ORIGINAL PAPER

DFV890: a new oral NLRP3 inhibitor—tested in an early phase 2a randomised clinical trial in patients with COVID-19 pneumonia and impaired respiratory function

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Abstract

Background Coronavirus-associated acute respiratory distress syndrome (CARDS) has limited effective therapy to date. NLRP3 inflammasome activation induced by SARS-CoV-2 in COVID-19 contributes to cytokine storm.

Methods This randomised, multinational study enrolled hospitalised patients (18–80 years) with COVID-19-associated pneumonia and impaired respiratory function. Eligible patients were randomised (1:1) via Interactive Response Technology to DFV890 + standard-of-care (SoC) or SoC alone for 14 days. Primary endpoint was APACHE II score at Day 14 or on day-of-discharge (whichever-came-first) with worst-case imputation for death. Other key assessments included clinical status, CRP levels, SARS-CoV-2 detection, other inflammatory markers, in-hospital outcomes, and safety.

Findings Between May 27, 2020 and December 24, 2020, 143 patients (31 clinical sites, 12 countries) were randomly assigned to DFV890 + SoC ($n = 71$) or SoC alone ($n = 72$). Primary endpoint to establish clinical efficacy of DFV890 vs. SoC, based on combined APACHE II score, was not met; LSM (SE), 8·7 (1.06) vs. 8·6 (1.05); $p = 0.467$. More patients treated with DFV890 vs. SoC showed ≥ 1-level improvement in clinical status (84.3% vs. 73.6% at Day 14), earlier clearance of SARS-CoV-2 (76.4% vs. 57.4% at Day 7), and mechanical ventilation-free survival (85.7% vs. 80.6% through Day 28), and there were fewer fatal events in DFV890 group (8.6% vs. 11.1% through Day 28). DFV890 was well tolerated with no unexpected safety signals.

Interpretation DFV890 did not meet statistical significance for superiority vs. SoC in primary endpoint of combined APACHE II score at Day 14. However, early SARS-CoV-2 clearance, improved clinical status and in-hospital outcomes, and fewer fatal events occurred with DFV890 vs. SoC, and it may be considered as a protective therapy for CARDS.

Trial registration ClinicalTrials.gov, NCT04382053.

Keywords Coronavirus-associated acute respiratory distress syndrome · DFV890 · NLRP3 inhibitors · Randomised controlled trial · SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) [1], is an enveloped virus with atypically large

positive-sense, single-stranded RNA genomes of approximately 30 kilobases in length [2]. Highly contagious in humans, the virus has infected more than 318 million individuals and caused more than 5.5 million deaths worldwide as of January 14, 2022 [3].

The clinical features of COVID-19 range from asymptomatic to mild respiratory symptoms, such as cough, fever, pneumonia, dyspnoea, myalgia, lymphopenia, fatigue, and diarrhoea, to even potentially life-threatening cardiovascular and pulmonary complications [4]. COVID-19-infected patients may develop lung injury, and respiratory distress that may progress to pneumonia and severe lung injury

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causing a distinctive form of acute lung injury named coronavirus-associated acute respiratory distress syndrome (CARDS) [5, 6]. Approximately 42% of patients with COVID-19 pneumonia develop CARDS, and 61–81% of these patients require intensive care [5, 7]. CARDS is characterised by pro-inflammatory cytokine release, inflammatory cellular infiltrate, and cell death due to dysregulated hyperinflammation, resulting in severe pulmonary damage and respiratory failure [5]. COVID-19 patients with moderate-to-severe CARDS may require invasive mechanical ventilation to sustain life and have a poor prognosis [7], with the mortality rate ranging from 26 to 61% in patients admitted to a critical care setting and 66 to 94% in patients who received mechanical ventilation [8].

SARS-CoV-2 encodes ion channel proteins called viroporins that cause intense and rapid stimulation of the innate immune response. This, in turn, triggers activation of the nucleotide oligomerisation domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome pathway via mechanisms such as lysosomal disruption and ion redistribution in the intracellular environment. These sensors initiate a protective response that produces inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF)-α, causing tissue inflammation during respiratory illness [9, 10]. This may contribute to vascular leakage and fluid accumulation, leading to pulmonary oedema and hypoxaemia [9, 11]. Due to its crucial role in triggering inflammatory response to infection, targeting the NLRP3 inflammasome pathway could represent an important and viable approach for the treatment of COVID-19-related complications and may improve patient outcomes [12].

DFV890 is a new, orally administered, potent, and selective low-molecular-weight compound designed to inhibit the activity of NLRP3 by directly binding to NLRP3 and locking the protein in an inactive conformation, thus preventing NLRP3 inflammasome assembly in response to sterile danger signals [13]. DFV890 thereby blocks the activation of NLRP3 that leads to the maturation of the pro-inflammatory cytokines, IL-1β, and IL-18, along with pyroptotic cell death.

The study aimed to evaluate the efficacy and safety of DFV890 administration in addition to the current standard-of-care (SoC) compared with SoC alone in controlling the inflammatory syndrome and resultant CARDS in hospitalised patients with COVID-19 pneumonia and impaired respiratory function.

Methods

Patients

Patients, aged 18–80 years, infected with SARS-CoV-2 and diagnosed within 7 days prior to randomisation, who were hospitalised and diagnosed with COVID-19-induced pneumonia, were eligible for inclusion in this study. COVID-19-associated pneumonia was evidenced by chest X-ray, computed tomography (CT) scan, or magnetic resonance imaging (MRI) performed within 5 days prior to randomisation and impaired respiratory function (peripheral oxygen saturation [SpO_2] $\leq 93\%$ on room air or partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2] < 300 mmHg). Other inclusion criteria were Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 10, C-reactive protein (CRP) ≥ 20 mg/L and/or ferritin level ≥ 600 µg/L, and body mass index of ≥ 18 to < 40 kg/m^2 at screening.

The key exclusion criteria included suspected active/chronic bacterial, fungal, viral, or other infection (except SARS-CoV-2), imminent and inevitable progression to death within the next 24 h (based on investigator's opinion), intubation prior to randomisation, and prior treatment with immunosuppressant and immunomodulatory drugs either within the past 2 weeks or within the past 30 days or 5 half-lives (whichever was longer) for immunomodulatory therapeutic antibodies or prohibited drugs, with the exception of hydroxychloroquine, chloroquine, or corticosteroids. Detailed inclusion/exclusion criteria are presented in supplementary Table 1.

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki [14] and all International Conference on Harmonisation Good Clinical Practice guidelines. All patients (or their representatives) signed an informed consent form, and the research protocol was reviewed and approved by an independent ethics committee or institutional review board.

