who were hospitalized for moderate COVID-19 were eligible for the study. Moderate COVID-19 was defined as fulfilling clinical status category 3 or 4 on the World Health Organization (WHO) 9-point ordinal scale [23]. Additional inclusion criteria included the presence of at least one symptom characteristic for COVID-19 (i.e., fever, cough, or respiratory distress). Key exclusion criteria were the inability to take drugs orally, pre-existing end-stage liver disease, acute or clinically relevant chronic renal failure, clinically relevant conditions leading to hyperuricemia, and a history or presence of serious or acute heart disease. Concomitant use of steroids was not

prohibited although recommended to be reserved for patients with developing severe disease or with special circumstances (e.g., underlying diseases requiring treatment). A list of the full inclusion and exclusion criteria, including prohibited medications, is provided in the Supplemental Materials.

Randomization and Blinding

Participants were randomly assigned (1:1) to receive twice daily oral 22.5 mg vidofludimus calcium (i.e., 45 mg per day) or placebo, with both treatment arms allowing standard-of-care treatment. Randomization was done using an interactive web-based response system (IWRS) and stratified by age (less than 65 years or 65 years and older) and antiviral therapy (no antiviral therapy or any concomitant antiviral therapy at randomization).

Participants, study investigators, and all other personnel directly involved in the conduct of the trial were blinded to the individual treatment assignments during the 28-day study period. Two unblinded safety analyses were performed and evaluated by an unblinded Independent Data Monitoring Committee (IDMC) after 30 participants and 60 participants, respectively, to identify treatment-emergent adverse events and serious adverse events.

Study Procedures

At enrollment, standard clinical assessments and laboratory assessments were conducted (see Supplementary Materials). SARS-CoV-2 titers, SARS-CoV-2 antibodies, and disease markers were also collected.

On day 1, participants took 45 mg vidofludimus calcium or placebo as a single dose; participants then took 45 mg vidofludimus calcium twice daily (22.5 mg BID, once in the morning and once in the evening) or placebo for an additional 13 days (14 total days of treatment). All participants received standard-of-care consistent with each trial site and local guidance. Continuous monitoring of clinical assessments occurred once or twice daily until the last day of treatment (day 14) and at a follow-up visit

(day 28). In case of hospital discharge before day 14, patients returned for clinic visit(s) at day 6 and/or day 14 but were allowed to skip other visits after released from hospitalization. A list of all assessments and a schedule of activities are provided in the Supplemental Materials. To assess change in patient symptoms (i.e., fatigue) at and after hospital discharge and following the end of the study, a questionnaire was completed by blinded investigators at the three highest enrolling sites in Ukraine. This was a post hoc analysis performed before unblinding of the sponsor, study participants, and investigators.

Adverse events were recorded and analyzed from the time of written informed consent until the end of the safety follow-up period (day 60) and assessed for relatedness and severity according to the National (US) Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. Treatment-emergent adverse events (TEAEs) were defined as any event not present prior to the first intake of study drug or any event already present that worsened in either intensity or frequency following study drug exposure.

Study Outcomes

The primary endpoint was the proportion of patients without a need for invasive ventilation until day 28 (as defined in the Supplementary Materials). Key secondary efficacy endpoints were the proportion of surviving patients without respiratory failure, the duration of hospitalization in the intensive care unit (ICU), and 28-day all-cause mortality. Other secondary efficacy endpoints included clinical status, renal impairment, oxygenation, hospitalization, concomitant vasoactive treatments, and clinical recovery. The effects of vidofludimus calcium on disease, virologic, and serological markers were also analyzed.

The intention-to-treat population consisted of all randomized patients who received at least one dose of vidofludimus calcium or placebo and were analyzed by the groups to which they were randomized to. The safety population consisted of all randomized patients who received at least one dose of vidofludimus calcium or placebo and were analyzed by the

treatment they received. The modified intention-to-treat population consisted of the intention-to-treat population with at least one positive SARS-CoV-2 test from the central laboratory. The per-protocol population consisted of the intention-to-treat population and those who did not violate major protocol criteria, were not incorrectly allocated to their respective treatment group, were not lost to follow-up or discontinued prior to day 14, or had no confirmed positive SARS-CoV-2 status post baseline.

Statistical Analysis

For the primary endpoint, the proportion of patients without a need for invasive ventilation until day 28 was calculated; patients who were lost to follow-up or discontinued the trial on or before day 13 (last treatment day) because of any other reason than death, and discontinued with a last observed WHO clinical status no lower than that at screening, and patients who died before day 28 were considered to have a need for invasive ventilation. The odds ratio with an exact two-sided 90% confidence interval (CI) was calculated taking adjustment for the stratification factors age (less than 65 years or 65 years and older) and antiviral therapy (no antivirals, hydroxychloroquine and chloroquine, all other antivirals) into account. The same procedure was performed to calculate the proportion (and corresponding 90% CI) of surviving patients without respiratory failure. For the duration of intensive care unit stay, a two-sided 90% confidence interval for the median of differences between treatment groups (location shift) was calculated. Kaplan–Meier procedures were conducted for time to event and correlation analyses (e.g., time to clinical improvement, time to clinical recovery, correlation between vidofludimus calcium trough concentrations and outcomes, etc.). In centers in Bulgaria, patients were required to remain hospitalized during the entire treatment period (day 0 to day 14) per hospital policy and were therefore excluded from analyses that used a derived WHO score.

