



# Objective measurement of cough in pulmonary fibrosis: a cohort study – ImpaCT

Copyright ©The authors 2024

This version is distributed under the terms of the Creative Commons Attribution Licence 4.0.

Received: 28 March 2024

Accepted: 2 May 2024

## To the Editor:

Among patients with interstitial lung disease (ILD), cough is a prevalent symptom and can persist over time, with chronic cough having a major impact on patients' quality of life [1–3]. Moreover, it has been hypothesised that cough may enhance fibrotic remodelling *via* cough-induced mechanical stress [1, 4]. However, while persistent cough is commonly reported in idiopathic pulmonary fibrosis (IPF) and is associated with worse prognosis [1, 3, 5], data are limited on the impact of cough in patients with pulmonary fibrosis other than IPF [2, 5]. This study aimed to assess the frequency and distribution of cough during the day and at night in patients with pulmonary fibrosis other than IPF, using objective cough monitoring as well as patient-reported severity and impact of cough.

ImpaCT was a multicentre, exploratory cohort study of patients aged  $\geq 18$  years who were diagnosed with pulmonary fibrosis other than IPF. Patients with IPF, those with cough due to causes other than fibrosis and individuals with sleep disordered breathing were excluded. Eligible patients were identified by participating physicians in the USA and Europe, and enrolled consecutively. The planned sample size was 100 patients. Patients provided written informed consent before study inclusion and could withdraw at any time. Ethical approval was obtained in each country and for each site from local review boards. The trial was registered with OnderzoekMetMensen.nl (identifier number NL79595.099.22).

Patients attended three study visits over 4 weeks (baseline, V1 and V2) (figure 1), and were followed prospectively from the time of enrolment until the end of the study period, loss to follow-up or death, whichever occurred first. Demographic and baseline variables collected from patient medical records and through routine clinical care were assessed at the initial visit. Cough was measured objectively after V1 and V2 for 24 h using the VitaloJAK cough monitor (Vitalograph, Inc.) [6], and subjectively with patient-reported outcome (PRO) measures (V1 and V2).

The primary objective was to assess frequency and daytime/night-time distribution of cough and coughing bouts (defined as three or more sequential coughs, each cough separated by  $\leq 2$  s). Secondary objectives included assessment of PROs, measured by the Leicester Cough Questionnaire (LCQ) and visual analogue scales (VAS) for cough severity, cough urgency and shortness of breath (V1 and V2), Living with Pulmonary Fibrosis (L-PF) cough Impact Item 18 (V1 and V2), and three-item Patient Global Impressions (PGI) scale assessing overall impression of change in cough over the preceding 2 weeks (V2). Log transformation of cough frequency was used for analysis of the relationship between cough frequency and PROs.

Overall, 28 patients (20 female and eight male) were enrolled across the USA and Europe (figure 1). Due to difficulties with enrolment, the study was terminated prematurely. In total, 35.7% of patients had connective tissue disease-associated ILD, 25.0% had fibrotic hypersensitivity pneumonitis, 21.4% had idiopathic nonspecific interstitial pneumonia, 10.7% had unclassifiable ILD and 7.2% had other ILD.

Objective cough counts at V1 and V2 are shown in figure 1. There was intra- and intersubject variation in the distribution of 24-h, daytime and night-time cough frequencies. Of the 24 patients who had recordings at both V1 and V2, the median (interquartile range (IQR)) difference between the two 24-h recording periods was  $-2.6$  ( $-9.7$  to  $0.1$ ) coughs per h. The median (IQR) difference in daytime and night-time cough frequency recordings was  $-4.3$  ( $-11.7$  to  $0.1$ ) and  $-0.3$  ( $-3.1$  to  $1.6$ ), respectively.