Study design

This was a phase 2, randomised, controlled, open-label, multicentre study (NCT04382053) conducted at 31 sites across 12 countries (supplementary Table 2) between May 27, 2020, and December 24, 2020. After a 24-h screening period, eligible patients were randomised (1:1) at baseline (Day 0) to receive either DFV890 in addition to SoC or SoC alone. DFV890 was administered twice daily (b.i.d.) orally for 14 days (28 doses) in addition to SoC, while patients in the control arm received SoC alone (e.g., hydroxychloroquine, chloroquine, remdesivir, faripivavir, ritonavir, lopinavir, or corticosteroids; supplementary Fig. 1). If patients were discharged from hospital prior to the end-of-treatment visit (Day 14), patients continued to take the investigational drug at home to complete the 14-day treatment period and returned to the site for Day 14 visit. After completion of 14-day treatment period,

patients were observed until Day 28 or discharge from hospital, whichever was sooner. A follow-up visit (Day 44) was conducted via telephone for the safety assessment.

Randomisation and masking

Patients were randomised via Interactive Response Technology that assigned a randomisation number and linked each patient to a treatment arm. The treatment was open to patients and investigator staff/persons performing the assessments. The randomisation scheme for patients was reviewed and approved by a member of the Novartis randomisation office.

Randomisation was stratified according to age (≤ 65/> 65 years); any antiviral therapy as SoC prior to randomisation (e.g., hydroxychloroquine, chloroquine, remdesivir, faripivavir, ritonavir, lopinavir, or corticosteroids); and presence of ≥ 1 of the following comorbidities: diabetes, hypertension, cardiovascular disease, and chronic lung disease.

For all analysis sets, patients were analysed according to the originally assigned randomised group. The safety analysis set included all randomised patients who attended at least one post-baseline visit. The pharmacokinetics (PK) analysis set included all patients with at least one available valid PK concentration measurement who received DFV890 and had no protocol deviations that would impact PK data. The pharmacodynamics (PD) analysis set included all randomised participants with no protocol deviations with relevant impact on PD data. For post hoc analyses, a compliant analysis set was defined to include all randomised participants who were part of the PD analysis set and with a calculated APACHE II score ≥ 10 at baseline and, if randomised to DFV890, with less than six doses of 50 mg DFV890 missed.

This multicentre randomised controlled trial (RCT) had trial reports fulfilling the CONSORT statement checklist, which comprises a minimum standard of recommendations for reporting RCTs [15].

Procedures

DFV890 50 mg was administered orally twice per day approximately 12 h apart (morning and evening). Patients discharged prior to Day 14 were provided with individual medication diary cards to record each administration of the investigational treatment at home. If a patient became intubated during the course of study and was unable to ingest tablets, the study drug was administered through a nasogastric tube (8 French or greater). DFV890, as 25 mg tablets, was supplied to the investigator as open-label, patient-specific kits. The SoC administered in addition to study treatment was supplied by the investigational site. SoC was administered as per local practice, and dose adjustments for SoC were permitted, while dose adjustments and/or interruptions were not permitted for DFV890.

Key efficacy and safety assessments were done at screening, baseline, and Days 1, 3, 5, 7, 9, 11, 13, and 14. For hospitalised patients, follow-up assessments were performed on site every 2 days (Days 16, 18, 20, 22, 24, 26, and 28). If the patient was discharged from the hospital, post-treatment follow-up was done via telephone call on Day 28. A safety follow-up call was made 30 days after the last study treatment together with Serious AE (SAE) data collection.

Outcomes

The primary objective of this study was to evaluate the effect of DFV890 in addition to SoC compared with SoC alone on the combined APACHE II severity of disease score on Day 14 or on day-of-discharge (whichever was earlier), with worst-case imputation for death. The APACHE II score was derived during the statistical analysis based on various parameters grouped under vital signs, oxygenation, chemistry, and haematology; in addition, age and Glasgow Coma Score are part of the APACHE II score [16]. The worst value for each parameter in the last 24 h was recorded. For the discharge visit, the value corresponding to the discharge was recorded, reflecting the patient's status when leaving the clinic. Furthermore, APACHE II scores over time were also reported for all time points up to 2 weeks.

The key secondary objectives were to evaluate the effect of DFV890 in addition to SoC compared with SoC alone on clinical status as assessed by the World Health Organization (WHO) 9-point ordinal scale and on endpoints derived from it (survival without the need for invasive mechanical ventilation and at least one-level improvement in clinical status on Days 14 and 28) and on inflammatory status (serum CRP levels).

The exploratory objectives of this study included:

– detection of SARS-CoV-2 [as measured using Polymerase Chain Reaction testing or by other approved diagnostic methodology available at screening (except for the patients who have had a valid test done within 7 days of randomisation), Day 7 and Day 14]
– mortality rate (death up to Day 28)
– in-hospital outcomes including time to discharge, Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II), and duration of hospitalisation, mechanical ventilation, intensive care unit (ICU) stay, oxygen support, extracorporeal membrane oxygenation (ECMO) therapy, and acute kidney injury (AKI) requiring renal replacement therapy
– plasma concentrations of DFV890 on Days 1, 3, and 14 or at day-of-discharge

– biomarker assessments conducted on the PD subset comprising inflammatory markers including IL-6, IL-1β, IL-8, IL-10, IL-18, interferon (IFN)-γ-inducible protein-10 (IP-10), IFN-γ, TNF-α, and IL-2RA and other cellular and liquid inflammatory, coagulation, and cardiac biomarkers including ferritin, D-dimer, lactate dehydrogenase (LDH), and troponin

A post hoc subgroup analysis was conducted on the compliant analysis set, in patients with high baseline CRP (greater than median baseline value [> 78.8 mg/L] of all patients), by low and high corticosteroid dose levels received during the first week following randomisation. The grouping into low and high corticosteroid doses was based on the average daily prednisone equivalent dose of all corticosteroids received in the first 7 days post-randomisation being > or ≤ 10 mg. Patients not receiving corticosteroids during the first 7 days following randomisation were included in the "low steroid" subgroup. This subgroup analysis investigated the treatment effect on biomarker parameters including APACHE II score, body temperature, IL-6, IP-10, and CRP over 2 weeks in the subpopulation with higher baseline inflammation levels.

Safety assessments included the incidence and severity of AEs, the number of patients with AEs, SAEs, and clinically significant changes in laboratory measures and vital signs.

Statistical analysis

The primary estimand, combined APACHE II score, was modelled using a mixed-effects model with treatment and stratification factors (age group, administration of any antiviral therapy at baseline, and presence of comorbidities ≥ 1) as fixed effects and the baseline combined APACHE II score as a continuous covariate. The mean differences of DFV890 in addition to SoC vs. SoC alone were reported with 90% confidence interval (CI) and one-sided p value for the treatment factor.

