# EU Risk Management Plan for Jascayd (nerandomilast)



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|---|---|
| **Global ID_version:** | 206893_10998033_5.0 |
| **RMP version to be assessed as part of this application:** | |
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# PART I PRODUCT OVERVIEW

PI.Table 1 Product Overview

| | |
|---|---|
| **Active substance (INN or common name)** | Nerandomilast (Jascayd) |
| **Pharmacotherapeutic group (ATC code)** | Selective Immunosuppressants<br>L04AA61 |
| **Marketing Authorisation Applicant** | Boehringer Ingelheim International GmbH |
| **Medicinal product to which this RMP refers** | 1 |
| **Invented name in the EEA** | Jascayd |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | *Chemical class*<br>Thienopyrimidine derivative |
| | *Summary of mode of action*<br>Nerandomilast is a selective inhibitor of PDE4 with preferential inhibition of the PDE4B isoenzyme over PDE4A, C and D. There is a 9-fold selectivity over PDE4D, 24-fold selectivity over PDE4A, and 870-fold selectivity over PDE4C based on *in vitro* data. At the recommended doses, inhibition of PDE4B and weaker inhibition of PDE4D can be expected. PDE4 hydrolyses and inactivates cAMP.<br>Nerandomilast exerts both anti-fibrotic and immunomodulatory effects as preferential PDE4B inhibition elevates intracellular cAMP levels and reduces the expression of pro-fibrotic growth factors and inflammatory cytokines, which are overexpressed in fibrotic lung disease. |
| | *Important information about its composition*<br>Not applicable |
| **Hyperlink to the Product Information** | <Product information (eCTD module 1.3.1)> |

| | |
|---|---|
| **Indications in the EEA** | *Current*<br>- Treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF)<br>- Treatment of adult patients with Progressive Pulmonary Fibrosis (PPF) |
| | *Proposed*<br>Not applicable |
| **Dosages in the EEA** | *Current*<br>- 18 mg b.i.d.<br>- 9 mg b.i.d., based on individual patient tolerability and anticipated benefit of treatment<br>- 9 mg b.i.d, when used concomitantly with strong CYP3A inhibitors<br>- 18 mg b.i.d., if used concomitantly with strong or moderate CYP3A inducers<br>- 18 mg b.i.d., when used concomitantly with pirfenidone |
| | *Proposed*<br>Not applicable |
| **Pharmaceutical form and strengths** | *Current*<br>Film-coated tablets for oral use, 9 mg or 18 mg |
| | *Proposed*<br>Not applicable |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

**ABBREVIATIONS**

| | |
|---|---|
| ATC | Anatomical therapeutic chemical |
| cAMP | Cyclic adenosine monophosphate |
| EEA | European Economic Area |
| EU | European Union |
| INN | International non-proprietary name |
| IPF | Idiopathic Pulmonary Fibrosis |
| PDE4 | Phosphodiesterase-4 |
| PPF | Progressive pulmonary fibrosis |
| RMP | Risk Management Plan |

# PART II SAFETY SPECIFICATION

# MODULE SI EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

## SI.1 IPF

The following section aims to provide an overview of the epidemiology of IPF, including patient characteristics, treatment patterns, and co-morbidities of interest. Nevertheless, the following potential limitations of the included studies have to be considered:

- Differences in the definition of clinical cases and the criteria used to diagnose IPF.
- Differences in the case definition and criteria used to identify the co-morbidities of interest, or in some cases the lack of a disease definition.
- Across the studies, IPF patients were in different stages of the disease. Newly diagnosed patients are likely to differ from patients at advanced stages, such as that they are awaiting lung transplantation. Hence, there may be differences in the prevalence of various co-morbidities among different stages of IPF severity.
- Only studies published in English language were included.
- The majority of the included studies were conducted based on existing data, which may be affected by information bias or misclassification.
- Differences in health care systems, population characteristics, and other factors such as local clinical practice and management of care guidelines may limit the generalisability of findings across countries.

### SI.1.1 Incidence

The annual incidence rates (per 100 000 of the population) of IPF vary globally. In the Asia-Pacific region, the incidence rate was 1.4, 2.23, and 13.0 in Taiwan, Japan, and South Korea, respectively [R13-2612; R16-1742; R24-1586], in North America 6.1 to 11.4 in the US and 21.7 to 25.8 in Canada [R16-2157; R24-1589; R24-4698] and in Europe 0.9 to 10.6 per 100 000 population per year (see SI.Table 1).

SI.Table 1 Incidence rates per 100 000 population per year for IPF in Europe, 2015-2023[¥]

| Reference | Country | Study period | Incident IPF sample size (n) | Incidence rate per 100 000 population per year |
|---|---|---|---|---|
| Hillberg 2022 [R22-0444] | Finland | 2014-2018 | NR | 3.5-7.1 |
| Hillberg 2022 [R22-0444] | Belgium | 2014-2018 | NR | 0.9-3.8 |
| Hillberg 2022 [R22-0444] | Denmark | 2014-2018 | NR | 0.4-10.6 |
| Hyldgaard 2014 [P16-01479] | Denmark | 2003-2009 | 121 | 1.3 |
| Hillberg 2022 [R22-0444] | Norway | 2014-2018 | NR | 2.2-5.5 |
| Hillberg 2022 [R22-0444] | Portugal | 2014-2018 | NR | 0.9-1.2 |
| Hillberg 2022 [R22-0444] | Greece | 2014-2018 | NR | 3.5-8.0 |
| Duchemann 2016 [R17-2810] | France | 2012 | 33 | 2.8 |
| Kreuter 2022 [P22-04814] | Germany | 2019 | 1737 | 9.6 |
| Iommi 2022 [P23-03984] | Italy | 2014-2019 | 528-766* | 6.8-9.8 |
| Agabiti 2016 [R16-1749] | Italy | 2005-2009 | 1752 | 7.5 |
| Harari 2016 [R16-1739] | Italy | 2005-2010 | 1309-2951* | 2.33-5.25 |
| Strongman 2018 [R18-1413] | UK | 2000-2012 | 1491-4527* | 2.85-8.65 |

[¥] Observational studies identified with literature search years of 2015-2023

[*] range in number of incident IPF cases depending on the definition of IPF.

### SI.1.2 Prevalence

Globally, the prevalence (per 100 000 of the population) of IPF is widely variable. In the Asia-Pacific region, the prevalence was 6.4, 27.0, and 35.2 in Taiwan, Japan, and South Korea, respectively [R13-2612; R23-2279; R24-1586]. In North America, administrative claims studies in the US have reported prevalence from 13.4 to 46.2 and in Canada it was

72.7 to 78.4 [R16-2157; R24-1589; R24-4698] and in Europe the range in prevalence was from 2.8 to 38.8 per 100 000 population (see SI.Table 2 below).

SI.Table 2 Prevalence per 100 000 population for IPF in Europe, 2015-2023¥

| Reference | Country | Study period | Prevalence IPF sample size (n) | Prevalence per 100 000 population |
|---|---|---|---|---|
| Hillberg 2022 [R22-0444] | Finland | 2014-2018 | NR | 11.2-22.8 |
| Salonen 2022 [P22-07486] | Finland | 2021 | 2317 | 36.0 |
| Hillberg 2022 [R22-0444] | Belgium | 2014-2018 | NR | 4.4-17.8 |
| Hillberg 2022 [R22-0444] | Denmark | 2014-2018 | NR | 2.7-27.7 |
| Hillberg 2022 [R22-0444] | Norway | 2014-2018 | NR | 8.1-20.7 |
| Hillberg 2022 [R22-0444] | Portugal | 2014-2018 | NR | 2.8-4.7 |
| Hillberg 2022 [R22-0444] | Greece | 2014-2018 | NR | 6.2-17.8 |
| Kreuter 2022 [P22-04814] | Germany | 2019 | NR | 24.1 |
| Strongman 2018 [R18-1413] | UK | 2012 | 1795 | 38.82 |
| Iommi 2022 [P23-03984] | Italy | 2014-2019 | 1037 | 13.3 |
| Agabiti 2016 [R16-1749] | Italy | 2005-2009 | 1212 | 25.6 |
| Harari 2016 [R16-1739] | Italy | 2005-2010 | 2097-5441* | 12.55-35.51 |
| Duchemann 2016 [R17-2810] | France | 2012 | 98 | 8.2 |

¥Observational studies published 2015 – 2023.

*Range in prevalent IPF cases depending on the definition of IPF.

### SI.1.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin, and risk factors for the disease

The incidence of IPF increases with advancing age, with a mean age of diagnosis at 65–70 years [P23-04248]. IPF is a disease with a male predominance. In multiple IPF cohorts, males account for more than 60% of all IPF cases. An overview of the age and gender

representation among IPF patients from a few European IPF registries are presented in SI.Table 3 below.

SI.Table 3 Demographic characteristics (age and gender) among patients with IPF in selected European registries

| Reference | Country/ Registry Name | Study Period | IPF n | Mean Age and % Male |
|---|---|---|---|---|
| Kalafiste 2017 [R19-4102] | Swedish IPF registry | 2014-2017 | 348 | 72.0 years*; 71.8% male |
| Wuyts 2018 [P18-12178] | Belgium PROOF IPF registry | 2013-2016 | 277 | 69.6 years; 76.9% male |
| Kaunisto 2019 [P19-06326] | Finnish IPF registry | 2011-2015 | 453 | 73 years; 65.1% male |
| Behr 2020 [P21-03230] | German INSIGHTS-IPF registry | 2012-2018 | 588 | 69.8 years; 81% male |
| Spencer 2021 [P24-02942] | UK British Thoracic Society IPF registry | 2013-2019 | 2,474 | 74 years; 79% male |
| Sese 2021 [R24-1588] | French COhorte Fibrose | 2007-2010 | 236 | 67.4 to 70.1 years; 78% male |

*Median age in years (mean age not provided).

A meta-analysis by Jalbert et al (2011-2021), of 4 observational IPF registry studies from US and Europe in which race was specifically reported, found that the weighted pooled proportion of non-white individuals in IPF studies was 14% with a range of 7% to 32% [R22-3214]. In a US study using a patient registry and 4 tertiary hospital registries (2003-2021) containing a cohort of 2322 IPF patients, the racial characteristics were: 2% Black; 92% White; and 6% Hispanic [R24-1585].

Potential factors for development of IPF include intrinsic risk factors (e.g. genetics, aging, male sex, lung microbiome), comorbidities (e.g. gastro-oesophageal reflux, obstructive sleep apnoea, diabetes mellitus, herpesvirus infection), and extrinsic risk factors (e.g. cigarette smoking, environmental exposures, air pollution) [R24-1591]. These risk factors may independently increase susceptibility for IPF or act in a synergistic fashion to contribute to an increased risk for disease development [R24-1591].