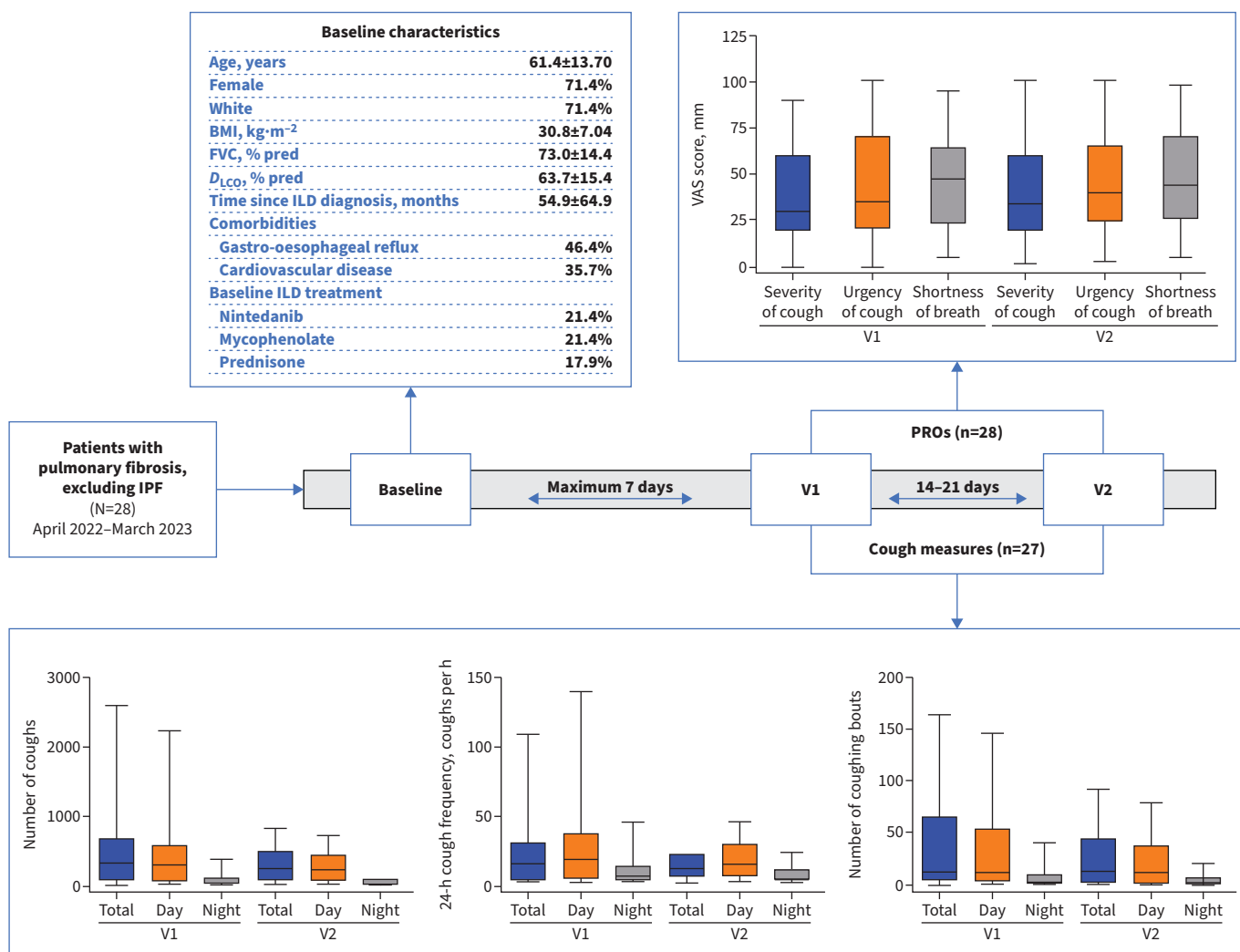


Shareable abstract (@ERSpublications)

Using both objective cough monitoring and patient-reported outcomes measures, this study describes the burden of cough for patients with non-IPF pulmonary fibrosis <https://bit.ly/3wFm0th>

Cite this article as: Kebbe J, Hart SP, Kaner RJ, *et al.* Objective measurement of cough in pulmonary fibrosis: a cohort study – ImpaCT. *ERJ Open Res* 2024; 10: 00310-2024 [DOI: 10.1183/23120541.00310-2024].





