8 September 2025
EMA/CHMP/290364/2025

Concept paper on new Guidance on the clinical investigation of medicinal products for the treatment of idiopathic pulmonary fibrosis (IPF)

Agreed by RIWP	15 July 2025
Adopted by CHMP for release for consultation	8 September 2025
Start of public consultation	30 September 2025
End of consultation (deadline for comments)	31 January 2026

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

Keywords	Idiopathic pulmonary fibrosis, clinical development, forced vital capacity

1. Introduction

There is currently no scientific guidance from the European Medicines Agency (EMA) on the clinical investigation of medicinal products for the treatment of idiopathic pulmonary fibrosis (IPF). A guidance document would facilitate development and support marketing authorisation applications for this condition.

2. Problem statement

IPF is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia (Raghu, 2022). IPF is characterised by irreversible loss of lung function due to fibrosis, which manifests as symptoms of increasing cough and dyspnoea and impaired quality of life. IPF is a rare disease with prevalence ranging from 7 to 1650 per 100 000 persons

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

worldwide (Gupta, 2023). In the European Union IPF has been considered as an orphan condition affecting no more than 5 in 10,000 people (EC Register). There is some evidence that the incidence of IPF is increasing worldwide (Hutchinson, 2015) but the reason for this is not entirely clear.

The prognosis of IPF is poor despite current treatment options. A meta-analysis of 62 studies (covering 63,307 patients) estimated that the overall 3-year and 5-year cumulative survival rates were 61.8% (95% CI 58.7-64.9) and 45.6% (95% CI 41,5-49.7), respectively (Zheng, 2022). Further, IPF is associated with a high disease burden with shortness of breath, fatigue and a persistent, dry cough being the most prevalent symptoms and severely impaired quality of life (Raghu, 2024).

Pharmacological anti-fibrotic therapies are available in the EU for the treatment of IPF. Non-pharmacological management of idiopathic pulmonary fibrosis involves oxygen supplementation, pulmonary rehabilitation, nutrition, and transplantation (Rozenberg, 2020).

3. Discussion (on the problem statement)

The following issues, related to the design of development programmes for the treatment of IPF will be addressed in the new guidance document:

- Overall design characteristics of studies in the IPF population, including duration of any double-blind randomised period and the required safety follow up period, also considering:
  - The claimed indications (chronic maintenance and/or symptomatic treatment)
  - Phase of development (proof of concept, dose finding, confirmatory).
- Relevance and limitations of outcome measures commonly used in IPF development programmes including:
  - Lung function tests such as forced vital capacity (FVC) (expressed as absolute change from baseline, change in percent predicted or proportion of subjects with a specified absolute decline in percent predicted), and measures of diffusing capacity (DLCO),
  - exercise capacity (six-minute walk test (6MWT)),
  - annual rate of acute pulmonary exacerbation,
  - respiratory-specific and all-cause hospitalisation rate,
  - extent of fibrosis (change in quantitative lung fibrosis on imaging),
  - patient-reported outcomes (symptoms, functional status; and quality of life assessments)
  - circulating biomarkers.
  - investigation of an effect on mortality (i.e. all-cause mortality and respiratory-cause mortality) acknowledging the challenges associated with such evaluations in a rare disease and the high degree of inter-individual variability with respect to disease extent, disease progression and survival time
- The choice of primary and secondary endpoints for confirmatory and dose finding studies. The potential place of composite endpoints for the use in IPF development programs may also be discussed.
- The choice of the comparator considering the intended place of new therapy in the overall management of patients (i.e. placebo on top of standard of care or active comparator).

- Key patient selection criteria for IPF studies considering stage of the disease at enrolment (mild, moderate or severe disease without/with pulmonary hypertension), and progression patterns.
- Standard of care for IPF studies and considerations for inclusion of patients on antifibrotic therapy.
- Considerations on the route of administration (oral, parenteral or inhalation route).
- Statistical considerations for IPF studies including estimand strategies, stratification factors and other relevant aspects, taking into account ICH E9(R1) addendum on estimands and sensitivity analysis.
- The number of pivotal studies recommended for approval also considering the rarity of the condition.
- The use of registries and real-world data as supporting evidence for IPF development programmes.
- The required size of the safety database at the time of application submission and approval.

Expansion of this upcoming guidance to also include topics relating to the clinical investigation of medicinal products for the treatment of progressive pulmonary fibrosis (PPF) is under consideration.