### SI.1.4 The main existing treatment options

The 2022 publication of the ATS, ERS, JRS, and ALAT clinical practice guideline recommends that treatment considerations should include both pharmacological (nintedanib and pirfenidone) and nonpharmacological (oxygen supplementation and/or pulmonary rehabilitation) therapies [P22-03204]. Patients at increased risk of mortality should be referred for lung transplantation at diagnosis [P22-03204].

Nintedanib and Pirfenidone

The 2 replicate 52 weeks Phase III trials (INPULSIS-1 and 2) included 1066 patients, which were randomly assigned in a 3:2 ratio to receive nintedanib versus placebo. Both trials showed that nintedanib reduced disease progression by significantly reducing the annual rate of decline in FVC compared to placebo. In addition, the INPULSIS-2 trial observed the following for the nintedanib group compared to the placebo: a) a benefit with regard to patient-reported outcomes (i.e. self-administered questionnaire to assess health-related quality of life) and b) increased time to first acute exacerbation (hazard ratio: 0.38 [95% CI 0.19, 0.77]; p = 0.005) [P14-07514].

A pooled analysis of data from the TOMORROW (Phase II randomised, placebo-controlled, 52-week, dose-finding trial of nintedanib in 428 patients with IPF) and both INPULSIS trials showed a trend towards a reduction in all-cause and respiratory mortality in patients treated with nintedanib. HRs for time to all-cause and on-treatment mortality were 0.70 (95% CI 0.46, 1.08; p = 0.0954) and 0.57 (95% CI 0.34, 0.97; p = 0.0274), respectively, in favour of nintedanib. The HR for time to first acute exacerbation was 0.53 (95% CI 0.34, 0.83; p = 0.0047). Adjusted mean change from baseline in SGRQ score at week 52 was 2.92 with nintedanib and 4.97 with placebo (difference: -2.05 [95% CI -3.59, -0.50]; p = 0.0095) [P16-04370].

The phase III ASCEND trial showed that pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with mild or moderate IPF [R14-2103].

A meta-analysis of 26 studies published up to 2020 (RCTs and cohort studies) comprising 12 956 patients (6425 with antifibrotic treatment [i.e. nintedanib, pirfenidone] and 6531 not treated with antifibrotics) reported decreased risk of all-cause mortality (pooled RR: 0.55 [0.45-0.66]) and acute exacerbation (pooled RR, 0.63 [0.53-0.76]) among those treated with antifibrotics [P21-06862].

Other treatments

Based on extrapolation from data from 2 large randomised COPD studies showing a survival benefit in patients with resting hypoxaemia who receive long-term oxygen therapy [R08-4073; R08-4108], patients with IPF should also receive supportive long-term oxygen supplementation in case of resting hypoxaemia [P11-07084]. However, appropriate data on benefit in patients with IPF is lacking.

In selected IPF patients, lung transplantation may be a treatment option, with optimal results in survival and quality of life [P24-01486]. Median survival after lung transplant in IPF patients is approximately 4.5 years. The 1-, 3- and 5-year survival ranged from 75%-81%, 59%-64% and 47%-53%, respectively [R14-4011]. A study that utilised data from the Irish National Lung Transplant Program (2005-2017) examined 156 IPF patients (mean age 63.3 years) selected for a single lung transplant. 84 out of 156 patients underwent lung transplants, 61 died while on the waiting list, and 11 were waiting and still alive at the time of data capture. The results of this study found that without transplantation, the median survival from time of listing was 0.68 years, but on the other hand, the estimated median survival was 9.6 years following transplantation [R24-1587]. The number of patients who have had lung

transplants due to IPF has increased steadily, particularly in the US, where IPF has become the most common indication for transplantation since the introduction of the Lung Allocation Score [R22-0458; R12-3676; R12-3680; R12-3474; R14-4011].

### SI.1.5 Natural history of the indicated condition in the population, including mortality and morbidity

The natural history of IPF is variable and difficult to predict [P23-04249]. For instance, some show a "rapid decline in lung function, others progress much more slowly, and some patients show periods of relative stability with acute deteriorations in respiratory function which are unpredictable and often fatal" [P23-04249]. Many of these events are considered as acute exacerbations which yearly occur in about 10% to 20% of the patients [P23-04249].

IPF has a poor prognosis, with an average life expectancy of 3-5 years from diagnosis, if left untreated [P23-01304]. Characterisations of IPF include irreversible loss of lung function due to lung fibrosis, with presentations of symptoms of chronic exertional dyspnoea and dry cough over a period of months to years and a gradual decline in ability to undertake activities of daily living [P23-01304]. Patients with IPF are also at increased risk for venous thromboembolism, lung cancer, and pulmonary hypertension [P23-04249].

To evaluate the prognosis of patients with IPF without antifibrotic therapy, a systematic review (publication year up to 2017) of cohort studies and the placebo arms of randomised controlled trials in IPF (participants ≥18 years untreated or not treated with nintedanib or pirfenidone) reported that within 2 years FVC and diffusing capacity of the lung for carbon monoxide declined by a mean of 6.76% predicted (95% CI -8.92-4.61) and 3% predicted (95% CI -5.14-1.52), respectively [R22-2436]. This review also found that the pooled mean overall survival was 4 years among studies with a follow-up duration of 10 years [R22-2436].

A retrospective, population-based cohort study (2010-2016; 5360 patients not treated with antifibrotic therapies) in France used claims data from the SNDS reported that, if untreated with antifibrotics, IPF is associated with a 50% all-cause mortality at 3 years [R24-1590].

A meta-analysis of 62 studies (covering 63307 patients from 20 countries) assessing IPF mortality and published in November 2021 estimated that the overall 3-year and 5-year CSRs were 61.8% (95% CI 58.7-64.9) and 45.6% (95% CI 41.5-49.7), respectively [R24-1593]. Prior to 2010, the pooled 3-year CSR was 59.9% (95% CI 55.8-64.1). After excluding studies in which no patients received antifibrotics after year 2010, the 3-year CSR was 67.4% (95% CI 63.9-70.9) [R24-1593]. These results should be interpreted in the context of the high heterogeneity (I2>50% represents high between-studies heterogeneity) [R24-1593].

### SI.1.6 Important co-morbidities

Publications of reviews including a systematic review [P24-02941; P20-00550; P15-10732] report the following frequent and relevant comorbidities among patients with IPF:

- Cardiovascular diseases
  - Arterial hypertension
  - Coronary artery disease

  - Myocardial infarction
  - Congestive heart failure
  - Pulmonary embolism
- Pulmonary hypertension
- Cerebrovascular diseases
- Pulmonary disease
  - Emphysema
  - COPD
- Metabolic co-morbidities
  - Diabetes mellitus
  - Hyperlipidaemia
- Psychiatric disease
  - Depression
  - Anxiety
- Lung cancer
- Sleep apnoea
- Gastro-oesophageal reflux

## SI.2 PPF

The following section aims to provide an overview of the epidemiology of PPF, including patient characteristics, treatment patterns, and co-morbidities of interest. Nevertheless, the same potential limitations of the included studies have to be considered as described in Section SI.1.

The term PPF refers to a number of fibrosing ILDs (excluding IPF) “which can develop a progressive phenotype, similar to IPF, characterised histologically by self-sustaining fibrosis, a process common to a variety of conditions, and which leads to worsening quality of life, decline in lung function and, eventually, early mortality” [P19-10166]. Non-IPF forms of ILD that develop PPF include iNSIP, unclassifiable idiopathic interstitial pneumonia, chronic HP, some autoimmune diseases-related ILDs such as SSc-ILD and RA-ILD, sarcoidosis, and lung occupational diseases [P22-08583].

### SI.2.1 Incidence

The estimated incidence rates of PPF ranged from 2.1 (Europe) to 108.7 (US) per 100 000 population per year. The variations in rates can be due to differences in study methodology, including PPF definitions and type of data (claims, medical records; see SI.Table 4).

In Europe, 2 studies were identified.

- The PERSEIDS retrospective cohort study (2014-2018) was conducted in pulmonary and rheumatology departments at 14 centres in Belgium, Denmark, Finland, Greece, Norway and Portugal. During the study period, the overall incidence rate for non-IPF PPF for the 6 countries ranged 4.4-9.0 per 100 000 population [R22-0444].

- The second study utilised the French healthcare database (2010-2017), the SNDS, which includes data for 98.8% of the population. A total of 14 119 new cases of PPF were identified. An increase in the incidence rates was seen from year 2010 (3.96 per 100 000 population) to year 2016 (4.59), with the highest in year 2014 (4.73) [P21-05688].

In the US, a study that utilised a medical and prescription commercial claims database estimated the incidence rate of PPF over a study period from 2012 to 2015. Out of 23 577 incidence fibrosing ILD patients, 57.3% were identified with PPF with a median time of 117 days from fibrosing ILD diagnosis to progression. This study used 2 different approaches to identify cases of PPF (for fibrosing ILD, 2 claims of diagnostic code for lung fibrosis versus 1 claim of diagnosis code). In this study, patients with progressive fibrosing ILD were a subgroup of the fibrosing ILD cohort. Patients were considered to have progressive fibrosing ILD (or PPF) if they satisfied any of the following criteria for progression: ≥2 pulmonary function tests or ≥2 oxygen titration tests within 90 days, ≥2 HRCT or ≥3 chest computed tomography scans within 360 days, respiratory hospitalisation, palliative care, lung transplant, any use of oxygen therapy or a corticosteroid >20 mg, or new use of immunosuppressive therapy. Thus, the adjusted (age and sex) incidence rates for PPF ranged between 32.55 to 108.17 per 100 000 population [R21-2387].

SI.Table 4 Incidence rates per 100 000 population per year for select studies conducted in Europe

| Reference | Country | Study Period | Incident PPF Sample size (n) | Incidence rate per 100 000 population per year˜ |
|---|---|---|---|---|
| Nasser 2021 [P21-05688] | France | 2010-2017 | 14 119 | 4.0 - 4.7 |
| Hillberg 2022 [R22-0444] | Belgium, Denmark, Norway, Portugal, Greece and Finland | 2014-2018 | NR | 4.4 – 9.0 |
| Hillberg 2022 [R22-0444] | Finland | 2014-2018 | NR | 5.0 - 10.1 |
| Hillberg 2022 [R22-0444] | Belgium | 2014-2018 | NR | 5.8 - 13.7 |
| Hillberg 2022 [R22-0444] | Denmark | 2014-2018 | NR | 8.5 - 14.4 |
| Hillberg 2022 [R22-0444] | Norway | 2014-2018 | NR | 2.7 - 6.8 |
| Hillberg 2022 [ R22-0444] | Portugal | 2014-2018 | NR | 2.1 - 2.9 |
| Hillberg 2022 [R22-0444] | Greece | 2014-2018 | NR | 2.1 - 5.2 |

NR: not reported

˜Ranges are provided if studies used multiple definitions for PPF or rates were provided for multiple years.

