21 May 2026
EMADOC-1829012207-55748 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jascayd

International non-proprietary name: nerandomilast

Procedure No. EMEA/H/C/006405/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BCS	Biopharmaceutics Classification System
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CPP	Critical process parameter
CQA	Critical Quality Attribute
DSC	Differential Scanning Calorimetry
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FP	Finished product
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectroscopy
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
LDPE	Low density polyethylene
MO	Major Objection
NMR	Nuclear Magnetic Resonance
PAR	Proven Acceptable Range
PD	Pharmacodynamics
PET	Polyethylene Terephthalate
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Process parameter
PRAC	Pharmacovigilance Risk Assessment Committee
PVC	Polyvinyl chloride
QTPP	Quality target product profile
RH	Relative Humidity
RMP	Risk management plan
SmPC	Summary of product characteristics
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy

USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction
AE	Adverse Event
AELD	Adverse Event Leading to Discontinuation
AESI	Adverse Event of Special Interest
AF	Antifibrotic
ALAT	Latin American Thoracic Association
ANCOVA	Analysis of Covariance
ARBS	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BI	Boehringer Ingelheim
Bid	bis in die (twice daily dosing)
BMI	Body Mass Index
CI	Confidence Interval
CO	Clinical Overview
CRF	Case Report Form
CT	Computed Tomography
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
CYP	Cytochrome P450
DBL	Database Lock
DLCO	Diffusing Capacity (of Lung) for Carbon Monoxide
eCRF	electronic Case Report Form
EOT	End of Treatment
ERS	European Respiratory Society
ES	Entered Set
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGO	Ground-glass Opacity
GI	Gastrointestinal
GORD	Gastro−oesophageal Reflux Disease
Hb	Haemoglobin
HR	Hazard Ratio
HRCT	High-resolution Computed Tomography
ID	Identification

ILD	Interstitial Lung Disease
iPD	Important Protocol Deviations
IPF	Idiopathic Pulmonary Fibrosis
IRT	Interactive Response Technology
JRS	Japanese Respiratory Society
LCQ	Leicester Cough Questionnaire
L-PF	Living with Fibrosis Symptoms and Impact Questionnaire
MACE	Major Adverse Cardiovascular Event
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model Repeated Measures
Nera	Nerandomilast
PDE4	Phosphodiesterase Enzyme 4
PDE4B	Phosphodiesterase 4B
PF	Pulmonary Fibrosis
PPF	Progressive Pulmonary Fibrosis
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SpO2	Oxygen Saturation
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UIP	Usual Interstitial Pneumonia
USA	United States of America
V	Visit
VAS	Visual Analogue Scale (Pain)
vs.	Versus

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Jascayd
Active substance	Nerandomilast
INN or common name	Nerandomilast
Applicant	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim Am Rhein GERMANY
EMA product number	EMEA/H/C/006405
ATC code and pharmacotherapeutic group	ATC code: L04AA61
Pharmaceutical form(s) and strength (s)	Film-coated tablet 9 mg and 18 mg
Packaging	blister (PVC/alu) and bottle (HDPE)
Package size(s)	10 x 1 tablets (unit dose), 30 x 1 tablets (unit dose), 60 x 1 tablets (unit dose), 180 tablets and 60 tablets
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Treatment of adult patients with idiopathic pulmonary fibrosis Treatment of adult patients with progressive pulmonary fibrosis
New active substance status	Granted

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
19 May 2022	Quality / non-clinical / clinical	EMA/SA/0000078671	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: • Active substance starting materials and specifications. The dissolution method for the release of Phase III and primary stability batches. The approach and control strategy justification for the tests in support of the proposed Phase III drug product specification. Studies on polymorphic identity, chiral purity and particle size distribution of BI 1015550 and need for testing of them in the active substance and/or finished product specifications at the time of registration. The proposed stability data package in support of a 24-month shelf life. The use of a delivery device in support of a paediatric formulation. • Nonclinical safety package in support of Phase 3 and MAA. Toxicity evaluation of major human metabolite BI 764333. Proposed non-clinical drug metabolism and pharmacokinetics characterization to support Phase 3. • Design of two pivotal Phase 3 trials, 1305-0014 (IPF patients) and 1305-0023 (other PF-ILD patients), including study population, endpoints (PEP - rate of FVC decline), trial duration (52 wks), background and concomitant treatments, placebo as comparator arm, stratification, dosing (18 mg bid), the statistical analysis strategy, interim analysis, conduct of the two pivotal trials within one master protocol for operational efficiency, definition of AESIs and other safety topics of interest, safety activities for minimization and monitoring of risks, the safety database, DDI studies, and studies in renal/hepatic impairment.
9 November 2023	Quality	EMA/SA/0000152243	The Scientific advice pertained to the following quality aspects: Omission of test from active substance specifications; the approach for specific impurity specification setting and to control residual solvents and water content in the active substance; the proposed control strategy for the finished

