# Response to: 'Correspondence on 'Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial'' by Bredemeier

Following the publication of data on the safety and tolerability of nintedanib in the SENSCIS trial,[1 2] and INBUILD trial,[3] Dr Bredemeier has raised the question of the risk of serious respiratory infections with nintedanib treatment in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) and other interstitial lung diseases (ILDs).[4] We have made a thorough investigation into this question and concluded that the evidence from clinical trials does not suggest an increased risk of infections in patients treated with nintedanib. Further, the mechanistic effects of nintedanib, an inhibitor of tyrosine kinases, do not suggest a plausible mechanism by which nintedanib would affect the risk of infection.[5]

We acknowledge that in the SENSCIS trial, there were numerical imbalances between the nintedanib and placebo groups in the percentages of patients with overall serious infections (6.6% vs 3.5%) or serious lower respiratory tract infections (3.5% vs 1.7%). This difference was driven largely by serious adverse events of pneumonia (2.8% (n=8) vs 0.3% (n=1)), when pneumonia was defined using the single preferred term 'pneumonia' from the Medical Dictionary for Regulatory Activities. A detailed review of the cases of serious pneumonia in patients treated with nintedanib revealed that none was considered related to nintedanib by the investigator. Most of the cases (6 of 8) occurred after nintedanib had been discontinued and an explanation for the infection was apparent in the majority of cases (predominantly the use of immunosuppressive drugs such as mycophenolate or cyclophosphamide). In the INPULSIS trials in patients with idiopathic pulmonary fibrosis (IPF),[6] there was no evidence of an increased risk of overall serious infections, serious lower respiratory tract infections or serious pneumonia with nintedanib versus placebo (8.5% vs 8.5%, 5.6% vs 5.4% and 3.6% vs 3.8%, respectively). Similarly, in the INBUILD trial in patients with progressive fibrosing ILDs other than IPF, the risk of these infections was similar between the nintedanib and placebo groups (8.7% vs 8.2%, 5.7% vs 6.3% and 3.6% vs 3.3%, respectively).

Dr Bredemeier queries whether nintedanib has a worse safety profile in patients with fibrosing ILDs who do not have a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT). When looking at data from the whole INBUILD trial, in patients who had other fibrotic patterns on HRCT, the frequencies of serious adverse events and fatal adverse events were similar between the nintedanib and placebo groups (42.9% vs 44.8% and 4.8% vs 7.2%, respectively). The heterogeneity of the patient population, with various comorbidities and comedications, needs to be borne in mind when interpreting the safety data from the INBUILD trial, but descriptive analyses suggest that nintedanib had a consistent safety profile between subgroups by fibrotic pattern on HRCT. Importantly, both in patients with a UIP-like fibrotic pattern on HRCT and in patients with other fibrotic patterns on HRCT, nintedanib was associated with a significant reduction in the rate of decline in forced vital capacity (mL/year) over 52 weeks compared with placebo (by 61% and 49%, respectively).[3]

In conclusion, our analyses indicate that in patients with SSc-ILD and with fibrosing ILDs with a progressive phenotype, nintedanib reduces the rate of progression of ILD, and the totality of the data does not suggest an increased risk of serious infections.

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**Patient consent for publication** Not required.

**Ethics approval** The study protocol was reviewed and approved by the Independent Ethics Committees and/or Institutional Review Boards of the participating centres. Written informed consent was obtained from all patients before study entry.

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## REFERENCES

1 Distler O, Highland KB, Gahlemann M, *et al*. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019;380:2518–28.
2 Seibold JR, Maher TM, Highland KB, *et al*. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217331. [Epub ahead of print: 05 Aug 2020].

3 Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–27.
4 Bredemeier M. Correspondence on 'Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial'. *Ann Rheum Dis*. doi:10.1136/annrheumdis-2020-218911.
5 Wollin L, Distler JHW, Redente EF, *et al*. Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2019;54. doi:10.1183/13993003.00161-2019. [Epub ahead of print: 19 Sep 2019].
6 Richeldi L, du Bois RM, Raghu G, *et al*. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.