### SI.2.2 Prevalence

In general, the proportion of PPF among those patients with ILD ranged from 13% to 40%, with studies in Canada and US reporting 50% and 60%, respectively [ P20-11493; P22-04608; R21-2387]. SI.Table 5 presents the proportion of patients with different ILDs that develop PPF based on a published review [P20-07871].

SI.Table 5 Estimated percentage of patients with a progressive fibrosing phenotype across different ILDs based on published review

| ILD subtype | Estimated % of ILD developing PPF |
|---|---|
| iNSIP | 32% |
| RA-ILD | 32% |
| SSc-ILD | 40% |
| Unclassifiable fibrotic ILD | 53% |
| Primary Sjögren syndrome-ILD | 24% |
| Drug induced ILD | 18% |
| Chronic fibrotic HP | 21% |
| Sarcoidosis | 13% |

Source: Wijsenbeek and Cottin 2020 [P20-07871]

Overall, the prevalence per 100 000 in Europe ranged from 5.4 to 65.3 (see SI.Table 6); in the US the range was 12.14 to 190.94 [R21-2387; R22-0312]; and in Australia it was approximately 15 [R20-3249]. These wide ranges can primarily be due to the various definitions being utilised to identify PPF in secondary databases.

SI.Table 6 Prevalence of PPF per 100 000 population in select observational studies from Europe

| Reference | Country | Study period | Prevalent PPF sample size (n) | Prevalence per 100 000 population |
|---|---|---|---|---|
| Nasser 2021 [P21-05688] | France | 2016 | 14 413 | 19.4 |
| Hillberg 2022 [R22-0444] | Belgium, Denmark, Norway, Portugal, Greece and Finland | 2014-2018 | NR | 14.5 - 35.1 |
| Hillberg 2022 [R22-0444] | Belgium | 2014-2018 | NR | 16.7 - 65.3 |
| Hillberg 2022 [R22-0444] | Denmark | 2014-2018 | NR | 25.3 - 40.4 |
| Hillberg 2022 [R22-0444] | Norway | 2014-2018 | NR | 13.1 - 33.3 |
| Hillberg 2022 [R22-0444] | Portugal | 2014-2018 | NR | 6.7 - 11.3 |
| Hillberg 2022 [R22-0444] | Greece | 2014-2018 | NR | 5.4 - 21.5 |
| Hillberg 2022 [R22-0444] | Finland | 2014-2018 | NR | 18.4 - 37.6 |

NR: not reported

### SI.2.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin, and risk factors for the disease

Studies that have examined the demographic characteristics of PPF patients report a median age of 60 years or older. There is no clear predominance in gender among PPF (see SI.Table 7). A US study which utilised an administrative database found increasing incidence rates of PPF as the age group increased, and the crude prevalence per 100 000 population was similar for males and females (males: 57.63; females: 57.98) [R21-2387].

SI.Table 7 Demographic characteristics (age and gender) in observational studies examining PPF in multiple countries

| Reference | Country | Study Period | PPF Sample Size | Median Age; % Male |
|---|---|---|---|---|
| Kilpeläinen 2023 [R23-0732] | Finland | 2014-2017 | 142 | 73 years; 65.5% male |
| Khor 2023 [R22-2616] | Canada and Australia | 2015-2020 | 403 | 59-61 years; 38-40% male |
| Gagliardi 2021 [P22-04607] | Belgium | 2017-2019 | 68 | 68 years; 38% male |
| Kwon 2021 [R22-3046] | South Korea | 2005-2015 | 135 | 58.7 years*; 43% male |
| Hambly 2022 [P22-04608] | Canada | 2015-2020 | 1376 | 64 years*; 52% male |
| Nasser 2021 [P21-05688] | France | 2010-2017 | 14,413 | 68.4 years*; 51.9% male |

*Mean years reported (not the median)

Published literature on the incidence or prevalence of PPF by race and ethnicity was not identified. The geographical data as reported in the prevalence section included South Korea, but further differences by race were not reported. A US study (2003-2021; n=4792 pulmonary fibrosis patients) reported the racial differences for pulmonary fibrosis in general (not PPF) by utilising the PFFR for the primary cohort and registries from 4 geographically distinct tertiary hospitals in the US. The study reported that within this cohort, Black patients more commonly had CTD-ILD, White patients had IPF and Hispanic patients had fibrotic hypersensitivity pneumonitis. The following are the detailed proportions by race and ethnicity for pulmonary fibrosis (see SI.Table 8) [R24-1585].

SI.Table 8 Race and ethnicity by ILD types in a US study, 2003-2021

| ILD type | Black (n= 488) | White (n=3985) | Hispanic (n=319) |
|---|---|---|---|
| CTD-ILD | 38.6%-54.3% | 12.6%-13.6% | 21.8%-27.2% |
| Fibrotic hypersensitivity pneumonitis | 5.7%-6.0% | 7.5%-13.9%; | 12.1%-14.4% |
| Unclassifiable or other pulmonary fibrosis | 23.8%-45.2% | 13.1%-27.3% | 16.4%-17.7% |
| IPF | 7.8%-16.2% | 45.5%-65.8% | 41.5%-48.4% |

Source: Adegunsoye 2023 [R24-1585]

Risk factors for progression include “older age, male sex, lower baseline pulmonary function, and radiographic honeycombing or usual interstitial pneumonia pattern of injury. Regardless of disease trigger, PPF progresses through mechanisms of self-sustained dysregulated cell

repair, fibroblast proliferation and alveolar dysfunction that can be targeted similarly" [P21-10421].

### SI.2.4 The main existing treatment options

There is no standardised management regimen that can be applied to all PPF types and aetiologies [P22-09890]. Antifibrotic therapy with nintedanib or pirfenidone to slow lung function decline is the backbone of treatment for IPF with an expanded indication of PPF for nintedanib. Nintedanib is approved for treatment of patients with chronic fibrosing ILDs with a progressive phenotype [P21-03105]. Immunosuppression is utilised for some subtypes of PPF, including connective tissue disease ILD and hypersensitivity pneumonitis [P21-10421]. Non-pharmacologic therapies for PPF can also include oxygen therapy, pulmonary rehabilitation, and lung transplantation [P21-10421].

The 2022 publication of the ATS, ERS, JRS, and ALAT clinical practice guideline suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD.

In the randomised controlled INBUILD trial, the annual rate of decline in FVC was significantly lower among patients who received nintedanib than among those who received placebo (−80.8 ml compared to −187.8 ml; with between-group difference 107.0 ml, 95% CI 65.4–148.5; P < 0.001) [P19-08802].

In the phase 2 RELIEF trial, the efficacy of pirfenidone was studied in CTD-ILD, fibrotic NSIP, chronic hypersensitivity pneumonitis, and asbestos-related progressive pulmonary fibrosis (e.g., ≥5% yearly FVC decline). Pirfenidone showed potential to slow decline in FVC in this population, though the trial was underpowered and terminated early [R21-1270].

### SI.2.5 Natural history of the indicated condition in the population, including mortality and morbidity

The natural course of untreated IPF is characterised by progression to respiratory failure in virtually every patient with a confirmed diagnosis [P20-07871]. In contrast, "more than half of all patients with a diagnosis of pulmonary fibrosis other than IPF have stable, chronic disease or improvement with immunomodulatory therapy. Despite treatment that is considered appropriate, a proportion of patients with PPF is associated with worsening respiratory symptoms, a decline in lung function, a decreased quality of life, and a risk of early death, independent of the classification of the ILD. Outcomes of PPF may be similar to those of IPF, especially in patients with a usual interstitial pneumonia pattern, such as those with RA–ILD, or with chronic hypersensitivity pneumonitis" [P20-07871].

Using data from the placebo groups of the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing ILDs, Brown et al. found that patients with fibrosing ILDs other than IPF, who are progressing despite management, have a subsequent clinical course similar to patients with untreated IPF, with a high risk of further ILD progression and early mortality [P20-02922]. According to an international survey among clinicians

managing patients with non-IPF ILDs, the average time from symptom onset to death was 61 to 80 months in these patients [R19-2487].

Based on the French healthcare database SNDS, a study (2010-2017) examining 14 413 patients with PPF reported the median overall survival was 3.7 years from the start of disease progression (see SI.Table 9). During the study period, 95.2% of patients had ≥ 1 hospitalisation for respiratory care and 34.3% were hospitalised in an intensive care unit [P21-05688]. When stratified by underlying disease, patients with sarcoidosis-ILD had the longest median overall survival (7.9 years) and patients with exposure-related ILD other than HP had the shortest (2.4 years).

SI.Table 9 Overall survival (median years and rates) by PPF subgroups as reported in France, SNDS, 2010-2017

| | PF-ILD (n=14 413) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **All** (n= 14 413) | **HP** (n= 728) | **IIP** (n= 3113) | **RA-ILD** (n= 2521) | **SSc-ILD** (n= 907) | **MCTD-ILD** (n= 655) | **Sarcoi-dosis-ILD** (n= 1500) | **Other auto-immune** (n=1503) | **Exposure-related ILD other than HP** (n=3486) |
| **Median OS, years** | 3.7 | 4.8 | 3.7 | 3.5 | 3.1 | 3.6 | 7.9 | 6.4 | 2.4 |
| **OS, %** | | | | | | | | | |
| 1 year | 73.7 | 81.4 | 70.7 | 72.4 | 73.6 | 71.5 | 85.2 | 81.0 | 67.7 |
| 3 years | 55.1 | 65.4 | 53.6 | 54.6 | 51.2 | 53.2 | 70.7 | 64.4 | 44.6 |
| 5 years | 42.0 | 49.2 | 44.3 | 39.8 | 38.8 | 41.1 | 59.0 | 53.6 | 27.8 |

OS: overall survival
Source: Nasser 2021 [P21-05688]

In a hospital-based study from China which assessed clinical outcomes such as mortality (2013-2014; n=132 PPF out of 608 ILD), the median time from diagnosis of ILD to PPF was 22.6 months. In this study, the 1, 3, and 5-years survival rates were 90.9%, 58.8% and 48.1% respectively, which were similar to those in the IPF group (89.4%, 68.1% and 43.9%, respectively), and significantly worse than those without PPF (99.4%, 96.4%, and 91.0% respectively; p <0.001) [R21-3890].

### SI.2.6 Important co-morbidities

In general, the comorbid conditions found among patients with PPF depend on the underlying disease that is associated with PPF. Data presented from observational studies list the

following as important comorbid conditions among patients with PPF [R24-1182; P22-05334; P21-05688]:

- Cardiovascular disease
  - Arterial hypertension
  - Congestive heart failure
  - Cardiac arrhythmias
  - Chronic coronary disease
- Psychiatric disease
  - Anxiety
  - Depression
- Lung cancer
- Gastro-oesophageal reflux disease
- Respiratory conditions

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### SI.3.2 Unpublished references

Not applicable.

