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Original research

TRPC6 inhibitor (BI 764198) to reduce risk and severity of ARDS due to COVID-19: a phase II randomised controlled trial

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ABSTRACT

Background Despite the availability of COVID-19 vaccinations, there remains a need to investigate treatments to reduce the risk or severity of potentially fatal complications of COVID-19, such as acute respiratory distress syndrome (ARDS). This study evaluated the efficacy and safety of the transient receptor potential channel C6 (TRPC6) inhibitor, BI 764198, in reducing the risk and/or severity of ARDS in patients hospitalised for COVID-19 and requiring non-invasive, supplemental oxygen support (oxygen by mask or nasal prongs, oxygen by non-invasive ventilation or high-flow nasal oxygen).

Methods Multicentre, double-blind, randomised phase II trial comparing once-daily oral BI 764198 (n=65) with placebo (n=64) for 28 days (+2-month follow-up). Primary endpoint: proportion of patients alive and free of mechanical ventilation at day 29. Secondary endpoints: proportion of patients alive and discharged without oxygen (day 29); occurrence of either in-hospital mortality, intensive care unit admission or mechanical ventilation (day 29); time to first response (clinical improvement/recovery); ventilator-free days (day 29); and mortality (days 15, 29, 60 and 90).

Results No difference was observed for the primary endpoint: BI 764198 (83.1%) versus placebo (87.5%) (estimated risk difference −5.39%; 95% CI −16.08 to 5.30; p=0.323). For secondary endpoints, a longer time to first response (rate ratio 0.67; 95% CI 0.46 to 0.99; p=0.045) and longer hospitalisation (+3.41 days; 95% CI 0.49 to 6.34; p=0.023) for BI 764198 versus placebo was observed; no other significant differences were observed. On-treatment adverse events were similar between trial arms and more fatal events were reported for BI 764198 (n=7) versus placebo (n=2). Treatment was stopped early based on an interim observation of a lack of efficacy and an imbalance of fatal events (Data Monitoring Committee recommendation).

Conclusions TRPC6 inhibition was not effective in reducing the risk and/or severity of ARDS in patients with COVID-19 requiring non-invasive, supplemental oxygen support.

Trial registration number NCT04604184.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Over 40% of patients hospitalised for COVID-19 develop acute respiratory distress syndrome (ARDS).
⇒ Therefore, there is a significant unmet need for a safe and effective treatment that reduces the risk and severity of ARDS in patients with severe COVID-19.

WHAT THIS STUDY ADDS

⇒ This is the first evaluation of TRPC6 inhibition as a potential treatment to reduce the risk and/or severity of ARDS in patients with COVID-19 requiring non-invasive, supplemental oxygen support.
⇒ BI 764198 did not improve outcomes in hospitalised patients and prolonged the duration of hospitalisation and recovery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite promising preclinical and phase I findings, further clinical trials of BI 764198 for the treatment of ARDS in COVID-19 are not justified based on the results of this study.

INTRODUCTION

COVID-19 is associated with a wide spectrum of symptoms of varying intensity, most notably affecting the respiratory system.[1] Studies estimate that up to 20% of COVID-19 cases are severe enough to warrant hospitalisation[2] and that 26%–32% of patients hospitalised with COVID-19 require medical care in an intensive care unit (ICU).[3]

At the time of this study, between 3% and 17% of all patients with COVID-19 developed acute respiratory distress syndrome (ARDS), a potentially deadly complication of severe COVID-19.[3] This figure increased to 42% among hospitalised patients, and between 61% and 85% among patients admitted to an ICU.[3–6] Therefore, preventing progression of COVID-19 to ARDS was of significant medical importance. Treatments available for patients hospitalised with COVID-19 included remdesivir, immunomodulators and corticosteroids.[7] Corticosteroids, such as dexamethasone, and interleukin (IL)-6 antagonists, such as tocilizumab, had been shown to improve outcomes in patients with COVID-19.[8–10] Janus kinase inhibitors such as baricitinib had also shown favourable outcomes but not a significant reduction in the

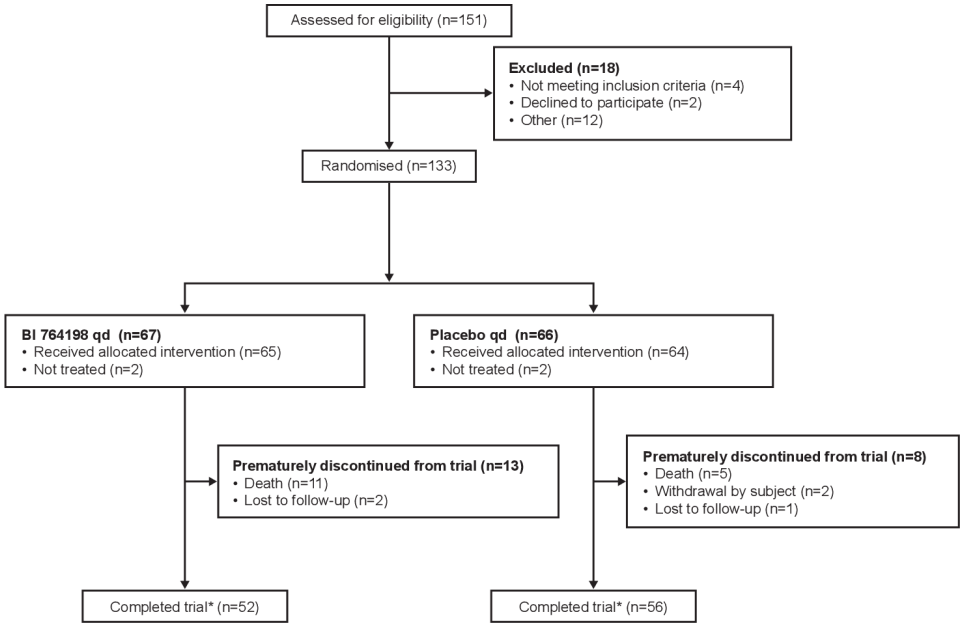

Figure 1 Patient flow diagram. *Patients completed visits through end of trial (day 90). qd, once daily.

development of ARDS in patients with COVID-19.[11–13] Since this trial, emergency use authorisation has been granted for several monoclonal antibody/antibody combinations[14–16] and two antiviral treatments[17 18]; these treatments have been authorised for patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19, but not for patients already hospitalised with COVID-19. In addition, numerous vaccines have been approved and are in use around the world.[19] Vaccinations reduce rates of infection as well as the intensity and adverse outcomes of infection, should it occur. However, breakthrough infections can occur in fully vaccinated individuals and in those who have received booster vaccines. New variants of concern, such as the Omicron variant (B.1.1.529) and the subvariant B.1.1.529.2 (BA.2), may present further challenges to vaccine-induced immune protection, highlighting the ongoing need for therapeutic options.[20 21]

The pathophysiology of developing ARDS in COVID-19 is heterogeneous and complex, involving various molecular pathways and a general imbalance between injurious and reparative mechanisms.[22 23] Endothelial injury can cause increased lung endothelial and alveolar epithelial permeability and a subsequent accumulation of pulmonary oedema fluid within the interstitium and alveolus.[22] In addition, injury to the lung epithelium facilitates leucocyte migration, reduces surfactant production and inhibits clearance of pulmonary oedema fluid. Other mechanisms, including deleterious effects of proinflammatory cytokines, oxidants and hypoxia, have also been identified as factors that can impair alveolar fluid clearance in ARDS.[22]

Transient receptor potential channel C6 (TRPC6) is highly expressed in human epithelial and endothelial cells within the lung[24] and is indirectly activated by hypoxia and reactive oxygen species; this results in calcium influx, leading to smooth muscle contraction and increased endothelial cell damage, which in turn increases endothelial permeability and oedema.[25] TRPC6 knockdown prevents thrombin-induced actin stress fibre formation and interendothelial junctional gap formation in human pulmonary arterial endothelial cells.[26]

BI 764198, a novel, potent, oral, small-molecule inhibitor of TRPC6, is being developed for the treatment of chronic kidney disease and has been shown to be well tolerated (data on file) in phase I studies in healthy adults.[27 28]

Due to the potential effect of TRPC6 inhibition in reducing lung oedema, the efficacy and safety of BI 764198 was investigated in a proof-of-concept phase II trial for the treatment of patients hospitalised for COVID-19 and requiring non-invasive, supplemental oxygen support.

METHODS

Trial design and participants

This parallel-group, randomised, double-blind, placebo-controlled, phase II trial was conducted across 25 trial sites in the USA, Brazil, Chile, Mexico and Spain (online supplemental table 1).