4. Recommendation

The Rheumatology/Immunology Working Party (RIWP) of the Committee for Human Medicinal Products (CHMP) recommends drafting a new guidance on the clinical investigation of medicinal products for the treatment of IPF taking into account the issues listed in section 3.

5. Proposed timetable

Release for consultation September 2025 (30 September 2025), deadline for comments (31 December 2025).

6. Resource requirements for preparation

The drafting of the new guidance document will involve experts from the national competent authorities (NCAs) and working parties. The RIWP should appoint a rapporteur and a drafting group. It is anticipated that at least one plenary session discussion at the RIWP will be needed.

7. Impact assessment (anticipated)

The aim is to consolidate the current scientific and regulatory view on the design of the clinical development programmes of medicinal products for the treatment of IPF. Considering also that a significant number of novel therapeutic approaches are currently being investigated (Koudstaal, 2023), it is anticipated that the new guidance document will promote the comparability of study results.

8. Interested parties

Pharmaceutical Industry, Academia, EU NCAs and patients and health care professional groups. Consultation with other working parties or committees will be initiated, as appropriate.

9. References to literature, guidelines, etc.

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022 May 1;205(9):e18-e47. doi: 10.1164/rccm.202202-0399ST. PMID: 35486072; PMCID: PMC9851481.

2. Shah Gupta R, Koteci A, Morgan A, George PM, Quint JK. Incidence and prevalence of interstitial lung diseases worldwide: a systematic literature review. BMJ Open Respir Res. 2023 Jun;10(1):e001291. doi: 10.1136/bmjresp-2022-001291. PMID: 37308252; PMCID: PMC10277538.

3. Community Register of orphan medicinal products, https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a

4. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015 Sep;46(3):795-806. doi: 10.1183/09031936.00185114. Epub 2015 May 14. PMID: 25976683.

5. Zheng Q, Cox IA, Campbell JA, Xia Q, Otahal P, de Graaff B, Corte TJ, Teoh AKY, Walters EH, Palmer AJ. Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. ERJ Open Res. 2022 Mar 14;8(1):00591-2021. doi: 10.1183/23120541.00591-2021. PMID: 35295232; PMCID: PMC8918939.

6. Raghu G, Ghazipura M, Fleming TR, Aronson KI, Behr J, Brown KK, Flaherty KR, Kazerooni EA, Maher TM, Richeldi L, Lasky JA, Swigris JJ, Busch R, Garrard L, Ahn DH, Li J, Puthawala K, Rodal G, Seymour S, Weir N, Danoff SK, Ettinger N, Goldin J, Glassberg MK, Kawano-Dourado L, Khalil N, Lancaster L, Lynch DA, Mageto Y, Noth I, Shore JE, Wijsenbeek M, Brown R, Grogan D, Ivey D, Golinska P, Karimi-Shah B, Martinez FJ. 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 Mar 15;209(6):647-669. doi: 10.1164/rccm.202312-2213SO. PMID: 38174955; PMCID: PMC12039048.

7. Rozenberg D, Sitzer N, Porter S, Weiss A, Colman R, Reid WD, Shapera S, Fisher J, Wentlandt K. Idiopathic Pulmonary Fibrosis: A Review of Disease, Pharmacological, and Nonpharmacological Strategies With a Focus on Symptoms, Function, and Health-Related Quality of Life. J Pain Symptom Manage. 2020 Jun;59(6):1362-1378. doi: 10.1016/j.jpainsymman.2019.12.364. Epub 2019 Dec 28. PMID: 31887400.

8. Hozumi H, Miyashita K, Nakatani E, Inoue Y, Yasui H, Suzuki Y, Karayama M, Furuhashi K, Enomoto N, Fujisawa T, Inui N, Suda T. Antifibrotics and mortality in idiopathic pulmonary fibrosis: external validity and avoidance of immortal time bias. Respir Res. 2024 Jul 31;25(1):293. doi: 10.1186/s12931-024-02922-y. PMID: 39085869; PMCID: PMC11293013.

9. Caminati A, Cassandro R, Torre O, Harari S. Severe idiopathic pulmonary fibrosis: what can be done? Eur Respir Rev. 2017 Sep 27;26(145):170047. doi: 10.1183/16000617.0047-2017. PMID: 28954763; PMCID: PMC9488930.

10. Koudstaal T, Funke-Chambour M, Kreuter M, Molyneaux PL, Wijsenbeek MS. Pulmonary fibrosis: from pathogenesis to clinical decision-making. Trends Mol Med. 2023 Dec;29(12):1076-1087. doi: 10.1016/j.molmed.2023.08.010. Epub 2023 Sep 14. PMID: 37716906.