A prior sample size calculation identified that to establish the clinical efficacy based on APACHE II score, a sample size of 60 patients per treatment group provides 80% power when testing on a 10% one-sided alpha level under the assumption that DFV890 in addition to SoC reduces APACHE II score by 3.6 points more than SoC alone (assumed standard deviation [SD] of 9.2 [17]). The type I error rate of 10% was considered an acceptable false-positive risk for this exploratory study. The primary objective was achieved if the null hypothesis that DFV890 in addition to SoC is not different to SoC alone was rejected using a one-sided alpha of 10%. A mixed-effects repeated-measures analysis of APACHE II scores over time was also conducted including all time points up to 2 weeks.

For the analysis of CRP, a sample size of 60 participants per treatment group provided 80% power when testing on a 1% one-sided alpha level under the assumption that DFV890 in addition to SoC reduces CRP by 44% more than SoC alone (assumed coefficient of variation of 1.3). Biomarker endpoints were analysed on the log scale by conducting a Mixed Model Repeated Measures analysis. The model included treatment, visit, and their interaction as well as three stratification factors as fixed factors and log-transformed baseline parameter as a covariate. A post hoc analysis using repeated-measures analysis was conducted on compliant analysis set in patients with high baseline CRP (CRP > 78.8 mg/L) by low and high corticosteroid dose levels received during the first week following randomisation. Due to a large percentage of patients being discharged by Day 14, all modelled analyses included data only until Day 14. Formal statistical testing was not performed for other exploratory endpoints including SARS-CoV-2 viral clearance.

Role of the funding source

Results

Baseline demographic and patient disease characteristics

A total of 143 patients were randomly assigned to receive either DFV890 + SoC ($n = 71$) or SoC alone ($n = 72$) across Argentina ($n = 3$), Brazil ($n = 13$), Denmark ($n = 5$), Germany ($n = 5$), Hungary ($n = 15$), India ($n = 12$), Mexico ($n = 9$), The Netherlands ($n = 7$), Peru ($n = 6$), South Africa ($n = 4$), Spain ($n = 10$), and the Russian Federation ($n = 54$). One patient randomised to the DFV890 group did not receive any

treatment. Out of 70 patients who received DFV890+SoC and 72 patients who received SoC alone, 88.6% (n=62) of DFV890 patients and 81.9% (n=59) of SoC patients completed the study. The primary reason for study discontinuation was death reported in six (8.6%) DFV890 and eight (11.1%) SoC patients (Fig. 1). In the DFV890 and SoC treatment groups, 26 (37.1%) and 38 (52.8%) patients were discharged prior to Day 14, respectively, while 40 (57.1%) and 46 (63.9%) were discharged prior to Day 28, respectively, as the patients' condition improved. The PD analysis set comprised 62 and 68 patients in the DFV890 and SoC groups, respectively, while the PK analysis set comprised 60 patients treated with DFV890.

Baseline demographics and disease characteristics were balanced across the DFV890 and SoC treatment arms. Overall, the mean (SD) day from onset of symptoms to randomisation was 10.3 (4.91), while from diagnosis to randomisation was 2.7 (2.41) days. Approximately 76.1% of patients had ≥1 comorbidity, with a lower number of patients in the DFV890 vs. SoC group (72.9% vs. 79.2%), and all the randomised patients had abnormal chest X-ray/CT scan/MRI. At baseline, approximately 93% of patients required any baseline oxygen support, with a higher number of patients requiring high-flow oxygen in the DFV890 vs. SoC group (31.4% vs. 16.7%). The mean (SD) APACHE II score at baseline was 11.5 (2.26) and 12.1 (2.66) for the DFV890 and SoC groups, respectively. There were marginal differences in biomarker levels between the groups at baseline (Table 1). The baseline biomarker values suggest that patients enrolled in this study presented on average with rather mild-to-moderately increased inflammatory parameters (i.e., no uncontrolled hyperinflammatory status) and no

signs of disseminated intravascular coagulation or hypoxic cardiac-stress events.

A higher number of patients in the DFV890 vs SoC group received corticosteroid therapy during the first week (80% vs 69.4%), with approximately 75% and 68% of patients receiving average doses of ≥10 mg daily in the DFV890 and SoC groups, respectively. The number of patients with corticosteroid use during the first week by dose category is presented in Supplementary Fig. 2.

Efficacy assessments (primary and key secondary outcomes)

The primary outcome measure was not met; patients receiving DFV890 vs. SoC alone did not reach the pre-specified significant difference at the one-sided 10% level in the primary estimand, combined APACHE II score (p=0.467). The adjusted least-squares mean (LSM; [SE] for the combined APACHE II score for DFV890 vs. SoC alone was 8.7 (1.06) vs. 8.6 (1.05) (LSM difference [LSMD] with 90% CI, 0.11 [−2.0, 2.3]). A supportive analysis of primary estimand of combined APACHE II score using the PD analysis set showed similar results with an adjusted LSM (SE) for DFV890 vs. SoC alone of 9.0 (1.2) vs. 8.8 (1.1) (LSMD [90% CI], 0.21 [−2.1, 2.5] with one-sided p value of 0.44. A mixed-effects repeated-measures analysis of APACHE II scores over time showed a decrease from baseline to Day 14 in both the DFV890 and SoC treatment arms. However, there was no significant overall treatment effect observed across timepoints (p=0.225). The mean APACHE II scores up to Day 14 are presented in Fig. 2.

After 2 weeks of the study, 84.3% vs. 73.6% (Day 14) and 87.1% vs. 83.3% (Day 28) of patients showed at least
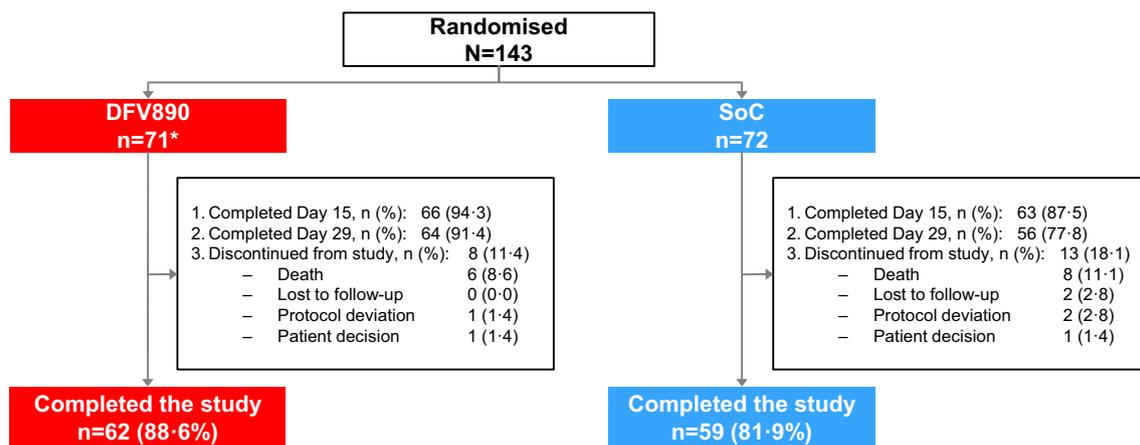
Fig. 1 CONSORT flowchart of trial participation. *N* number of patients, *SoC* standard-of-care. *One patient randomised to the DFV890 arm did not receive any study treatment