Eligible patients were aged ≥50 years old, hospitalised for COVID-19 (SARS-CoV-2 infection confirmed by PCR or approved point-of-care test) with a clinical score of 5 (hospitalised; oxygen by mask or nasal prongs) or 6 (hospitalised; oxygen by non-invasive ventilation or high-flow nasal oxygen (HFNO)), as defined on the WHO Clinical Progression Scale at the time of study screening.[29] Other scores were not eligible for inclusion. Patients were not vaccinated against SARS-CoV-2. Patients aged 50 years and older were included in this trial as these patients are at a higher risk of developing severe lung complications as a result of SARS-CoV-2 infection, and as such, are clinically important. Additionally, patients with a WHO Clinical Progression Scale score of 5 or 6 were included as, at the time of screening, there was a lack of physiological differentiation between the two scores as well as variability in local clinical decision-making regarding the choice between oxygen by mask (clinical score of 5) or HFNO (clinical score of 6). The inclusion of patients with a clinical score of 5 or 6 was also consistent with regulatory agency guidance at the time of screening.

An independent and unblinded Data Monitoring Committee (DMC; composed of field experts and supported by an independent statistician) with full access to efficacy and safety data oversaw conduct of the trial; they reviewed data snapshots at

Table 1 Demographics and clinical characteristics at baseline

	BI 764198 n=65	Placebo n=64	Total N=129
Male, n (%)	41 (63.1)	39 (60.9)	80 (62.0)
Age, mean (SD), years	63.8 (8.3)	63.6 (7.9)	63.7 (8.1)
Race, n (%)			
White	53 (81.5)	47 (73.4)	100 (77.5)
American Indian or Alaskan native	5 (7.7)	7 (10.9)	12 (9.3)
Black or African American	3 (4.6)	3 (4.7)	6 (4.7)
Native Hawaiian or other Pacific islander	2 (3.1)	0 (0)	2 (1.6)
Asian	0 (0)	3 (4.7)	3 (2.3)
Missing	2 (3.1)	4 (6.3)	6 (4.7)
Geographical region, n (%)			
North America	36 (55.4)	36 (56.3)	72 (55.8)
Europe	17 (26.2)	20 (31.3)	37 (28.7)
South America	12 (18.5)	8 (12.5)	20 (15.5)
BMI, mean (SD, kg/m^2)	31.9 (6.5)	30.6 (5.6)	31.2 (6.1)
Tobacco history, n (%)			
Never	44 (67.7)	44 (68.8)	88 (68.2)
Former	18 (27.7)	18 (28.1)	36 (27.9)
Current	3 (4.6)	2 (3.1)	5 (3.9)
Duration of symptom before hospitalisation, mean days (SD)	8.6 (3.6)	8.0 (4.1)	8.3 (3.8)
Score on WHO Clinical Progression Scale at baseline, n (%)			
5: Hospitalised; oxygen by mask or nasal prongs	45 (69.2)	46 (71.9)	91 (70.5)
6: Hospitalised; oxygen by NIV or HFNO	20 (30.8)	18 (28.1)	38 (29.5)
Medical history, n (%)			
Diabetes	19 (29.2)	22 (34.4)	41 (31.8)
Chronic cardiac disease (not hypertension)	7 (10.8)	7 (10.9)	14 (10.9)
Asthma	6 (9.2)	5 (7.8)	11 (8.5)
Chronic obstructive pulmonary disease	5 (7.7)	4 (6.3)	9 (7.0)
Chronic liver disease	4 (6.2)	3 (4.7)	7 (5.4)
Medication at baseline, n (%)			
Corticosteroids	58 (89.2)	59 (92.2)	117 (90.7)
Dexamethasone	50 (76.9)	48 (75.0)	98 (76.0)
Antivirals	30 (46.2)	30 (46.9)	60 (46.5)
Remdesivir	29 (44.6)	28 (43.8)	57 (44.2)
Anti-inflammatories	4 (6.2)	0 (0.0)	4 (3.1)
Tocilizumab	4 (6.2)	0 (0.0)	4 (3.1)

None of the patients enrolled was vaccinated against SARS-CoV-2.
BMI, body mass index; HFNO, high-flow nasal oxygen; NIV, non-invasive ventilation.

frequent intervals and provided recommendations on trial continuation, modification or termination.

Procedures

Eligible patients were randomised 1:1 to receive once-daily BI 764198 or placebo orally, or by nasogastric tube, for up to 28 days. Patients were hospitalised during the duration of treatment (up to 28 days). If a patient was well enough to be discharged from the hospital, treatment was stopped prior to the maximum treatment period of 28 days. Patients were followed up for 90 days from randomisation.

Trial medication was added on to COVID-19 standard of care according to local COVID-19 treatment guidelines at the time of trial conduct.[30–32] Patients were excluded if they had received experimental, or off-label usage of, medicinal products for COVID-19.

Outcomes

The primary endpoint was the proportion of patients alive and free of mechanical ventilation at day 29. Secondary endpoints included (1) proportion of patients alive and discharged without supplemental oxygen at day 29; (2) proportion of patients with occurrence of any component of a composite of in-hospital mortality, ICU admission or mechanical ventilation at day 29; (3) time to response, defined as 2-point decrease in score (from randomisation) on the WHO Clinical Progression Scale, discharge from the hospital or being considered fit for discharge (score of 0, 1, 2 or 3 on the Clinical Progression Scale), whichever comes first, by day 29; (4) number of ventilator-free days by day 29; and (5) mortality at days 15, 29, 60 and 90.

Safety and tolerability assessments were based on occurrence of on-treatment (defined as start of drug treatment to 4 days after last drug treatment – the residual effect time) adverse events (AEs), safety laboratory parameters, physical examination, vital sign measurements and 12-lead ECG.

Randomisation, blinding and sample size

Patients were block randomised (block size: 4) in a 1:1 ratio to double-blind treatment and stratified by baseline disease severity (WHO Clinical Progression Score 5 vs 6). The trial sponsor was responsible for arranging the randomisation, packaging and labelling of the trial medication, and the randomisation list was generated using a pseudorandom number generator to ensure reproducibility and non-predictability. Access to the randomisation codes was restricted to keep the investigators, patients, reviewers and any other individuals involved in conducting the trial blinded to the treatment allocation, with the exception of the independent DMC.

The proportion of patients assumed to be alive and free of mechanical ventilation at day 29 in the placebo group was expected to be ~81%. Assuming BI 764198 would increase this proportion by 9%, the probability of observing ≥5% improvement in the primary endpoint would be 72% if 130 patients were randomised (online supplemental table 2).

Further details on exclusion criteria, dosage, clinical, physiology and AE monitoring, statistical analyses and sample size determination are provided in the online supplemental file 1.

RESULTS

Trial population

Patient recruitment opened on 3 November 2020; the first patient was screened and randomised on 12 November 2020, and recruitment ended on 24 February 2021. The trial ended on 31 May 2021.

This trial screened a total of 151 patients; of these, 133 patients were eligible, consented to being involved in the trial and were enrolled (figure 1). Patients were randomised to receive either BI 764198 once daily (n=67) or placebo once daily (n=66). Four patients, two in each treatment group, were not treated due to withdrawal (n=1, BI 764198; n=1, placebo), meeting

