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
USA	54	Male	Asian	6	2-Well	Placebo	13	22	Hypotension, bradycardia, right ventricular dilatation, right ventricular

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.

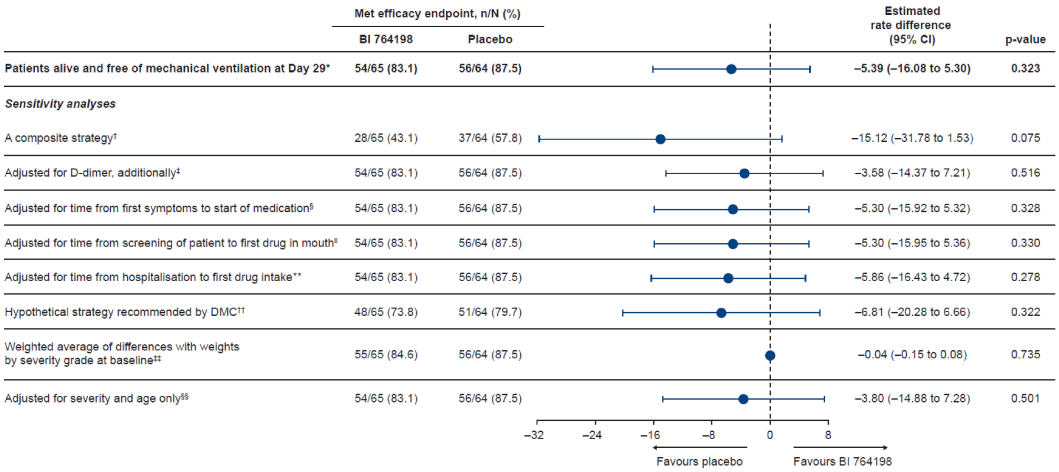
*Treatment stopped on February 24, 2021 per trial treatment termination letter.

Table 5. Treatment status of patients at the time notification of study discontinuation was implemented

	BI 764198 n=65	**Placebo n=64**	**Total n=129**
Patients randomised but not treated*	3	2	5
Patients receiving active treatment*	8	9	17
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

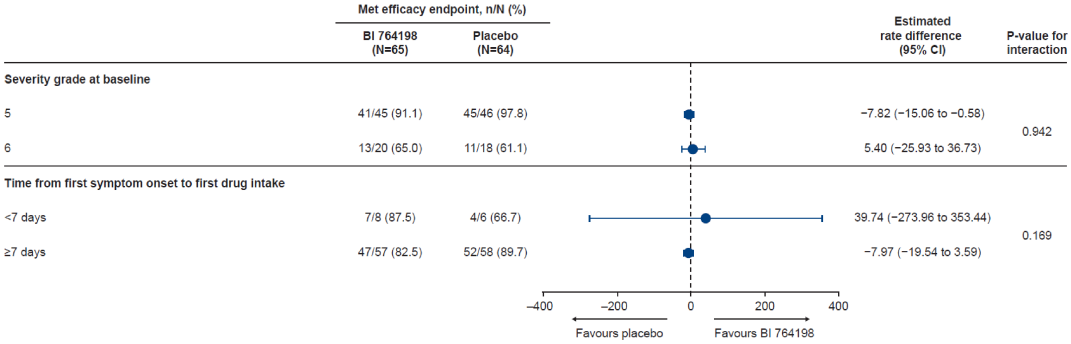


*The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline and duration of symptoms before hospitalization as covariates. †A composite strategy considers patients with treatment discontinuation, death and use of standard of care after initiation with BI 764198 as treatment failures. ‡The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline, D-dimer at baseline and duration of symptoms before hospitalization as covariates. §The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline and time from first symptoms to start medication as covariates. ‖The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline and time from screening of patient to first drug in mouth as covariates. **The logistic regression model includes treatment, severity grade at baseline, age, creatinine at baseline and time from hospitalization to first drug intake as covariates. ††Hypothetical estimate of treated patients who stopped treatment due to sponsor´s request as non-responders. ‡‡Severity grade at baseline is used for weights. §§The logistic regression model includes treatment,

severity grade at baseline and age.

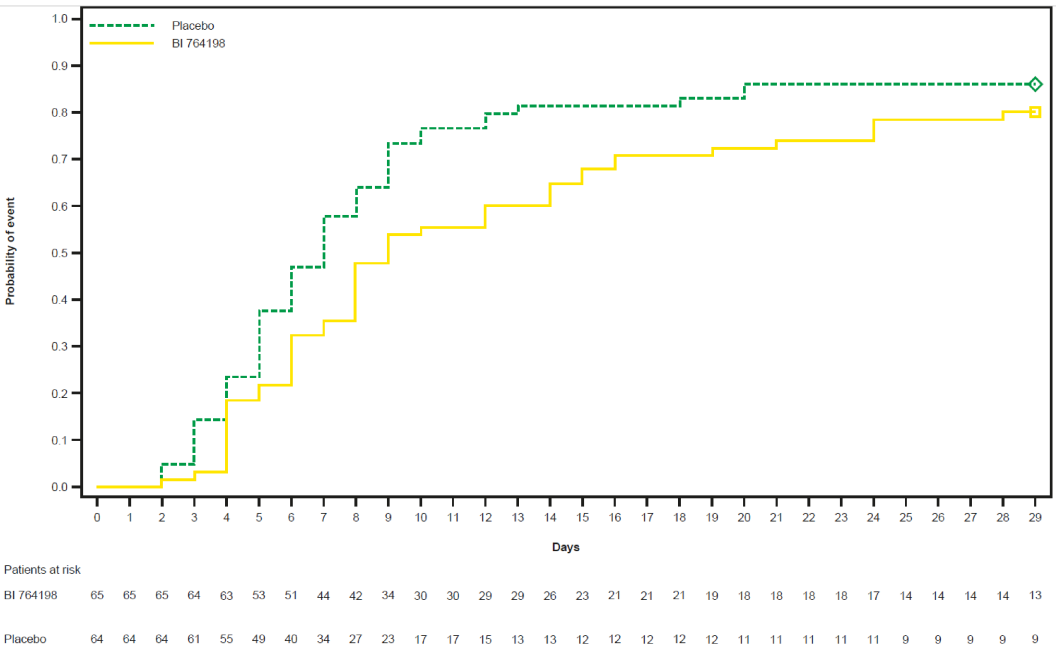
CI, confidence interval; DMC, Data Monitoring Committee.

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.