# A phase 2 multiple ascending dose study of the inhaled pan-JAK inhibitor nezulcitinib (TD-0903) in severe COVID-19



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*To the Editor:*

Severe coronavirus disease 2019 (COVID-19) is characterised by pneumonia with excessive systemic inflammation, referred to as a "cytokine storm" [1–3]. Dexamethasone treatment decreases mortality in patients with COVID-19 receiving respiratory support and is standard of care for severe COVID-19 [4, 5]. However, pulmonary inflammation, which drives COVID-19 morbidity and mortality [3], can persist despite corticosteroid use [6, 7]. Janus kinase (JAK) inhibition blocks signalling by many cytokines in diverse cell types, offering broad immunomodulation [8]. The oral JAK-1/2 inhibitor baricitinib combined with the antiviral remdesivir shows clinical efficacy in patients with severe COVID-19 [9]. Direct delivery of JAK inhibition to the lung *via* inhalation could overcome corticosteroid-resistant pulmonary inflammation [10], offering the potential for improved responses while minimising risk of excessive systemic immunosuppression. The novel inhaled pan-JAK inhibitor nezulcitinib (TD-0903) was designed to target all JAK isoforms (JAK1, JAK2, JAK3, TYK2; −log inhibition constant ⩾9.2) and optimise delivery to the lungs while limiting systemic exposure (R. Sana and co-workers; unpublished results: abstract submitted to ERS International Congress, 2021). We report results from the completed part 1 of a 2-part phase 2 trial (NCT04402866) in hospitalised patients with severe COVID-19.

The study was designed with separate data reporting for parts 1 and 2. Part 1 was a randomised, double-blind, placebo-controlled, multiple-ascending-dose trial conducted in the UK, Moldova and Ukraine. The study documents were approved by independent ethics committees at each site. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients provided informed consent. Hospitalised patients aged 18 to 80 years with PCR-confirmed symptomatic COVID-19 (symptoms for 3–14 days) who required supplemental oxygen to maintain saturation >90% were eligible; patients receiving JAK inhibitors or anti-interleukin-6 therapy were excluded (full inclusion/exclusion criteria: https://www.clinicaltrials.gov/ct2/show/NCT04402866). Patients were sequentially enrolled in three ascending-dose cohorts (n=6 active and 2 placebo per cohort) and received once-daily nezulcitinib 1 mg (day 1 loading dose 2 mg), 3 mg (day 1 loading dose 6 mg), or 10 mg (no loading dose) or matched placebo *via* inhalation (Aerogen Solo+Ultra nebuliser system, Galway, Ireland) for up to 7 days, with follow-up through day 28. Day 1 loading doses for nezulcitinib 1 mg and 3 mg were administered to rapidly achieve pseudo-steady state in the lung.

Peripheral blood arterial oxygen saturation ($S_{aO_2}$) was collected *via* pulse oximetry, and fraction of inspired oxygen ($F_{IO_2}$), vital signs, adverse events, and clinical status using an 8-point ordinal scale (OS) [11] were recorded daily through day 7 and on days 14, 21 and 28 and/or at hospital discharge. Physical examination and blood collection were performed on days 1 and 7; patient care-related laboratory evaluations through day 28 were included. Safety was assessed from vital signs, laboratory results, and treatment-emergent adverse events (TEAEs; coded per Medical Dictionary for Regulatory Activities v23.1). Plasma pharmacokinetic parameters were evaluated on days 1 and 7. The key pharmacodynamic outcome was change from baseline $S_{aO_2}/F_{IO_2}$ ratio; other clinical outcomes were considered exploratory.

A sample size of six active- and two placebo-treated patients per cohort was deemed appropriate to assess nezulcitinib safety and tolerability during dose escalation. Safety, $S_{aO_2}/F_{IO_2}$ ratio, and efficacy data were summarised as descriptive statistics using SAS v9.4 (SAS Institute, Cary, NC, USA).

Shareable abstract (@ERSpublications)
**The inhaled lung-selective pan-JAK inhibitor nezulcitinib appears generally well tolerated in hospitalised patients with severe #COVID-19, with trends for improved oxygenation and clinical status, shortened hospitalisation, and fewer deaths *versus* placebo** https://bit.ly/35Xs1Rf

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**TABLE 1** Key baseline data and outcomes