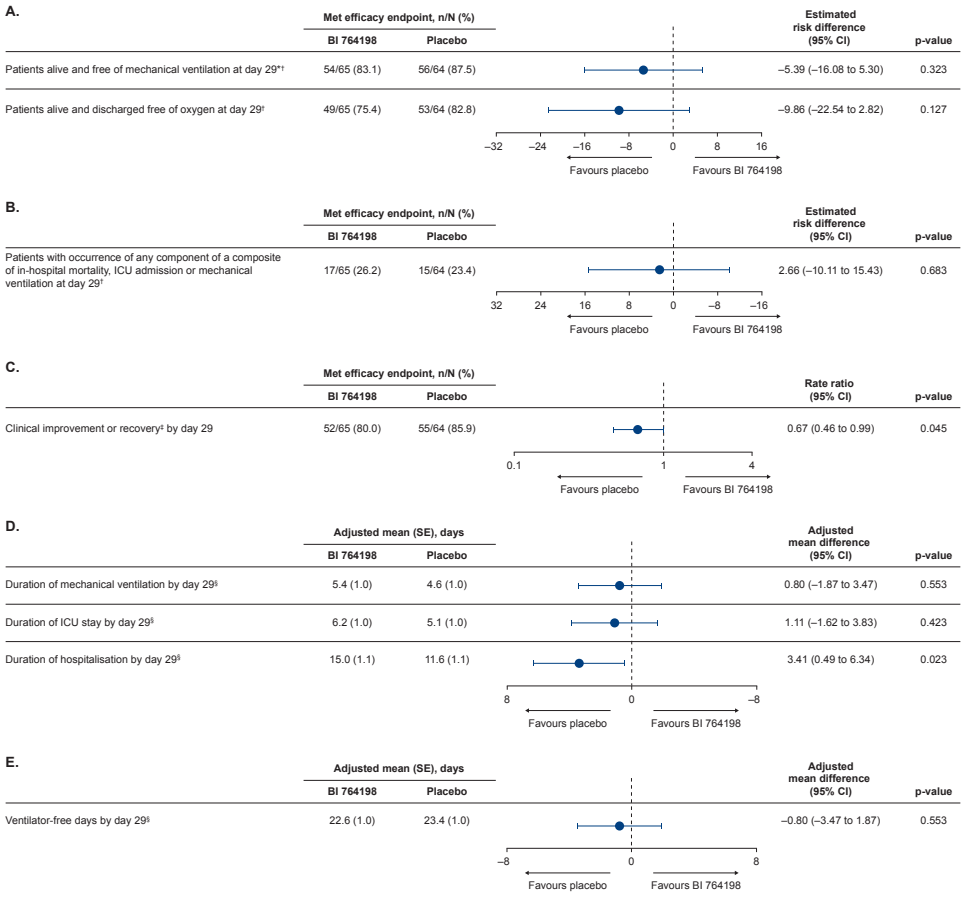

Figure 2 Key efficacy results for patients treated with BI 764198 versus placebo. The following endpoints are presented: (A) patients alive and free of mechanical ventilation and patients alive and discharged free of oxygen free of oxygen; (B) patients with occurrence of any component of a composite of in-hospital mortality, ICU admission or mechanical ventilation; (C) clinical improvement or recovery; (D) duration of mechanical ventilation, ICU stay and hospitalisation; (E) and ventilator-free days. *Sensitivity analyses support these data. †The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalisation as covariates. ‡Covariates in the Cox model are treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalisation; first response of clinical improvement or recovery defined as a 2-point decrease in score (from randomisation) on the WHO Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (scores of 0, 1, 2 or 3), whichever comes first, by day 29. §Patients analysed using analysis of covariance with fixed effects of treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalisation as covariates. ICU, intensive care unit.

an exclusion criterion (n=1, BI 764198) or clinical worsening (n=1, placebo). The total number of patients enrolled and included in the full analysis set was 65 in the BI 764198 group and 64 in the placebo group.

In the BI 764198 and placebo groups, 52 and 56 patients, respectively, completed the trial. In both groups, the main reason for discontinuation was death (n=11, BI 764198; n=5, placebo). Five patients (two in the BI 764198 group and three in the placebo group) missed one dose of treatment and an additional patient in the BI 764198 group missed two consecutive doses. Although the trial completed enrolment, based on advice from the DMC (following their periodic review of unblinded safety and efficacy data), treatment was discontinued early for patients receiving ongoing treatment when the trial was terminated by the DMC. This included nine patients in the BI 764198 group and seven in the placebo group. Further details are provided in the DMC section.

Table 2 Mortality by days 15, 29, 60 and 90

Mortality by time point, n (%)	BI 764198 n=65	Placebo n=64	% treatment difference (95% CI)
Day 15	4 (6.2)	1 (1.6)	5.32 (−1.01 to 11.65)
Day 29	8 (12.3)	5 (7.8)	6.06 (−3.19 to 15.31)
Day 60	10 (15.4)	5 (7.8)	8.93 (−0.76 to 18.62)
Day 90	11 (16.9)	5 (7.8)	10.35 (0.41 to 20.28)

Patient baseline characteristics are shown in table 1. Overall, baseline characteristics, medical history and standard of care received were well balanced between treatment groups. The majority of patients were white (77.5%) and over half were from North America. Diabetes was the most common comorbidity (31.8%), followed by chronic cardiac disease (10.9%) and asthma (8.5%). About 91% of patients were prescribed corticosteroid treatment for COVID-19. Specifically, 76% were prescribed dexamethasone. Remdesivir and tocilizumab were used in 44% and 3% of patients, respectively.

Efficacy

There was no statistically significant difference in the proportion of patients alive and free of mechanical ventilation at day 29 (figure 2A) between active and placebo treatment arms (83.1%

Table 3 Adverse events

	BI 764198 n=65	Placebo n=64	Total N=129
On-treatment AEs overall summary, n (%)			
Any AE	30 (46.2)	35 (54.7)	65 (50.4)
AE leading to discontinuation	5 (7.7)	5 (7.8)	10 (7.8)
Serious AE	15 (23.1)	16 (25.0)	31 (24.0)
Resulting in death	7 (10.8)	2 (3.1)	9 (7.0)
Life-threatening	5 (7.7)	8 (12.5)	13 (10.1)
Requires or prolongs hospitalisation	6 (9.2)	9 (14.1)	15 (11.6)
On-treatment AEs (≥2% in either treatment group), n (%)			
Respiratory failure	13 (20)	10 (15.6)	23 (17.8)
Infective pneumonia	7 (10.8)	5 (7.8)	12 (9.3)
Acute renal failure	5 (7.7)	4 (6.3)	9 (7.0)
Fatal AEs, n (%)			
On-treatment fatal AEs	7 (10.8)	2 (3.1)	9 (7.0)
Post-treatment fatal AEs	5 (7.7)	3 (4.7)	8 (6.2)

AEs, adverse events.

vs 87.5%; estimated risk difference –5.39%; 95% CI –16.08 to 5.30; p=0.323). This result was consistent across a number of sensitivity analyses (online supplemental figure 1) and subgroup analyses based on WHO Clinical Progression Scale score at baseline (5 vs 6; p value for interaction 0.942) and time from first symptom onset to first drug intake (<7 days vs ≥7 days; p value for interaction 0.169) (online supplemental figure 2). Of the patients receiving corticosteroids as standard of care (BI 764198: n=58; placebo: n=59), 47 patients in the BI 764198 group (81.0%) and 51 patients in the placebo group (86.4%) met the primary endpoint.

No statistically significant difference was observed either in the proportion of patients alive and discharged free of oxygen (75.4% vs 82.8%; estimated risk difference –9.86; 95% CI −22.54 to 2.82; p=0.127) (figure 2A) or the proportion of patients with occurrence of any one of: hospital mortality, ICU admission or mechanical ventilation at day 29 (26.2% vs 23.4%; estimated risk difference 2.66; 95% CI –10.11 to 15.43; p=0.683) (figure 2B).

Patients treated with active treatment had a longer time to recovery than patients treated with placebo (rate ratio 0.67; 95% CI 0.46 to 0.99; p=0.045) (figure 2C and online supplemental figure 3).

Treatment with BI 764198 versus placebo increased the duration of hospitalisation by 3.4±1.5 days (95% CI 0.49 to 6.34; p=0.023) (figure 2D) and increased the duration of oxygen use up to day 29 after treatment start by 3.4±1.7 days (95% CI 0.13 to 6.76; p=0.042) (online supplemental table 3). There were numeric but not significant differences in the duration of mechanical ventilation and stay in an ICU at day 29 (figure 2D). The difference in number of ventilator-free days by day 29 was also not significantly different between treatment groups (figure 2E).

By days 15, 29, 60 and 90, the number of deaths was numerically higher in patients treated with BI 764198 compared with placebo (day 29: BI 764198: n=8; placebo: n=5) (table 2). All 16 patients who died during the study period were receiving corticosteroids as standard of care.

Safety

The frequency of patients with any AE was similar between the two treatment groups (46.2% in the BI 764198 group vs 54.7% in the placebo group) (table 3).

The frequency of patients with serious AEs—with the exception of fatal events—was also similar between treatment arms (23.1% in the BI 764198 group vs 25.0% in the placebo group) (table 3). The most common on-treatment AEs were respiratory, thoracic and mediastinal disorders (22.5%), metabolism and nutrition disorders (17.8%) and gastrointestinal disorders (15.5%).

In total, there were 16 deaths due to fatal AEs during the trial (11 in the BI 764198 group vs five in the placebo group). Infections (six in the BI 764198 group vs two in the placebo group), as well as respiratory, thoracic and mediastinal disorders (four in the BI 764198 group vs three in the placebo group), were the most common fatal AEs. With regard to fatal AEs, there were nine patients with onset of AEs leading to death during the treatment period (seven in the BI 764198 group vs two in the placebo group) (table 3). After treatment, there were eight patients with an onset of AEs leading to death (five in the BI 764198 group vs three in the placebo group) (table 3). One patient had fatal AEs with an onset during treatment and after treatment (table 4).

Cause of death and clinical characteristics are shown in online supplemental table 4. Fatal events were typically directly related to the deterioration of COVID-19 culminating in respiratory failure.