## ABBREVIATIONS

| | |
|---|---|
| ALAT | Asociatión Latinoamericana de Tórax |
| ASCEND | Trial: A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis |
| ATS | American Thoracic Society |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CSR | Cumulative survival rates |
| CTD-ILD | Connective tissue disease-associated interstitial lung disease |
| DLCO | Diffusing capacity of the lung for carbon monoxide) |
| ERS | European Respiratory Society |
| FVC | Forced vital capacity |
| Hb | Haemoglobin |
| HCRT | High-resolution computed tomography |
| HP | Hypersensitivity pneumonitis |
| HR | Hazard ratio |

| | |
|---|---|
| IIP | Idiopathic interstitial pneumonia |
| ILD | Interstitial lung disease |
| INBUILD | Trial: Nintedanib in Progressive Fibrosing Interstitial Lung Diseases |
| INPULSIS | Trial: Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis |
| IPF | Idiopathic pulmonary fibrosis |
| (i)NSIP | (idiopathic) non-specific interstitial pneumonia |
| JRS | Japanese Respiratory Society |
| MCTD-ILD | Mixed connective tissue disease-associated interstitial lung disease |
| NR | Not reported |
| OS | Overall survival |
| PFFR | Pulmonary Fibrosis Foundation Registry |
| PF-ILD | Progressive fibrosing interstitial lung disease |
| PERSEIDS | Study title: Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries |
| PPF | Progressive pulmonary fibrosis |
| RA-ILD | Rheumatoid arthritis-associated interstitial lung disease |
| RELIEF | Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (clinical trial) |
| RR | Risk ratio |
| SGRQ | St George's Respiratory Questionnaire |
| SNDS | Système National des Données de Santé |
| SSc-ILD | Systemic sclerosis associated interstitial lung disease |
| TOMORROW | Trial: A 12 Month, Double Blind, Randomized, Placebo-controlled Trial Evaluating the Effect of BIBF 1120 Administered at Oral Doses of 50 mg qd, 50 mg Bid, 100 mg Bid and 150 mg Bid on Forced Vital Capacity Decline During One Year, in Patients With Idiopathic Pulmonary Fibrosis, With Optional Active Treatment Extension Until Last Patient Out. |
| US | United States of America |

# MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

## SII.1 KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE

### SII.1.1 Toxicity

The toxic potential of nerandomilast was assessed in a comprehensive non-clinical toxicology programme that included safety pharmacology, repeat-dose general toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicology studies.

No acute toxicity studies were conducted with nerandomilast. Pivotal repeat-dose toxicity and toxicokinetic studies were conducted in rats for up to 26 weeks, and in minipigs and cynomolgus monkeys for up to 39 weeks [U11-3445, U12-1580, n00232817, n00259627, n00221777, n00269853, n00290939, n00307319]. In rats, a dose level of 2 mg/kg/day did not result in adverse changes and exposure was equivalent to (1-fold) humans at the MRHD (18 mg twice daily). In minipigs a dose level of 3 mg/kg/day was judged a low observed adverse effect level, with exposure equivalent to humans at the MRHD. No adverse effects were observed in cynomolgus monkeys at dose levels up to 30 mg/kg/day administered over 39 weeks (10-fold human exposure at the MRHD). The exposure margin in monkeys, considered the most relevant species to humans, suggests that primates are less sensitive to nerandomilast-related toxicity than other species.

In a dose escalation/6-week DRF study in monkeys, emesis was observed in a dose-responsive manner in several animals per group at ≥60 mg/kg/day [n00280519]. The frequency of emesis was low in monkeys receiving 30 mg/kg/day (10-fold human AUC at the MRHD) in pivotal repeat-dose toxicity studies of 13 or 39 weeks [n00290939, n00307319]. Emesis in monkeys is thought to be related to inhibition of PDE4D that is caused by the high nerandomilast exposure levels achieved in toxicology studies. Emesis in monkeys related to nerandomilast administration is considered of human relevance, but in view of the adequate exposure multiple is judged low risk. This is supported by clinical trials in humans.

In repeat-dose general toxicity studies, vasculopathy (inflammation, haemorrhage, and necrosis of in and around blood vessels) was the primary nerandomilast-related adverse finding observed in rats and minipigs. Vasculopathy is a known class effect of PDE4is in non-clinical models and is thought to be a consequence of vascular tone dysregulation and subsequent inflammatory response. Species dissimilarities in PDE4 expression and response to PDE4 inhibition are believed to be the cause of species-related differences in target tissues. In rats and minipigs, the mesentery and heart were the respective target organs, but inflammation, degeneration, necrosis, and/or haemorrhage around and within blood vessel walls were observed in multiple organs in both species in more severe cases. At times vasculopathy led to moribundity/mortality. Vasculopathy was reversible in rats and minipigs. In one male monkey receiving 500/300 mg/kg/day (at 300 mg/kg/day, 39-fold human AUC exposure at the MRHD) in a dose escalation/6-week DRF study, vasculitis was observed unilaterally in the epididymal blood vessels but was considered non-adverse due to its limited

nature and lack of effect on adjacent tissues; no other instances of vasculopathy were noted in monkeys. Adverse vascular effects observed in the rat and minipig pivotal repeat-dose toxicology studies do not preclude administration of nerandomilast to humans. The singular finding of a vascular change in monkeys coupled with high nerandomilast exposure levels supports a lower likelihood of this effect in humans than was observed in rats and minipigs at exposure levels equivalent to humans at the MRHD. Regardless, vasculopathy is considered a potential risk of nerandomilast administration to humans, based on the nonclinical results.

Clinical pathology changes indicating a dose-related inflammatory profile were noted in pivotal repeat-dose toxicity studies in rats and occasionally in individual minipigs. This consisted of increased neutrophil counts and fibrinogen levels, along with a decreased albumin/globulin ratio, the latter due to a change in either parameter. A similar clinical pathology profile was not observed in monkeys in pivotal repeat-dose toxicity studies.

In one monkey per group administered 100 or 300 mg/kg/day (17 and 39-fold human AUC exposure at the MRHD) in a dose escalation/6-week DRF study, microscopic focal myocardial degeneration or necrosis, respectively, was observed in the interventricular septum near the apex of the heart but was not accompanied by vasculopathy [n00280519]. These heart findings were limited (focal) and evident at exposure levels well exceeding human exposure at the MRHD. No nerandomilast-related heart muscle changes were observed at 30 mg/kg/day (10-fold human AUC exposure at the MRHD) in monkey studies up to 39 weeks duration, suggesting a low potential for a similar effect in humans.

Inflammation around and within the covering surrounding the tibia, and more rarely new bone formation around the tibia, were observed in a few rats receiving ≥4 mg/kg/day following 26 weeks of administration and in a few rats at 2 mg/kg/day for 104 weeks (4- and 2-fold human AUC exposure at the MRHD) [n00259627, n00308868]. Similar changes have been noted in the literature in rodent studies with other PDE3/PDE4i and PDE4i. Although a similar finding was not seen in minipigs, degeneration in and around blood vessels was observed in connective tissues around the tarsus of a few minipigs receiving 25/20 mg/kg/day (6-fold human AUC exposure at the MRHD) [n00269853]. In both species, limb inflammation occasionally led to severely impaired locomotion and moribundity with subsequent humane euthanasia. Inflammation surrounding the tibia was reversible in rats, whereas new bone formation was partially reversible. Connective tissue inflammation around the tarsus in minipigs was reversible. Similar findings were not observed in monkeys. Based on observations across species, exposure margins, and information in literature, these findings are not considered relevant to adult humans at the MRHD.

During administration of nerandomilast to mature female monkeys over 39 weeks, sporadic prolongation of menstrual cycles was observed at 10 and 30 mg/kg/day (3 and 10-fold human AUC exposure at the MRHD) [n00307319]. Menstrual cycles were not affected at 3 mg/kg/day (equivalent to human AUC exposure at the MRHD). This finding is of potential relevance to humans.

Nerandomilast showed no immunotoxic potential in repeat-dose toxicity studies in rats, minipigs, or monkeys. Nerandomilast showed no evidence of phototoxic potential [U13-5052].

SII.1.1.1 Reproductive and developmental toxicity

A comprehensive programme assessing reproductive and developmental toxicity was completed with nerandomilast in rats and rabbits. No adverse effects on fertility in male and female rats were noted at 6 mg/kg/day (3 to 4-fold human AUC exposure at the MRHD) [n00290709, n00304275]. Nerandomilast administered during the period of organogenesis was not teratogenic in rats and rabbits at the highest dose levels tested of 9 and 15 mg/kg/day (7- and 4-fold human AUC exposure at the MRHD) [n00289050, n00292761]. Embryo-foetal lethality in the form of prenatal embryo-foetal loss (post-implantation loss due to early resorptions) was observed in rats at 6 mg/kg/day (5-fold human AUC exposure at the MRHD) but was not observed in rats at 3 mg/kg/day (3-fold human AUC exposure at the MRHD) [n00289050, n00290709] or in rabbits at 15 mg/kg/day (4-fold human AUC exposure at the MRHD) [n00292761]. In summary, nerandomilast-related adverse reproductive and developmental effects included prenatal embryo-foetal loss in rats. These results suggest a potential risk to pregnancy viability in humans.

In a dose range-finding pre- and postnatal development study in rats, a maternal dose of 6 mg/kg/day (approximately 5 to 6-times human AUC exposure at the MRHD) resulted in lower pup weights [n00301452]. A pre- and postnatal development study in rats showed no adverse effects on maternal performance or toxicity at the high-dose of 3 mg/kg/day, which corresponded to 2-times human AUC exposure at the MRHD [n00310068]. Offspring ($F_1$) development, behaviour, and reproductive performance were not affected. The presence of nerandomilast in the plasma of rat pups during the nursing period suggested secretion into rat milk, which was supported by the presence of radioactivity in milk of lactating rats that had been administered radioactive-labelled nerandomilast [n00310068, n00300902]. It is not known whether nerandomilast, or its metabolites, are excreted in human milk.

SII.1.1.2 Genotoxicity

Nerandomilast is non-genotoxic as assessed in a standard battery of *in vitro* tests of gene mutation (bacterial reverse mutation) and chromosomal damage (chromosomal aberration) and an *in vivo* (rat bone marrow micronucleus) assay for genotoxicity [n00073838, n00201043, U11-3395].

SII.1.1.3 Carcinogenicity

No increase in tumour formation was observed in transgenic mice (TgrasH2) or rats orally administered nerandomilast for 26 and 104 weeks, respectively [n00296852, n00308868]. Therefore, nerandomilast is not carcinogenic in either species. Nerandomilast exposure at the highest dose levels of 60/100 mg/kg/day in mice and of 2 mg/kg/day in rats corresponded to male/female AUC levels that were 47/57-fold and 1.6/2.2-fold human exposure at the MRHD, respectively.