| | Placebo (n=6) | Nezulcitinib | | |
|---|---|---|---|---|
| | | 1 mg (n=6) | 3 mg (n=7)[#] | 10 mg (n=6) |
| **Baseline characteristics** | | | | |
| Sex, male | 3 (50.0) | 5 (83.3) | 4 (57.1) | 5 (83.3) |
| Age, years | 54.2±17.0 | 59.5±15.5 | 62.0±3.3 | 52.8±13.4 |
| Race, white | 5 (83.3) | 6 (100) | 7 (100) | 6 (100) |
| Country of enrolment | | | | |
| Moldova | 3 | 6 | 6 | 3 |
| Ukraine | 2 | 0 | 0 | 2 |
| UK | 1 | 0 | 1 | 1 |
| Body mass index, $kg \cdot m^{-2}$ | 27.2±3.6 | 32.6±7.1 | 31.8±2.7 | 34.3±3.4 |
| Comorbidities | | | | |
| Hypertension | 4 (66.7) | 6 (100) | 4 (57.1) | 3 (50.0) |
| Sleep apnoea | 1 (16.7) | 4 (66.7) | 3 (42.9) | 3 (50.0) |
| Diabetes mellitus | 3 (50.0) | 3 (50.0) | 3 (42.9) | 1 (16.7) |
| COVID-19 symptom duration, days, median (IQR) | 7.5 (3.0) | 6.5 (3.0) | 8.0 (4.0) | 7.5 (2.0) |
| $S_{aO_2}/F_{IO_2}$ ratio | 284.5±63.6 | 295.0±28.2 | 282.5±55.5 | 270.0±61.5 |
| **Concomitant medication** | | | | |
| Dexamethasone | 5 (83.3) | 6 (100) | 7 (100) | 5 (83.3) |
| Heparin group[¶] | 4 (66.7) | 6 (100) | 7 (100) | 6 (100) |
| Remdesivir | 1 (16.7) | 0 | 1 (14.3) | 1 (16.7) |
| **Summary of TEAEs**[+] | | | | |
| All TEAEs | 6 (100) | 5 (83.3) | 2 (28.6) | 5 (83.3) |
| Related to study treatment | 1 (16.7) | 2 (33.3) | 0 | 3 (50.0) |
| **Clinical endpoints**[§] | | | | |
| Change in $S_{aO_2}/F_{IO_2}$ from day 1 to 7 | −49.5±65.3 | 108.9±87.9 | 106.4±87.8 | 11.2±106.3 |
| Alive and respiratory failure-free on day 28 | 4 (66.7) | 5 (83.3) | 6 (85.7)[f] | 6 (100) |
| Time to hospital discharge, days[##] | 22.5±6.4 | 18.8±6.8 | 15.3±6.7 | 15.2±4.4 |
| Clinical status OS[f,¶¶] | | | | |
| Day 7 | | | | |
| 1 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 |
| 3 | 1 (16.7) | 0 | 1 (16.7) | 0 |
| 4 | 0 | 4 (66.7) | 2 (33.3) | 2 (33.3) |
| 5 | 2 (33.3) | 2 (33.3) | 3 (50.0) | 4 (66.7) |
| 6 | 0 | 0 | 0 | 0 |
| 7 | 3 (50.0) | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 | 0 |
| Day 28[f] | | | | |
| 1 | 3 (50.0) | 5 (83.3) | 5 (83.3) | 5 (83.3) |
| 2 | 0 | 0 | 0 | 1 (16.7) |
| 3 | 0 | 0 | 0 | 0 |
| 4 | 1 (16.7) | 0 | 1 (16.7) | 0 |
| 5 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 |
| 8 | 2 (33.3) | 1 (16.7) | 0 | 0 |

Data are shown as mean±SD or n (%), unless otherwise specified. [#]: one patient discontinued the study due to subsequent negative PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was replaced but included in analyses as available data permitted. [¶]: includes heparins, enoxaparin, bemiparin and nadroparin. [+]: including patients who received ⩾1 dose of study drug analysed as treated. [§]: including all randomised patients analysed as randomised (intent-to-treat population). [f]: the patient who discontinued the study due to negative PCR test for SARS-CoV-2 was known to be alive but with unknown clinical status at day 28. Thus, this patient was not counted as alive and respiratory failure-free and was not included in analyses of ordinal scale (OS) on days 7 and 28. [##]: for patients who died or were still hospitalised on day 28, a time to discharge of 28 days was assigned. [¶¶]: 8-point OS: 1, not hospitalised, no limitations on activities; 2, not hospitalised, but with limitation on activities and/or requiring home oxygen; 3, hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (including hospitalisation for infection control); 4, hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (whether related or not to coronavirus disease 2019 (COVID-19)); 5, hospitalised, requiring supplemental oxygen; 6, hospitalised, on noninvasive ventilation or high-flow oxygen devices; 7, hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 8, death. IQR: interquartile range; $S_{aO_2}/F_{IO_2}$: ratio of oxygen saturation measured by pulse oximetry to fraction of inspired oxygen; TEAE: treatment-emergent adverse event.