**FIGURE 1** Baseline characteristics, objective cough monitoring and patient-reported outcomes for patients with pulmonary fibrosis. Baseline characteristics are presented as mean±SD or %. Cough measures and patient-reported outcome (PRO) data are shown as median (horizontal line) with interquartile range (box). Whiskers represent range. The cough-evaluable set (n=27) included all patients with at least one recording through the VitaloJAK monitor. The PRO-evaluable set (n=28) included all patients with at least one of the PRO measures completed. In total, 24 patients had data available at both visit (V)1 and V2. BMI: body mass index; DL<sub>CO</sub>: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; VAS: visual analogue scale.

VAS scores showed similar trends to cough counts. For the L-PF (Impact Item 18), the proportion of patients with a score  $\leq 2$  (negative effect of cough on quality of life) ranged from 46.5% to 64.3% across visits. On the LCQ, total median (IQR) scores were 13.5 (11.8 to 19.3) at V1 and 14.8 (10.3 to 16.8) at V2. In total, 16 (57.1%) patients experienced no impression of change in cough over the preceding 2 weeks using the PGI. For all PRO measures, the total and subdomain scores were similar at V1 and V2.

The overall relationship between cough frequency and VAS items showed moderate correlation, based on Pearson correlation: severity of cough,  $\rho=0.6$  (95% CI 0.3 to 0.7); urgency of cough,  $\rho=0.5$  (95% CI 0.3 to 0.7); shortness of breath,  $\rho=0.5$  (95% CI 0.2 to 0.7).

This study shows a high cough burden observed for patients in this cohort with pulmonary fibrosis other than IPF, as measured objectively by cough frequency over 24 h and subjectively by PROs.

There was a relatively low percentage of patients treated with nintedanib at baseline (21.4%) (figure 1), which may reflect the inclusion criteria (disease progression was not required for enrolment) and/or a lag between nintedanib approval and treatment initiation. The baseline forced vital capacity (FVC) % predicted

and diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ) % predicted suggest that patients were not as severely affected by their disease as those in the INBUILD trial of nintedanib in patients with progressive fibrosing ILD (FVC 69.0% predicted;  $D_{LCO}$  46.1% predicted).



The median cough counts in this study (13.1 and 9.7 coughs per h at V1 and V2, respectively) are in line with those observed in IPF studies reporting median baseline objective cough counts of 11.4–16.0 coughs per h [7, 8]. To our knowledge, this is the first study to assess coughing bouts in patients with pulmonary fibrosis other than IPF (figure 1). While the definition of coughing bouts is not standardised, episodes of continuous coughing may impact patient quality of life [9]. Recognising the importance of incorporating patient insights into clinical trial design, we would advocate including a measure of cough bouts as an outcome for future studies [10].

Cough severity VAS scores (mean±SD) at V1 (39.9±26.7) and V2 (41.2±26.5) and 24-h cough frequency (median (IQR)) at V1 (13.1 (2.8–28.4) coughs per h) and V2 (9.7 (4.1–20.8) coughs per h) were similar to what was found for IPF in a systematic literature review [11].

PRO findings were not always consistent with observed patterns of cough measurements for these patients with non-IPF pulmonary fibrosis, similar to observations in patients with IPF [8, 12]. The presence of moderate, but not strong, correlation between cough frequency and VAS scores is consistent with previous reports in patients with chronic cough [13]. This underlines that we likely need to take a multidimensional approach to assessing cough in trials and daily care.

Study limitations include the small sample size, affecting the generalisability of the results. Eligibility criteria were broad and no specific cough threshold was required for inclusion. However, there may have been selection bias, with some investigators potentially enrolling patients with a high degree of cough symptoms.

In conclusion, cough is a significant burden for patients with pulmonary fibrosis other than IPF. To our knowledge, this is the first study to describe cough using objective and subjective metrics in patients with pulmonary fibrosis other than IPF. These data support the inclusion of patients with non-IPF forms of pulmonary fibrosis, in addition to those with IPF, in future cough studies. Such studies may be more attuned to patient experiences to gain insights into cough mechanisms in fibrotic lung diseases and identify effective treatments.