DMC

Based on the DMC's fourth unblinded snapshot data review (inclusive of 101 patients with eight fatal events), a recommendation was made to the sponsor to stop enrolment, discontinue administration of trial drug and continue blinded evaluation of patients already enrolled in the trial.

Following this recommendation, the sponsor advised that the trial sites immediately implement the DMC recommendations as a result of the lack of efficacy (with regard to primary and secondary endpoints) and numerical imbalance of fatal events (although not statistically significant) between the active treatment and placebo groups. As there was a lag time from the fourth data snapshot being captured to review of data by the DMC, an additional five patients were randomised and treated after the fourth data snapshot (22 February 2021). At the time the recommendation was implemented, treatment had not been completed in all patients and was discontinued in those receiving ongoing treatment and in the additional five patients randomised/treated on or after 22 February 2021 (nine patients in the BI 764198 group and seven in the placebo group were discontinued due to the sponsor's decision). Further details of the treatment status of patients at the time of study discontinuation are provided in online supplemental table 5.

DISCUSSION

This phase II proof-of-concept clinical trial investigated the efficacy and safety of a TRPC6 inhibitor aimed at reducing the risk and/or severity of ARDS associated with severe COVID-19.

The trial did not meet any of its primary or secondary endpoints, and the TRPC6 inhibitor (BI 764198) did not reduce the risk or severity of ARDS associated with severe COVID-19. In general, patients had a trend towards worse outcomes with active therapy. At day 29, no statistically significant difference was observed in the proportion of patients alive and free of mechanical ventilation, alive and discharged free of oxygen, or

Table 4 On-treatment and post-treatment serious AEs with a fatal outcome

Serious AE	Exposure to trial drug, days	Serious AE start date*	Time of death*	Intensity of AE	Drug-related, Y/N
On-treatment serious AEs					
BI 764198					
Respiratory failure	7	Day 3	Day 7	Severe	N
Septic shock†	8	Day 9	Day 10	Severe	N
Diarrhoea	13	Day 11	Day 14	Moderate	N
COVID-19‡		Day 14	Day 14	Severe	N
ARDS	18	Day 6	Day 19	Severe	N
Respiratory failure	16	Day 3	Day 20	Severe	N
COVID-19 pneumonia	8	Day 6	Day 37§	Severe	N
COVID-19 pneumonia	6	Day 6	Day 65§¶	Severe	N
Acute respiratory failure		Day 6	Day 65§¶	Severe	N
Placebo					
Septic shock	10	Day 8	Day 11	Severe	N
Acute kidney disease		Day 9	Day 11	Severe	N
Pneumothorax		Day 11	Day 11	Severe	Y
Respiratory failure		Day 8	Day 11	Severe	N
ARDS	5	Day 1	Day 31§	Severe	N
Post-treatment serious AEs					
BI 764198					
Pneumonia	1	Day 12	Day 12	Severe	N
Acute myocardial infarction	4	Day 23	Day 23	Severe	N
Aspergillus infection	4	Day 18	Day 26	Severe	N
Death	6	Day 59	Day 59	Severe	N
COVID-19 pneumonia	6	Day 17	Day 65¶	Severe	N
Acute respiratory failure		Day 17	Day 65¶	Severe	N
Septic shock		Day 48	Day 65¶	Severe	N
Placebo					
Bradycardia	13	Day 22	Day 22	Severe	N
Right ventricular dilation		Day 22	Day 22	Severe	N
Right ventricular dysfunction		Day 22	Day 22	Severe	N
Hypotension		Day 22	Day 22	Severe	N
COVID-19 pneumonia	7	Day 27	Day 27	Severe	N
Respiratory failure	8	Day 30	Day 30	Severe	N

Each bordered row represents a single patient with a fatal outcome.
*Relative to the start of trial drug.
†The serious AE started within 4 days of the last drug intake.
‡Missed trial drug on the day of AE onset.
§Death occurred during the post-treatment period; however, the serious AE that led to death started during the on-treatment period.
¶This patient experienced various serious AEs that led to death, some of which started during the on-treatment period, whereas others started during the post-treatment period; details for this patient are therefore listed as both on-treatment and post-treatment serious AEs.
AE, adverse event; ARDS, acute respiratory distress syndrome; N, no; Y, yes.

with any one of a composite of in-hospital mortality, ICU admission or mechanical ventilation. Compared with BI 764198, more patients in the placebo group achieved clinical improvement or recovery. In addition, for patients treated with BI 764198 versus placebo, both the duration of hospitalisation and the duration of oxygen use were longer by an average of approximately 3 days.

In terms of safety, the number of patients with on-treatment AEs and serious AEs were similar in both treatment arms; however, more patients treated with BI 764198 had fatal AEs compared with placebo. The safety monitoring of the trial worked as planned, with close monitoring by the DMC resulting in an immediate early stop in enrolment and treatment of patients when signals pointed towards potential worsening under treatment.

Although this trial did not meet its primary or secondary endpoints, it was initiated on the basis of strong scientific rationale. The therapeutic premise for this study in terms of TRP channel involvement in acute lung injury and potentially COVID-19 has been previously postulated.[33 34] Inhibition of TRPC6 has been studied in detail as a potential mechanism to

reduce pulmonary oedema[25 35 36] and was supported by preclinical findings of TRPC6 inhibition in mouse models of lung injury wherein TRPC6 inhibition led to marked reduction in alveolar leakage, endothelial cellular damage and apoptosis (data not shown). Additionally, in phase I studies, BI 764198 was well tolerated by healthy adults (data on file). This is not the first time that strong evidence for reduction in inflammation and oedema from preclinical models has not been replicated in the clinic. There was preclinical evidence that the bradykinin inhibitor BI 1026706 reduced lung inflammation.[37–39] However, clinical studies went on to show numerical signs of increased inflammation or oedema in chronic obstructive pulmonary disease and a human pulmonary endotoxin challenge model in early exploratory studies.[40 41]

The trial was designed in response to an unprecedented unmet need to find a safe and effective treatment to reduce the risk and severity of ARDS in patients hospitalised for severe COVID-19. In patients hospitalised with COVID-19, up to 42% are reported to develop ARDS.[3] At the time of the trial, there were no validated and effective treatments recommended for the management of ARDS in patients with COVID-19.[42–44] Treatments shown to be effective in patients hospitalised for COVID-19 included immune modulators, namely, corticosteroids (eg, dexamethasone) and anti-inflammatories (eg, tocilizumab).[45] Good clinical management, adequate ventilatory support and the use of systemic corticosteroids were considered the most effective methods to reduce mortality and duration of hospitalisation at the time this trial was conducted.[43] As of September 2022, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines[46] recommend the use of dexamethasone plus the antiviral remdesivir for most patients that are hospitalised and require oxygen supplementation, replacing antivirals with anti-inflammatory antibody-based treatment as oxygen supplementation needs become more invasive with disease progression. This phase II proof-of-concept study was initiated in November 2020 and was terminated in February 2021, before the NIH recommendations. Even then, only a small fraction of patients (~10%) did not receive corticosteroids.

The scope of this trial was exploratory in nature, and it was conducted in a relatively small number of participants. The main objective was to assess if TRPC6 inhibition, based on promising preclinical findings, could improve outcomes in patients aged ≥50 years, hospitalised for COVID-19 and requiring non-invasive, supplemental oxygen at the time of trial inclusion. The clear lack of benefit with BI 764198 treatment relative to placebo in this patient population cannot be fully explained given the supportive preclinical data. The patient numbers were relatively small, with only 106 patients completing the trial. However, it is not expected that a larger or longer duration trial would have demonstrated a different outcome given the relative consistency of results towards worsening of outcome.

The time point of administration of treatment and the disease severity of the patients recruited (including their inflammatory status) could have resulted in the lack of efficacy observed with BI 764198. COVID-19 infection may be broadly considered in terms of two stages: the first, early stage, in which viral load plays the major role and antiviral therapies are generally effective; and the second, later stage, dominated by the immune response (in particular, the hyperinflammatory response) and for which dexamethasone is the current standard of care.[2] Particularly for this latter stage, the time point of administration of anti-inflammatory therapies is critical.[2] In this trial, patients were recruited later on in the disease course (WHO Clinical Scale 5 and 6 at the time of screening), at which point they were already hypoxaemic and likely to have had damage to their lung endothelial barrier. Therefore, it may have been too late for BI 764198 to be effective. Earlier intervention might have been more effective but would be challenging to study, particularly given the outcome of the current trial.