### SII.1.2 Safety pharmacology

No adverse findings were associated with nerandomilast administration in a battery of single dose secondary pharmacodynamic studies and safety pharmacology assessments of central nervous system or respiratory function in male rats up to dose levels of 12 mg/kg [U11-2031, n00201167, n00201168], or of cardiovascular functions in male rats or minipigs up to dose levels of 3 mg/kg or 30 mg/kg, respectively [U11-2031, U11-2032, n00201598]. $C_{max}$ and $AUC_{0-24}$ levels at high-dose levels of 12 mg/kg in rats and 30 mg/kg in minipigs were between 5 to 7-fold human exposure at the MRHD, when estimated based on TK results from repeat-dose studies. Nerandomilast caused no effects *in vitro* on the hERG potassium ion channel or on the action potential configuration or contractility of the guinea pig papillary muscle at concentrations relevant to human exposure at the MRHD [U11-2027]. In secondary pharmacology studies, no relevant changes in gastric emptying, intestinal transit, renal, or liver function were noted following a single dose of nerandomilast to rats [U11-2028, U11-2033].

Heart rate and ECGs recorded during minipig and monkey repeat-dose toxicity studies of up to 39 weeks duration showed no adverse changes related to oral administration of nerandomilast [n00269853, n00290939, n00291907, U12-1580].

### SII.1.3 Other toxicity-related information or data

**Metabolite**
The major human metabolite of nerandomilast is formed *in vivo* in mice, rats, minipigs, and monkeys, but studies have shown its contribution to pharmacological activity or toxicity is low. Therefore, its formation is judged to have no contribution to efficacy or to adverse effects. This is supported by repeat-dose general toxicity studies in rats, minipigs, and monkeys where formation of this metabolite was adequate to assess toxicity [n00259627, n00269853, n00307319]. In addition, this metabolite showed no genotoxicity in standard *in vitro* assays (bacterial reverse mutation and chromosomal aberration) and its formation in carcinogenicity studies in mice and rats showed no potential for carcinogenic activity [n00261504, n00261516, n00296852, n00308868]. Results of a hERG assay indicated a minimal likelihood of an effect on the potassium channel [n00303479].

Full details of the non-clinical safety data for nerandomilast are presented in the registration dossier.

## SII.2 REFERENCES

### SII.2.1 Published references

Not applicable.

## SII.2.2 Unpublished references

n00073838 BI 1015550 rat micronucleus test. Charles River Laboratories Preclinical Services Montreal study no. 963770. Boehringer Ingelheim Pharmaceuticals, Inc., study no. 11R006.

n00201043 BI 1015550 chromosome aberration test. Charles River Laboratories Preclinical Services Montreal study no. 963769. Boehringer Ingelheim Pharmaceuticals, Inc., study no. 11R005.

n00201167 Pharmacological assessment of the effect of BI 1015550 on the central nervous system of the Wistar (Han) rat. Charles River Laboratories Preclinical Services Montreal study no. 694117. BI study no. 11R001.

n00201168 A pharmacological assessment of the effect of BI 1015550 on the respiratory system of the Wistar (Han) rat. Charles River Laboratories Preclinical Services Montreal study no. 694118. Boehringer Ingelheim Pharmaceuticals, Inc., study no. 11R002.

n00201598 Safety pharmacology assessment of BI 1015550 on the cardiovascular system of the naïve Gottingen mini-pig using telemetry. CRL study no 694119, BI no. 11R003.

n00221777 A 13-week study of BI 1015550 by oral gavage in minipigs with a 1-month recovery period. CRL study no. 20035317, BI no. 13R002.

n00232817 BI 1015550: a 13-week oral (gavage) toxicity and toxicokinetic study in rats with a 4-week recovery period, including a 2-week satellite group. HLS study no. 12-2330, BI no. 13R008.

n00259627 BI 1015550: a 26-week oral (gavage) toxicity study in rats with a 13-week recovery period. Covance study no. MN71VB, BI no. 17R081.

n00261504 BI 764333: Bacterial reverse mutation assay with an independent repeat assay. BioReliance study no. AF23DB.5002002ICH.BTL, BI no. 18R065.

n00261516 BI 764333: *In vitro* mammalian chromosomal aberration assay in Human peripheral blood lymphocytes (HPBL). BioReliance study no. AF23DB.341ICH.BTL, BI no. 18R066.

n00269853 A 39-week study of BI 1015550 by oral gavage in minipigs with a 28-day recovery period. CRL study no. 20124371, BI no. 17R062.

n00280519 BI 1015550: An oral (gavage) dose escalation followed by a six-week dose range-finding study in the monkey. BI study no. 20R145.

n00289050 An embryo-fetal development study of BI 1015550 by oral gavage in rats. CRL study no. 9001784, BI no. 21R015.

| | |
|---|---|
| n00290709 | A fertility and early embryonic development to implantation study of BI 1015550 by oral gavage in male and female rats. CRL study no. 9001829, BI no. 21R070. |
| n00290939 | BI 1015550: A 13-week oral (gavage) toxicity and toxicokinetic study in Cynomolgus monkeys with a 8-week recovery period. Labcorp study no. 8455063, BI no. 21R001. |
| n00291907 | BI 1015550: Thirteen-Week Oral (Gavage) Toxicity and Toxicokinetics Study in the Rat. BI Study no. 22R048. |
| n00292761 | An embryo-fetal development study of BI 1015550 by oral gavage in rabbits. CRL study no. 9001785, BI no. 21R016. |
| n00293932 | [$^{14}$C]BI 1015550: Metabolite profiling and tentative metabolite identification in humans. |
| n00296852 | BI 1015550: A 26-Week Once Daily Oral Gavage Carcinogenicity and Toxicokinetic Study in Transgenic RasH2 Mice. Labcorp study no. 8494975, BI no. 22R079. |
| n00300902 | Transfer of [$^{14}$C]BI 1015550 drug-related radioactivity to milk after oral (gavage) administration to lactating rats. 10 Apr 2024. |
| n00301452 | A Dose Range-Finding Pre and Postnatal Development Study of BI 1015550 by Oral Gavage in Rats. CRL study no. 9002186, BI no. 22R115. |
| n00303479 | BI 764333: Effect on hERG inactivating Tail Currents recorded from Stably Transfected HEK 293 cells at near Physiological Temperature. B'SYS Study no. B'SYS A3409, BI no. 23R063. |
| n00304275 | A Fertility and Early Embryonic Development to Implantation Study of BI 1015550 by Oral Gavage in Male Rats. CRL Study no. 9002081, BI no. 22R080. |
| n00307319 | BI 1015550: A 39-week oral (gavage) toxicity and toxicokinetic study in Cynomolgus monkeys with a 8-week recovery period. Labcorp study no. 8468639, BI no. 21R096. Amendment 1. |
| n00308868 | BI 1015550: A 104-Week Oral (Gavage) Carcinogenicity Study in Rats. Labcorp study no. 8448462. BI no. 20R152. |
| n00310068 | A Pre and Postnatal Development Study of BI 1015550 by Oral Gavage in Rats. Final Report Amendment No. 1. Charles River Study no. 9002002. BI no. 23R030. |

| | |
|---|---|
| U11-2026 | Effects of BI 1015550 on behavior assessed by observation in a modified IRWIN-test and on nocturnal activity in rats after oral administration of 0.3, 1 and 3 mg/kg. BI study no. GP2010/0178/0179/PH3. |
| U11-2027 | Influence of BI 1015550 on hERG-mediated potassium current in HEK293 cells and on action potential configuration in isolated guinea pig papillary muscle. BI study no. GP2010/0118/0120/PH2. |
| U11-2028 | Effects of BI 1015550 (0.3, 1 and 3 mg/kg p.o.) on gastric emptying and intestinal transit in rats. BI study no. GP2010/0122/PH4. |
| U11-2031 | Influence of BI 1015550 (0.3, 1 and 3 mg/kg PO) on vital physiological function in conscious rats using a telemetry / plethysmography system. BI study no. GP2010/0100/PH5. |
| U11-2032 | Effects of single, therapeutic doses of BI 1015550 (0.3, 1 and 3 mg/kg) on hemodynamic and electrocardiographic parameters in conscious minipigs. BI study no. GP2010/0205/PH5. |
| U11-2033 | Effects of BI 1015550 (0.3, 1 and 3 mg/kg p.o.) on renal and liver function in conscious rats. BI study no. GP2010/0188/PH4. |
| U11-3395 | BI 1015550: Bacterial reverse mutation test in Salmonella Typhimurium and Escherichia Coli. Charles River Laboratories Preclinical Services Montreal study no. 963768. Boehringer Ingelheim Pharmaceuticals, Inc., study no. 11R004. |
| U11-3445 | BI 1015550: four-week oral (gavage) toxicity and toxicokinetics study in the Wistar Han IGS rat followed by a four-week recovery period. BI study no. 10R150. |
| U12-1580 | BI 1015550: 2-week oral (gavage) toxicity study in the Göttingen minipig. BI study no. 11B008. |
| U13-5052 | Neutral red uptake phototoxicity assay of BI 1015550 in Balb/c 3T3 mouse fibroblasts. CRL study no. 20037605, BI no. 13R018. |

**ABBREVIATIONS**

| | |
|---|---|
| AUC | Area under the curve |
| DRF | Dose range finding |
| ECG | Electrocardiogram |
| hERG | Human Ether-à-go-go-related gene |
| MRHD | Maximum recommended human dose |

| | |
|---|---|
| PDE3 | Phosphodiesterase-3 |
| PDE4 | Phosphodiesterase-4 |
| PDE4i | Phosphodiesterase-4-inhibitor |
| TK | Toxicokinetic |

# MODULE SIII CLINICAL TRIAL EXPOSURE

For this RMP, the following safety analysis sets were analysed for the presentation of the clinical trial exposure:

- **SAF3**: all trials of any duration, any dose, any target indication, in healthy subjects or patients.
  SAF3 includes the following trials:
  1305-0001, -0002, -0011, -0012, -0013, -0014, -0015, -0016, -0017, -0020, -0023, -0024, -0025, -0026, -0027, -0028, -0029, -0030, -0031, -0033, -0034, -0037, -0038, -0039, -0051.
- **SAF1:** randomised, double-blind, placebo-controlled trials with a duration of at least 52-weeks, any target indication.
  SAF1 includes the following trials:
  1305-0014, 1305-0023
- **Trial 1305-0014**: phase III trial in IPF indication.[1]
- **Trial 1305-0023**: phase III trial in PPF indication.

[1] In addition to trial 1305-0014, 2 further trials were conducted for the indication IPF (trials 1305-0012 and 1305-0013) in which the 18 mg dose of nerandomilast was used. The total 18 mg exposure across all 3 IPF trials (1305-0012, -0013, and -0014) is N=499 (501.96 person years).