All endpoints were analyzed descriptively and no formal hypothesis testing was conducted. Thus, no sample size calculation was conducted. In a previous version of the protocol, a pooling of

p values for parts 1 and 2 was planned with an adaptive design and required a sample size of 200 participants, applying an overall information rate of 20% for the interim analysis after part 1. Using a three-stage group sequential test design with O'Brien and Fleming shaped boundaries and assuming a one-sided $\alpha = 0.05$, a difference in proportion of patients with a need for invasive ventilation of 8% (40% in the placebo group and 32% in the vidofludimus calcium group), and a 6% withdrawal rate, we calculated that approximately 200 patients (100 per group) were required for 80% power on the primary endpoint. Following regulatory guidance, the pooled adaptive design of parts 1 and 2 was later withdrawn but the previously planned sample size of 200 was assumed to provide a robust estimation of all efficacy and safety parameters for part 1 and therefore a change to the sample size was not considered necessary.

Ethical Review and Funding Source

Trial conduct was consistent with all applicable regulatory authorities and international regulations including International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki (1996) in addition to applicable local laws and regulations. The study protocol and amendments were reviewed by institutional review boards/independent ethics committees. An IDMC safeguarded the interests of trial participants and provided recommendations on trial conduct, sample size, and safety. The IDMC also fulfilled the role of the Data Safety Monitoring Board. All participants provided written consent prior to the conduct of any trial-related procedures. The study is registered with ClinicalTrials.gov (NCT04379271) and EudraCT (2020-001264-28).

RESULTS

Participant Disposition, Demographics, and Baseline Clinical Characteristics

Of 234 patients assessed for eligibility, 223 were randomized to receive either placebo plus

standard-of-care ($n = 112$) or vidofludimus calcium plus standard-of-care ($n = 111$). Three patients in total withdrew consent and were not treated ($n = 2$ in the placebo group and $n = 1$ in the vidofludimus calcium group). A total of 220 patients received at least one dose of placebo or vidofludimus calcium which made up the intention-to-treat and safety populations (Fig. 1); 190 patients (86%) completed the study and study completion rates were similar between placebo-treated patients ($n = 97$ [88%]) and vidofludimus calcium-treated patients ($n = 93$ [85%]). Premature study discontinuations were also similar between placebo-treated patients ($n = 13$ [12%]) and vidofludimus calcium-treated patients ($n = 17$ [15%]). The most common reason for study discontinuation was withdrawal of consent for any reason ($n = 18$ [8%]). Five patients (2%) withdrew because of an adverse event or a COVID-19-related adverse event and four patients (2%) died during the study.

Baseline demographics and clinical characteristics were generally similar between both groups (Table 1). The study population was predominately White (99%) with a mean age of 53.7 and 54.5 for placebo- and vidofludimus-treated patients, respectively. The vidofludimus calcium group had slightly more women (50%) compared to the placebo group (42%). In addition, the prevalence of pre-existing cardiovascular disease, a risk factor for COVID-19-related respiratory failure, was the most frequently reported risk factor in both treatment groups and was higher in the vidofludimus calcium group (52%) compared to the placebo group (43%).

Standard-of-Care Therapy

Standard-of-care therapy was similar between both groups, with 71 (65%) and 69 (63%) of patients receiving systemic corticosteroid therapy in the placebo and vidofludimus calcium groups, respectively. At randomization, 15 (14%) and 16 (15%) patients were on antiviral therapy in the placebo and vidofludimus calcium groups, which increased to 41 (37%) and