Another potential variable was the standard of care patients received. In terms of concomitant treatments permitted during the trial, medications prescribed to patients were consistent with the Infectious Diseases Society of America-recommended guidelines for standard of care[30] and over 90% of patients were receiving corticosteroids at baseline. However, concomitant medications were generally well balanced, with the exception that more patients in the BI 764198 arm received anti-IL-6 blockade than in the placebo arm (4 vs 0, respectively). All four patients were receiving tocilizumab; emergency use authorisation had not yet been granted when the trial was conducted, thus accounting for the low number of patients on this treatment.[47] All four patients were alive and free of mechanical ventilation at day 29.

A limitation of the trial was the fact that only a single dose of active treatment was investigated; therefore, the evaluation of a dose range was not feasible in the context of this accelerated development.

Patients who had been enrolled in vaccine studies were excluded from this trial as their course of disease was expected to be modified based on vaccination, a finding now scientifically well established. As patient enrolment began before COVID-19 vaccinations were approved or widely used in the study countries, none of the patients in this trial were vaccinated for COVID-19 on a post-release basis.

In conclusion, this is the first time that inhibition of TRPC6 has been evaluated as a potential treatment modality with an aim to reduce the risk and/or severity of ARDS secondary to COVID-19 requiring hospitalisation and receiving non-invasive, supplemental oxygen. Despite promising preclinical data and a sound mechanistic treatment rationale, BI 764198 did not improve outcomes in patients hospitalised for COVID-19 and prolonged the duration of hospitalisation and recovery.

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Contributors Conception and design: LW, NS, DFM, RK, WC, AG and TW. Acquisition of data/design of data acquisition platform: LW, NS, VE, GAD, PL, RK, WC and AG. Principal investigators at study sites: VE, GAD and PL. Statistical analysis: NS, RK, WC and AG. Data interpretation, edited and reviewed the manuscript, and approved the final version of the manuscript: LW, NS, DFM, VE, GAD, PL, RK, WC, AG and TW. LW accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests LW reports receipt of research support from Boehringer Ingelheim, Genentech and CSL Behring and consulting fees from Merck, Citius, Foresee and Quark. NS, WC and AG are employees of Boehringer Ingelheim. DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, SOBI and Eli Lilly, and from sitting on Data Monitoring and Ethics Committees for trials undertaken by Vir Biotechnology and Faron Pharmaceuticals. DFM's institution has received funds from grants from the NIHR Wellcome Trust, MRC, Innovate UK and NIHSC R&D, and others for studies in patients with ARDS and COVID-19; he also has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. DFM is the MRC/NIHR EME Programme Director; DFM's spouse is joint Editor-in-Chief for *Thorax*. VE reports clinical trial support and consulting fees from Gilead. GAD reports receipt of clinical trial research support from Boehringer Ingelheim, Edesa Biotech, Gilead Sciences, Regeneron and Roche, and scientific advisory board membership for Safeology.

Patient consent for publication Obtained.

Ethics approval This has been uploaded as a supplemental file named "TRPC6i in COVID-19 IRB approval list". Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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ONLINE SUPPLEMENT

TRPC6 inhibitor (BI 764198) to reduce risk and severity of ARDS due to COVID-19: a Phase II randomised controlled trial

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Supplementary Methods

Exclusion criteria

The exclusion criteria included: pulmonary oedema/respiratory failure due to cardiogenic insult; long-term oxygen therapy prior to current hospitalization; a history of cardiac conditions (myocardial infarction <3 months prior to first dose, unstable angina, and/or a prolonged QTc interval [as observed on an electrocardiogram or a family history of this]); received experimental, or off-label usage of, medicinal products as specific treatments for COVID-19; or any confounding condition.

Screening and dosage

Patients who are already hospitalised for COVID-19 were identified and screened. For patients who met the inclusion criteria, a confirmatory SARS-CoV-2 test (confirmed by polymerase chain reaction or an approved point-of-care test) was performed during the screening period (Day –3 to Day 1), after which study medication was administered on Day 1. Efforts were made to minimise the time between patient identification, screening and treatment initiation. Patients received daily BI 764198 or placebo in the form of an oral capsule or, only if needed, via nasogastric intubation, following overnight fasting and 1.5 hours prior to breakfast. Dose reductions or down-titrations were not permitted; however, trial treatment could be restarted following a temporary reason for treatment discontinuation. Drug administration was in-hospital and overseen by the clinical staff. For each dose of BI 764198 or placebo administered, the date, time and route (orally or via nasogastric intubation) was recorded in the electronic care report forms (eCRFs). Any missed doses were also recorded in the eCRFs.

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Clinical, physiology and adverse events monitoring

Assessments of concomitant therapy and procedures, hospitalization status, WHO Clinical Progression Scale, ventilation and oxygen parameters (respiratory rate, fraction of inspired oxygen [FiO_2], oxygen saturation [SpO_2]) and blood gases/partial pressure of oxygen (PaO_2) (if captured as part of routine care) were carried out daily until hospital discharge (up to Day 28). All except blood gases/PaO_2 were also carried out during follow-up. Adverse events (AEs) were recorded daily and by telephone call following discharge from hospital 4 days after the end of treatment and on Days 15, 29, 60 and 90 (counted from Day 1 of the trial). Vital status was recorded at each follow-up visit. Follow-up visits were conducted by telephone calls. For patients that remained hospitalised after the end of the treatment period, follow-up visits were conducted in hospital until discharge and thereafter by telephone call. Trial completion was defined as the completion of all follow-up visits.

Statistical analysis

The proportions of patients alive and free of mechanical ventilation at Day 29 (primary endpoint) was analysed using a logistic regression model with covariates of treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalization. The logistic regression for the primary endpoint analysis was used for all other binary endpoints, whereas time-to-event endpoints were analysed using a Cox regression, which included the same covariates used for the primary endpoint analysis. The difference in ventilator-free days between BI 764198 and placebo groups was analysed using ANCOVA model including the same covariates as in the primary endpoint analysis.

Efficacy analyses were performed according to a prespecified analysis plan in all randomized patients documented to have received at least one dose of trial medication (full analysis

set). The intent-to-treat principle was applied to the randomized set, including all observed data in the primary analysis regardless of treatment discontinuation.

Sensitivity and subgroup analyses

A sensitivity analysis was conducted with a logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, D-dimer at baseline, and duration of symptoms before hospitalisation. Subgroup analysis was performed using descriptive statistics.

Determination of sample size

The proportion of patients assumed to be alive and free of mechanical ventilation at Day 29 in the placebo group is expected to be ~81%. It is assumed that BI 764198 would increase this proportion by 9% (from 81% to 90%). The probability of observing ≥5% improvement in the primary endpoint (≥86% in BI 764198 group as opposed to 81% in placebo group) is 72% under this assumption with a total of 130 patients (65 patients per group). If there is no treatment effect (81% in both BI 764198 and placebo group), the probability of observing ≥5% improvement is 22% as depicted in Table E2. As the treatment policy is used to analyse the primary endpoint, early discontinuation is not considered in the sample size calculation.

Table 1. Trial site locations

Country	Sites
United States (n=61)	Dr. Richard A Lee, University of California Irvine, Orange, California, United States, 92868 Dr. Naseem A Jaffrani, Rapides Regional Medical Center, Alexandria, Louisiana, United States, 71301 Dr. Peter LaCamera, St. Elizabeth's Medical Center, Boston, Massachusetts, United States, 02135 Dr. Harry M Schrager, Newton-Wellesley Hospital, Newton, Massachusetts, United States, 02462 Dr. Salil Avasthi, Mercy Health St. Vincent Medical Center, Toledo, Ohio, United States, 43608 Dr. George A Diaz, Providence Regional Medical Center, Everett, Washington, United States, 98201 Dr. Patrick S Meehan, MultiCare Tacoma General Hospital, Tacoma, Washington, United States, 98405 Dr. Alvaro U Aranda-Rodriguez, Hospital Auxilio Mutuo, Hato Rey, Puerto Rico, 00919 Dr. Ricardo Fernandez-Gonzalez, Hospital Municipal de San Juan, Rio Piedras, Puerto Rico, 00936

Country	**Sites**
Spain (n=37)	Dr. Enrique Míguez, Hospital A Coruña, A Coruña, Spain, 15006 Dr. Sergio Reus, Hospital General Universitario de Alicante, Alicante, Spain, 03010 Dr. Jesús Troya García, Hospital Universitario Infanta Leonor, Madrid, Spain, 28031 Dr. Vicente Estrada, Hospital Clínico San Carlos, Madrid, Spain, 28040 Dr. Cristina de la Calle, Hospital Universitario 12 de Octubre, Madrid, Spain, 28041 Dr. Melchor Riera Jaume, Hospital Son Espases, Palma de Mallorca, Spain, 07120
Brazil (n=16)	Dr. Frederico B Carvalho, Hospital Luxemburgo, Belo Horizonte, Brazil, 32380-490 Dr. José Francisco K Saraiva, IPECC - Instituto de Pesquisa Clínica de Campinas, Campinas, Brazil, 13060-080 Juliana C Fernandes, M.D., Hospital Ernesto Dornelles, Porto Alegre, Brazil, 90160-092 Dr. Conrado R Hoffman Filho, Hospital Regional Hans Dieter Schmidt, Santa Catarina, Brazil, 89227