			product manufacturing process; adequacy of the proposed data package to bridge between different formulations of film-coated tablets as well as filing strategy for MAA and to support the bioequivalence of these two formulations; whether the product design features presented for BI 1015550 film-coated tablets provide sufficient product strength differentiation to prevent medication errors.
27 June 2024	Quality / clinical	EMA/SA/0000171693	The Scientific advice pertained to the following quality and clinical aspects: • Classification of the dosage form; definition of tablet "unit dose" for the purpose of content uniformity and weight variation. • Appropriateness of the proposed formulation and dispensing method for the intended patient population; safety and effectiveness of the proposed formulation and dispensing method; benefits and potential harms of using the proposed delivery device; suitability of the expected tablet burden; acceptable limit for hand-counting of tablets.

1.3. Eligibility to the centralised procedure

The applicant Boehringer Ingelheim International GmbH submitted on 29 April 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Jascayd (Nerandomilast), through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision P/0459/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0459/2021 had not yet been completed as some

measures had been deferred.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. New active substance status

The applicant requested the active substance Nerandomilast contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that nerandomilast is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Finbarr Leacy
Co-rapporteur:	Peter Mol

The application was received by the EMA on	29 April 2025
The procedure started on	22 May 2025
The CHMP rapporteur's first assessment report was received on	11 August 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	13 August 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	25 August 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	18 September 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	30 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 February 2026

The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 February 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	23 March 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint Preliminary assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	08 April 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint Updated assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	17 April 2026
The CHMP agreed on a 2nd list of outstanding issues (LoOI) to be sent to the applicant on	23 April 2026
The applicant submitted the responses to the 2nd CHMP list of outstanding issues on	27 April 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint Preliminary assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	06 May 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint Updated assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	13 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jascayd on	21 May 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	21 May 2026

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has deferred a paediatric development have also been included.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 2.6 of this report.

1.9.3. CHMP opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jascayd is favourable in the following indications:

- Jascayd is indicated for the treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF)
- Jascayd is indicated for the treatment of adult patients with Progressive Pulmonary Fibrosis (PPF)

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.9.8. Proposed list of recommendations

Table 2: Proposed list of recommendations

Description of recommendation(s)
Conduct water solubility test, dissociation constant and partition coefficient and provide final report by July 2026.
The Applicant should submit the results of the proposed DDI study (1305-0035), evaluating the impact of pirfenidone on nerandomilast PK, by July 2027.

2. Introduction

2.1. Therapeutic context

Disease or condition

Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) is the most common disease with a progressive fibrosing phenotype and is characterised by a decline in lung function and worsening dyspnoea. IPF occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). The incidence of IPF increases with older age, with presentation typically consisting of insidious onset of dyspnoea in the sixth and seventh decades. Idiopathic pulmonary fibrosis (IPF) carries significant mortality and unpredictable progression, with limited therapeutic options. Patients with diagnosis of IPF generally follow one of three courses: 1) most patients follow the pathway of slow decline over 3–5 years since the diagnosis ("slow progression"); 2) some patients experience a more rapid decline in lung function over several months ("rapid progression"); and 3) others remain stable over several years before progressing. IPF is more common in men than women and the majority of patients have a history of past cigarette smoking.

The proposed indication is: *Jascayd is indicated for the treatment of adult patients with idiopathic pulmonary fibrosis*.

Progressive Pulmonary Fibrosis (PPF)

The term interstitial lung disease (ILD) encompasses a large group of over 200 pulmonary disorders and a large category of diseases that have either fibrosis, inflammation, or both, in the walls of the air sacs in the lung. While IPF is considered to be universally progressive, there is a group of patients with different underlying clinical ILD diagnoses who develop a progressive phenotype (termed PPF) similar to patients with IPF during the course of their disease [Wells et al. 2018].

The proposed indication is: *Jascayd is indicated for the treatment of adult patients with Progressive Pulmonary Fibrosis (PPF)*.