Jad Kebbe <sup>1</sup>, Simon P. Hart <sup>2</sup>, Robert J. Kaner<sup>3</sup>, Tejaswini Kulkarni<sup>4</sup>, Lutz Wollin<sup>5</sup>, Carl Coeck<sup>6</sup>, Richard Vinisko<sup>7</sup>, Nina Patel<sup>7</sup> and Marlies S. Wijsenbeek<sup>8</sup>

<sup>1</sup>Section of Pulmonary, Critical Care and Sleep Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA. <sup>2</sup>Hull York Medical School, University of Hull, Hull, UK. <sup>3</sup>Division of Pulmonary and Critical Care Medicine and Department of Genetic Medicine, Weill Cornell Medicine, New York, NY, USA. <sup>4</sup>University of Alabama at Birmingham, Birmingham, AL, USA. <sup>5</sup>Boehringer Ingelheim Pharma GmbH & Co, KG, Biberach an der Riß, Germany. <sup>6</sup>Boehringer Ingelheim SComm, Brussels, Belgium. <sup>7</sup>Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA. <sup>8</sup>Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.

Corresponding author: Marlies S. Wijsenbeek ([m.wijsenbeek-lourens@erasmusmc.nl](mailto:m.wijsenbeek-lourens@erasmusmc.nl))

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors would like to thank all the patients whose data contributed to this manuscript.

Data availability: To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major Regulatory Authorities or after termination of the development programme. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

This study is registered at OnderzoekMetMensen.nl with identifier number NL79595.099.22.

Ethics statement: Ethical approval was obtained in each country and for each site from local review boards.

Author contributions: The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. Concept and design: L. Wollin, C. Coeck, N. Patel and M.S. Wijsenbeek; methodology: C. Coeck, N. Patel and M.S. Wijsenbeek; data collection: J. Kebbe, T. Kulkarni and M.S. Wijsenbeek; data analysis: J. Kebbe and R. Vinisko; data interpretation: all authors; writing and reviewing manuscript: all authors; final approval of version to be published: all authors.

Conflict of interest: J. Kebbe reports research contracts with Boehringer Ingelheim, CSL Behring, United Therapeutics, Genentech, Insilico and ATYR Pharma. S.P. Hart reports grants or contracts with Boehringer Ingelheim; consulting fees from Trevi Therapeutics; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim and Chiesi; support for attending meetings and/or travel from Boehringer Ingelheim, Chiesi and Trevi Therapeutics; and is a trustee for Action for Pulmonary Fibrosis and is an associate editor of this journal. R.J. Kaner reports institutional grants or contacts with National Institutes of Health, Boehringer Ingelheim, Chiesi, CSL Behring, Genentech, Respiant, Toray, Bellerophon and the US Department of Defense; personal royalties or licences from UpToDate; personal payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim, Genentech, Vindico and France Foundation; support for attending meetings and/or travel from United Therapeutics and Boehringer Ingelheim; participation on a data safety monitoring board or advisory board for PureTech, Pliant, Boehringer Ingelheim, Genentech, United Therapeutics, Verona Pharma, Galapagos (Endpoint Adjudication Committee) and AstraZeneca (Endpoint Adjudication Committee); unpaid leadership or fiduciary roles with Pulmonary Wellness Foundation and Stony Wold Foundation; personal stock or stock options with Doximity and Air Cycle Systems; and receipt of medical writing support from Boehringer Ingelheim, Genentech, Galapagos and AstraZeneca. T. Kulkarni reports consulting fees from Boehringer Ingelheim Inc., Puretech Inc., United Therapeutics Corp and Aileron Inc.; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim Inc. and Veracyte; and participation on a Data Safety Monitoring Board or Advisory Board for Boehringer Ingelheim Inc. and Puretech Inc. L. Wollin, C. Coeck, R. Vinisko and N. Patel are employees of Boehringer Ingelheim. M.S. Wijsenbeek reports institutional grants or contracts with The Netherlands Organisation for Health Research and Development, The Dutch Lung Foundation, The Dutch Pulmonary Fibrosis Organisation, Sarcoidosis.nl, Boehringer Ingelheim, Hoffmann-La Roche and AstraZeneca-Daiichi; consulting fees paid to their institution from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Galapagos, Galeco, GSK, Hoffmann-La Roche, Horizon Therapeutics, Kinevant Sciences, Molecure, Nerre Therapeutics, Novartis, PureTech Health, Thyron, Trevi and Vicore; payment or honoraria to their institution for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim, CSL Behring, Hoffmann-La Roche and Novartis; support for attending meetings and/or travel from Boehringer Ingelheim, GSK, Hoffmann-La Roche and Galapagos; and leadership or fiduciary roles as Chair of the Idiopathic Interstitial Pneumonia group of the European Respiratory Society, member of the board of the Netherlands Respiratory Society, member of the scientific advisory board of the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation, Chair of the Educational Committee of the European Reference Network for Rare Lung Diseases and member of an advisory board of the Dutch Lung-Fibrosis and Sarcoidosis Patient Associations.