SIII.Table 1 Duration of exposure (SAF3, SAF1, trial 1305-0014, trial 1305-0023) – TS

**Cumulative, any target indication and healthy volunteers (person-time)** – SAF3

| **Duration of exposure (weeks)** | **Placebo N (%)** | **Person-time (years)** | **Nerandomilast N (%)** (all doses) | **Person-time (years)** |
|---|---|---|---|---|
| >0 to <4 wks | 96 (10.4) | 1.30 | 557 (20.3) | 14.07 |
| ≥4 wks to <12 wks | 37 (4.0) | 5.91 | 298 (10.9) | 53.84 |
| ≥12 wks to <26 wks | 86 (9.3) | 24.66 | 493 (18.0) | 140.68 |
| ≥26 wks to <52 wks | 72 (7.8) | 52.14 | 121 (4.4) | 87.60 |
| ≥52 wks | 635 (68.6) | 887.88 | 1269 (46.3) | 1852.31 |
| **Total person-time** | 926 (100.0) | 971.69 | 2738 (100.0) | 2148.50 |

SIII.Table 1 (cont'd) Duration of exposure (SAF3, SAF1, trial 1305-0014, trial 1305-0023) – TS

**Cumulative, indications IPF and PPF (person-time)** – SAF1

| **Duration of exposure (weeks)** | **Placebo N (%)** | **Person-time (years)** | **Nerandomilast N (%)** (all doses) | **Person-time (years)** |
|---|---|---|---|---|
| >0 to <4 wks | 9 (1.1) | 0.27 | 37 (2.4) | 1.60 |
| ≥4 wks to <12 wks | 29 (3.7) | 4.13 | 68 (4.3) | 10.16 |
| ≥12 wks to <26 wks | 40 (5.1) | 13.86 | 73 (4.7) | 25.50 |
| ≥26 wks to <52 wks | 72 (9.2) | 52.14 | 121 (7.7) | 87.60 |
| ≥52 wks | 635 (80.9) | 887.88 | 1269 (80.9) | 1780.48 |
| **Total person-time** | 785 (100.0) | 958.28 | 1568 (100.0) | 1905.34 |

**Indication IPF** – trial 1305-0014

| **Duration of exposure** | **Placebo N (%)** | **Person-time** (years) | **Nera N (%)** (9 mg b.i.d.) | **Person-time** (years) | **Nera N (%)** (18 mg) b.i.d. | **Person-time** (years) | **Nera N (%)** total | **Person-time** (years) |
|---|---|---|---|---|---|---|---|---|
| >0 to <4 wks | 5 (1.3) | 0.12 | 11 (2.8) | 0.42 | 12 (3.1) | 0.49 | 23 (2.9) | 0.90 |
| ≥4 wks to <12 wks | 15 (3.8) | 2.32 | 13 (3.3) | 1.97 | 14 (3.6) | 2.04 | 27 (3.4) | 4.01 |
| ≥12 wks to <26 wks | 17 (4.3) | 5.62 | 13 (3.3) | 4.67 | 20 (5.1) | 6.68 | 33 (4.2) | 11.35 |
| ≥26 wks to <52 wks | 37 (9.4) | 25.61 | 35 (8.9) | 25.98 | 31 (7.9) | 22.46 | 66 (8.4) | 48.44 |
| ≥52 wks | 319 (81.2) | 451.34 | 320 (81.6) | 453.47 | 315 (80.4) | 448.17 | 635 (81.0) | 901.63 |
| **Total person time for indication IPF** | 393 (100.0) | 485.01 | 392 (100.0) | 486.51 | 392 (100.0) | 479.83 | 784 (100.0) | 966.34 |

**Indication PPF** – trial 1305-0023

| **Duration of exposure** | **Placebo N (%)** | **Person-time** (years) | **Nera N (%)** (9 mg b.i.d.) | **Person-time** (years) | **Nera N (%)** (18 mg b.i.d.) | **Person-time** (years) | **Nera N (%)** total | **Person-time** (years) |
|---|---|---|---|---|---|---|---|---|
| >0 to <4 wks | 4 (1.0) | 0.15 | 7 (1.8) | 0.32 | 7 (1.8) | 0.38 | 14 (1.8) | 0.70 |
| ≥4 wks to <12 wks | 14 (3.6) | 1.82 | 19 (4.8) | 2.63 | 22 (5.6) | 3.52 | 41 (5.2) | 6.15 |
| ≥12 wks to <26 wks | 23 (5.9) | 8.24 | 20 (5.1) | 7.16 | 20 (5.1) | 6.99 | 40 (5.1) | 14.15 |
| ≥26 wks to <52 wks | 35 (8.9) | 26.52 | 25 (6.4) | 18.40 | 30 (7.7) | 20.76 | 55 (7.0) | 39.16 |
| ≥52 wks | 316 (80.6) | 436.54 | 322 (81.9) | 447.44 | 312 (79.8) | 431.40 | 634 (80.9) | 878.84 |
| **Total person time for indication PPF** | 392 (100.0) | 473.26 | 393 (100.0) | 475.96 | 391 (100.0) | 463.05 | 784 (100.0) | 939.00 |

Data source: data on file, x1305p3_rmp--01--study-report-body, tables 1.1.1.1, 1.1.4.1, 1.1.6.1 and 1.1.7.1.

SIII.Table 2 Age group and gender (SAF3, SAF1, trial 1305-0014, trial 1305-0023) – TS

| **Age group (all indications and healthy volunteers**– SAF3) | **Placebo (N)** | | **Person-time (years)** | | **Nerandomilast (N)** (all doses) | | **Person-time (years)** | |
|---|---|---|---|---|---|---|---|---|
| | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| <65 years | 235 | 99 | 203.91 | 101.03 | 742 | 306 | 410.40 | 216.56 |
| ≥65 years | 437 | 155 | 490.85 | 176.10 | 1232 | 458 | 1079.42 | 442.12 |
| **Total** | 672 | 254 | 694.76 | 277.13 | 1974 | 764 | 1377.22 | 658.69 |
| **Age group (indications IPF and PPF** – SAF1) | **Placebo (N)** | | **Person-time (years)** | | **Nerandomilast (N)** (all doses) | | **Person-time (years)** | |
| | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| <65 years | 158 | 77 | 200.27 | 100.68 | 291 | 164 | 361.29 | 206.98 |
| ≥65 years | 410 | 140 | 484.70 | 172.63 | 772 | 341 | 929.23 | 407.83 |
| **Total** | 568 | 217 | 684.97 | 273.31 | 1063 | 505 | 1290.52 | 614.81 |
| **Age group (indication IPF** – trial 1305-0014) | **Placebo (N)** | | **Person-time (years)** | | **Nerandomilast (N)** total | | **Person-time (years)** | |
| | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| <65 years | 73 | 13 | 91.79 | 19.33 | 137 | 24 | 177.46 | 31.76 |
| ≥65 years | 264 | 43 | 316.65 | 57.23 | 503 | 120 | 617.46 | 139.66 |
| **Total** | 337 | 56 | 408.45 | 76.57 | 640 | 144 | 794.92 | 171.42 |
| **Age group (indication PPF** – trial 1305-0023) | **Placebo (N)** | | **Person-time (years)** | | **Nerandomilast (N)** total | | **Person-time (years)** | |
| | **M** | **F** | **M** | **F** | **M** | **F** | **M** | **F** |
| <65 years | 85 | 64 | 108.48 | 81.35 | 154 | 140 | 183.83 | 175.23 |
| ≥65 years | 146 | 97 | 168.04 | 115.40 | 269 | 221 | 311.78 | 268.17 |
| **Total** | 231 | 161 | 276.52 | 196.74 | 423 | 361 | 495.61 | 443.40 |

Data source: data on file, x1305p3_rmp--01--study-report-body, tables 1.2.1.1.1, 1.2.1.3.1, 1.2.4.1.1, 1.2.4.3.1, 1.2.6.1.1, 1.2.6.3.1, 1.2.7.1.1, 1.2.7.3.1

SIII.Table 3 Dose (SAF3, SAF1, trial 1305-0014, trial 1305-0023) – TS

| **Dose of exposure, target indications and healthy volunteers** (SAF3) | **Nerandomilast N** | **Person-time (years)** |
|---|---|---|
| **Single dose** | | |
| <9 mg | 58 | 1.16 |
| 9 mg | 82 | 2.30 |
| >9 mg and <18 mg | 12 | 0.03 |
| 18 mg | 207 | 5.05 |
| >18 mg | 81 | 0.77 |
| **b.i.d.** | | |
| <9 mg | 26 | 1.40 |
| 9 mg | 785 | 962.46 |
| >9 mg and <18 mg | 8 | 0.31 |
| 18 mg | 1479 | 1175.02 |
| **Total** | 2738 | 2148.50 |
| **Dose of exposure, indications IPF and PPF** (SAF1) | **Nerandomilast N** | **Person-time (years)** |
| 9 mg b.i.d. | 785 | 962.46 |
| 18 mg b.i.d. | 783 | 942.87 |
| **Total** | 1568 | 1905.34 |
| **Dose of exposure, indication IPF (**trial 1305-0014) | **Nerandomilast N** | **Person-time (years)** |
| 9 mg b.i.d. | 392 | 486.51 |
| 18 mg b.i.d. | 392 | 479.83 |
| **Total** | 784 | 966.34 |
| **Dose of exposure, indication PPF (**trial 1305-0023) | **Nerandomilast N** | **Person-time (years)** |
| 9 mg b.i.d. | 393 | 475.96 |
| 18 mg b.i.d. | 391 | 463.05 |
| **Total** | 784 | 939.00 |

Data source: data on file, x1305p3_rmp--01--study-report-body, tables 1.1.1.1, 1.1.4.1, 1.1.6.1, 1.1.7.1

SIII.Table 4 Ethnic origin (SAF3, SAF1, trial 1305-0014, trial 1305-0023) – TS

| **Ethnic origin, target indications and healthy volunteers** (SAF3) | **Placebo N** | **Person-time (years)** | **Nerandomilast** (all doses) **N** | **Person-time (years)** |
|---|---|---|---|---|
| Asian | 286 | 337.68 | 811 | 779.05 |
| Black or African American | 11 | 11.78 | 23 | 17.11 |
| White | 624 | 617.56 | 1889 | 1338.53 |
| Other | 5 | 4.88 | 15 | 13.81 |
| **Total** | 926 | 971.89 | 2738 | 2148.50 |
| **Ethnic origin, indications IPF and PPF** (SAF1) | **Placebo N** | **Person-time (years)** | **Nerandomilast** (all doses) **N** | **Person-time (years)** |
| Asian | 272 | 335.79 | 561 | 703.92 |
| Black or African American | 9 | 11.73 | 13 | 15.94 |
| White | 499 | 605.87 | 983 | 1172.07 |
| Other | 5 | 4.88 | 11 | 13.41 |
| **Total** | 785 | 958.28 | 1568 | 1905.34 |
| **Ethnic origin, indication IPF** (trial 1305-0014) | **Placebo N** | **Person-time (years)** | **Nerandomilast** (all doses) **N** | **Person-time (years)** |
| Asian | 118 | 141.14 | 255 | 319.46 |
| Black or African American | 2 | 3.09 | 4 | 4.61 |
| White | 273 | 340.78 | 524 | 640.96 |
| Other | 0 | - | 1 | 1.31 |
| **Total** | 393 | 485.01 | 784 | 966.34 |
| **Ethnic origin, indication PPF** (trial 1305-0023) | **Placebo N** | **Person-time (years)** | **Nerandomilast** (all doses) **N** | **Person-time (years)** |
| Asian | 154 | 194.65 | 306 | 384.47 |
| Black or African American | 7 | 8.64 | 9 | 11.33 |
| White | 226 | 265.09 | 459 | 531.10 |
| Other | 5 | 4.88 | 10 | 12.10 |
| **Total** | 392 | 473.26 | 784 | 939.00 |

Data source: data on file, x1305p3_rmp--01--study-report-body, tables 1.1.1.1, 1.1.4.1, 1.1.6.1, 1.1.7.1, 1.2.1.4.1, 1.2.4.4.1, 1.2.6.4.1, 1.2.7.4.1

## SIII.1 REFERENCES

Not applicable.