Table 1 Baseline and disease characteristics of patients

Variable, mean (SD) unless otherwise specified	DFV890 (N=70)	SoC (N=72)
Age (years); range	59.9 (13.34); 19–79	61.5 (10.38); 33–79
Male, n (%)	48 (68.6)	48 (66.7)
Female, n (%)	22 (31.4)	24 (33.3)
White, n (%)	55 (78.6)	57 (79.2)
Weight (kg)	85.6 (17.39)	84.5 (15.97)
BMI (kg/m^2)	29.9 (4.99)	29.0 (4.90)
Days from onset of symptoms to randomisation	10.5 (4.92)	10.0 (4.93)
Days from diagnosis to randomisation	2.8 (2.58)	2.7 (2.25)
Days from hospital admission to randomisation	3.3 (3.05)	3.4 (3.90)
Presence of comorbidities, n (%)		
Any comorbidities	51 (72.9)	57 (79.2)
Cerebrovascular disorder	6 (8.6)	1 (1.4)
Cardiac disorder	8 (11.4)	9 (12.5)
Hypertension	42 (60.0)	44 (61.1)
Chronic kidney disease	2 (2.9)	1 (1.4)
Neoplasm malignant	3 (4.3)	6 (8.3)
Diabetes	22 (31.4)	15 (20.8)
Chronic lung disease	4 (5.7)	10 (13.9)
APACHE II score	11.5 (2.26)	12.1 (2.66)
Chest X-ray/CT scan/MRI abnormal, n (%)	70 (100.0)	72 (100.0)
Inflammatory biomarkers		
CRP (mg/L), plasma/serum	101.5 (86.3)	88.0 (67.3)
D-dimers (mg/L), blood	23.6 (89.2)	6.5 (41.6)
Ferritin (μg/L), serum	1110.5 (1177.2)	1092.4 (854.2)
LDH	435.8 (254.0)	443.9 (225.2)
N-terminal proB-type natriuretic peptide, (pmol/L), serum/plasma	39.8 (64.4)	60.0 (132.0)
Neutrophils (10E9/L), blood	5.9 (3.7)	6.8 (3.6)
Troponin (μg/L), serum	1.3 (4.1)	1.0 (3.3)
Clinical status (9-point ordinal scale score), n (%)		
Hospitalisation: no oxygen	1 (1.4)	0 (0.0)
Hospitalisation: oxygen mask	47 (67.1)	54 (75.0)
Hospitalisation: non-invasive ventilation	22 (31.4)	18 (25.0)
Oxygen support, n (%)		
Any oxygen support	65 (92.9)	67 (93.1)
Low-flow nasal oxygen	33 (47.1)	41 (56.9)
High-flow nasal oxygen	22 (31.4)	12 (16.7)
Oxygen via face mask	8 (11.4)	11 (15.3)
Non-invasive ventilation	2 (2.9)	2 (2.8)
Mechanical ventilation	0 (0.0)	1 (1.4)
Use of corticosteroids at randomisation, n (%)	54 (77.1)	47 (65.3)
Antiviral treatment at randomisation, n (%)	44 (62.9)	53 (73.6)
Anti-infective treatment at randomisation, n (%)	56 (80.0)	58 (80.6)
Anti-coagulant treatment at randomisation, n (%)	63 (90.0)	57 (79.2)

The DFV890 arm consisted of patients treated with DFV890 in addition to SoC, while patients in the SoC arm received SoC alone

APACHE Acute Physiology and Chronic Health Evaluation, *BMI* body mass index, *CRP* C-reactive protein, *CT* computed tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging, *n* number of patients in the group, *N* number of patients randomised, *SD* standard deviation, *SoC* standard-of-care
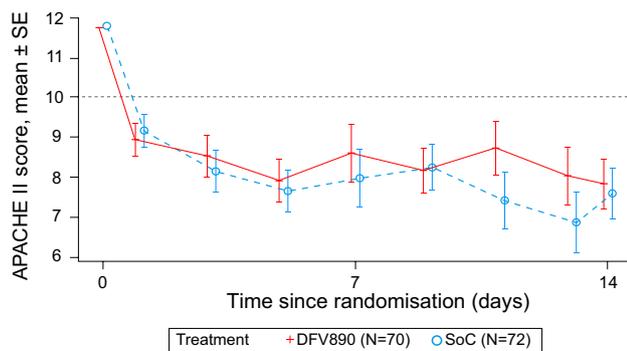
Fig. 2 APACHE II scores up to 2 weeks (safety analysis set). APACHE II scores were modelled using a mixed-effects model with treatment, visit, stratification factors, visit*treatment, and visit*stratification factors as fixed effects and baseline score and visit*baseline as continuous covariates. Stratification factors were age group (≤ 65 years, > 65 years), administration of any antiviral therapy (yes/no), and presence of comorbidities ≥ 1 (yes/no). The one-sided p value for the overall treatment factor was $p = 0.225$. The safety analysis set included all randomised patients who attended at least one post-baseline visit. *APACHE* Acute Physiology and Chronic Health Evaluation, *SE* standard error, *SoC* standard-of-care

one-level improvement in clinical status on a 9-point ordinal scale in the DFV890 and SoC groups, respectively. The evolution of weekly changes in categorical clinical status (i.e., "worsening", "no change", and "improvement") from baseline by Sankey plots in the DFV890 and SoC groups is shown in Fig. 3a. Based on the WHO clinical status scale, a lower number of patients receiving DFV890 ($n = 10$) required mechanical ventilation vs. SoC ($n = 14$). On Day 14, 85.7% vs. 81.9% of patients survived without mechanical ventilation with DFV890 vs. SoC; corresponding values were 85.7% vs. 80.6% on Day 28, respectively. Kaplan–Meier curves for mechanical ventilation-free survival by treatment group are presented in Fig. 3b.

Mean CRP levels decreased over time in both the DFV890 and SoC groups over 2 weeks following randomisation; lower mean CRP values were observed in the DFV890 vs. SoC during Week 1, with no notable difference observed during the further course of the study ($p = 0.237$; supplementary Fig. 3a).

