Supplemental material

Manuscript title

Efficacy and safety of an inhaled pan-Janus kinase inhibitor, nezulcitinib, in hospitalised patients with COVID-19: Results from a Phase 2 clinical trial

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Belperio J, *et al. BMJ Open Respir Res* 2023; 10:e001627. doi: 10.1136/bmjresp-2023-001627

SUPPLEMENTAL METHODS

Patients

Patients receiving invasive mechanical ventilation at screening were excluded, as were patients who in the investigator's opinion were unlikely to survive for 24 hours or longer or who had a significant comorbidity predisposing them to mortality such as New York Heart Association Class IV Heart Failure, hepatic dysfunction, or renal dysfunction. Renal dysfunction was defined as estimated glomerular filtration rate <50 mL/min or receiving renal replacement therapy. Other exclusion criteria included requiring continuous oxygen supplementation for underlying cardiorespiratory disease in the past 90 days; evidence of serious active infections other than COVID-19; presence of an active malignancy (skin cancer was an exception); septic shock at enrolment; current diagnosis of human immunodeficiency virus or hepatitis B or C; active or incompletely treated pulmonary tuberculosis (or known history of non-tuberculosis mycobacterium over the past 12 months); hypersensitivity to nezulcitinib or its components (or to other Janus kinase [JAK] inhibitors); haemoglobin <80 g/L; neutropaenia (<1000 cells/μL), lymphopaenia (<200 cells/μL), or thrombocytopaenia (<50 x 10^9/L); history of venous thromboembolism, deep venous thrombosis, pulmonary embolism, or hypercoagulable state; or body mass index ≥40 kg/m^2. Treatment with anti–interleukin (IL)-6, anti–IL-1, or anti–T-cell antibodies; IL-6 receptor antagonists; supplemental interferon therapy, tyrosine kinase inhibitors, or JAK inhibitors within the past 30 days; or planning to receive a JAK inhibitor during the study were not permitted. Patients did not receive methotrexate, cyclosporine, mycophenolate, tacrolimus, penicillamine, or sulfasalazine within 2 weeks; tumour necrosis factor-α inhibitors within 4 weeks; or azathioprine, cyclophosphamide, or monoclonal antibodies targeting B cells within 12 weeks before enrolment. Patients receiving any live vaccine within 4 weeks before study Visit 1, planning to receive a live vaccine during the study period, or participating in other clinical trials involving any other experimental treatment for COVID-19 except in the context of a single-arm antiviral or convalescent plasma compassionate-use protocol were also excluded. All participants agreed to not donate sperm or ova through 30 days of the last dose of study medication, and women who were pregnant, thought to be pregnant, or breastfeeding, were excluded.

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Procedures

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) were recorded after the patient had rested in a semirecumbent position for approximately 5 minutes before the first daily dose on Days 1 through 7 and on Days 14, 21, and 28 and/or at hospital discharge. Physical examination including documentation of hepatomegaly or splenomegaly was performed on Days 1 and 7. Concomitant medications and adverse events were recorded as was clinical status. Blood was collected for haematology and serum chemistry evaluations on Day 1 and Day 7; results of any laboratory evaluations performed for patient care through Day 28 were also recorded. Minimum laboratory evaluations included a complete blood count with differential, renal function assessments (creatinine and blood urea nitrogen), liver function assessments (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin), and triglycerides. If feasible, additional blood samples and upper respiratory tract swabs were collected on Day 1 (ideally, predose) and 3 hours ± 2 hours postdose on Days 5 (Part 2 only) and 7, and at discharge (Part 2 only) to assess biomarkers and infection status.

Statistical analysis

Efficacy analyses were anticipated to be stratified by concurrent antiviral use, but this was not performed after blinded internal review indicated the majority of patients did not receive antiviral treatment. Treatment comparison of nezulcitinib vs placebo for the primary efficacy endpoint of number of respiratory failure-free (RFF) days through Day 28 was evaluated from the proportional odds (PO) ordinal regression model adjusting for baseline age strata (≤60 vs >60 years). The *P*-value was based on the Van Elteren test adjusted for baseline age strata since the PO assumption was not met; the difference between nezulcitinib-treated and placebo-treated patients was summarised based on median number of days. Change in SaO_2/FiO_2 ratio at Day 7 was compared between patients receiving nezulcitinib and placebo using a mixed model repeated measures including fixed effects for treatment, study day, treatment group by study day interaction, baseline SaO_2/FiO_2 ratio, treatment group by baseline SaO_2/FiO_2 ratio interaction and baseline age group, and a random effect for each patient. Covariance of within-patient

scores was estimated using an unstructured covariance matrix, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. Least squares means, standard errors, treatment differences in least squares means, and 95% confidence intervals were estimated from the model, and a 2-sided nominal *P*-value for the comparison between patients receiving nezulcitinib and placebo was reported. Proportion of patients in each clinical status category at Days 7, 14, 21, and 28 was evaluated using a PO ordinal regression model adjusting for baseline age group with *P*-value based on Van Elteren test since the PO assumption was not met. Treatment comparisons for binary endpoints of 28-day mortality rate and proportion of patients alive and RFF on Day 28 were analysed using an unstratified Cochran-Mantel-Haenszel (CMH) chi-square test, and CMH test stratified by baseline age group, respectively. For time-to-event endpoints (time to recovery and ventilator-free survival), within-group summaries (median and third-quartile time) were analysed using over time (postbaseline) Kaplan-Meier estimates, and treatment comparison was evaluated using a Cox proportional hazards model adjusting for baseline age strata with *P*-value based on log-rank test (stratified by baseline age group). Statistical tests of treatment effects were performed at a 2-sided significance level of 0.05. No multiplicity adjustment was performed due to the hypothesis-generating nature of this Phase 2 study.

Supplemental Table 1: Ordinal 8-point clinical status scale

Status/Criteria	Score
Death	8
Hospitalised, on invasive mechanical ventilation or ECMO	7
Hospitalised, on noninvasive ventilation or high-flow oxygen device	6
Hospitalised, requiring supplemental oxygen	5
Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care[a]	4
Hospitalised, not requiring supplemental oxygen or ongoing medical care[b]	3
Not hospitalised, but with limitation on activities and/or requiring home oxygen	2
Not hospitalised, no limitations on activities	1

[a]Whether or not related to COVID-19.
[b]Including hospitalisation for infection control.
ECMO, extracorporeal membrane oxygenation.

Supplemental Table 2: Baseline demographics for subgroups of baseline CRP <150 and ≥150 mg/L[a]

	Baseline CRP <150 mg/L (N = 171)[a]		Baseline CRP ≥150 mg/L (N = 30)[a]	
	Placebo (n = 85)	**Nezulcitinib (n = 86)**	**Placebo (n = 13)**	**Nezulcitinib (n =17)**
Age, years, mean ± SD	57.6 ± 12.6	57.8 ± 12.9	61.8 ± 10.8	59.9 ± 10.6
Ethnicity				
Hispanic or Latino	7 (8.2)	8 (9.3)	2 (15.4)	5 (29.4)
Not Hispanic or Latino	75 (88.2)	76 (88.4)	11 (84.6)	12 (70.6)
Unknown	0	1 (1.2)	0	0
Not reported	3 (3.5)	1 (1.2)	0	0
Sex				
Male	50 (58.8)	53 (61.6)	8 (61.5)	11 (64.7)
Female	35 (41.2)	33 (38.4)	5 (38.5)	6 (35.3)
Race				
White	83 (97.6)	86 (100)	13 (100)	16 (94.1)
Black or African American	0	0	0	1 (5.9)
Other	1 (1.2)	0	0	0
Multiple	1 (1.2)	0	0	0
BMI, kg/m^2, mean ± SD	30.0 ± 4.06	29.9 ± 3.55	32.0 ± 4.31	31.3 ± 4.20
Comorbidities				
None	24 (28.2)	28 (32.6)	3 (23.1)	3 (17.6)
One	22 (25.9)	19 (22.1)	3 (23.1)	6 (35.3)
Two or More	39 (45.9)	39 (45.3)	7 (53.8)	8 (47.1)
Clinical status (ordinal scale)				
5	69 (81.2)	73 (84.9)	8 (61.5)	12 (70.6)
6	16 (18.8)	13 (15.1)	5 (38.5)	5 (29.4)
Oxygen flow rate, L/min, mean ± SD	6.49 ± 2.33	6.94 ± 5.32	7.62 ± 3.91	9.75 ± 13.6
SaO_2/FiO_2 ratio, mean ± SD	242.43 ± 59.94	244.43 ± 64.74	216.52 ± 81.71	222.08 ± 67.13