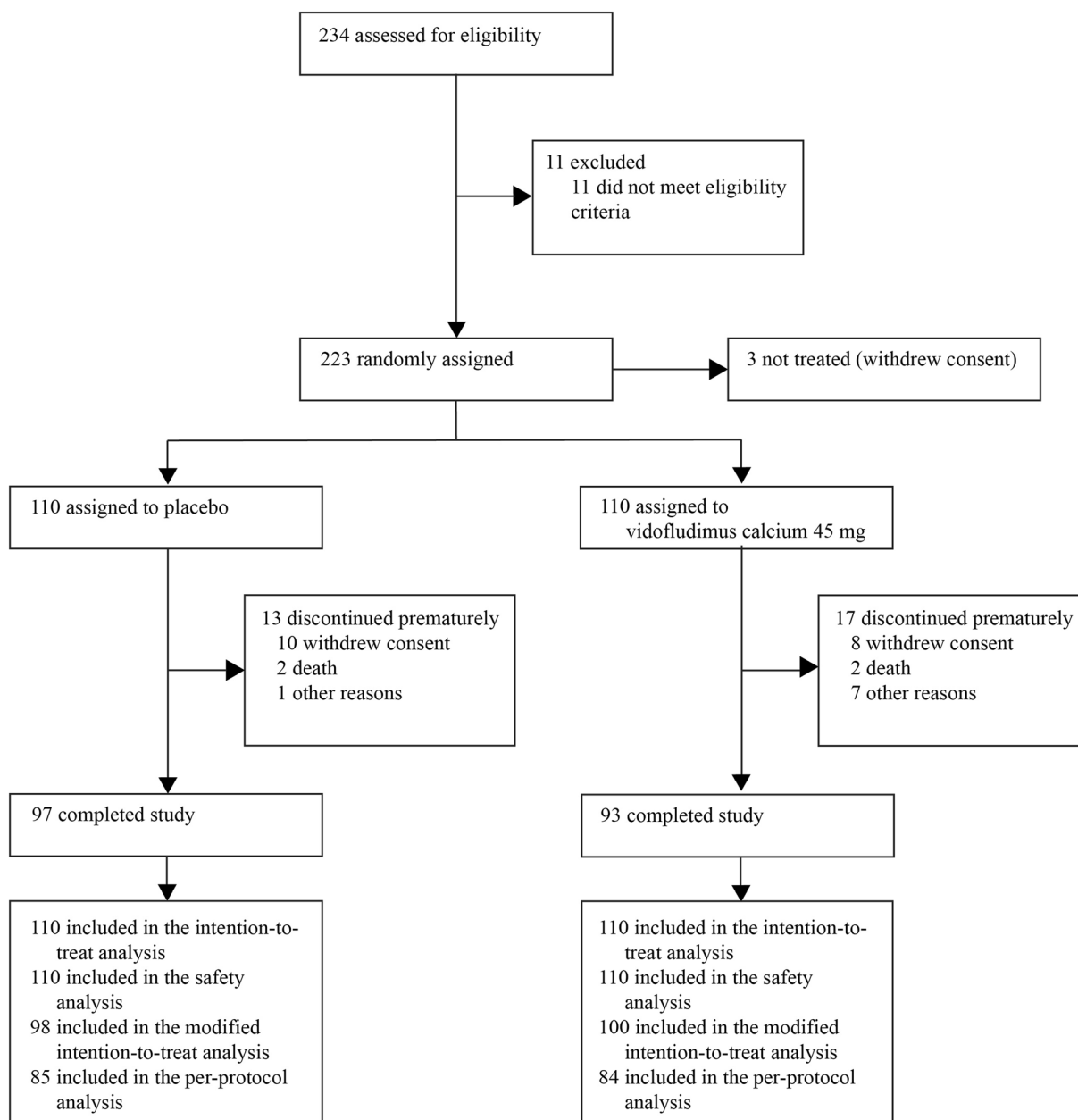


Fig. 1 CONSORT diagram

36 (33%) during the study as part of standard-of-care therapy, respectively (Table 1).

Primary and Key Secondary Efficacy Outcomes

The actual observed number of patients receiving invasive ventilation was 6 (5%) in the

placebo group and 6 (5%) in the vidofludimus calcium group during the 28-day study period. With imputation, 8 (9%) patients in the placebo group and 12 (11%) patients in the vidofludimus calcium group were recorded as requiring invasive ventilation. The observed need for invasive ventilation was substantially lower than the anticipated frequencies of 32% and 40% reported during early studies of

Table 1 Baseline demographics and clinical characteristics

	Placebo (<i>n</i> = 110)	Vidofludimus calcium (<i>n</i> = 110)
Age, years	53.7 (20–85)	54.5 (24–83)
Female	46 (42%)	55 (50%)
Race		
White	107 (97%)	110 (100%)
Black	1 (1%)	0
Asian	1 (1%)	0
Other	1 (1%)	0
BMI, kg/m ²	28.3 (19.5–46.9)	29.3 (19.5–46.9)
Risk factor for respiratory failure		
≥ 65 years	26 (24%)	27 (25%)
Cardiovascular disease	47 (43%)	57 (52%)
Immunosuppressive therapy ^a	1 (1%)	3 (3%)
Diabetes	20 (18%)	19 (17%)
Malignancy	1 (1%)	1 (1%)
Immunodeficiency	0	0
Pre-existing pulmonary disease	8 (7%)	8 (7%)
Time since first COVID-19 symptoms, days		
≤ 9	65 (59%)	68 (62%)
> 9	41 (37%)	41 (37%)
Unknown	4 (4%)	1 (1%)
Antiviral therapy at randomization	16 (15%)	15 (14%)
COVID-19 standard-of-care therapy		
Systemic corticosteroids ^b	71 (65%)	69 (63%)
Current or recent immunosuppressive therapy	1 (1%)	3 (3%)
Disease markers ^c		
CRP (nmol/L)	4.5 (5.2)	4.6 (5.0)
IL-6 (ng/L)	5.1 (6.5)	6.2 (8.3)
D-dimer (ng/L)	654 (787)	971 (2070)

Data are presented as *n* (%) or mean (range)

CRP C-reactive protein, IL-6 interleukin-6

^aCurrent or recent therapy

^bIncludes dexamethasone

^cPresented as mean (standard deviation)

patients hospitalized with COVID-19 [24]. Given that the rate of invasive ventilation was substantially lower than assumed, hypothesis testing was not conducted for the primary endpoint or any secondary endpoint and are reported descriptively. The effect of sex on clinical outcomes was also not analyzed for this reason.

For the key secondary endpoint, the actual number of patients who survived, but experienced respiratory failure, defined as ICU admission, need for invasive ventilation or high-flow oxygen, or extracorporeal membrane oxygenation (ECMO), during the 28-day study period was similar between placebo-treated patients (7 [6%]) and vidofludimus calcium-treated patients (7 [6%]). With imputation, the numbers of patients meeting these criteria were 11 (10%) and 14 (13%) in the placebo and vidofludimus calcium group, respectively. Nine patients (5 [5%] in the placebo group and 4 [4%] in the vidofludimus calcium group) were admitted to the intensive care unit during the trial. The mean duration of time in the intensive care unit was also similar between both groups (2.33 days in the placebo group and 2.54 days in the vidofludimus calcium group). Without imputation, the actual observed mean duration of time in the intensive care unit was 0.6 days in the placebo group and 0.4 days in the vidofludimus calcium group.

Death was confirmed in four patients during the study ($n = 2$ [2%] in the placebo group and $n = 2$ [2%] in the vidofludimus calcium group). The per-protocol definition of all-cause mortality occurred in 8 (7%) patients in the placebo group and 9 (8%) patients in the vidofludimus calcium group. These numbers included patients for whom an outcome at the end of the trial could not be determined or was not available and were considered to have died in the intention-to-treat all-cause mortality analysis. Other secondary efficacy outcomes are listed in the Supplementary Material.

Other Efficacy Endpoints

Estimates for endpoints including hospitalization duration/status are reported as the 50th

percentile (median) and the 75th percentile. The study's design of (1) requiring in-person visit at day 14 independent of hospitalization status and (2) requiring to hospitalize patients for a minimum of 14 days in some countries introduced bias as evidenced by a disproportional amount of patients that were released from the hospital on day 14. This suggested that the investigator's decision regarding hospitalization was made on day 14 and was driven more by convenience than patient need; therefore, endpoints including hospitalization duration/status are better interpreted after day 14. Fourteen days was the median duration of hospitalization in both treatment arms but at the 75% percentile, duration of hospitalization was shorter for vidofludimus calcium-treated patients (15.9 days) compared to placebo-treated patients (19.0 days).