Support statement: The ImpaCT trial was supported by Boehringer Ingelheim International GmbH. The authors did not receive payment related to the development of the manuscript. Writing, editorial support and formatting assistance was provided by Helen Keyworth of Nucleus Global, and was contracted and funded by Boehringer Ingelheim. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. Funding information for this article has been deposited with the Crossref Funder Registry.

## References

- 1 van Manen MJG, Wijsenbeek MS. Cough, an unresolved problem in interstitial lung diseases. *Curr Opin Support Palliat Care* 2019; 13: 143–151.
- 2 Cheng JZ, Wilcox PG, Glaspole I, et al. Cough is less common and less severe in systemic sclerosis-associated interstitial lung disease compared to other fibrotic interstitial lung diseases. *Respirology* 2017; 22: 1592–1597.
- 3 Wu Z, Smith DJF, Yazbeck L, et al. Cough severity visual analogue scale assesses cough burden and predicts survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2024; 209: 1165–1167.
- 4 Froese AR, Shimbori C, Bellaye PS, et al. Stretch-induced activation of transforming growth factor- $\beta$ 1 in pulmonary fibrosis. *Am J Respir Crit Care Med* 2016; 194: 84–96.
- 5 Lee J, White E, Freiheit E, et al. Cough-specific quality of life predicts disease progression among patients with interstitial lung disease: data from the Pulmonary Fibrosis Foundation Patient Registry. *Chest* 2022; 162: 603–613.

- 6 McGuinness K, Holt K, Dockry R, *et al.* P159: validation of the VitaloJAK™ 24 hour ambulatory cough monitor. *Thorax* 2012; 67: Suppl. 2, A131.
- 7 Maher TM, Avram C, Bortey E, *et al.* Nalbuphine tablets for cough in patients with idiopathic pulmonary fibrosis. *NEJM Evid* 2023; 2: EVIDoa2300083.
- 8 Yousaf N, Monteiro W, Matos S, *et al.* Cough frequency in health and disease. *Eur Respir J* 2013; 41: 241–243.
- 9 Mann JMV, Holland AE, Goh NSL, *et al.* Understanding patient experience of chronic cough in interstitial lung disease. *ERJ Open Res* 2023; 9: 00039-2023.
- 10 Raghu G, Ghazipura M, Fleming TR, *et al.* Meaningful endpoints for idiopathic pulmonary fibrosis (IPF) clinical trials: emphasis on ‘feels, functions, survives’. Report of a collaborative discussion in a symposium with direct engagement from representatives of patients, investigators, the National Institutes of Health, a patient advocacy organization, and a regulatory agency. *Am J Respir Crit Care Med* 2024; 209: 647–669.
- 11 Green R, Baldwin M, Pooley N, *et al.* PCR253: The burden of persistent cough in idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILD): a systematic evidence synthesis. *Value Health* 2023; 26: S498.
- 12 Martinez FJ, Wijsenbeek MS, Raghu G, *et al.* Phase 2B study of inhaled RVT-1601 for chronic cough in idiopathic pulmonary fibrosis: a multicenter, randomized, placebo-controlled study (SCENIC trial). *Am J Respir Crit Care Med* 2022; 205: 1084–1092.
- 13 Boulet LP, Coeytaux RR, McCrory DC, *et al.* Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. *Chest* 2015; 147: 804–814.