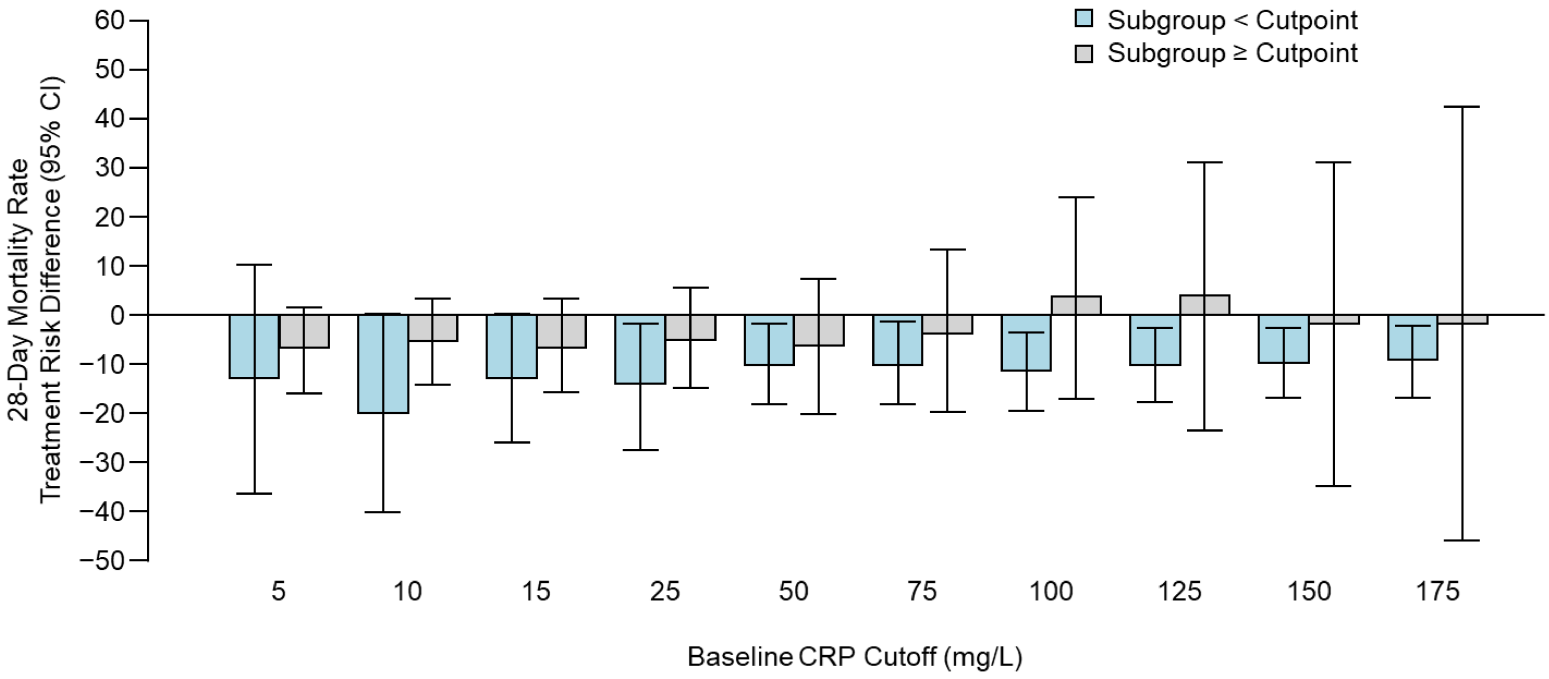
Data are shown as n (%) unless otherwise specified.

[a]Baseline CRP values were available for 98 patients in the placebo arm and 103 in the nezulcitinib arm.

BMI, body mass index; CRP, C-reactive protein; FEU, fibrinogen-equivalent units; FiO_2, fraction of inspired oxygen; ITT, intent-to-treat; LDH, lactate dehydrogenase; SaO, peripheral oxygen saturation; SD, standard deviation.

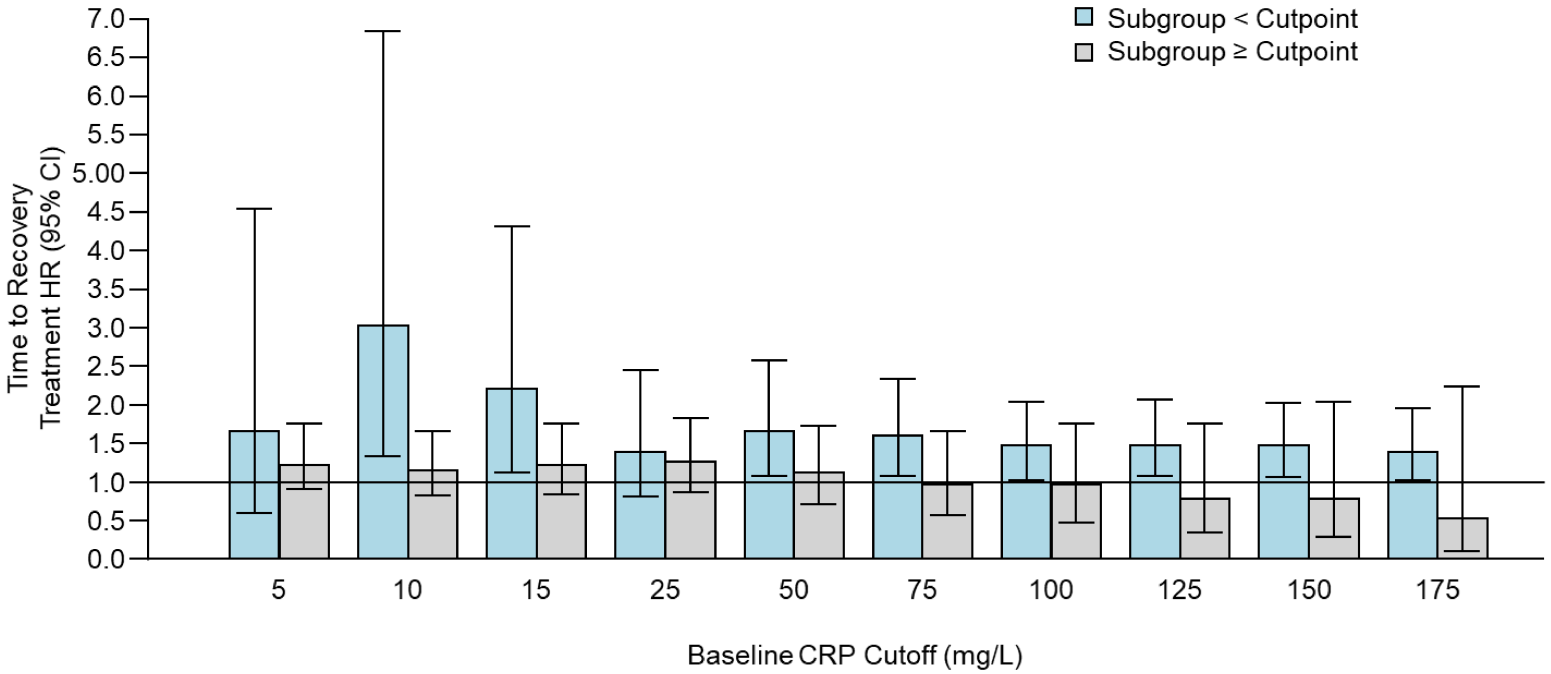
Supplemental Figure 1. Supporting analyses of the CRP threshold of 150 mg/L for subgroup analyses showing the treatment risk difference for nezulcitinib vs placebo for **A)** 28-day mortality rate, **B)** time to recovery, and **C)** 28-day invasive mechanical ventilation or death in the ITT population.

a)