Other assessments

Patients receiving DFV890 cleared SARS-CoV-2 earlier compared with those receiving SoC alone. At Day 7, a higher proportion of participants receiving DFV890 (76.4%) achieved SARS-CoV-2 clearance vs. SoC (57.4%), while on Day 14, the proportion of patients testing positive for SARS-CoV-2 was comparable between the groups (23.6% vs. 22.4% in DFV890 vs. SoC). The incidence of death was 5.7% and 6.9% in the DFV890 and SoC groups, respectively, up to Day 14. A lower number of patients died in the

DFV890 group compared with the SoC group up to Day 28 (8.6% vs. 11.1%). A Kaplan–Meier plot with time to death by treatment group is presented in supplementary Fig. 3b. The median duration of hospitalisation was 14 days in the DFV890 group and 11 days in the SoC group. No relevant treatment differences were observed in the SOFA and SAPS II scores between the treatment groups, and no patient in the study required renal replacement therapy.

Patients receiving DFV890 50 mg b.i.d. rapidly achieved stable steady-state PK concentrations, as illustrated by relatively stable troughs over time after 72 h of treatment with no further accumulation during the 2-week treatment period (supplementary Fig. 4). Then, mean trough concentrations on Days 1 and 3, and at end-of-treatment were 1340 ng/mL, 1550 ng/mL, and 1690 ng/mL, respectively, with % coefficient of variation between 64.2 and 67.7%.

Overall, both DFV890 and SoC groups showed comparable reduction in the inflammatory biomarkers and normalisation through Week 2. IL-6 levels were lower in the DFV890 group on Day 3 with no notable difference between treatment groups on Day 14. IL-1β levels were below the limit of quantification in 99% of the samples. The levels of other inflammatory markers, including IL-8, IL-10, IL-18, IP-10, IFN-γ, TNF-α, and IL-2RA, were similar in both treatment groups on Day 3; however, on Day 14, there was an increase in all of these markers observed in the DFV890 group. At Week 2, the mean IL-6, IL-8, IL-10, IL-18, IP-10, IFN-γ, TNF-α, and IL-2RA levels were 6.1, 27.9, 3.0, 669.0, 2045.1, 29.1, 3.6, and 3981.1 pg/mL in the DFV890 group and 3.7, 39.0, 0.5, 567.7, 682.4, 12.8, 2.5, and 3289.4 pg/mL in the SoC group. Other cellular and liquid inflammatory, coagulation and cardiac biomarkers such as neutrophils, ferritin, D-dimers, LDH, and troponin showed similar levels and no significant differences on Day 14 in both groups. The adjusted geometric mean for neutrophils, D-dimer, ferritin, LDH, and troponin at Week 2 was 3.5, 0.9, 357.0, 263.7, and 0.01 pg/mL for DFV890 and 4.2, 1.0, 400.9, 252.6, and 0.01 pg/mL for SoC.

A post hoc analysis in patients with more severe inflammation (CRP↑) but lower corticosteroid doses showed faster reduction and normalisation of inflammatory markers in the DFV890 group compared with the SoC group. Lower mean APACHE II scores and an early reduction in the body temperature were observed over 2 weeks with DFV890 vs. SoC, but did not reach statistical significance. Additionally, an earlier reduction and lower levels of CRP, IL-6, and IP-10 were observed with DFV890 vs. SoC in patients with more severe inflammation at baseline and low corticosteroid doses (Fig. 4).

Responders, n (%)	DFV890 (N=70)	SoC (N=72)	% Difference (90% CI)
Day 14	59 (84·3)	53 (73·6)	10·67 (-0·47, 21·82)
Day 28	61 (87·1)	60 (83·3)	3·81 (-5·96,13·58)
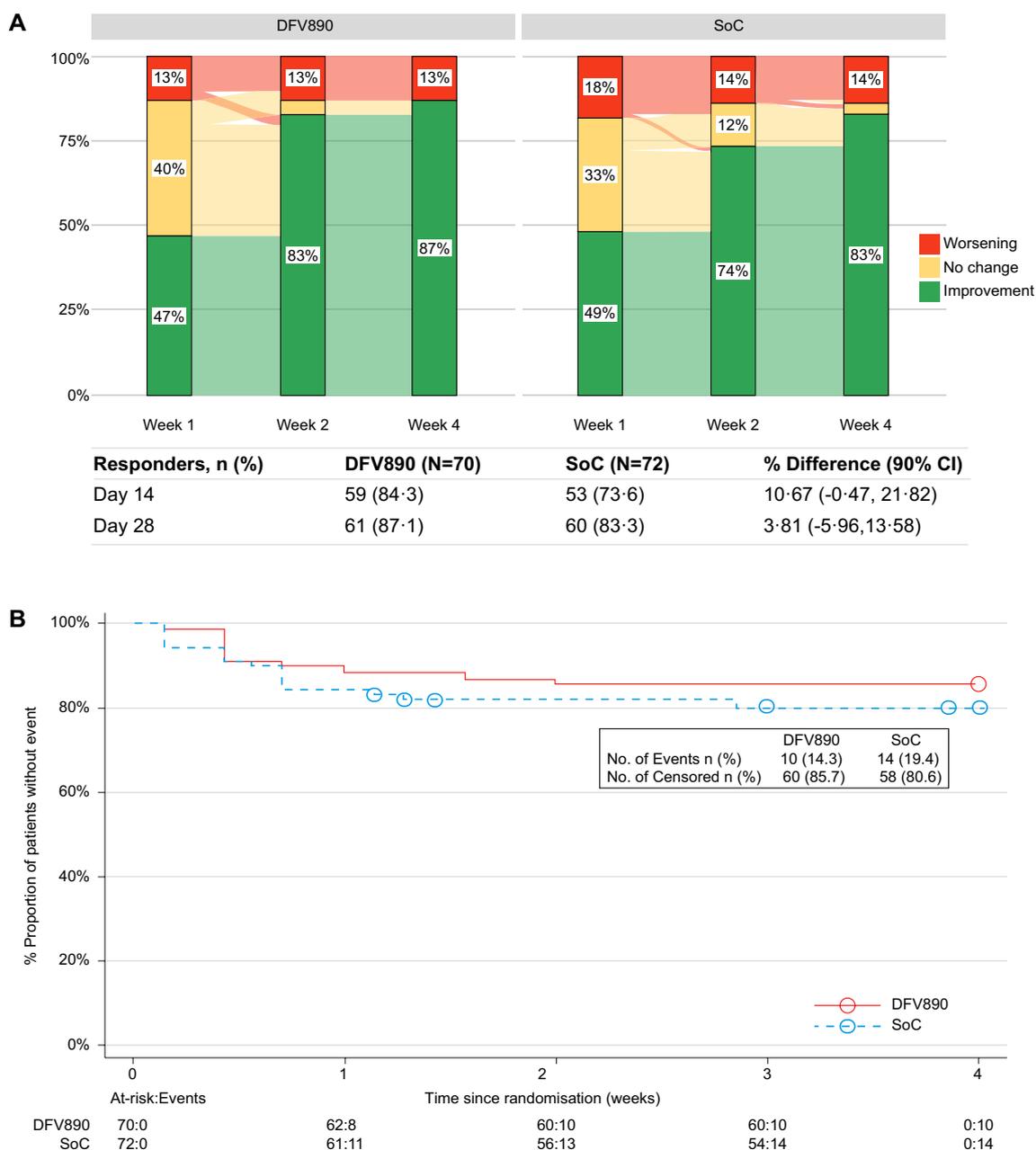
Fig. 3 **a** Sankey plot of change from baseline in clinical status and summary of at least one-level improvement in clinical status (WHO 9-point ordinal scale; safety analysis set); **b** Kaplan–Meier plot for mechanical ventilation-free survival. The safety analysis set included all randomised patients who attended at least one post-baseline visit. **a** Responders were defined as patients with a reduction of ≥ 1 on a 9-point ordinal scale score from screening to Day 14/28. 90% CI was based on Fisher's exact test. The two-sided *p* value for the treatment effect on Day 14 and Day 28 was 0.1509 and 0.6380, respectively; **b** Mechanical ventilation-free survival was defined as a 9-point ordinal scale score of < 6 points. *CI* confidence interval, *SoC* standard-of-care, *WHO* World Health Organization