While the median time to clinical improvement was similar between placebo- and vidofludimus calcium-treated patients in the intention-to-treat population (13.8 vs. 13.9 days, respectively), time to clinical improvement at the 75% percentile was shorter by approximately 1 day in the vidofludimus group (15.0 days [90% CI 14.8–15.9]) compared to the placebo group (15.9 days [90% CI 14.9–19.9]). This observation was consistent in patients with at least one risk factor for respiratory failure and those who were at least 65 years of age (Table 2). The largest effect favoring patients treated with vidofludimus calcium was seen in patients who received therapy within 9 days of COVID-19 symptom onset as compared to those patients who started therapy later (Table 2). When we assessed the proportion of patients with clinical improvement, more patients treated with vidofludimus calcium achieved early clinical improvement at day 14 (44/99 [44%]) compared to placebo (39/97 [40%]) and was near complete at day 28 in both groups (placebo, 93/97 [96%]; vidofludimus calcium, 95/97 [98%]).

A similar proportion of patients in the vidofludimus calcium group achieved clinical recovery at day 28 (61/88 [69%]) compared to the placebo group (61/93 [66%]). Kaplan–Meier analysis showed that higher trough concentrations of vidofludimus calcium were associated with quicker time to clinical recovery (Fig. 2c).

No consistent effect of trough concentration was observed between time to negative SARS-CoV-2 status or time to clinical improvement (Supplementary Material).

Virological, Immunological, and Disease Markers

SARS-CoV-2 viral load decreased over time during the trial (Supplementary Material). At

Table 2 Time to clinical improvement according to percentile

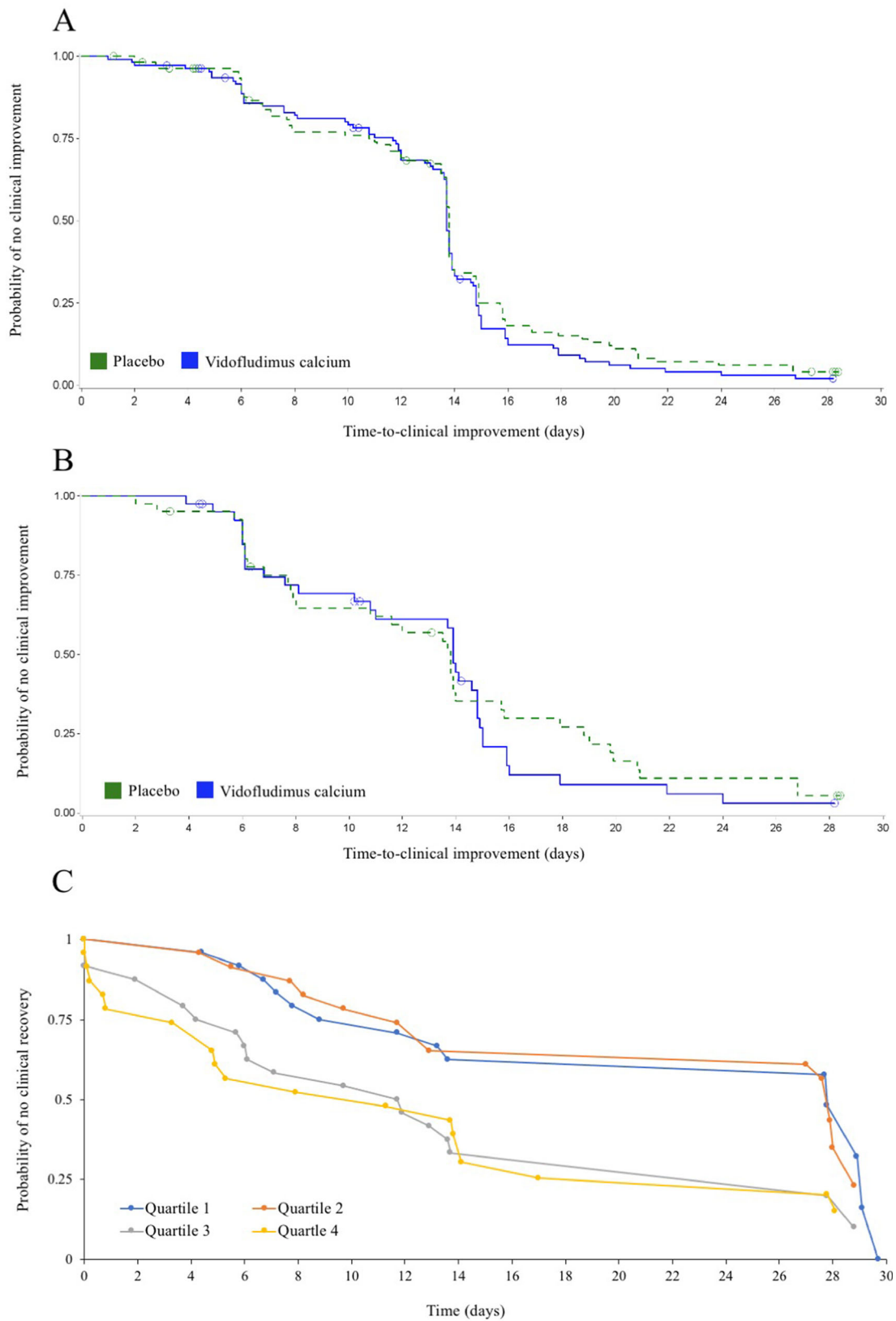
	Time to clinical improvement [†]	
	50% (90% CI)	75% (90% CI)
All patients		
Placebo (<i>n</i> = 74), days	13.8 (12.0–14.9)	15.9 (14.9–19.9)
Vidofludimus calcium (<i>n</i> = 70), days	13.9 (13.6–14.1)	15.0 (14.8–15.9)
Difference, days	– 0.1	0.9
Patients with at least 1 risk factor for respiratory failure*		
Placebo (<i>n</i> = 45), days	13.7 (8.0–13.9)	17.9 (13.9–19.9)
Vidofludimus calcium (<i>n</i> = 46), days	13.9 (10.8–14.6)	15.0 (14.6–16.0)
Difference, days	– 0.2	2.9
Patients ≥ 65 years		
Placebo (<i>n</i> = 19), days	13.9 (13.5–15.8)	18.8 (14.0–NE)
Vidofludimus calcium (<i>n</i> = 19), days	14.8 (13.7–14.9)	15.0 (14.8–24.0)
Difference, days	– 0.9	3.8
Patients receiving concomitant antiviral therapy		
Placebo (<i>n</i> = 20), days	13.5 (10.8–13.8)	15.7 (13.6–21.6)
Vidofludimus calcium (<i>n</i> = 17), days	13.7 (7.6–14.8)	14.8 (13.7–24.0)
Difference, days	– 0.2	0.9
Start of treatment ≤ 9 days of first symptoms [‡]		
Placebo (<i>n</i> = 40), days	14.9 (13.8–15.8)	19.8 (15.8–23.9)
Vidofludimus calcium (<i>n</i> = 43), days	13.9 (13.7–14.9)	15.9 (14.9–18.9)
Difference, days	1.0	3.9