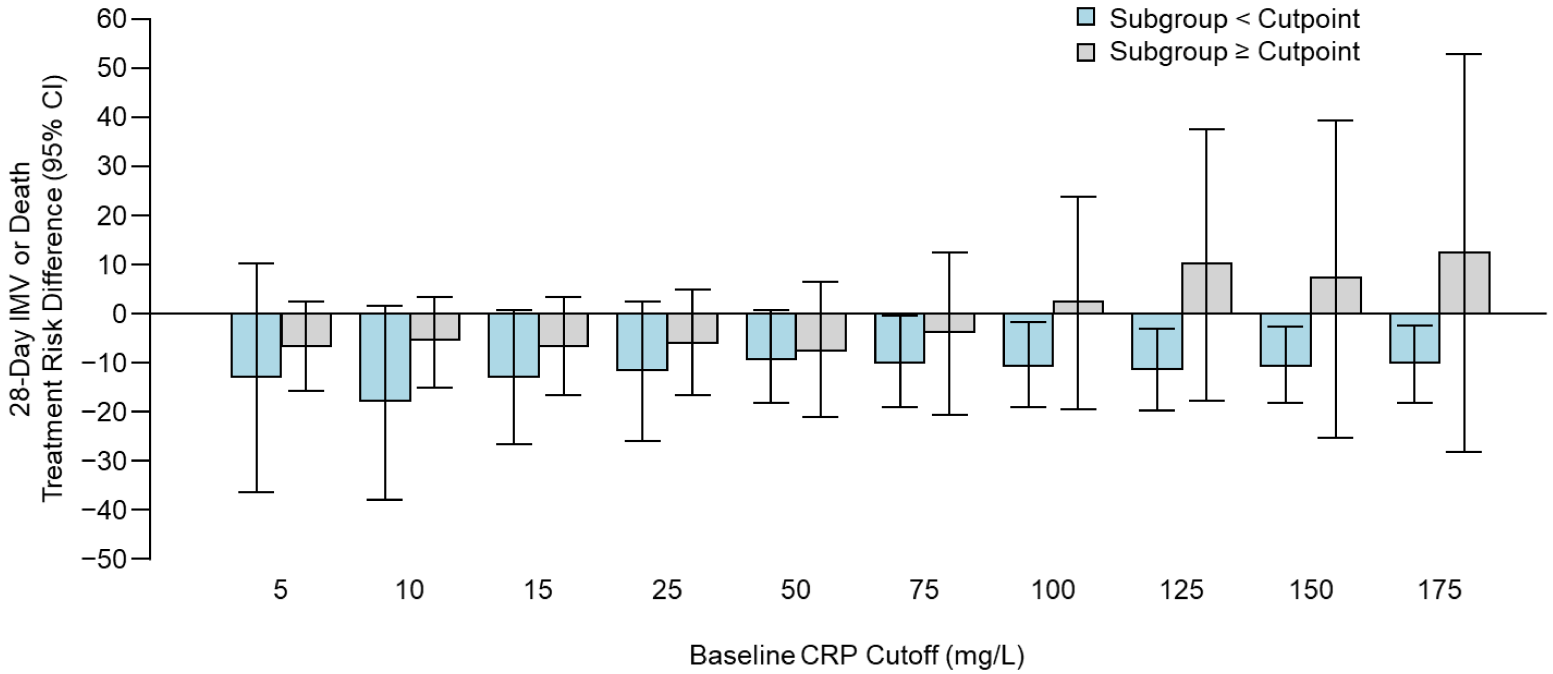
Subgroup size	19	182	31	170	44	157	57	144	99	102	127	74	149	52	164	37	171	30	182	19
RD (vs. PBO)	−12.50	−6.81	−20.00	−5.15	−12.50	−6.28	−14.29	−4.75	−9.80	−6.11	−9.75	−3.51	−11.20	3.85	−10.06	4.09	−9.43	−1.36	−8.94	−1.14
RD 95% CL	−35.42	−15.46	−40.24	−13.95	−25.73	−15.86	−27.25	−14.76	−17.97	−19.65	−18.18	−19.75	−19.25	−16.69	−17.36	−23.49	−16.35	−34.50	−16.08	−45.11
RD 95% CU	10.42	1.84	0.24	3.65	0.73	3.29	−1.32	5.26	−1.64	7.43	−1.33	12.73	−3.15	24.38	−2.76	31.68	−2.50	31.79	−1.79	42.84
P-val	0.241	0.125	0.064	0.252	0.105	0.195	0.036	0.353	0.027	0.374	0.024	0.674	0.006	0.717	0.007	0.775	0.009	0.937	0.015	0.961

b)



Subgroup size	19	182	31	170	44	157	57	144	99	102	127	74	149	52	164	37	171	30	182	19
HR (vs. PBO)	1.68	1.27	3.07	1.18	2.24	1.24	1.39	1.28	1.68	1.13	1.61	0.99	1.47	0.96	1.50	0.80	1.48	0.78	1.43	0.50
HR 95% CL	0.62	0.92	1.36	0.85	1.15	0.87	0.79	0.89	1.09	0.73	1.11	0.59	1.04	0.51	1.08	0.36	1.07	0.30	1.04	0.11
HR 95% CU	4.57	1.75	6.90	1.64	4.35	1.75	2.45	1.84	2.58	1.75	2.35	1.66	2.07	1.81	2.08	1.75	2.04	2.01	1.95	2.26
Log-rank p-val	0.186	0.146	0.002	0.351	0.012	0.230	0.250	0.174	0.018	0.603	0.013	0.982	0.036	0.971	0.018	0.636	0.020	0.549	0.030	0.254

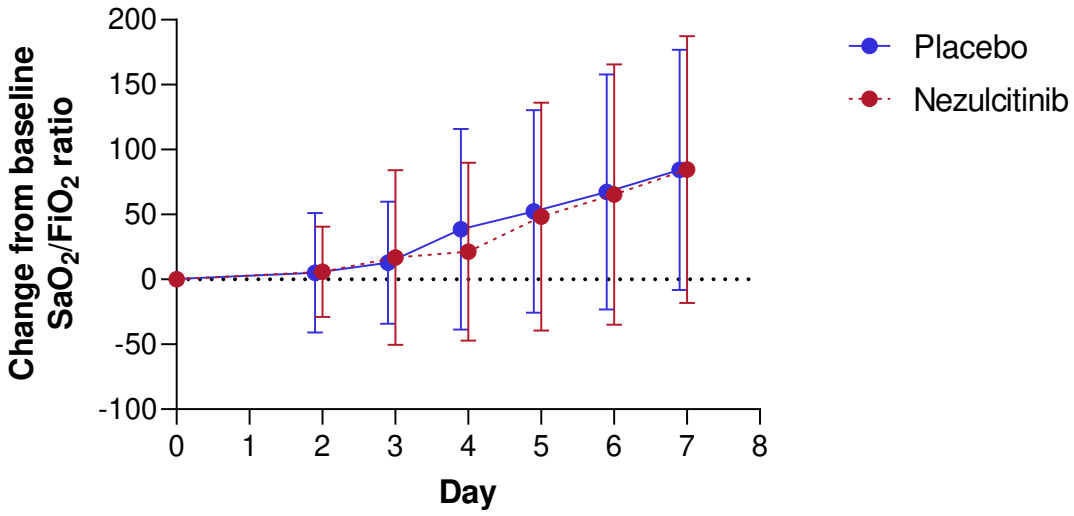
c)



Subgroup size	19	182	31	170	44	157	57	144	99	102	127	74	149	52	164	37	171	30	182	19
RD (vs. PBO)	−12.98	−6.86	−18.25	−5.61	−13.12	−6.48	−11.53	−6.02	−9.12	−7.48	−9.73	−4.13	−10.85	2.20	−11.54	10.11	−10.82	7.30	−10.20	12.36
RD 95% CL	−36.22	−16.03	−38.09	−15.06	−26.59	−16.73	−25.85	−16.52	−18.64	−21.30	−18.86	−20.99	−19.36	−19.74	−19.63	−17.53	−18.53	−25.24	−17.97	−28.83
RD 95% CU	10.26	2.30	1.59	3.84	0.35	3.76	2.79	4.48	0.40	6.34	−0.61	12.73	−2.33	24.14	−3.44	37.75	−3.11	39.94	−2.43	53.55
P-val	0.221	0.145	0.080	0.247	0.082	0.214	0.122	0.263	0.073	0.289	0.037	0.636	0.012	0.848	0.005	0.486	0.007	0.669	0.011	0.589