Safety assessments

The proportion of patients with any AE was 58.6% in the DFV890 group and 54.2% in the SoC group. Overall, most of the patients experienced AEs of mild intensity (40.1%); AE of moderate and severe intensities were observed in 23.2% and 16.9% of patients, respectively. Fatal events were reported in 8.6% and 11.1% of patients, while SAE were reported in 22.9% and 15.3% of patients in the DFV890 and SoC groups, respectively. No drug-related SAE was reported in any of the treatment arms.

Overall, the most frequent AEs (reported in ≥ 10% of patients) in any of the treatment group by primary system organ class included infections and infestations (*n* = 22,
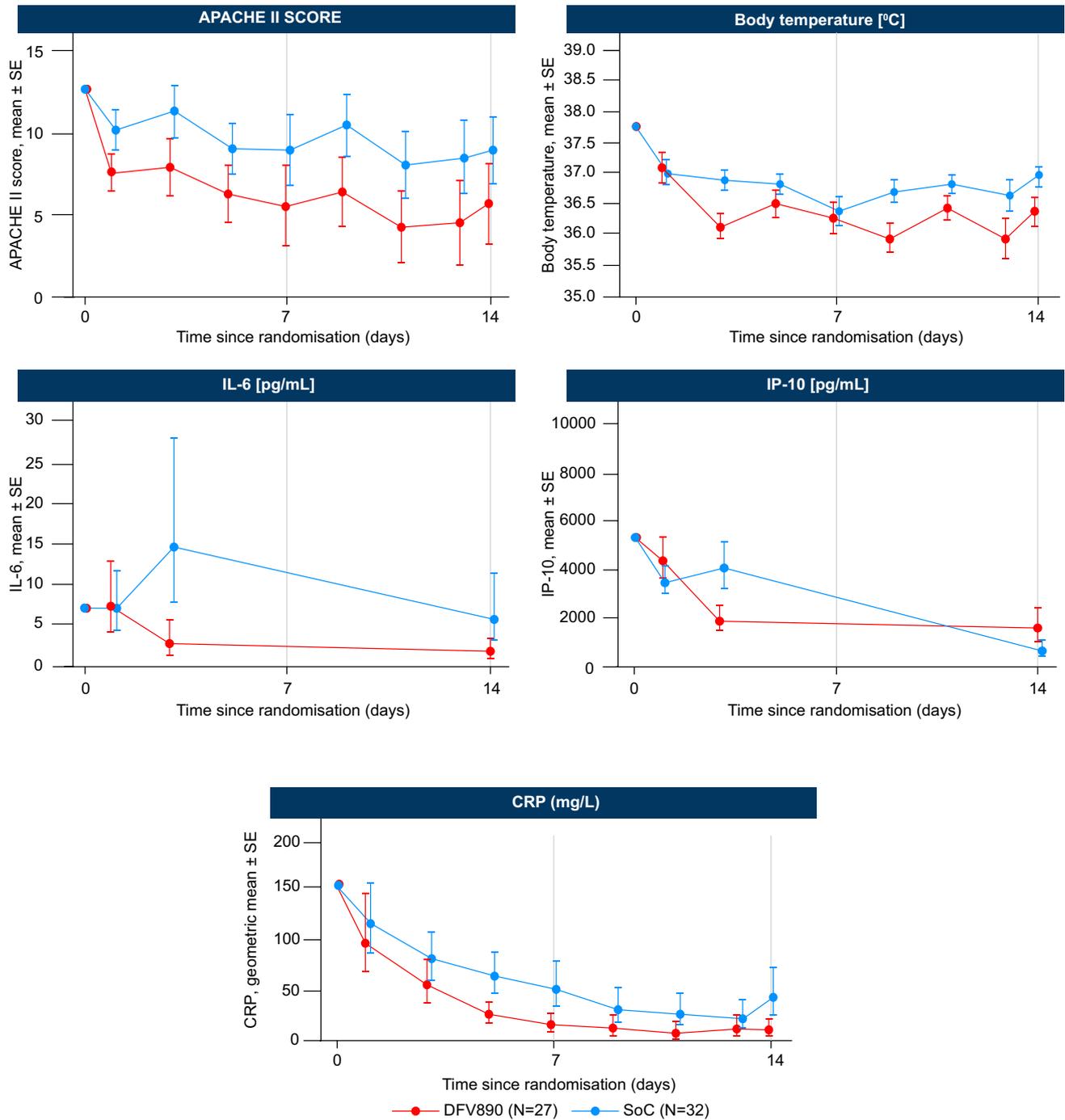
Fig. 4 Subgroup analysis of inflammatory markers in patients with more severe inflammation (CRP↑) who received lower corticosteroid doses in the first week (compliant analysis set). Only patients with baseline CRP greater than median baseline CRP (> 78.8 mg/L) and an average daily dose of corticosteroids ≤ 10 mg during the first week after randomisation were included. The analysis was based on the compliant analysis set (patients with confirmed SARS-COV-2 infection were included and patients with APACHE II score < 10 at baseline and ≥ 6 missed doses of study drug were excluded). The model adjusted the results to the average markers and clinical status at baseline. Dotted line represents APACHE II score < 10 at baseline. *APACHE* Acute Physiology and Chronic Health Evaluation, *IL* interleukin, *IP-10* interferon-γ-inducible protein-10, *CRP* C-reactive protein, *SoC* standard-of-care