NE not estimable

*Risk factors were age ≥ 65, cardiovascular disease (including hypertension), pre-existing pulmonary disease, diabetes, malignancy, medical condition leading to immunodeficiency, current or recent (within 3 months) immunosuppressive treatment

[†]Clinical improvement was defined as an at least 2-point improvement on the WHO 9 category ordinal scale (as assessed by the investigator), or live discharge from hospital without oxygen supplementation, whichever comes first. Patients in Bulgaria had a fixed hospitalization period of a minimum of 14 days as requested by their local regulatory agency. For that reason, patients in Bulgaria are not included in the assessment of clinical improvement (placebo *n* = 33 and vidofludimus calcium *n* = 37)

[‡]Modified intention-to-treat analysis



◀**Fig. 2** Time to clinical improvement in the intention-to-treat analysis (a), in patients with at least one risk factor for respiratory failure (b), and association between plasma trough vidofludimus calcium concentration at day 6 and clinical recovery (c). Risk factors were age 65 years and older, cardiovascular disease (including hypertension), pre-existing pulmonary disease, diabetes, malignancy, medical condition leading to immunodeficiency, current or recent (within 3 months) immunosuppressive treatment. Clinical improvement was defined as an at least 2-point improvement on the WHO 9-category ordinal scale (as assessed by the investigator), or live discharge from hospital without oxygen supplementation, whichever comes first. Patients in Bulgaria had a fixed hospitalization period of a minimum of 14 days as requested by their local regulatory agency. For that reason, patients in Bulgaria are not included in the assessment of clinical improvement (placebo $n = 33$ and vidofludimus calcium $n = 37$). Quartile 1, $< 2.6 \mu\text{g/mL}$; quartile 2, $2.6\text{--}4.0 \mu\text{g/mL}$; quartile 3, $4.0\text{--}5.5 \mu\text{g/mL}$; quartile 4, $\geq 5.5 \mu\text{g/mL}$

day 28, 57% (57/100) of the patients in the vidofludimus calcium group and 61% (60/98) of the patients in the placebo group were negative for SARS-CoV-2 using nasopharyngeal samples analyzed by the central laboratory. By day 6, more than 80% of all patients had developed IgA and/or IgG antibodies for SARS-CoV-2, which increased to almost all patients by day 28 (Fig. 3). The rate and timing of appearance of IgA and IgG antibodies were not markedly different between treatment groups (Table 3).

Fatigue

Three investigator sites with an overall enrollment of 36 patients were able to evaluate 27 patients (15 in the placebo group and 12 in the vidofludimus calcium group) for long-term fatigue. At hospital discharge, 12 (80%) patients who received placebo reported fatigue compared to 6 (50%) patients in the vidofludimus calcium group. Fatigue decreased in both groups 9–17 weeks after hospital discharge (5 [33%] in placebo and 2 [17%] in vidofludimus calcium groups).

Safety Outcomes

Safety outcomes are summarized in Table 4. Of 560 adverse events affecting 150 (68%) patients in the safety population ($n = 220$), 69 (63%) and 81 (74%) patients experienced any adverse event in the placebo and vidofludimus calcium group, respectively. Although the rate of patients that experienced any treatment-emergent adverse event was slightly higher in vidofludimus calcium-treated patients (81 [74%]) than placebo-treated patients (68 [62%]), the number of serious adverse events was low; seven adverse events, occurring in 4 (4%) patients of the placebo group and 2 (2%) of the vidofludimus calcium group, were considered serious (Supplementary Materials). No serious adverse event was considered related to study treatment.

Most treatment-emergent adverse events were mild or moderate; the incidence of grade 3 or greater treatment-emergent adverse events were similar for the placebo and vidofludimus calcium group (10 [9%] and 7 [6%], respectively). The most frequently reported treatment-emergent adverse event was hypertriglyceridemia (12% for placebo and 21% for vidofludimus calcium), increased glycosylated hemoglobin (6% for placebo and 9% for vidofludimus calcium), hyperglycemia (7% for placebo and 5% for vidofludimus calcium), and headache (5% for placebo and 7% for vidofludimus calcium). Any treatment-emergent adverse event leading to withdrawal of study treatment was similar between placebo (2 [3%]) and vidofludimus calcium (3 [3%]) group. Relatedness of treatment-emergent adverse events to the study treatment is summarized in the Supplementary Materials. The total number of treatment-emergent adverse events of increased severity related to COVID-19 was lower in the vidofludimus calcium group (10) compared to the placebo group (17) and are summarized in Table 5. Other safety outcomes including concomitant infections, hepatic events, and hematological adverse events are described in the Supplementary Materials.