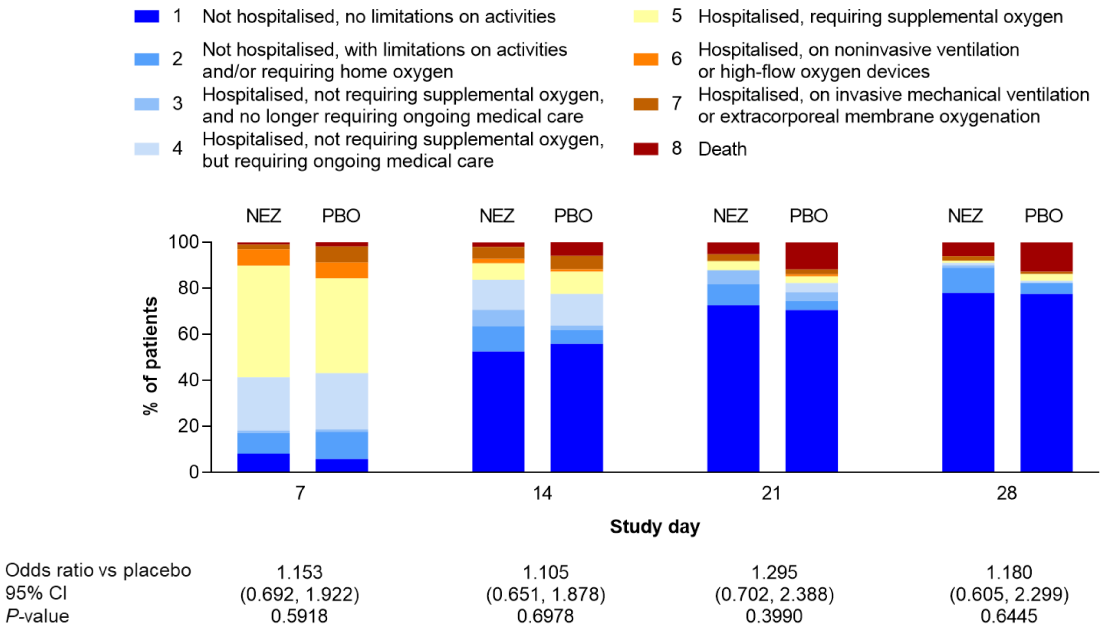
CI, confidence interval; CL, confidence interval lower bound; CRP, C-reactive protein; CU, confidence interval upper bound; HR, hazard ratio; IMV, invasive mechanical ventilation; ITT, intent-to-treat; PBO, placebo; P-val, *P*-value; RD, risk difference.

Supplemental Figure 2: Least squares means for change from baseline in SaO_2/FiO_2 ratio in the ITT analysis set.



Least squares means for change from baseline in SaO_2/FiO_2 ratio were obtained from MMRM model. FiO_2, fraction of inspired oxygen; ITT, intent-to-treat; MMRM, mixed model repeated measures; SaO_2, oxygen saturation.

Supplemental Figure 3: Proportion of patients in each category of the 8-point clinical status scale in the ITT population

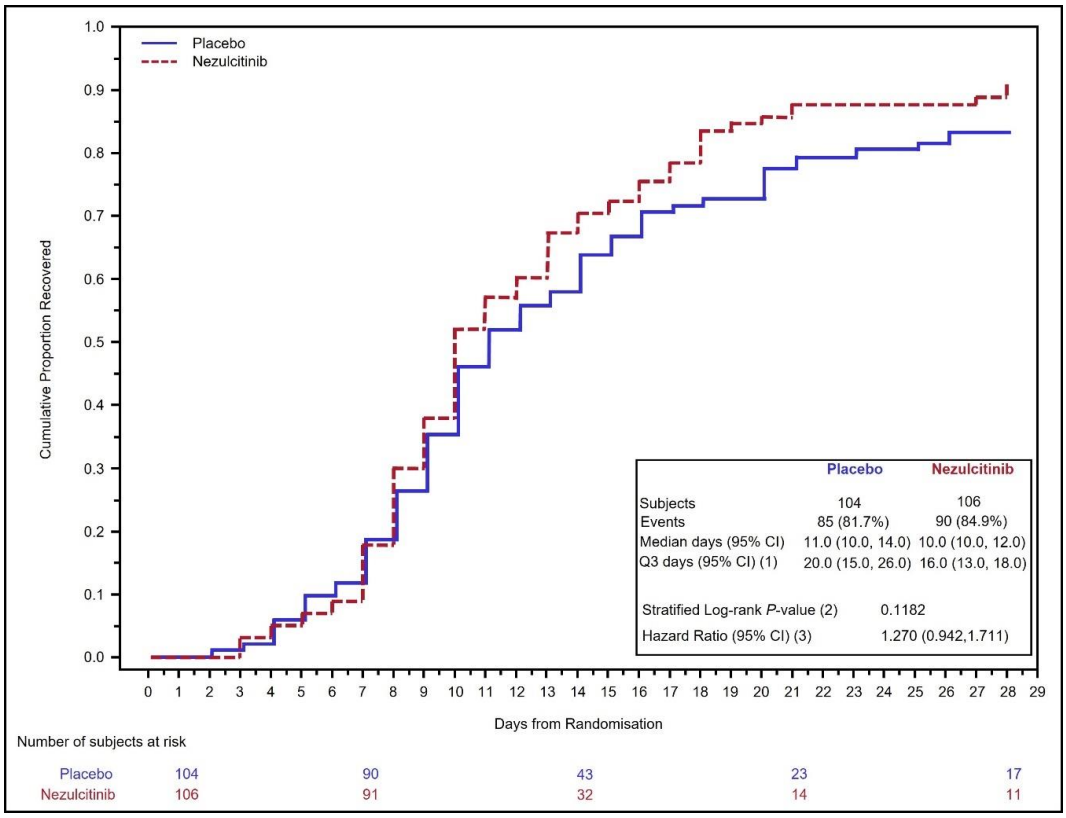


Treatment effect OR and 95% CI (nezulcitinib 3 mg vs placebo) was assessed from the PO ordinal regression model adjusting for baseline age strata (≤60 vs >60 years). *P*-values are based on the Van Elteren test stratified by baseline age strata.

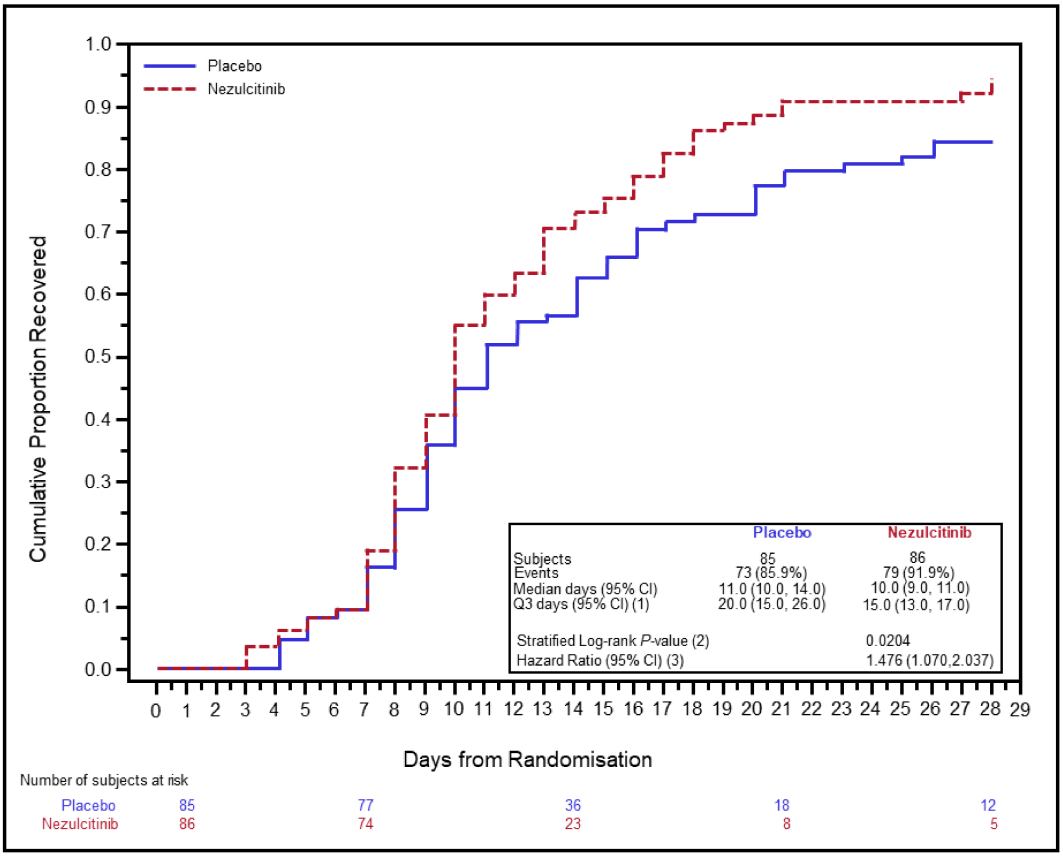
CI, confidence interval; ITT, intent-to-treat; NEZ, nezulcitinib 3 mg; OR, odds ratio; PBO, placebo; PO, proportional odds.