Country	**Sites**
	Suzana Lobo, M.D., Hospital de Base - Fac Med de Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil, 15090-000
Mexico (n=11)	Dr. Francisco Marquez Díaz, Hospital Cardiologica Aguascalientes, Aguascalientes, Mexico, 20230 Dr. Jorge A Zamudio Lerma, Hospital General de Culiacán "Dr. Bernardo J. Gastellum", Culiacán, Mexico, 80230 Dr. Luis Adrian Rendon Perez, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico, 64460
Chile (n=4)	María Schnettler, M.D., Hospital Padre Alberto Hurtado, Santiago, Chile, 8880465 Claudia M Cartagena Salinas, M.D., Hospital Carlos Van Buren, Valparaiso, Chile, 2341131

Table 2. Probabilities of observing an improvement of 5% under different scenarios

Assumed true value	**<5%**	**≥5%**
Negative scenario: Delta = 0%	78%	22%
Positive scenario: Delta = 9%	28%	72%

Table 3. Duration of oxygen use days by Day 29

	BI 764198 **n=65**	**Placebo** **n=63**
Duration of oxygen use by Day 29		
Days, mean (SD)	12.6 (10.8)	9.4 (10.1)
95% CI	12.3–17.1	8.8–13.7

Patients were analysed using ANCOVA with fixed effects of treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalization as covariates.

CI, confidence interval; SD, standard deviation.

Table 4. Patient characteristics, duration of treatment and time to death for patients who died

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
BR	76	Male	Black or African American	5	6-Moderately frail	BI 764198	1	12	Distributive shock, pneumonia, respiratory failure
CL	77	Male	White	5	6-Moderately frail	BI 764198	4*	26	Aspergillus infection

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
ES	75	Male	White	5	3-Managing well	BI 764198	8	10	Septic shock
MX	75	Male	American Indian or Alaskan Native	6	3-Managing well	BI 764198	18	19	Acute respiratory distress syndrome, pneumomediastinum, pneumothorax, haemothorax

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
MX	63	Male	American Indian or Alaskan Native	5	2-Well	BI 764198	13	14	Diarrhoea, COVID-19
USA	85	Male	Black or African American	6	6-Moderately frail	BI 764198	7	7	Respiratory failure, acute kidney injury
USA	75	Male	White	5	3-Managing well	BI 764198	6	59	Death (cause unknown,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									found at home in bed)
USA	68	Male	White	6	3-Managing well	BI 764198	16	20	Respiratory failure, liver injury, acute kidney injury
USA	62	Male	White	6	1-Very fit	BI 764198	8*	37	COVID-19 pneumonia, cardiac tamponade,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									acute respiratory failure, multiple organ dysfunction syndrome, acute kidney injury, pulmonary hypertension

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	60	Male	White	6	3-Managing well	BI 764198	4*	23	Acute myocardial infarction, COVID-19 pneumonia, respiratory failure, pneumomediastinum

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	54	Male	White	6	1-Very fit	BI 764198	6	65	Acute respiratory failure, COVID-19 pneumonia, septic shock, acute kidney injury, electrocardiogram QT prolonged

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	67	Male	White	6	3-Managing well	Placebo	10	11	Respiratory failure, septic shock, sepsis, acute kidney injury, pneumothorax
BR	56	Male	White	5	6-Moderately frail	Placebo	8*	30	Respiratory failure

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
MX	67	Male	American Indian or Alaskan Native	6	2-Well	Placebo	5	31	Acute respiratory distress syndrome, pneumomediastinum
USA	62	Female	Not given	6	3-Managing well	Placebo	7	27	COVID-19 pneumonia, respiratory failure,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									pulmonary hypertension, sepsis, acute kidney injury
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Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									dysfunction, respiratory failure, COVID-19 pneumonia, septic shock, acute respiratory failure, acute kidney injury, pulmonary

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									embolism, cardiac ventricular thrombosis

BR, Brazil; CL, Chile; ES, Spain; MX, Mexico; USA, United States.

*Treatment stopped on February 24, 2021 per trial treatment termination letter.

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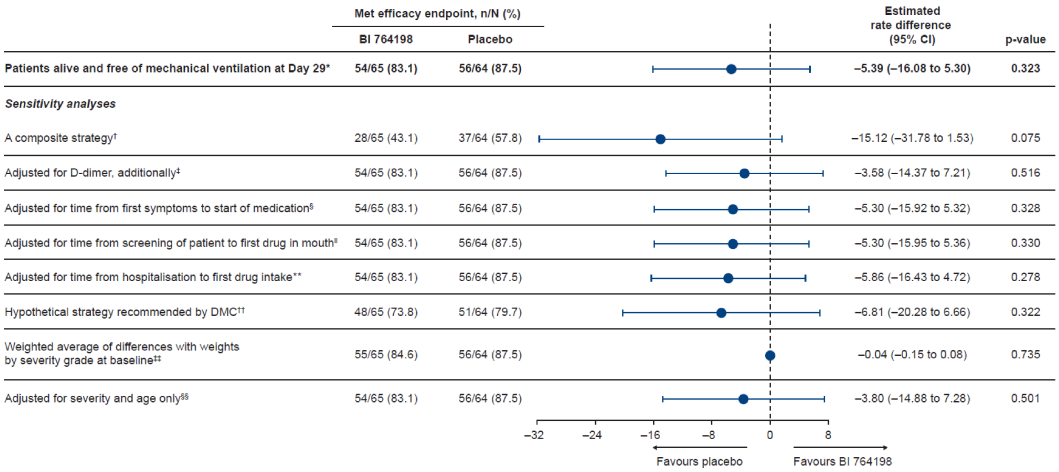
Patients who had completed treatment or were off-treatment†	54	53	107

*As of 22 February 2021. †Prior to 22 February 2021.

Figure S1. Sensitivity analyses of proportion of patients alive and free of mechanical ventilation at Day 29



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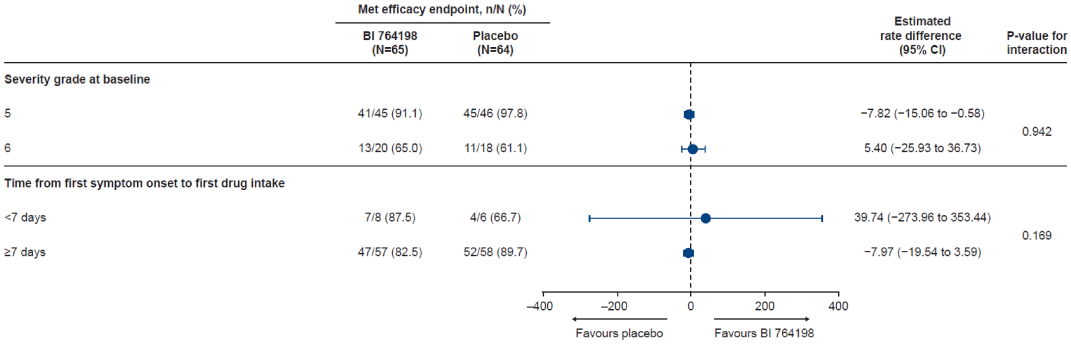
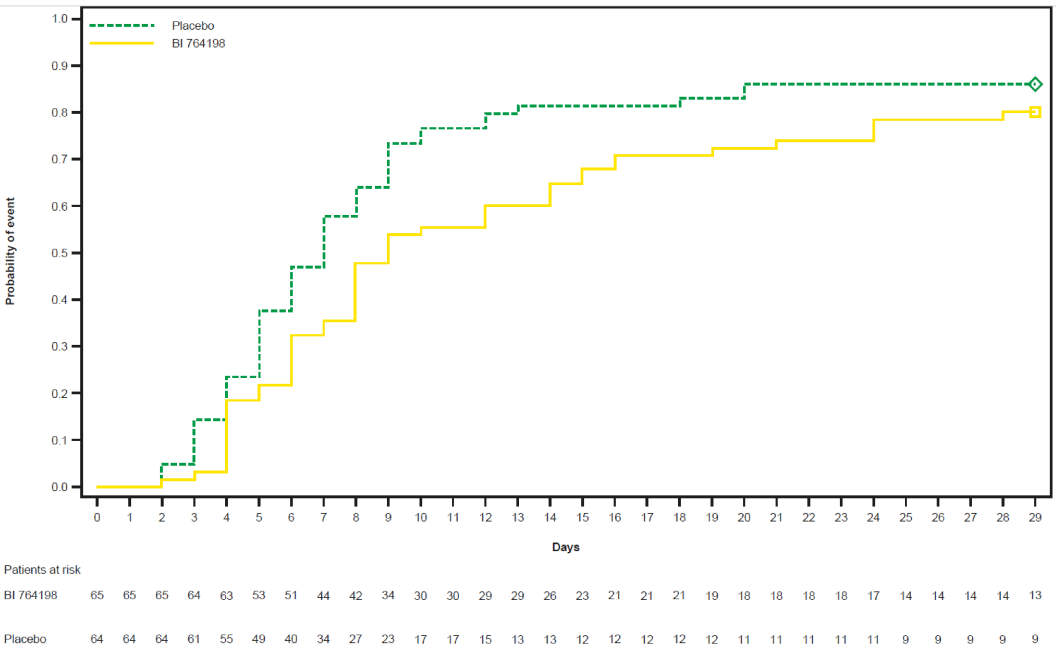
CI, confidence interval; DMC, Data Monitoring Committee.