DISCUSSION

Here we report the first placebo-controlled, randomized phase 2 trial investigating a DHODH inhibitor for the treatment of COVID-19. The number of hospitalized patients who needed invasive ventilation during the 28-day study was low and similar between patients receiving placebo and vidofludimus calcium. When the study was planned, the assumed need for invasive ventilation was 40% based on published data from the first COVID-19 wave [24]. The low event rate in both arms, however, prevents a meaningful interpretation of this endpoint. A similar interpretation was made for key secondary endpoints, which showed an intensive care unit admission rate of less than 5% and a mortality rate of 2%.

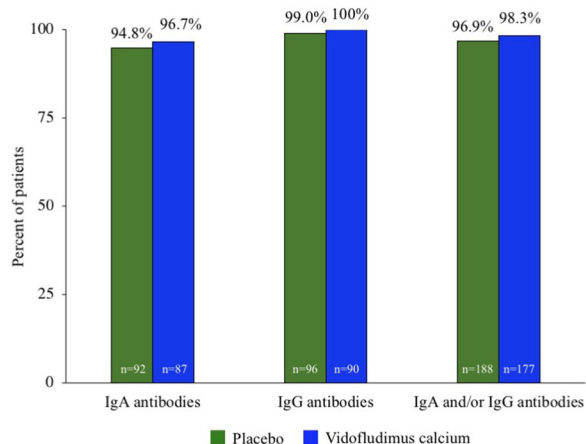


Fig. 3 Percentage of patients who developed IgA antibodies, IgG antibodies, and/or both at day 28. Patients are from the intention-to-treat population who provided evaluable samples at day 28

Despite low rates of invasive ventilation, evidence of clinical activity following vidofludimus calcium treatment was observed. Time to clinical improvement at the 75% percentile was shorter by approximately 1 day in the vidofludimus group compared to the placebo group; a similar difference of approximately 1 day favoring vidofludimus calcium was also observed in patients with at least one risk factor for respiratory failure and in patients at least 65 years of age. The largest difference in time to clinical improvement was in patients who initiated therapy within 9 days of symptom onset (3.8 days shorter in the vidofludimus calcium group). This observation may be explained, in part, by antiviral properties of vidofludimus calcium because direct-acting antivirals, such as molnupiravir and nirmatrelvir, are typically effective when initiated early and/or before hospitalization presumably by limiting viral replication and subsequent disease progression [4, 5]. SARS-CoV-2 viral load decreased during CALVID-1 but was not notably different between both groups so it is unclear whether the effect of vidofludimus calcium on clinical improvement was mechanistically driven by its antiviral or anti-inflammatory properties, or both. Thirty-five percent of patients received antiviral therapy as part of standard-of-care during the study with no identifiable effect on any efficacy endpoint. Shortening time to clinical improvement by approximately 1–4 days appears to be slightly lower or comparable to trials of molnupiravir (4 days) and remdesivir (5 days), although cross-trial comparison is difficult because of differences in study design, timing (e.g., predominant SARS-CoV-2 strain when the study was conducted), and baseline clinical severity of the study population [25, 26].

Table 3 Percentage of patients with anti-SARS-CoV-2 IgA or IgG antibodies

	Day 6		Day 14		Day 28	
	IgA (%)	IgG (%)	IgA (%)	IgG (%)	IgA (%)	IgG (%)
Placebo	84	88	94	94	97	99
Vidofludimus calcium	86	93	97	97	95	100

Table 4 Summary of adverse events (intention-to-treat population)

	Placebo (<i>n</i> = 110)	Vidofludimus calcium (<i>n</i> = 110)
Any adverse event	69 (63%)	81 (74%)
Any serious adverse event	4 (4%)	2 (2%)
Any treatment-emergent adverse event	68 (62%)	81 (74%)
Any treatment-emergent adverse event grade \geq 3	10 (9%)	7 (6%)
Any treatment-emergent adverse event \geq 5% in any treatment group by preferred term		
Hypertriglyceridemia	13 (12%)	23 (21%)
Hyperglycemia	8 (7%)	5 (5%)
Bradycardia	7 (7%)	4 (3%)
Hepatocellular injury	7 (6%)	3 (3%)
Anemia	6 (6%)	4 (4%)
Alanine aminotransferase increased	6 (6%)	5 (5%)
Glycosylated hemoglobin increased	6 (6%)	10 (9%)
Sinus bradycardia	5 (5%)	6 (6%)
Headache	5 (5%)	8 (7%)
Hematuria	4 (4%)	7 (6%)
Hypertension	4 (4%)	6 (6%)
Hypertensive crisis	3 (3%)	6 (6%)
Tachycardia	2 (2%)	7 (6%)

Data are presented as *n* (%)

Patients with higher vidofludimus calcium plasma concentrations recovered quicker, suggesting a concentration–effect relationship as shown in Fig. 2c. A 45-mg dose of vidofludimus calcium was selected on the basis of available in vitro and clinical data. Serum trough concentrations following a 20-mg dose is approximately equivalent to the in vitro IC₅₀ of cytokine release in human lymphocytes with active doses between 20 and 45 mg observed in clinical trials to treat autoimmune diseases [17, 21, 27, 28]. Evaluation at other doses may be helpful to better define a concentration–effect relationship, which is supported by an encouraging safety and tolerability profile observed in the present study and in phase 1 repeat-dose studies of up to 50 mg [27].