Supplemental Figure 4: Kaplan-Meier estimates of time to recovery in the **a)** ITT analysis set and post hoc subgroups defined by **b)** baseline CRP <150 mg/L and **c)** baseline CRP ≥150 mg/L

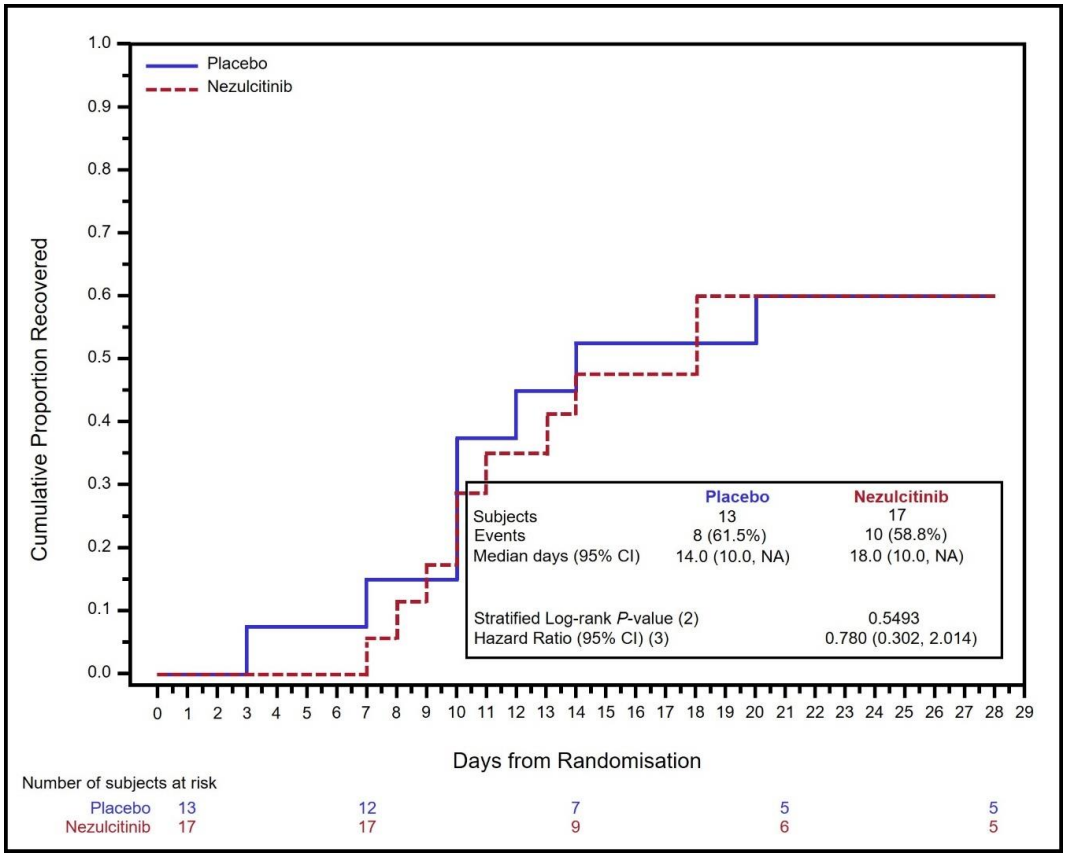
a)



b)


Placebo
Nezulcitinib
Cumulative Proportion Recovered
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Days from Randomisation
Placebo Nezulcitinib
Subjects 85 86
Events 73 (85.9%) 79 (91.9%)
Median days (95% CI) 11.0 (10.0, 14.0) 10.0 (9.0, 11.0)
Q3 days (95% CI) (1) 20.0 (15.0, 26.0) 15.0 (13.0, 17.0)
Stratified Log-rank P-value (2) 0.0204
Hazard Ratio (95% CI) (3) 1.476 (1.070,2.037)
Number of subjects at risk
Placebo 85 77 36 18 12
Nezulcitinib 86 74 23 8 5

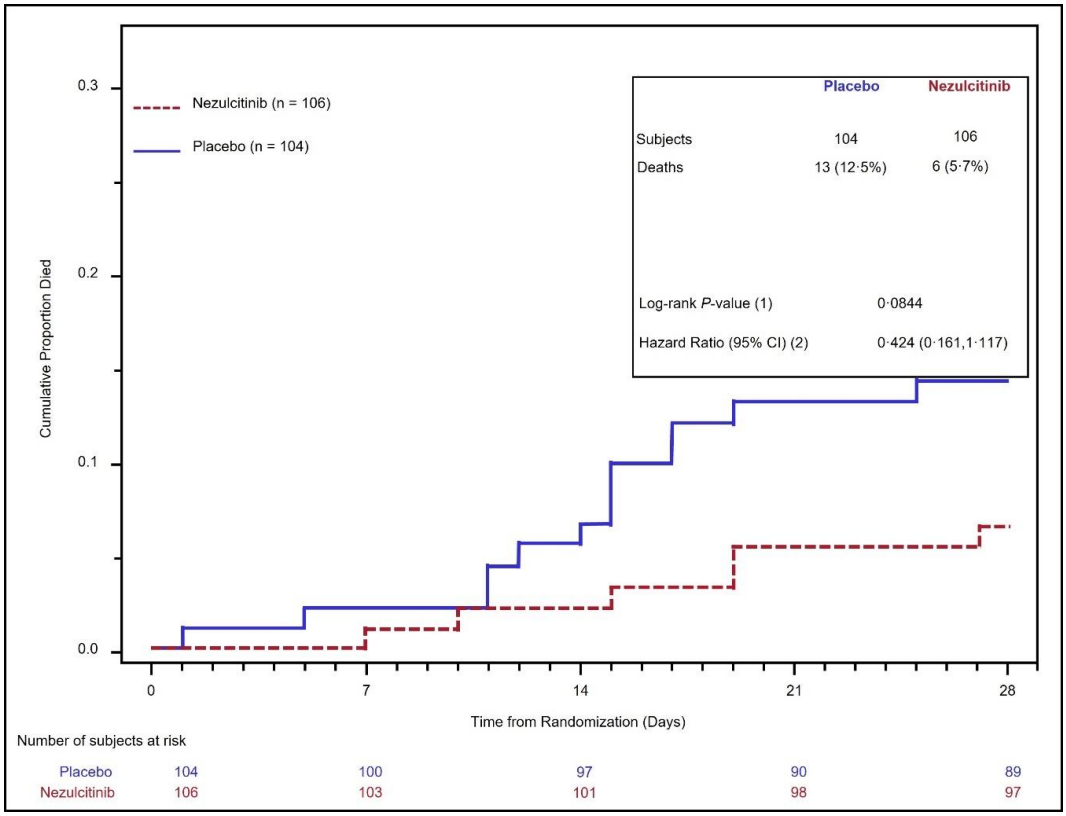
c)