## ABBREVIATIONS

| | |
|---|---|
| b.i.d. | *Bis in die*, twice daily |
| F | Female |
| IPF | Idiopathic pulmonary fibrosis |
| M | Male |
| N | Number |
| Nera | Nerandomilast |
| PPF | Progressive pulmonary fibrosis |
| RMP | Risk Management Plan |
| SAF | Safety analysis set |
| TS | Treated set |
| wks | Weeks |

# MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL TRIALS WITHIN THE DEVELOPMENT PROGRAMME

**Relevant chronic or acute infections including HIV and viral hepatitis**

| | |
|---|---|
| Reason for exclusion: | Standard exclusion criterion in clinical trials.<br>Patients with relevant acute or chronic infections are excluded from clinical trials for safety reasons, to safeguard the wellbeing of susceptible patients and to improve interpretability of data by reducing confounding factors like pre-existing infections |
| Is it considered to be included as missing information? | No |
| Rationale: | Available clinical data do not provide evidence for an increased risk of infections under nerandomilast treatment. |

**Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to visit 2, or planned during the trial period**

(e.g. hip replacement. Registration on lung transplantation list would not be considered as planned major surgery)

| | |
|---|---|
| Reason for exclusion: | Standard exclusion criterion related to subject compliance during a trial. This criterion was selected in order to limit any potential bias on the efficacy and safety results in a trial. |
| Is it considered to be included as missing information? | No |
| Rationale: | Standard exclusion criterion for clinical trials, not applicable for medical practice/in a real-life setting. There is no evidence to suggest that the efficacy or safety of nerandomilast is affected by a major surgical procedure within 6 weeks prior initiation, or during treatment with nerandomilast. |

**Any documented active or suspected malignancy or history of malignancy within 5 years prior to visit 1, except appropriately treated basal cell carcinoma of the skin, in situ squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix**

| | |
|---|---|
| Reason for exclusion: | Standard exclusion criterion in clinical trials.<br>Patients with active or suspected malignancy or a history of malignancy are excluded from clinical trials for safety reasons and to improve interpretability of data by reducing interfering factors like pre-existing or relapsing malignancies. |
| Is it considered to be included as missing information? | No |
| Rationale: | Patients with malignancies have been excluded from the clinical trials conducted with nerandomilast. Available clinical data do not provide evidence for an association between nerandomilast and malignancy. |

**Patients with AST or ALT >2.5 x ULN or total Bilirubin >1.5 x ULN and/or underlying liver cirrhosis (Child Pugh A, B or C hepatic impairment).**

| | |
|---|---|
| Reason for exclusion: | To improve the detectability of potential changes in hepatic function during treatment with nerandomilast, patients with pre-existing elevations of liver enzymes were excluded. |
| Is it considered to be included as missing information? | No |
| Rationale: | Nerandomilast is predominately metabolised via CYP3A and ~60% are excreted via faeces. Pharmacokinetic data from the hepatic impairment trial did not show a clinically relevant increase in exposure of nerandomilast in patients with Child Pugh A and B. Population PK analysis did not show an impact of baseline liver enzyme elevations on nerandomilast exposure. Based on all safety data obtained so far, no new safety concern is expected in this population. Treatment with nerandomilast in patients with hepatic impairment is covered in the respective section in the prescribing information/SmPC (Section 4.2 Posology and method of administration, Special populations). |

**eGFR ≤30 ml/min/1.73 $m^2$ at Visit 1. (CKD-EPI formula or Japanese version of CKD-EPI for Japanese patients)**

| | |
|---|---|
| Reason for exclusion: | To improve the detectability of potential changes in renal function during treatment with nerandomilast, patients with pre-existing severe renal impairment were excluded. |
| Is it considered to be included as missing information? | No |
| Rationale: | Less than half (~8-40%) of nerandomilast is renally excreted. Pharmacokinetic data from the renal impairment study and from a population PK analysis did not show a clinically relevant increase in exposure of nerandomilast in patients with mild to severe renal impairment. There was no indication for a difference in the safety profile of nerandomilast in patients with mild and moderate renal impairment in FIBRONEER-IPF or FIBRONEER-ILD. Based on all safety data obtained so far, no new safety concern is expected in this population. Treatment with nerandomilast in patients with renal impairment is covered in the respective section in the prescribing information/SmPC (Section 4.2 Posology and method of administration, Special populations). |

**Cardiovascular diseases, any of the following:**

- Severe hypertension (uncontrolled under treatment ≥160/100 mmHg at multiple occasions) within 3 months of visit 1
- Myocardial infarction, stroke or transient ischaemic attack within 6 months of visit 1
- Unstable cardiac angina within 6 months of visit 1

| | |
|---|---|
| Reason for exclusion: | Patients that experienced these events in the recent past may have been in a clinical condition unsuitable for trial participation. |
| Is it considered to be included as missing information? | No |
| Rationale: | Clinical trial data, investigator reported events, as well as adjudicated events did not indicate that patients treated with nerandomilast have an increased risk of experiencing the above cardiovascular events. |

**IPF:**

**Patients who are treated with immunomodulatory medications (other than oral corticosteroids) or prednisone >15 mg/day or equivalent for respiratory or pulmonary reasons**

**PPF:**

**Treated with prednisone >15mg/day or equivalent within 4 weeks; cyclophosphamide, tocilizumab, MMF, pirfenidone within 8 weeks; rituximab within 6 months**

| | |
|---|---|
| Reason for exclusion: | Immunomodulatory medications could confound the efficacy assessments for nerandomilast. To improve interpretability of data these medications were excluded. |
| Is it considered to be included as missing information? | No |
| Rationale: | There is no indication of a difference in the safety profile of nerandomilast in patients on the mentioned background medication as compared to the remaining patients, although clinical data are limited. |

**Women who are pregnant, nursing, or who plan to become pregnant while participating in the trial**

| | |
|---|---|
| Reason for exclusion: | Clinical trials in pregnant or breast-feeding women cannot be conducted for ethical reasons. |
| Is it considered to be included as missing information? | No |
| Rationale: | Experience from clinical trials is not available and post-marketing data on use of nerandomilast in pregnant and lactating woman are not yet available and not expected to be obtained as a result of the existing implemented risk minimisation measures. Nerandomilast is not recommended during pregnancy or lactation and woman of childbearing potential have to use effective contraceptive methods due to the non-clinical observation of loss of pregnancy. |

## SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

## SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

SIV.Table 1 Exposure of special populations included or not in clinical trial development programmes

| Type of special population | Exposure | |
|---|---|---|
| | **Number** | **Person-time** |
| Pregnant women | Not included in the clinical development programme. | - |
| Breastfeeding women | Not included in the clinical development programme. | - |
| Patients with relevant comorbidities: | | - |
| • Patients with hepatic impairment | Hepatic impairment trial (1305-0027):<br>8 Patients with Child Pugh A and 8 Patients with Child Pugh B were exposed to a single dose of 18 mg nerandomilast in the hepatic impairment trial. | - |
| • Patients with renal impairment | FIBRONEER-IPF (1305-0014)<br>*Baseline eGFR <30ml/min/1.73m² **<br>- 1 patient on placebo<br>- 1 patient on 18mg nerandomilast b.i.d.<br>*Baseline eGFR <60ml/min/1.73m²*<br>- 40 patients on placebo<br>- 42 patients on 9 mg nerandomilast b.i.d.<br>- 55 patients on 18 mg nerandomilast b.i.d.<br>*Baseline eGFR 60 - <90 ml/min/1.73m²*<br>- 254 patients on placebo<br>- 254 patients on 9 mg nerandomilast b.i.d.<br>- 244 patients on 18 mg nerandomilast b.i.d.<br>*Baseline eGFR ≥90 ml/min/1.73m²*<br>- 99 patients on placebo<br>- 96 patients on 9 mg nerandomilast b.i.d.<br>- 93 patients on 18 mg nerandomilast b.i.d. | - |

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

| Type of special population | Exposure | |
|---|---|---|
| | **Number** | **Person-time** |
| Patients with relevant comorbidities (continued): | | - |
| • Patients with renal impairment (continued) | FIBRONEER-ILD (1305-0023)<br>*Baseline eGFR <30ml/min/1.73m² **<br>- 1 patient on placebo<br>- 1 patient on 18 mg nerandomilast b.i.d<br>*Baseline eGFR <60ml/min/1.73m²*<br>- 38 patients on placebo<br>- 40 patients on 9 mg nerandomilast b.i.d.<br>- 42 patients on 18 mg nerandomilast b.i.d.<br>*Baseline eGFR 60 - <90 ml/min/1.73m²*<br>- 231 patients on placebo<br>- 219 patients on 9 mg nerandomilast b.i.d.<br>- 214 patients on 18 mg nerandomilast b.i.d.<br>*Baseline eGFR ≥90 ml/min/1.73m²*<br>- 123 patients on placebo<br>- 134 patients on 9 mg nerandomilast b.i.d.<br>- 135 patients on 18 mg nerandomilast b.i.d.<br><br>Renal impairment trial (1305-0025)<br>8 patients with moderate renal impairment and 8 patients with severe renal impairment were exposed to a single dose of 18 mg nerandomilast. | - |
| • Patients with cardiovascular impairment | Not specifically addressed in the clinical development programme. | - |
| • Immuno-compromised patients | Not specifically addressed in the clinical development programme. | - |
| • Patients with a disease severity different from inclusion criteria in clinical trials | Not specifically addressed in the clinical development programme. | - |
| Population with relevant different ethnic origin | See SIII.Table 4 for information on ethnic origin. | - |
| Subpopulations carrying relevant genetic polymorphisms | Not specifically addressed in the clinical development programme. | - |

SIV.Table 1 (cont'd) Exposure of special populations included or not in clinical trial development programmes

| Type of special population | Exposure | |
|---|---|---|
| | Number | Person-time |
| Paediatric patients | Not addressed in the clinical development programme to date.<br>A dedicated trial (1305-0022) in paediatric patients with Children interstitial lung disease (chILD) is planned once a positive benefit-risk profile of nerandomilast has been established in adult patients. | - |

Data source: data on file, iss-output (v2.0), Table 3.6.1.1.1.1.; c42811255-01.