Vidofludimus calcium was well tolerated: although a slightly lower proportion of placebo-treated patients (62%) experienced a treatment-emergent adverse event compared to vidofludimus calcium-treated patients (74%), premature study discontinuations for any reason (12% and 16%, respectively) or related to the study treatment (2% and 3%, respectively) were similar between both groups. Likewise, treatment-emergent adverse events of grade 3 or higher and serious adverse events were low and comparable between both groups consistent with other trials of vidofludimus calcium [28]. Hypertriglyceridemia occurred more frequently in the patients treated with vidofludimus calcium compared to placebo although the reason for this observation is not clear.

Table 5 Patients with treatment-emergent adverse events of increased severity related to COVID-19 (intention-to-treat population)

	Placebo (<i>n</i> = 110)	Vidofludimus calcium (<i>n</i> = 110)
Total	13 (12%)	8 (7%)
Cardiac disorders		
Bradycardia	2 (2%)	1 (1%)
General disorders and administration site conditions		
Pyrexia	4 (4%)	1 (1%)
Infections and infestations		
COVID-19	1 (1%)	1 (1%)
COVID-19 pneumonia	4 (4%)	3 (3%)
Respiratory, thoracic, and mediastinal disorders		
Acute respiratory distress syndrome	0	1 (1%)
Acute respiratory failure	1 (1%)	0
Dyspnea	2 (2%)	2 (2%)
Hypoxia	1 (1%)	1 (1%)
Respiratory distress	1 (1%)	0
Respiratory failure	1 (1%)	0

Data are presented as *n* (%)

Treatment-emergent adverse events of increased severity due to COVID-19 were defined as symptoms present at baseline which continued during the trial, but which worsened in a way which was considered as clinically unusual. Events with severity grade 2 or higher were validated during blind data review

Hypertriglyceridemia has not been associated with DHODH inhibitors, including vidofludimus calcium, so the apparent higher incidence of hypertriglyceridemia in patients treated with vidofludimus calcium is unlikely to be related to inhibition of DHODH [27, 29–32]. All non-published clinical studies investigating vidofludimus calcium also have no reported adverse events of hypertriglyceridemia. Of the 23 adverse events of hypertriglyceridemia occurring in the vidofludimus calcium group, 21 (91%) were mild, 2 (9%) were moderate, and all were considered unrelated to vidofludimus calcium, suggesting that this observation is not clinically significant.

A notable finding in this study is that development and concentrations of anti-SARS-CoV-2 antibodies were not different between

vidofludimus calcium and placebo groups. This implies that vidofludimus calcium can be safely administered without impairing humoral response, and vaccination efficacy is likely maintained after treatment with a DHODH inhibitor [33, 34]. Targeting DHODH could represent an alternative to broad-acting immunosuppressives used in the treatment of patients with COVID-19 that may result in Epstein–Barr viral reactivation and subsequent risks of long COVID-19 symptoms [35]. Vidofludimus calcium was not associated with viral reactivation in CALVID-1 consistent with other clinical trials and has shown antiviral effects against Epstein–Barr virus [36].

There are several limitations associated with this study. As noted earlier, unexpected low rates of invasive ventilation and major

complications in this phase 2 trial prevent adequate interpretation of clinically relevant endpoints in this population of hospitalized patients with non-severe COVID-19. Second, the study design potentially biased efficacy endpoints that included hospitalization status. The study required an in-person day 14 follow-up visit, which may have led to patients remaining hospitalized when close to day 14 whom may have otherwise been discharged. In addition, some countries mandated a minimum of 14 days of hospitalization when admitted for COVID-19. To help adjust for this bias, we reported efficacy endpoints that included hospitalization as the 75th percentile rather than the median. Lastly, increasing data support that antiviral treatments are generally effective when used early during infection [4, 5, 37, 38]. Because CALVID-1 was not designed to intervene during early infection, the efficacy of vidofludimus calcium may be greater in this setting, which is supported by subgroup analysis in patients who initiated therapy within 9 days of symptom onset.

CONCLUSIONS

Vidofludimus calcium was safe and evidence of clinical antiviral activity was observed while preserving SARS-CoV-2 humoral response. Further studies, particularly during the early viral replication cycle, are warranted to assess the efficacy of vidofludimus calcium in patients with COVID-19.

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Compliance with Ethics Guidelines. This study's conduct was consistent with all applicable regulatory authorities and international regulations including International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki (1996) in addition to applicable local laws and regulations. The study protocol and amendments were reviewed by institutional review boards/independent ethics committees. An IDMC safeguarded the interests of trial participants and provided recommendations on trial conduct, sample size, and safety. The Independent Data Monitoring Committee (IDMC) also fulfilled the role of the Data Safety Monitoring Board. All participants provided written consent prior to the conduct of any trial-related procedures.

Data Availability. Data will be shared with qualified researchers who submit a research proposal following approval by an independent review board and a signed data sharing agreement. Requests for data can be made 6 months after the indication studied has been approved in the USA and EU with no expiration date on requests. De-identified data, including the study protocol, statistical analysis plan, clinical study report, and case report forms will be provided in a secure sharing environment.

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REFERENCES

1. Gordan AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491–502.
2. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–45.
3. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med*. 2020;383(24):2333–44.
4. Bernal AJ, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386:509–20.
5. Paxlovid [package insert]. New York: Pfizer; 2021. <https://www.fda.gov/media/155050/download>. Accessed June 30, 2022.
6. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med*. 2020;383(19):1813–26.
7. Feuillet V, Canard B, Trautmann A. Combining antivirals and immunomodulators to fight COVID-19. *Trends Immunol*. 2021;42(1):31.
8. Chen LYC, Quach TTT. Combining immunomodulators and antivirals for COVID-19. *Lancet Microbe*. 2021;2(6): e233.
9. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2021;384(9):795–807.
10. Biron KK, Stanat SC, Sorrell JB, et al. Metabolic activation of the nucleoside analog 9-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]guanine in human diploid fibroblasts infected with human