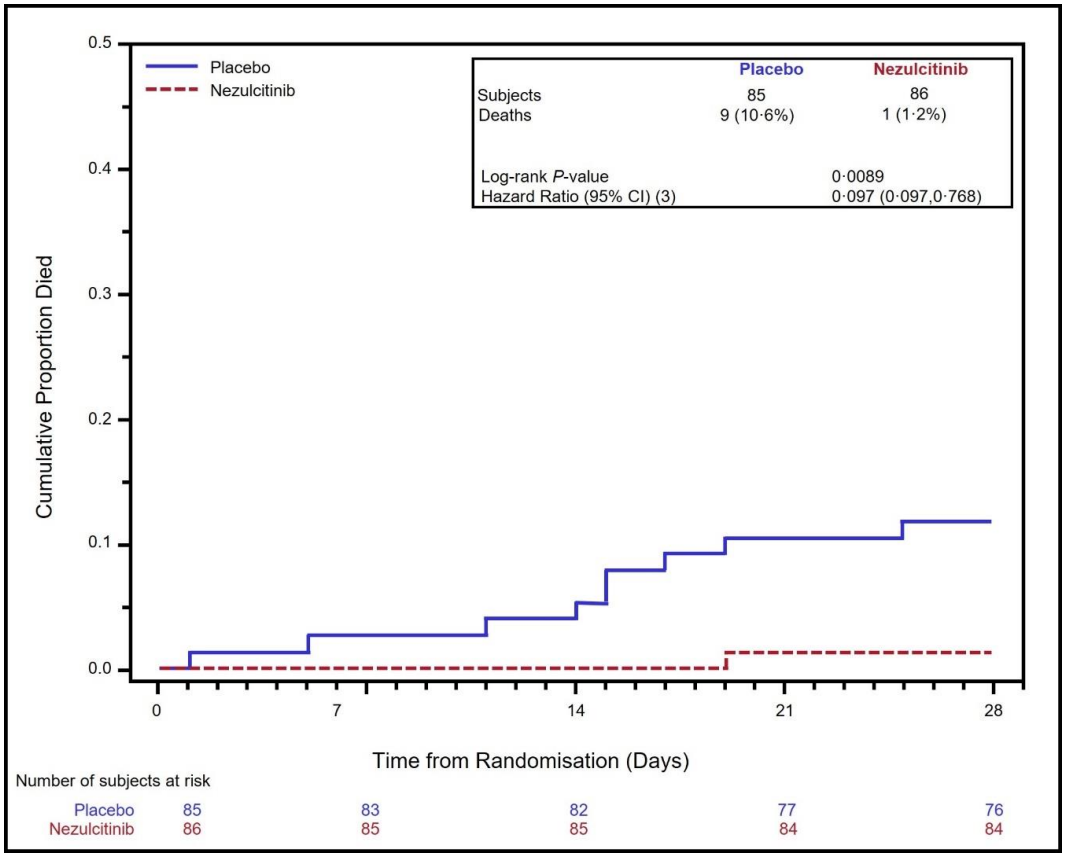
Baseline CRP values were available for 98 patients in the placebo arm and 103 in the nezulcitinib arm. Median and Q3 times are based on Kaplan-Meier estimate; HR (nezulcitinib vs placebo) and 95% CI are calculated from the Cox proportional hazards model adjusting for baseline age strata (≤60 vs >60 years); *P*-value is based on stratified log-rank test stratified by baseline age strata.
CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ITT, intent-to-treat; NA, not assessed
Q3, third quartile.

Supplemental Figure 5: Kaplan-Meier estimates of time to mortality in the **a)** ITT analysis set and post hoc subgroups defined by **b)** baseline CRP <150 mg/L and **c)** baseline CRP ≥150 mg/L

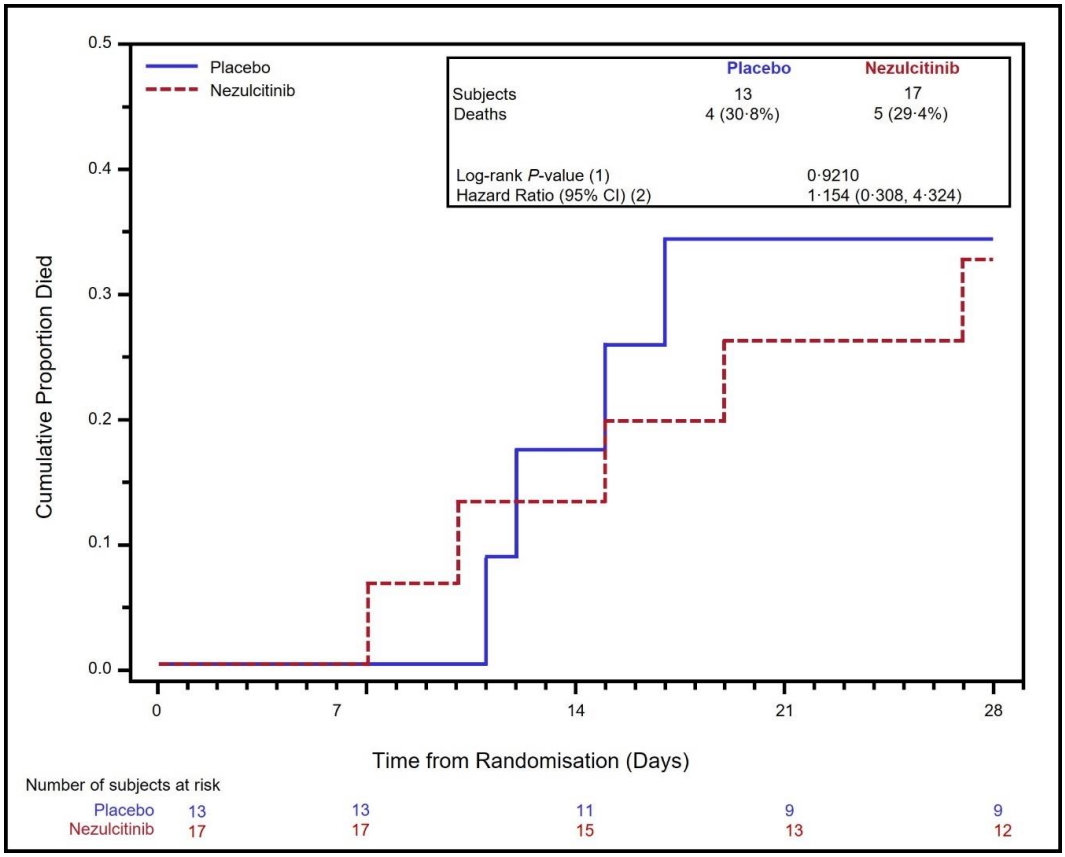
a)



b)


Placebo
Nezulcitinib
Placebo
Nezulcitinib
Subjects
85
86
Deaths
9 (10·6%)
1 (1·2%)
Log-rank P-value
0·0089
Hazard Ratio (95% CI) (3)
0·097 (0·097,0·768)
Cumulative Proportion Died
0.5
0.4
0.3
0.2
0.1
0.0
0
7
14
21
28
Time from Randomisation (Days)
Number of subjects at risk
Placebo 85 83 82 77 76
Nezulcitinib 86 85 85 84 84