Figure S2. Subgroup analyses of proportion of patients alive and free of mechanical ventilation at Day 29



CI, confidence interval

Figure S3. Time to first response of clinical improvement or recovery*



*First response of clinical improvement or recovery defined as the first of any one of: a 2-point decrease in score (from randomization) on the WHO Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (a score of 0, 1, 2, or 3 on the Clinical Progression Scale), whichever comes first, by Day 29.

ONLINE SUPPLEMENT

TRPC6 inhibitor (BI 764198) to reduce risk and severity of ARDS due to COVID-19: a Phase II randomised controlled trial

Lorraine B. Ware, Nima Soleymanlou, Danny F. McAuley, Vicente Estrada, George A. Diaz, Peter LaCamera, Renee Kaste, Wansuk Choi, Abhya Gupta, Tobias Welte

Supplementary Methods

Exclusion criteria

The exclusion criteria included: pulmonary oedema/respiratory failure due to cardiogenic insult; long-term oxygen therapy prior to current hospitalization; a history of cardiac conditions (myocardial infarction <3 months prior to first dose, unstable angina, and/or a prolonged QTc interval [as observed on an electrocardiogram or a family history of this]); received experimental, or off-label usage of, medicinal products as specific treatments for COVID-19; or any confounding condition.

Screening and dosage

Patients who are already hospitalised for COVID-19 were identified and screened. For patients who met the inclusion criteria, a confirmatory SARS-CoV-2 test (confirmed by polymerase chain reaction or an approved point-of-care test) was performed during the screening period (Day –3 to Day 1), after which study medication was administered on Day 1. Efforts were made to minimise the time between patient identification, screening and treatment initiation. Patients received daily BI 764198 or placebo in the form of an oral capsule or, only if needed, via nasogastric intubation, following overnight fasting and 1.5 hours prior to breakfast. Dose reductions or down-titrations were not permitted; however, trial treatment could be restarted following a temporary reason for treatment discontinuation. Drug administration was in-hospital and overseen by the clinical staff. For each dose of BI 764198 or placebo administered, the date, time and route (orally or via nasogastric intubation) was recorded in the electronic care report forms (eCRFs). Any missed doses were also recorded in the eCRFs.

Ware LB, *et al. Thorax* 2023;0:1–9. doi: 10.1136/thorax-2022-219668

Clinical, physiology and adverse events monitoring

Assessments of concomitant therapy and procedures, hospitalization status, WHO Clinical Progression Scale, ventilation and oxygen parameters (respiratory rate, fraction of inspired oxygen [FiO_2], oxygen saturation [SpO_2]) and blood gases/partial pressure of oxygen (PaO_2) (if captured as part of routine care) were carried out daily until hospital discharge (up to Day 28). All except blood gases/PaO_2 were also carried out during follow-up. Adverse events (AEs) were recorded daily and by telephone call following discharge from hospital 4 days after the end of treatment and on Days 15, 29, 60 and 90 (counted from Day 1 of the trial). Vital status was recorded at each follow-up visit. Follow-up visits were conducted by telephone calls. For patients that remained hospitalised after the end of the treatment period, follow-up visits were conducted in hospital until discharge and thereafter by telephone call. Trial completion was defined as the completion of all follow-up visits.

Statistical analysis

The proportions of patients alive and free of mechanical ventilation at Day 29 (primary endpoint) was analysed using a logistic regression model with covariates of treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalization. The logistic regression for the primary endpoint analysis was used for all other binary endpoints, whereas time-to-event endpoints were analysed using a Cox regression, which included the same covariates used for the primary endpoint analysis. The difference in ventilator-free days between BI 764198 and placebo groups was analysed using ANCOVA model including the same covariates as in the primary endpoint analysis.

Efficacy analyses were performed according to a prespecified analysis plan in all randomized patients documented to have received at least one dose of trial medication (full analysis

Ware LB, *et al. Thorax* 2023;0:1–9. doi: 10.1136/thorax-2022-219668

set). The intent-to-treat principle was applied to the randomized set, including all observed data in the primary analysis regardless of treatment discontinuation.

Sensitivity and subgroup analyses

A sensitivity analysis was conducted with a logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, D-dimer at baseline, and duration of symptoms before hospitalisation. Subgroup analysis was performed using descriptive statistics.

Determination of sample size

The proportion of patients assumed to be alive and free of mechanical ventilation at Day 29 in the placebo group is expected to be ~81%. It is assumed that BI 764198 would increase this proportion by 9% (from 81% to 90%). The probability of observing ≥5% improvement in the primary endpoint (≥86% in BI 764198 group as opposed to 81% in placebo group) is 72% under this assumption with a total of 130 patients (65 patients per group). If there is no treatment effect (81% in both BI 764198 and placebo group), the probability of observing ≥5% improvement is 22% as depicted in Table E2. As the treatment policy is used to analyse the primary endpoint, early discontinuation is not considered in the sample size calculation.

Table 1. Trial site locations

Country	Sites
United States (n=61)	Dr. Richard A Lee, University of California Irvine, Orange, California, United States, 92868 Dr. Naseem A Jaffrani, Rapides Regional Medical Center, Alexandria, Louisiana, United States, 71301 Dr. Peter LaCamera, St. Elizabeth's Medical Center, Boston, Massachusetts, United States, 02135 Dr. Harry M Schrager, Newton-Wellesley Hospital, Newton, Massachusetts, United States, 02462 Dr. Salil Avasthi, Mercy Health St. Vincent Medical Center, Toledo, Ohio, United States, 43608 Dr. George A Diaz, Providence Regional Medical Center, Everett, Washington, United States, 98201 Dr. Patrick S Meehan, MultiCare Tacoma General Hospital, Tacoma, Washington, United States, 98405 Dr. Alvaro U Aranda-Rodriguez, Hospital Auxilio Mutuo, Hato Rey, Puerto Rico, 00919 Dr. Ricardo Fernandez-Gonzalez, Hospital Municipal de San Juan, Rio Piedras, Puerto Rico, 00936

Country	**Sites**
Spain (n=37)	Dr. Enrique Míguez, Hospital A Coruña, A Coruña, Spain, 15006 Dr. Sergio Reus, Hospital General Universitario de Alicante, Alicante, Spain, 03010 Dr. Jesús Troya García, Hospital Universitario Infanta Leonor, Madrid, Spain, 28031 Dr. Vicente Estrada, Hospital Clínico San Carlos, Madrid, Spain, 28040 Dr. Cristina de la Calle, Hospital Universitario 12 de Octubre, Madrid, Spain, 28041 Dr. Melchor Riera Jaume, Hospital Son Espases, Palma de Mallorca, Spain, 07120
Brazil (n=16)	Dr. Frederico B Carvalho, Hospital Luxemburgo, Belo Horizonte, Brazil, 32380-490 Dr. José Francisco K Saraiva, IPECC - Instituto de Pesquisa Clínica de Campinas, Campinas, Brazil, 13060-080 Juliana C Fernandes, M.D., Hospital Ernesto Dornelles, Porto Alegre, Brazil, 90160-092 Dr. Conrado R Hoffman Filho, Hospital Regional Hans Dieter Schmidt, Santa Catarina, Brazil, 89227

Country	**Sites**
	Suzana Lobo, M.D., Hospital de Base - Fac Med de Sao Jose do Rio Preto, Sao Jose do Rio Preto, Brazil, 15090-000
Mexico (n=11)	Dr. Francisco Marquez Díaz, Hospital Cardiologica Aguascalientes, Aguascalientes, Mexico, 20230 Dr. Jorge A Zamudio Lerma, Hospital General de Culiacán "Dr. Bernardo J. Gastellum", Culiacán, Mexico, 80230 Dr. Luis Adrian Rendon Perez, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico, 64460
Chile (n=4)	María Schnettler, M.D., Hospital Padre Alberto Hurtado, Santiago, Chile, 8880465 Claudia M Cartagena Salinas, M.D., Hospital Carlos Van Buren, Valparaiso, Chile, 2341131

Table 2. Probabilities of observing an improvement of 5% under different scenarios

Assumed true value	**<5%**	**≥5%**
Negative scenario: Delta = 0%	78%	22%
Positive scenario: Delta = 9%	28%	72%

Table 3. Duration of oxygen use days by Day 29

	BI 764198 **n=65**	**Placebo** **n=63**
Duration of oxygen use by Day 29		
Days, mean (SD)	12.6 (10.8)	9.4 (10.1)
95% CI	12.3–17.1	8.8–13.7

Patients were analysed using ANCOVA with fixed effects of treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalization as covariates.