- cytomegalovirus. *Proc Natl Acad Sci USA*. 1985;82(8):2473.
11. Bonavia A, Franti M, Keaney EP, et al. Identification of broad-spectrum antiviral compounds and assessment of the druggability of their target for efficacy against respiratory syncytial virus (RSV). *Proc Natl Acad Sci USA*. 2011;108(17):6739–44.
 12. Kim YJ, Cubitt B, Cai Y, et al. Novel dihydroorotate dehydrogenase inhibitors with potent interferon-independent antiviral activity against mammarenaviruses in vitro. *Viruses*. 2020;12(8):821.
 13. Xiong R, Zhang L, Li S, et al. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. *Protein Cell*. 2020;11(10):723–39.
 14. Hahn F, Wangen C, Häge S, et al. IMU-838, a developmental DHODH inhibitor in phase II for autoimmune disease, shows anti-SARS-CoV-2 and broad-spectrum antiviral efficacy in vitro. *Viruses*. 2020;12(12):1394.
 15. Lucas-Hourani M, Dauzonne D, Jorda P, et al. Inhibition of pyrimidine biosynthesis pathway suppresses viral growth through innate immunity. *PLoS Pathog*. 2013;9(10): e1003678.
 16. Hayek S, Pietrancosta N, Hovhannisyan AA, et al. Cerpegin-derived furo[3,4-c]pyridine-3,4(1H,5H)-diones enhance cellular response to interferons by de novo pyrimidine biosynthesis inhibition. *Eur J Med Chem*. 2020;186: 111855.
 17. Muehler A, Peelen E, Kohlhof H, Gröppel M, Vitt D. Vidofludimus calcium, a next generation DHODH inhibitor for the treatment of relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2020;43: 102129.
 18. Fitzpatrick LR, Deml L, Hofmann C, et al. 4SC-101, a novel immunosuppressive drug, inhibits IL-17 and attenuates colitis in two murine models of inflammatory bowel disease. *Inflamm Bowel Dis*. 2010;16(10):1763–77.
 19. Phase 2 dose-finding IMU-838 for ulcerative colitis (CALDOSE-1). *ClinicalTrials.gov Identifier NCT03341962*. Updated February 24, 2021. <https://clinicaltrials.gov/ct2/show/NCT03341962>. Accessed March 21, 2019.
 20. Vidofludimus calcium for primary sclerosing cholangitis (PSC). *ClinicalTrials.gov Identifier NCT03722576*. Updated November 25, 2020. <https://clinicaltrials.gov/ct2/show/NCT03722576>. Accessed March 21, 2019.
 21. Muehler A, Kohlhof H, Groeppel M, Vitt D. The selective oral immunomodulator vidofludimus in patients with active rheumatoid arthritis: safety results from the COMPONENT study. *Drugs R D*. 2019;19(4):351–66. <https://doi.org/10.1007/s40268-019-00286-z>.
 22. Fox RJ, Wiendl H, de Stefano N, Sellner J, Muehler A. Safety and tolerability of IMU-838, a next-generation DHODH inhibitor in EMPHASIS: a randomized, placebo-controlled phase 2 trial in relapsing multiple sclerosis. *Neurology*. 2021;96(15 Suppl):2872.
 23. World Health Organization (WHO) WHO R&D Blueprint—COVID-19 Therapeutic Trial Synopsis. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf. Accessed Dec 4, 2021.
 24. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med*. 2020;382(24):2372–4.
 25. Garibaldi BT, Wang K, Robinson ML, et al. Comparison of time to clinical improvement with vs without remdesivir treatment in hospitalized patients with COVID-19. *JAMA Netw Open*. 2021;4(3): e213071.
 26. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabetes Metab Syndr*. 2021;15(6): 102329.
 27. Muehler A, Kohlhof H, Groeppel M, Vitt D. Safety, tolerability and pharmacokinetics of vidofludimus calcium (IMU-838) after single and multiple ascending oral doses in healthy male subjects. *Eur J Drug Metab Pharmacokinet*. 2020;45(5):557–73.
 28. Herrlinger KR, Diculescu M, Fellermann K, et al. Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study. *J Crohns Colitis*. 2013;7(8): 636–43.
 29. Fox RJ, Wiendl H, Wolf C, et al. A double-blind, randomized, placebo-controlled phase 2 trial evaluating the selective dihydroorotate dehydrogenase inhibitor vidofludimus calcium in relapsing-remitting multiple sclerosis. *Ann Clin Transl Neurol*. 2022. <https://doi.org/10.1002/acn3.51574>.
 30. Carey EJ, Eaton J, Clayton M, et al. A pilot study of vidofludimus calcium for treatment of primary sclerosing cholangitis. *Hepatol Commun*. 2022;6(7):1589–97.
 31. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing

- multiple sclerosis. *N Engl J Med.* 2011;365(14):1293–303.
32. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2014;13(3):247–56.
 33. Bar-Or A, Freedman MS, Kremenchutzky M, et al. Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. *Neurology.* 2013;81(6):552.
 34. Bar-Or A, Wiendl H, Miller B, et al. Randomized study of teriflunomide effects on immune responses to neoantigen and recall antigens. *Neurol Neuroimmunol Neuroinflamm.* 2015;2(2): e70.
 35. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein–Barr virus reactivation. *Pathogens.* 2021;10(6):763.
 36. Marschall M, Peelen P, Müller R, et al. IMU-838, a small molecule DHODH inhibitor in phase 2 clinical trial for multiple sclerosis, shows potent anti-EBV activity in cell-culture-based systems: potential additional benefits in multiple sclerosis treatment. ECTRIMS, Poster P37; 2021.
 37. Yu T, Tian C, Chu S, et al. COVID-19 patients benefit from early antiviral treatment: a comparative, retrospective study. *J Med Virol.* 2020;92(11):2675–83.
 38. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2022;386:305–15.