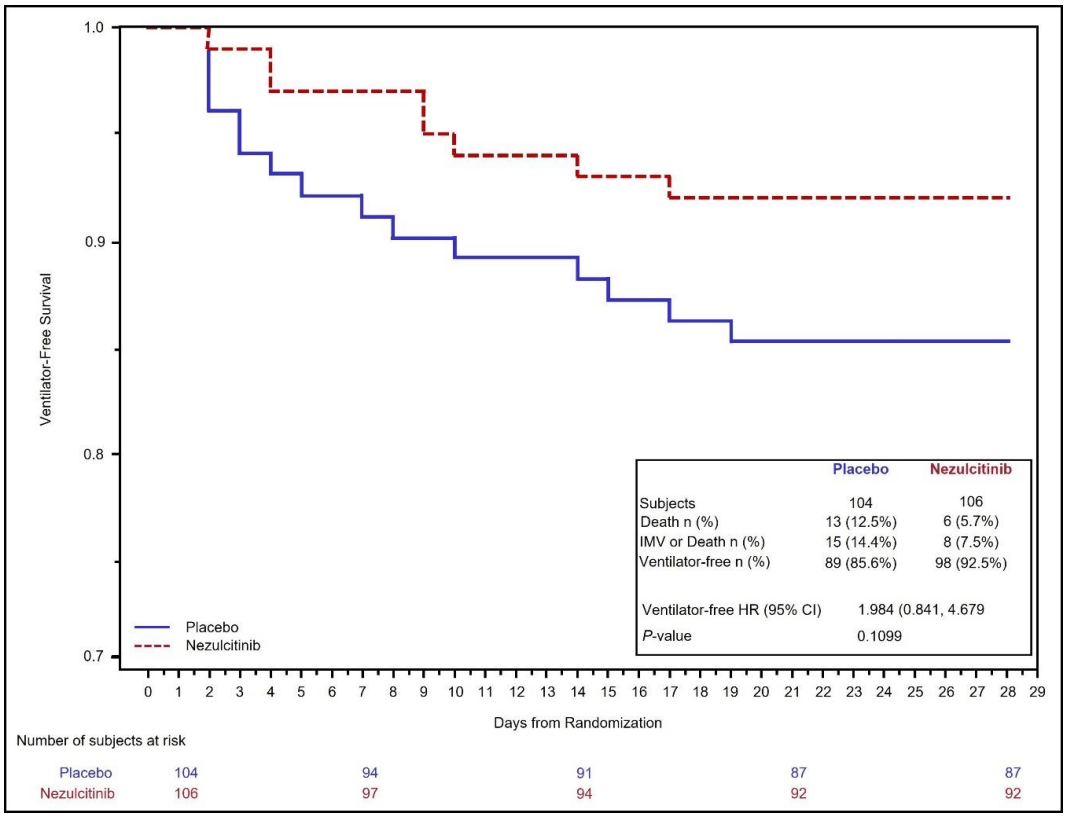
c)



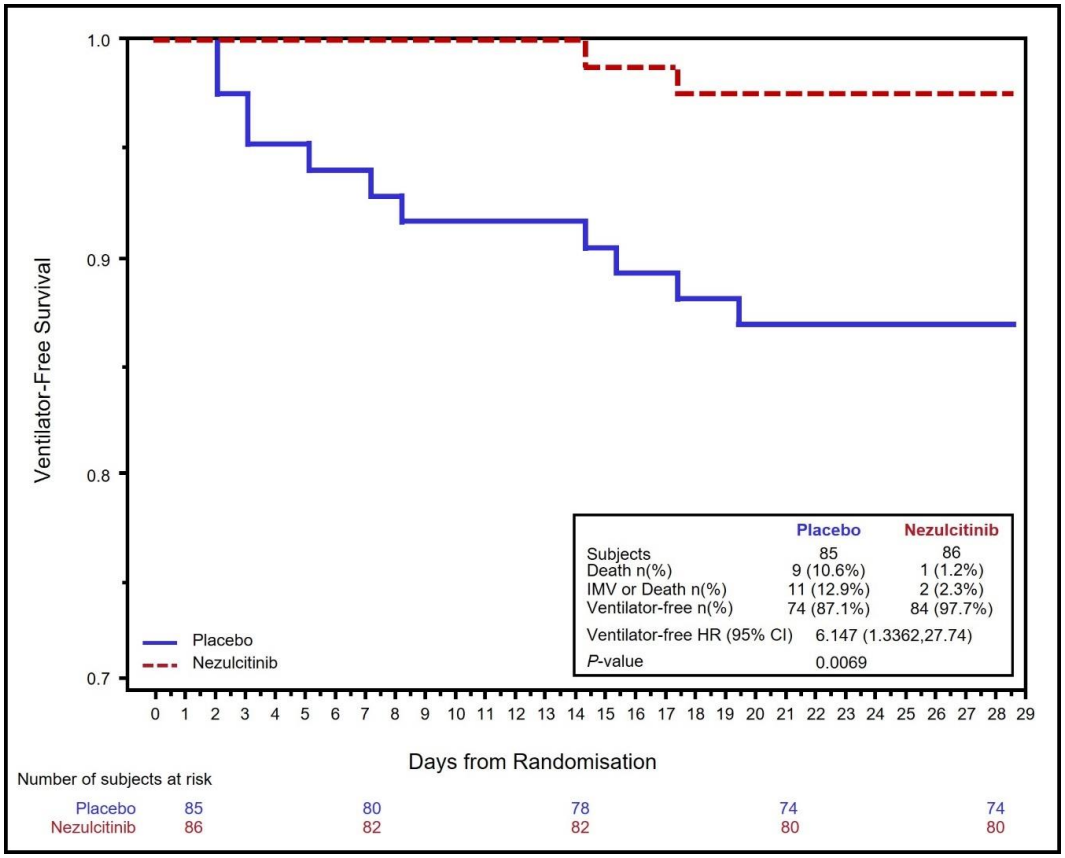
Median and Q3 times are based on Kaplan-Meier estimate; HR (nezulcitinib vs placebo) and 95% CI are calculated from the Cox proportional hazards model adjusting for baseline age strata (≤60 vs >60 years); *P*-value is based on stratified log-rank test stratified by baseline age strata.
CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ITT, intent-to-treat; Q3, third quartile.

Supplemental Figure 6: Kaplan-Meier estimates of VFS in the **a)** ITT analysis set and in post hoc subgroups defined by **b)** baseline CRP <150 mg/L and **c)** baseline CRP ≥150 mg/L

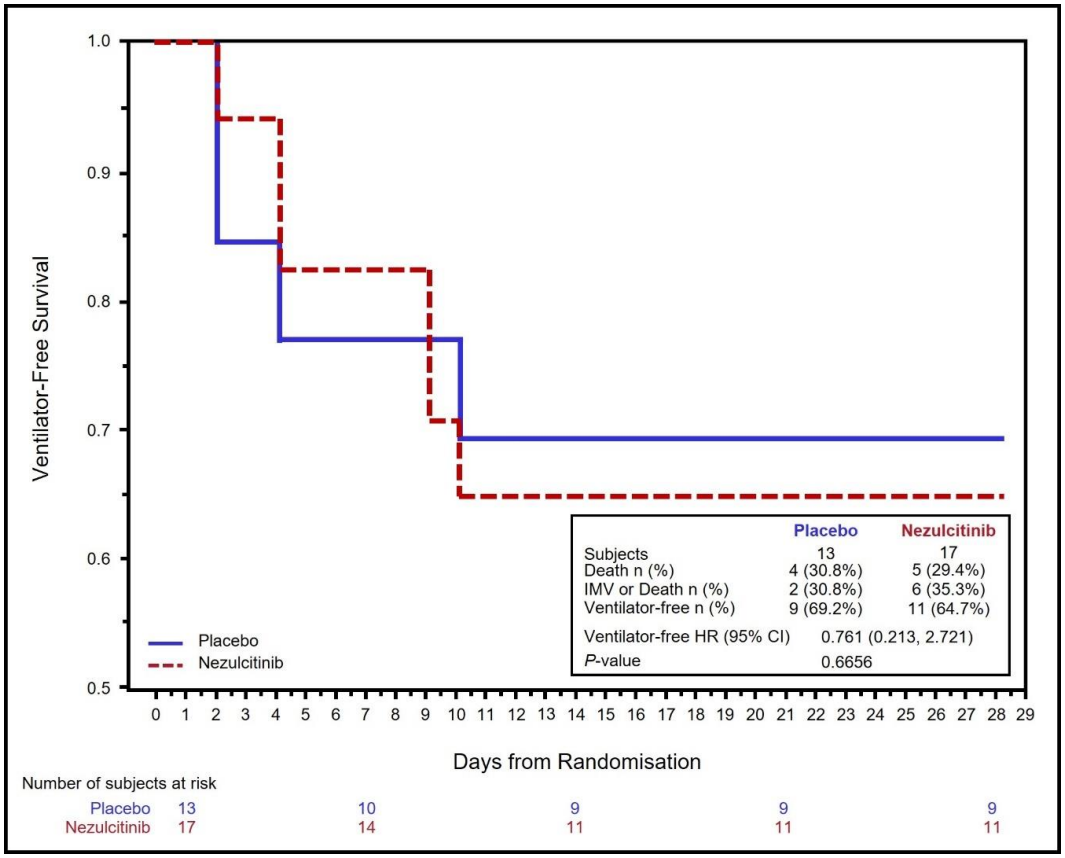
a)



b)