Table 2 Summary of clinical safety until Day 28

Variable, n (%) unless otherwise specified	DFV890 (N=70)	SoC (N=72)
Any AE	41 (58.6)	39 (54.2)
Any SAE	16 (22.9)	11 (15.3)
Study drug-related AE	15 (21.4)	0
Study drug-related SAE	0	0
AE leading to discontinuation	8 (11.4)	0
Study drug-related AE leading to discontinuation	0	0
Fatal events leading to death	6 (8.6)	8 (11.1)
Infections and infestations	3 (4.3)	3 (4.2)
Respiratory, thoracic, and mediastinal disorders	1 (1.4)	4 (5.6)
Cardiac disorders	0	1 (1.4)
General disorders and administration site conditions	1 (1.4)	0
Vascular disorders	1 (1.4)	0
Most frequent treatment-emergent AEs		
Infections and infestations*	9 (12.9)	13 (18.1)
Gastrointestinal disorders	12 (17.1)	9 (12.5)
Investigations#	9 (12.9)	11 (15.3)
Metabolism and nutrition disorders	11 (15.7)	9 (12.5)
Respiratory, thoracic, and mediastinal disorders	9 (12.9)	11 (15.3)
Blood and lymphatic system disorders	8 (11.4)	5 (6.9)
Vascular disorders	4 (5.7)	9 (12.5)
Skin and subcutaneous tissue disorders	11 (15.7)	1 (1.4)
Cardiac disorders	3 (4.3)	7 (9.7)
Most frequent treatment-emergent SAEs		
Respiratory, thoracic, and mediastinal disorders	6 (8.6)	8 (11.1)
Infections and infestations	5 (7.1)	4 (5.6)
Vascular disorders	2 (2.9)	3 (4.2)
Cardiac disorders	0	3 (4.2)

A patient with multiple AEs was counted only once in the category. Only treatment-emergent (on treatment) AEs were considered, i.e., from the date of randomisation to Day 28. The DFV890 arm consisted of patients treated with DF890 in addition to SoC, while patients in the SoC arm received SoC alone

AE adverse event, number of patients in the group, *N* number of patients randomised, *SAE* serious AE, *SoC* standard-of-care

*Infections and infestations in DFV890 and SoC group mainly included COVID-19 pneumonia [n (%), 3 (4.3) and 2 (2.8)], sepsis [n (%), 1 (1.4) and 2 (2.8)], septic shock [n (%), 1 (1.4) and 1 (1.4)], pneumonia [n (%), 1 (1.4) and 1 (1.4)], and urinary tract infection [n (%), 0 (0.0) and 2 (2.8)]; #investigations mainly included an increase in any of the following: alanine aminotransferase, amylase, aspartate aminotransferase, lipase, or transaminases (occurrence in > 1% patients overall)

Discussion

In various inflammatory indications including atherosclerosis [18], Alzheimer's disease [19], gout [20], Parkinson's disease [21], rheumatoid arthritis [22], and non-alcoholic steatohepatitis [23], NLRP3 is a key node in innate immune signalling that modulates the assembly of an inflammasome and downstream inflammatory signalling. Over the last decade, research has substantiated an expanding list of indications where NLRP3 inhibitors play a beneficial role [18–23].

DFV890, by inhibiting NLRP3, blocks IL-1β and IL-18 secretions and pyroptotic cell death in vitro and in mechanistic mouse models, thus suggesting its potential use in COVID-19 pneumonia.

In this study, although DFV890 in addition to SoC compared with SoC alone did not show a significant reduction in combined APACHE II score on Day 14 or day-of-discharge, the mean profile of the APACHE II scores up to 2 weeks decreased from baseline in both treatment groups. APACHE II score (range 0–71), a widely used ICU prognostic scoring model, is shown to be an accurate measurement of disease severity and correlates strongly with outcome in critically ill patients [16]. The primary estimand was based on this score to provide a comprehensive structured assessment of the clinical, physiological, and laboratory parameters that have been routinely employed by physicians to access the overall clinical status of COVID-19 patients with pneumonia and respiratory failure [17, 24].

On the 9-point ordinal scale recommended by the WHO and used in various randomised trials involving patients with COVID-19 to measure clinical progression outcomes [25, 26], DFV890 showed at least one-step improvement in clinical status compared with baseline with a 10% intergroup difference in favour of DFV890 at Week 2. Furthermore, DFV890 showed more rapid viral clearance as early as Day 7 and a slightly lower mortality compared with SoC. Early initiation of DFV890 treatment in hospitalised patients with severe COVID-19 infection may lead to better treatment outcomes and reduced complications.

The design of this study supports the assessment of preliminary efficacy and safety of DFV890 in addition to SoC in critically ill COVID-19 population. The stratification for age (≤ 65/> 65 years), administration of any antiviral therapy, and presence of comorbidities was justified as these were identified as the key risk factors associated with more severe outcomes of SARS-CoV-2 infection, e.g., invasive ventilation or death. A 14-day study duration was selected taking into account literature indicating a 12-day median hospital stay for COVID-19 (interquartile range 1–14 days) [27]. As expected, over the 14-day treatment

15.5%), gastrointestinal disorders (n=21, 14.8%), investigations (n=20, 14.1%), metabolism and nutrition disorders (n=20, 14.1%), and respiratory, thoracic, and mediastinal disorders (n=20, 14.1%; Table 2).

period, DFV890 at a dose of 50 mg b.i.d. was generally well tolerated, and steady-state trough concentrations were reached in around 72 h of treatment, with no further accumulation during the study.

Several studies have shown an association of inflammatory markers, such as IL-6, IL-10, and IP-10, with the development of severe COVID-19 and mortality [28, 29]. Hence, the timely measurement of these markers may assist clinicians to monitor the severity and prognosis of COVID-19. In this study, lower mean levels of IL-6 were observed with DFV890 on Day 3 compared with SoC alone, with no difference between treatment groups on Day 14. No reduction was observed in other biomarkers at any time points assessed.