25 patients enrolled (UK, 3; Ukraine, 4; Moldova, 18) and were randomised to receive nezulcitinib 1 mg (n=6), 3 mg (n=7), 10 mg (n=6), or placebo (n=6). One patient receiving nezulcitinib 3 mg was discontinued due to a negative SARS-CoV-2 PCR screening test returned after randomisation and was replaced per protocol. Baseline data, concomitant medications, TEAEs and clinical outcomes are summarised in table 1. Mean body mass index and proportion of men were lower in patients receiving placebo *versus* nezulcitinib, and mean age was lower in patients receiving placebo or nezulcitinib 10 mg *versus* nezulcitinib 1 mg or 3 mg. Almost all patients (92%) received dexamethasone; three (12%) received remdesivir. The majority of TEAEs were mild to moderate and resolved by end of study, with no apparent dose relationship. Serious TEAEs occurred in five patients through day 28, including COVID-19 progression in one placebo-treated patient; acute respiratory distress syndrome (ARDS) and fatal multiple organ dysfunction syndrome (MODS) in one placebo-treated patient; ARDS and fatal cardiac arrest in one placebo-treated patient; acute respiratory failure, ventricular fibrillation, and fatal MODS in one nezulcitinib 1 mg-treated patient; and ischaemic stroke in one nezulcitinib 3 mg-treated patient. No serious TEAEs were considered related to study treatment by the investigator. One patient receiving nezulcitinib 10 mg discontinued treatment on day 4 due to elevated alanine aminotransferase that resolved without consequence. No other changes in vital signs or laboratory safety measures, including creatinine and haematologic parameters, were attributed to treatment. On day 7, mean systemic levels of inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) and lung injury marker soluble receptor for advanced glycation end products (sRAGE) were lower *versus* baseline in patients treated with nezulcitinib 3 mg and 10 mg (range: hsCRP, 52%–75% reduction; sRAGE, 54%–83% reduction) *versus* placebo (41% increase and 37% reduction, respectively). The mean steady state maximal plasma concentration of nezulcitinib at the highest dose was 19.0 $ng \cdot mL^{-1}$, well below levels predicted to produce systemic JAK inhibition.

At baseline, all patients received supplemental oxygen *via* nasal prongs or mask (OS 5). During the 7-day treatment period, three (50%) placebo-treated patients progressed to invasive mechanical ventilation (OS 7), but no nezulcitinib-treated patient declined in clinical status. After day 7, one patient treated with nezulcitinib 1 mg and two placebo-treated patients died (OS 8; nezulcitinib 1 mg-treated patient on day 23 and placebo-treated patients on days 11 and 14), whereas clinical status remained stable or improved through day 28 in all patients treated with nezulcitinib 3 mg or 10 mg. $S_{aO_2}/F_{IO_2}$ ratio improved from baseline to day 7, proportion of patients alive and respiratory failure-free at day 28 was higher and mean time to hospital discharge was shorter in patients treated with nezulcitinib *versus* placebo (table 1).

This is the first clinical trial of an inhaled JAK inhibitor for COVID-19 treatment. Once-daily inhaled nezulcitinib for 7 days was generally well tolerated in patients with severe COVID-19. There were trends towards improvement in $S_{aO_2}/F_{IO_2}$ ratio, respiratory failure-free survival at day 28, and mean time to hospital discharge in patients treated with nezulcitinib *versus* placebo. Overall mortality was 33% in placebo-treated patients *versus* 5% in nezulcitinib-treated patients. The small size of this early-phase clinical trial and consequent baseline differences in clinical characteristics limited evaluation of efficacy through between-group comparisons and formal control for potential confounders. Nevertheless, the low mortality and pattern of earlier clinical recovery with nezulcitinib *versus* placebo treatment suggests promise for targeting cytokine-driven pulmonary inflammation in patients with severe COVID-19 through pan-JAK inhibition. Notably, JAK inhibition may have additive anti-inflammatory effects in combination with corticosteroid treatment [10, 12], which almost all patients in the study received, and, thus, inhaled nezulcitinib may complement dexamethasone for treatment of patients with COVID-19.

Based on all evidence, inhaled nezulcitinib 3 mg was advanced for further evaluation in part 2, a larger (n≈200) double-blind, placebo-controlled parallel-group phase 2 study in hospitalised COVID-19 patients requiring supplemental oxygen (OS 5–6) (NCT04402866).

**Dave Singh[1], Maxim Bogus[2], Valentyn Moskalenko[3,4,5], Robert Lord[6], Edmund J. Moran[7], Glenn D. Crater[7], David L. Bourdet[7], Nathan D. Pfeifer[7], Jacky Woo[7], Elad Kaufman[7], David A. Lombardi[7], Emily Y. Weng[7], Tuan Nguyen[7], Ashley Woodcock[6], Brett Haumann[8] and Rajeev Saggar[7]**

[1]Medicines Evaluation Unit, University of Manchester, Manchester University NHS Foundations Trust, Manchester, UK. [2]Arensia Exploratory Medicine SRL, Timofei Moșneaga Republican Clinical Hospital, Chișinău, Moldova. [3]Arensia Exploratory Medicine, LLC, Kyiv City Clinical Hospital #12, Kyiv, Ukraine. [4]Oleksandrivska Kyiv City Clinical Hospital, Kyiv, Ukraine. [5]Brovary Multidisciplinary Clinical Hospital, Brovary, Ukraine. [6]University of Manchester, Manchester University NHS Foundations Trust, Manchester, UK. [7]Theravance Biopharma US, Inc., South San Francisco, CA, USA. [8]Theravance Biopharma UK Limited, London, UK.

Corresponding author: Rajeev Saggar (rsaggar@theravance.com)

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