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

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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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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inhibition constant ⩾9.2) and optimise delivery to the lungs while limiting systemic exposure (R. Sana and co-workers; unpublished results: abstract submitted to ERS International Congress, 2021).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.