* 2 patients violated the exclusion criterion in FIBRONEER-IPF of eGFR ≤30ml/min/1.73m², and 2 patients violated the exclusion criterion in FIBRONEER-ILD of eGFR ≤30 ml/min/1.73m$^2$. Data on file, 1305-0014--16205--compliance-and-drug-concentration-data (v1.0), 1305-0023--16205--compliance-and-drug-concentration-data (v1.0).

## SIV.4 REFERENCES

Not applicable.

## ABBREVIATIONS

| | |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate Aminotransferase |
| b.i.d. | *Bis in die*, twice daily |
| child | Children interstitial lung disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CYP3A4 | Cytochrome P3A4 |
| eGFR | Estimated glomerular filtration rate |
| FIBRONEER-ILD | A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs) |
| FIBRONEER-IPF | Trial: A Double Blind, Randomized, Placebo-controlled Trial Evaluating the Efficacy and Safety of nerandomilast Over at Least 52 Weeks in Patients with Idiopathic Pulmonary Fibrosis (IPF) |
| HIV | Human immunodeficiency virus |
| IPF | Idiopathic pulmonary fibrosis |
| MMF | Mycophenolate Mofetil |
| mmHG | Millimeters Mercury |
| PK | Pharmacokinetic |

| | |
|---|---|
| PPF | Progressive pulmonary fibrosis |
| SmPC | Summary of Product Characteristics |
| ULN | Upper limit of normal |

# MODULE SV POST-AUTHORISATION EXPERIENCE

## SV.1 POST-AUTHORISATION EXPOSURE

Jascayd is not marketed yet.

# MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Jascayd is available as prescription medicine only. Pharmacological properties, non-clinical, and clinical data do not indicate an impact on the central nervous system suggestive for stimulant, depressant, hallucinogenic, or mood-elevating effects, or other effects that might lead to dependency. Abuse for illegal purpose is not expected with Jascayd.

## SVI.2 REFERENCES

Not applicable.

## ABBREVIATIONS

| | |
|---|---|
| EU | European Union |

# MODULE SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The analyses of safety, including safety analysis sets and criteria, are described in Section SVII.3.

### SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

The following risks are ADRs that require no further characterisation and are followed up via routine pharmacovigilance (signal detection, adverse reaction reporting):

- Diarrhoea
- Decreased appetite
- Weight decreased
- Nausea
- Back pain

Other reasons for considering risks not important:

- Foetal loss:
  Foetal loss is a known finding for PDE4is, originating from non-clinical studies in rats. The relevance of this important potential risk for the target populations (mainly elderly patients) is considered low. Effective routine risk minimisation measures (addressed in the prescribing information, section on fertility, pregnancy and lactation) are in place and expected to be adhered to by prescribers (contraception as part of standard clinical practice). This topic was characterised based on all available data to date to the extent that is achievable considering the specific nature of the topic. It will continue to be monitored via routine pharmacovigilance activities (signal detection, adverse reaction reporting), which are considered sufficient for the understanding and management of this topic.

- Vasculitis:
  Vasculitis is a known finding for PDE4is (originating from non-clinical studies) including marketed apremilast and roflumilast. For apremilast it is considered an important potential risk. Human relevance of this non-clinical finding has not been established so far and apremilast is indicated in Behcet’s disease, a systemic vasculitis. For nerandomilast, vasculitis was considered an important potential risk during clinical development (i.e. in DSURs) based on non-clinical findings in rodents and minipigs. In monkeys, adverse vascular findings were not observed. In clinical trials with nerandomilast few events of vasculitis were reported, without an imbalance

between the nerandomilast and placebo groups for investigator-reported events, as well as for adjudicated events of vasculitis. The majority of these events were serious due to hospitalisation or due to medical significance, no life-threatening events were reported. There was 1 fatal case of vasculitis reported in phase II, where the diagnosis of vasculitis could not be confirmed by the external data monitoring committee. Review of individual cases did not indicate a causal relationship of vasculitis events with nerandomilast. In addition, no pattern in regard to the type of vasculitis, e.g. small or large vessel vasculitis, was detected, and confounders were present in all cases. Available evidence does not support a causal relationship between vasculitis and nerandomilast treatment. Vasculitis will be monitored via routine pharmacovigilance activites (signal detection, adverse reaction reporting), which are considered sufficient for the understanding and management of this topic.

The following hypothetical risks were specifically monitored during the clinical development program of nerandomilast because they are important potential or identified risks for compounds of the same pharmacological class. However, review of clinical data for nerandomilast did not reveal an imbalance towards nerandomilast nor a trigger case indicating a causal association with nerandomilast for any of these topics. Therefore, they are not considered to be risks and require no further monitoring.

- MACE,
- Serious depression, suicidal ideation and behaviour,
- Nervousness and anxiety,
- Malignancies,
- Severe, serious and opportunistic infections including mycobacterium tuberculosis.

### SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Based on all available data, there are no important identified risks, important potential risks, or missing information for nerandomilast to be included in the RMP.

## SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

This section is not applicable as the granting of the marketing authorisation has not yet been obtained.

## SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The evaluation of safety is based on the treated set of patients, i.e. representing all patients who received at least 1 dose of the trial medication. The analysis of AEs is based on the concept of treatment emergent AEs. This means that all AEs with an onset date between first drug intake until 7 days after last drug intake (end of REP) are assigned to the study drug taken for reporting AEs occurring on-treatment.

Data from the clinical development programme of nerandomilast were analysed in different safety analysis sets, each representing a particular stratum of safety data. For the evaluation of risks, the following data sets were analysed:

SVII.Table 1 Overview of safety analysis sets

| Analysis set | Description | Included trials | Indication |
|---|---|---|---|
| SAF2 | BI 1015550 (nerandomilast) vs. placebo in randomised, double-blind, placebo-controlled trials, any treatment duration, any target indication (nerandomilast 18 mg, placebo). | 1305-0012<br>1305-0013<br>1305-0014<br>1305-0023 | IPF, PPF |
| Trial 1305-0014 | Phase III trial in IPF (nerandomilast 9 mg, nerandomilast 18 mg, placebo). | 1305-0014 | IPF |
| Trial 1305-0023 | Phase III trial in PPF (nerandomilast 9mg, nerandomilast 18mg, placebo) | 1305-0023 | PPF |

Data source: SAP for RMP for nerandomilast IPF [c44717048-01], Table 5.1.2:1

### SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified or potential risks for nerandomilast.

### SVII.3.2 Presentation of the missing information

There is no missing information for nerandomilast.

## SVII.4 REFERENCES

### SVII.4.1 Published references

Not applicable.

### SVII.4.2 Unpublished references

c44717048-01 Risk Management Plan Statistical Analysis Plan for nerandomilast (1305.P3). 21 Aug 2024.

## ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |

| | |
|---|---|
| IPF | Idiopathic pulmonary fibrosis |
| MACE | Major adverse cardiovascular event |
| PDE4i | Phosphodiesterase 4 inhibitor |
| PPF | Progressive pulmonary fibrosis |
| REP | Residual effect period |
| RMP | Risk Management Plan |
| SAF | Safety Analysis Set |

# MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

SVIII.Table 1 Summary of safety concerns

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

## SVIII.1 REFERENCES

Not applicable.

## ABBREVIATIONS

Not applicable.

# PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## PART III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires:**
  None.

- **Other forms of routine pharmacovigilance activities:**
  None.

## PART III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered sufficient to address all safety topics, with the aim to obtain and analyse relevant safety data from post-marketing experience to fully assess the safety of the product.

## PART III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered sufficient to address all safety topics, with the aim to obtain and analyse relevant safety data from post-marketing experience to fully assess the safety of the product.

## PART III.4 REFERENCES

Not applicable.

## ABBREVIATIONS

Not applicable.

# PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This part is not applicable as there are no planned or ongoing post-authorisation efficacy studies imposed for Jascayd.

# PART V RISK MINIMISATION MEASURES

## RISK MINIMISATION PLAN

## PART V.1 ROUTINE RISK MINIMISATION MEASURES

PV.Table 1 Description of routine risk minimisation measures by safety concern

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Important identified risks** | |
| None | |
| **Important potential risks** | |
| None | |
| **Missing information** | |
| None | |

## PART V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable as there are no safety concerns for nerandomilast.

## PART V.3 SUMMARY OF RISK MINIMISATION MEASURES

PV.Table 2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |
| None | | |
| **Important potential risks** | | |
| None | | |
| **Missing information** | | |
| None | | |

## PART V.4 REFERENCES

Not applicable.

## ABBREVIATIONS

Not applicable.

# PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

## SUMMARY OF RISK MANAGEMENT PLAN FOR JASCAYD (NERANDOMILAST)

This is a summary of the risk management plan (RMP) for Jascayd. The RMP details important risks of Jascayd, how these risks can be minimised and how more information will be obtained about Jascayd's risks and uncertainties (missing information).

Jascayd's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jascayd should be used.

This summary of the RMP for Jascayd should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Jascayd's RMP.

## I. THE MEDICINE AND WHAT IT IS USED FOR

Jascayd is authorised for the treatment of idiopathic pulmonary fibrosis (IPF) and for the treatment of progressive pulmonary fibrosis (PPF) (see SmPC for the full indication). It contains nerandomilast as the active substance and it is given by oral administration.

Further information about the evaluation of Jascayd’s benefits can be found in Jascayd’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

## II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Jascayd, together with measures to minimise such risks and the proposed studies for learning more about Jascayd's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A List of important risks and missing information

Important risks of Jascayd are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jascayd. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

**List of important risks and missing information**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

## II.B Summary of important risks

**Important identified risks**

None

**Important potential risks**

None

**Missing information**

None

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Jascayd.

### II.C.2 Other studies in post-authorisation development plan

There are no studies required for Jascayd.

# PART VII APPENDICES

# PART VII TABLE OF CONTENTS

# APPENDIX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse event follow-up forms for Jascayd.

# APPENDIX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

There are no proposed additional risk minimisation activities for Jascayd.