Ventilator-Free Survival
1.0
0.9
0.8
0.7
Placebo
Nezulcitinib
Placebo Nezulcitinib
Subjects 85 86
Death n(%) 9 (10.6%) 1 (1.2%)
IMV or Death n(%) 11 (12.9%) 2 (2.3%)
Ventilator-free n(%) 74 (87.1%) 84 (97.7%)
Ventilator-free HR (95% CI) 6.147 (1.3362,27.74)
P-value 0.0069
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Days from Randomisation
Number of subjects at risk
Placebo 85 80 78 74 74
Nezulcitinib 86 82 82 80 80

c)



Baseline CRP values were available for 98 patients in the placebo arm and 103 in the nezulcitinib arm. HR (nezulcitinib vs placebo) and 95% CI are calculated from the Cox proportional hazards model adjusting for baseline age strata (≤60 vs >60 years); *P*-value is based on stratified log-rank test stratified by baseline age strata.

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IMV, invasive mechanical ventilation; ITT, intent-to-treat; VFS, ventilator-free survival.

Participant Information Sheet and Informed Consent Form

PART 2

<Add site specific header>

Participant Information Sheet and Informed Consent Form
PART 2

Study Protocol Code:	**TD-0903-0188**
Sponsor Name:	**Theravance Biopharma Ireland Limited**
Principal Investigator:	**<name of Principal Investigator>**
Investigational Site Name and Address:	**< name and address of investigational site>**

Study title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-centre Study of an Inhaled Pan-Janus Kinase Inhibitor, TD-0903, to Treat Symptomatic Acute Lung Injury Associated with COVID-19.

Short title: TD-0903 for Acute Lung Injury Associated with COVID-19.

Invitation to participate

We are inviting adults (aged between 18 and 80 years) who have been admitted to hospital with Coronavirus Disease 2019, COVID-19, to join a clinical research study to test a possible treatment. This information sheet describes the study and invites you to participate in the study.

Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Your participation in this study is voluntary. If you do not wish to participate in the study or you later withdraw your consent this will not lead to any disadvantage for you.

Information about this study will be made available on the public website, www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. The website will include details of the study design. You can search this website at any time.

1. What is the purpose of the study?

The Sponsor, Theravance Biopharma Ireland Limited, is developing a new investigational medication, TD-0903, to treat acute lung injury associated with COVID-19.

Investigational means the medicine is not approved by Health Authorities like <country authority> or the European Medicines Agency (EMA) in the European Union (EU) and is still being tested.

This study is divided into two parts:

- ***Part 1*** will look at increasing strengths of the study medication, given over 7 days either once or twice-a-day. The first group of patients will be given 1 milligram (mg), then 3 mg to the next group of patients, then 10 mg to the final group of patients. The participation in this part will last up to 28 days. Up to 24 patients will participate in Part 1.
- ***Part 2*** will look at comparing 2 different strengths of the study drug, over 7 days either once or twice-a-day. The participation in this part will last up to 28 days. Approximately 135 patients will participate in Part 2.

You are being invited to participate in **Part 2** of the study**.**

Some patients will receive TD-0903 (active study medication) and others will receive placebo ('dummy' drug with no active ingredients), to prevent the study results from being influenced in any way. Whether you receive the active study medication or placebo will be decided at random by a computer (like flipping a coin). You will have a 1 in 3 chance of receiving placebo. Neither you or the site staff will know whether you are taking the active or placebo medication, but this information can be obtained if deemed necessary for safety reasons.

2. Why have I been invited?

You have been invited because you have COVID-19 confirmed by a laboratory test (or considered highly likely by your doctor) and are hospitalised, and the doctor thinks you are suitable for the trial. You may not be able to take part in this study if you're already taking part in another study. It is important that you inform the doctor if you are taking part in another study.

3. Do I have to take part?

No. It is up to you whether-or-not to take part. A decision not to take part will not affect your treatment and care.

You can also agree to be in the study now and change your mind later without prejudice and without giving any reason if you do not wish to provide any. The study doctor will discuss with you any other treatment options.

In the event that you will lose capacity during the study you will continue to participate in the study, unless your study doctor feels the situation it is not medically appropriate. If you do not agree to this condition you cannot participate in this study.

4. What will happen to me if I take part?

If you decide to join, you will be asked to sign the consent form at the end of this document. You will then be asked to answer a few questions about your health and medical conditions. You will then have some tests performed that are in addition to your standard care tests. All of these tests will be done during your hospital stay. On Day 1, these tests will determine whether you are eligible to take part in the study. If the study doctor determines you to be eligible for the study, you will then receive the study medication once or twice-a-day for up to 7 days in a row. The study medication will be given in addition to your usual standard of care. Some more additional tests will be performed on the days you receive the study medication and some follow-up tests will be performed after you have finished taking the study medication. The duration of the study is about 28 days. No additional testing will be performed once you are discharged from the hospital or after Day 28.

See section 7, below, for a list of what tests are done on each day of the study.

5. What are the possible benefits of being included in the study?

We do not know whether the treatment being tested will benefit you. We hope that information we get from this study will help us treat patients more effectively in the future.

6. What are the alternative treatments?

Your study doctor will discuss with you other treatments, including the benefits and risks, which are available for COVID-19.

7. What are the possible risks of being included in the study?

Risks associated with study medication:

The study medication is currently in the early stages of development and has been given to 42 healthy volunteers. Preliminary data has shown to be safe and well tolerated in healthy volunteers in single and multiple doses of 1mg, 3 mg, and 10mg. However, the full side effects in humans are unknown. Almost all medicines can cause side effects. Many are mild, but some can become life threatening if they are not treated. You must report any new symptoms/signs of illness to the staff.

Studies in animals indicate the drug was adequately tolerated with mild inflammation of the airways

being observed. It is important to note that animal studies do not always predict the side effects people may experience.

Patients receiving repeated oral doses of similar medications to the study medication on a longer term basis have shown changes in cholesterol, liver function tests, decreased levels of blood cells (which can cause problems with bleeding or infection), headache, diarrhoea, runny nose, sore throat, and a small increase in the rates of intestinal perforation, cancer and risk of infection, and blood clots of the lungs and limbs. These risks are anticipated to be minimal in this study due to the short duration of treatment and administering the study medication via inhalation.

Because the study medication is given by breathing into the lungs, there is a chance that the drug may irritate the lung and breathing airways. We will be watching for things like coughing, wheezing, chest tightness, shortness of breath, and other lung problems.

As with any drug, there is a chance you may experience an allergic reaction, such as hives, swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing. You will be under close observation during and after administration of the study medication and would be treated promptly if any allergic reaction was experienced.

As with any investigational drug, there may also be other side effects that we cannot predict and as this is a new drug, our current knowledge regarding all potential harms and the probability of the occurrence of all harm is limited. However, we will provide you with any new information that becomes available during the course of the study that may affect your decision to take part/ remain in the study.

Whether you are allocated to take active study medication or placebo, there are some potential side effects which may occur. You will be treated as appropriate and supported by the medical staff until you feel well again.

Risks associated with study procedures:

Blood Sampling: On study days where a number of blood samples are collected over the day, a cannula (thin plastic tube inserted into a vein) may be used to collect blood samples. Placing a cannula and/or drawing blood via a needle may cause some discomfort, bleeding or bruising. Rarely, fainting or local inflammation or infection may occur.

8. What happens on each day?

If you decide to join the study and sign the consent form, the following tests will be performed. Please, refer also to Table 1 at the end of this document:

Day 1

- Medical history and medication review
- Vital signs measurements (body temperature, blood pressure, pulse rate and breathing rate)
- Clinical status (what hospital device, if any, is being used to provide additional oxygen and help aid in breathing)
- Physical Examination

Height and Weight measurement (if not already in your hospital notes)