CI, confidence interval; SD, standard deviation.

Table 4. Patient characteristics, duration of treatment and time to death for patients who died

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
BR	76	Male	Black or African American	5	6-Moderately frail	BI 764198	1	12	Distributive shock, pneumonia, respiratory failure
CL	77	Male	White	5	6-Moderately frail	BI 764198	4*	26	Aspergillus infection

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
ES	75	Male	White	5	3-Managing well	BI 764198	8	10	Septic shock
MX	75	Male	American Indian or Alaskan Native	6	3-Managing well	BI 764198	18	19	Acute respiratory distress syndrome, pneumomediastinum, pneumothorax, haemothorax

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
MX	63	Male	American Indian or Alaskan Native	5	2-Well	BI 764198	13	14	Diarrhoea, COVID-19
USA	85	Male	Black or African American	6	6-Moderately frail	BI 764198	7	7	Respiratory failure, acute kidney injury
USA	75	Male	White	5	3-Managing well	BI 764198	6	59	Death (cause unknown,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									found at home in bed)
USA	68	Male	White	6	3-Managing well	BI 764198	16	20	Respiratory failure, liver injury, acute kidney injury
USA	62	Male	White	6	1-Very fit	BI 764198	8*	37	COVID-19 pneumonia, cardiac tamponade,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
									acute respiratory failure, multiple organ dysfunction syndrome, acute kidney injury, pulmonary hypertension

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	60	Male	White	6	3-Managing well	BI 764198	4*	23	Acute myocardial infarction, COVID-19 pneumonia, respiratory failure, pneumomediastinum

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	54	Male	White	6	1-Very fit	BI 764198	6	65	Acute respiratory failure, COVID-19 pneumonia, septic shock, acute kidney injury, electrocardiogram QT prolonged

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
USA	67	Male	White	6	3-Managing well	Placebo	10	11	Respiratory failure, septic shock, sepsis, acute kidney injury, pneumothorax
BR	56	Male	White	5	6-Moderately frail	Placebo	8*	30	Respiratory failure

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
MX	67	Male	American Indian or Alaskan Native	6	2-Well	Placebo	5	31	Acute respiratory distress syndrome, pneumomediastinum
USA	62	Female	Not given	6	3-Managing well	Placebo	7	27	COVID-19 pneumonia, respiratory failure,

Country	Age	Sex	Race	Score on WHO clinical scale at baseline	Clinical frailty scale	Treatment arm	Time on treatment, days	Time to death after start of treatment, days	AEs (preferred term)
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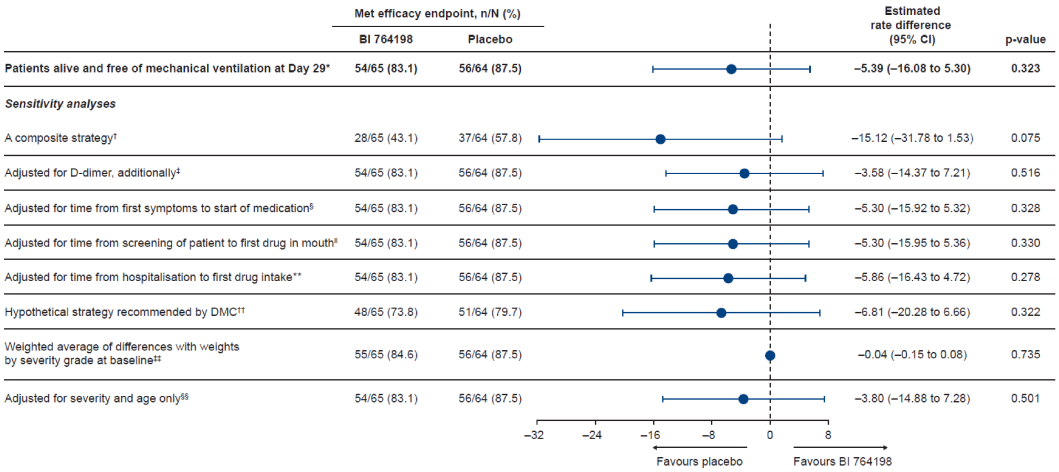

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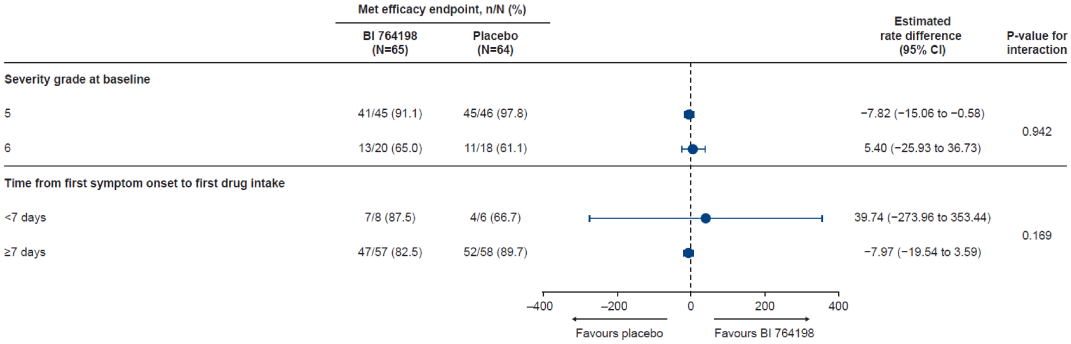

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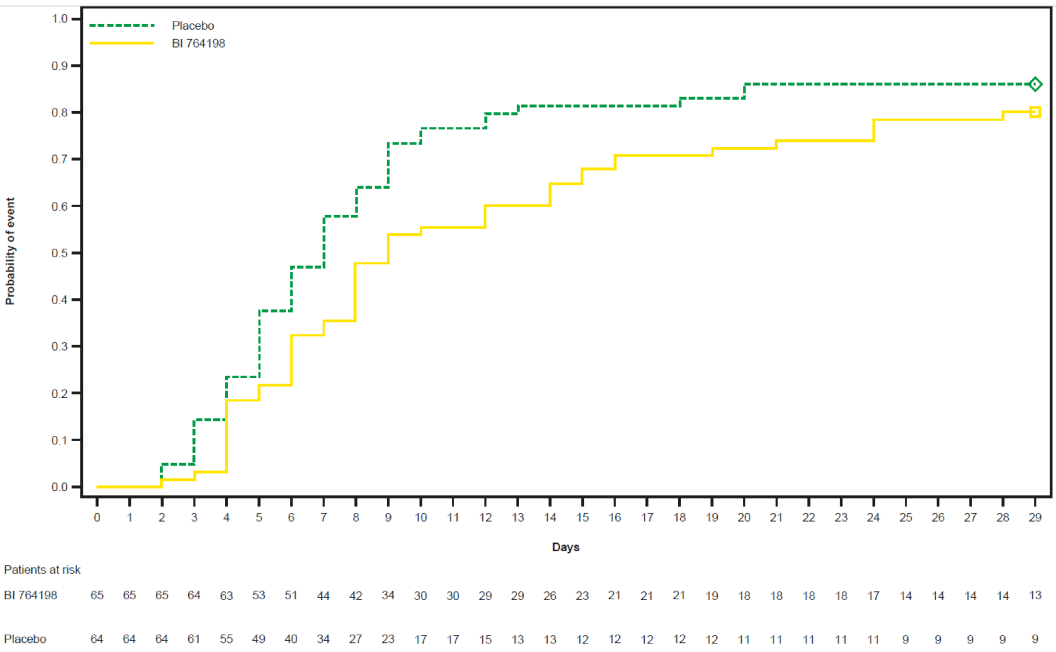
Figure S3. Time to first response of clinical improvement or recovery*



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