In this study, a significantly large proportion of patients were receiving high corticosteroid doses at the start of and during the trial. In the literature, various trials have indicated a poor disease course in patients with hepatitis B viral infection, where the use of corticosteroids or immunosuppressant drugs may increase viral replication, exacerbate inflammation, and worsen the underlying chronic viral hepatitis [30]. A post hoc analysis was performed to investigate the treatment effect in a subpopulation of COVID-19-infected patients with elevated CRP levels reflecting more severe inflammation at baseline and to understand the influence of concomitant corticosteroid treatment. DFV890 treatment showed lower mean APACHE II scores for most time points in patients with higher baseline inflammation treated with low-dose corticosteroids, suggesting that in the overall study population (and in the high corticosteroid dose group), the DFV890 therapeutic effect may have been masked by a broad anti-inflammatory effect of high corticosteroid doses. It was also observed that these patients showed an earlier reduction in body temperature and lower levels of inflammatory biomarkers, e.g., CRP, IL-6, and IP-10 with DFV890 treatment compared with SoC over 2 weeks. However, due to a low sample size and large variability, no statistical significance was reached in these analyses.

Mutations are neither new nor unexpected in viruses. SARS-CoV-2, via different mutations, is also gradually evolving over time to replace the original strains worldwide with new variants which are likely to cause severe disease, evade diagnostic tests, or resist antiviral treatment. Majorly, the alpha, beta, gamma, delta and omicron variants of the virus were classified as variants of concern. These shifts in the properties of SARS-CoV-2, mainly concerned with the spike protein which is a key component to design the vaccine candidate, may render a majority of these vaccines less effective against these variants [31]. However, DFV890, by interfering with the molecular mechanism leading to cytokine storm and not viral particle levels, may be expected to work independently irrespective of underlying variants.

The number and severity of AEs and SAEs were balanced among the DFV890 and SoC groups. DFV890 was associated with fewer infections and vascular complications but a higher number of maculopapular/pruritic skin rashes of mild and moderate intensity. Additionally, the time to fatal events and mechanical ventilation-free survival was comparable in both treatment groups while marginally favouring DFV890 treatment, with numerically fewer fatal events and a lower number of patients requiring mechanical ventilation during the study. Overall, DFV890 was well tolerated with no unexpected new safety signals identified for this COVID-19 population.

The current study has several limitations. It was difficult to observe the treatment effect, because most patients enrolled in this trial were on high-dose corticosteroids despite having low inflammation, which can potentially mask the expected treatment effect of NLRP3 inhibition. Furthermore, in this study, no specific data were collected on the use of various methods used for diagnosis and detection of COVID-19. The changing recommendations in SoC therapy, geographical differences, and COVID-19 mitigation measures impacted the conduct of the clinical trial. The distribution of different variables that compose the APACHE II score showed that many significant disease indicators, mainly for inflammation, systemic organ failure, and kidney failure and the resulting electrolyte imbalance, such as white blood cells, creatinine, sodium, potassium, or arterial pH, were not exacerbated in this milder study population. The factors mainly contributing to the treatment effect were the invasiveness of oxygen support, respiratory rate, and temperature. Thus, this study population comprised patients with low-to-medium inflammation, which is in conflict with the hypothesis of treating hyperinflammation via NLRP3 inhibition in the clinical setting. Also, the stratification for age group, administration of any antiviral therapy at baseline, and presence of comorbidities ≥ 1 was reflected in the statistical model for this analysis. However, the analysis did not adjust for other potential confounding factors such as patients' sex, age distribution, and type of respiratory support, due to the limited sample size in this proof-of-concept trial. The results should be considered preliminary and interpreted with caution.

Research investigating NLRP3-targeted treatments for multiple diseases is rapidly progressing. Further studies are also underway to explore the potential role of DFV890 as therapeutic option for various NLRP3-related inflammatory conditions such as cryopyrin-associated periodic syndromes (CAPS) and osteoarthritis.

Conclusion

In conclusion, although DFV890 did not show a significant difference in combined APACHE II scores compared with SoC alone, DFV890 was associated with comparable or

numerically higher improvements in the clinical status and faster clearance of SARS-CoV-2 compared with SoC alone in COVID-19-infected patients who were hospitalised and diagnosed with COVID-19 pneumonia and impaired respiratory function. DFV890 may offer benefits during the NLRP3 activation phase of the disease. However, neither DFV890 nor other selective inhibitors of NLRP3 have previously been studied in patients with COVID-19 pneumonia. The role of DFV890 in preventing or treating CARDS warrants further research.

Research in context

Evidence before this study

As of October 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had infected more than 242 million people worldwide, with more than 4.9 million deaths reported. Approximately 5–10% of COVID-19 patients develop lung injury and respiratory distress progressing to coronavirus-associated acute respiratory distress syndrome (CARDS). COVID-19 patients with moderate-to-severe CARDS are characterised by pro-inflammatory cytokine release and dysregulated hyperinflammation and may require invasive mechanical ventilation. In hospitalised patients with COVID-19 pneumonia, most cases of mortality are linked to the presence of a cytokine storm caused by the virus.

We searched PubMed from inception up to October 25, 2021, using the terms ("NLRP3") AND ("SARS-CoV-2" OR "COVID-19") AND ("randomised controlled trial") for clinical trials evaluating the effectiveness of NLRP3 inhibitors in patients hospitalised with COVID-19, without language restrictions. We simultaneously searched ClinicalTrials.gov for these search terms. No relevant trials were identified through the PubMed search, while ten trials were identified through ClinicalTrials.gov. Among the ten retrieved trials, three were not yet recruiting patients, five were currently recruiting/enrolling patients, and two trials were completed. Only one of the completed trials evaluated the effectiveness of colchicine in inhibiting the activation of NLRP3 inflammasomes in COVID-19 patients, with results not yet available.

Added value of this study

Due to their crucial role in triggering the inflammatory response to infection, targeting the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathway, and cytokines, such as interleukin (IL)-1β and IL-18, could represent an important and viable approach in the treatment of COVID-19-related complications. This, in turn, may reduce the requirement for mechanical ventilation and

improve clinical outcomes while also significantly reducing the demand on healthcare systems. DFV890 is a new, potent, and selective low-molecular-weight inhibitor of NLRP3 being tested for the first time in this proof-of-mechanism study in patients with severe COVID-19 pulmonary disease. The key objectives of this study were to assess the efficacy of DFV890 in addition to standard-of-care (SoC) vs. SoC alone in reducing inflammation, reversing lung pathology, reducing ventilation support, and improving clinical outcomes.

Implications of all the available evidence

This study presents efficacy and safety data on DFV890. Although DFV890 treatment did not show a significant difference in combined Acute Physiology and Chronic Health Evaluation II (APACHE II) scores compared with SoC, we observed numerically higher improvements in clinical status and faster clearance of SARS-CoV-2 (as early as Day 7) compared with SoC alone in COVID-19-infected patients who were hospitalised and diagnosed with COVID-19 pneumonia and impaired respiratory function.

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Declarations

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