Epidemiology

IPF

IPF occurs worldwide and the prevalence of the disease appears to be increasing with increasing rates of hospital admissions and deaths due to IPF suggesting an increasing burden of disease, although it is unclear whether this reflects increased recognition or a true increase in incidence. The incidence of IPF appears to be higher in North America and Europe (3 to 9 cases per 100,000 person-years) than in South America and East Asia (fewer than 4 cases per 100,000 person-years).

PPF

Disease onset during adulthood is most common [Kang et al. 2023], but onset can range over multiple decades with some cases reported in the pediatric population [Rajan et al. 2023]. The estimated prevalence for PPF were 2.2–20.0 per 100 000 in Europe and 28.0 per 100 000 in the USA (Olson et al. 2021). Non-IPF PF-ILD is associated with a considerable mortality risk with an average median survival rate of around 3-5 years varying by countries (Cottin et al. 2022).

PPF is a serious and debilitating conditions with a poor prognosis and early mortality. Even with guideline-directed standard of care, significant morbidity and mortality remain. Current approved treatments are also associated with side effects that limit their use.

Biologic features

The major abnormality across ILDs is the disruption of the distal lung parenchyma. It is generally agreed that some form of injury of the alveolar epithelial cells initiates an inflammatory response coupled with repair mechanisms. The injury-repair process is reflected pathologically as inflammation, fibrosis, or a combination of both. Irrespective of the underlying pathophysiology, the resulting alteration of the interstitial space leads to clinical symptoms such as dyspnoea and cough, and results in restrictive ventilatory and gas exchange deficits on pulmonary function testing.

Clinical presentation, diagnosis

IPF

Diagnosis of IPF requires the following: An exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, drug toxicity), and either the presence of the HRCT pattern of UIP or specific combinations of HRCT patterns and histopathology patterns in patients subjected to lung tissue sampling. IPF is characterised by an increasing extent of pulmonary fibrosis on imaging, declining lung function, worsening respiratory symptoms (such as dyspnoea and cough), quality of life despite disease management, and ultimately, early mortality. It has been shown that a decline in forced vital capacity (FVC) is associated with increased mortality in patients with IPF.

PPF

The term interstitial lung disease (ILD) encompasses a large group of over 200 pulmonary disorders, including IPF. While IPF is considered to be universally progressive, there is a group of patients with different underlying clinical ILD diagnoses who develop a progressive phenotype similar to patients with IPF during the course of their disease. The progressive phenotype is characterised by increasing extent of pulmonary fibrosis on imaging, declining lung function, worsening respiratory symptoms (such as dyspnoea and cough) and quality of life despite disease management, and ultimately, early mortality.

In study 1305-0023, PPF diagnosis was based on the presence of fibrotic lung disease on HRCT as confirmed by central review and progression according to predefined criteria within 24 months before screening (patients either had to have a clinically meaningful decline in FVC [relative decline ≥10% predicted] or a combination of at least two of the following features: a marginal decline in FVC [relative decline ≥5 to <10% predicted], worsening of respiratory symptoms, and/or an increase in fibrotic changes on imaging). These criteria were similar to those used in the Phase III INBUILD trial investigating nintedanib in patients with progressive fibrosing ILD.

Management

IPF

IPF carries a poor prognosis, with a median survival of approximately 3-5 years after diagnosis. Real-world data from studies of previously approved drug treatments, Nintedanib and Pirfenidone, have been shown to improve survival and lung function in patients. However, no therapy is currently available that can stop or reverse disease progression and as such IPF remains a deadly disease. Other than nonpharmacological therapies and treating comorbidities, nintedanib and pirfenidone are the only drugs registered in several countries for the treatment of IPF and both treatments are recommended by the ATS/ERS/JRS/ALAT clinical practice guideline for the treatment of IPF and are approved by CHMP. Current treatments for IPF may slow disease progression but cannot stop or reverse fibrosis. Thus, despite existing treatments, significant morbidity and mortality remain in patients with IPF. There remains a high unmet need for new treatments for IPF, which can be added to approved treatments or given as monotherapy and can result in greater efficacy and fewer side effects than existing therapies.

PPF

Other than nonpharmacological therapies (Symptom management, pulmonary rehabilitation, and preventive strategies) and glucocorticosteroids, immunosuppressant treatments, the antifibrotic agents nintedanib is recommended for the treatment of children and adults with PPF and is approved in the US and the European Union for the treatment of other fibrosing ILDs with progressive phenotype [Raghu et al. 2022]. Current treatments for PPF may slow disease progression but cannot stop or reverse fibrosis or provide symptomatic benefit [Ghumman et al. 2021]. Thus, despite existing treatments, significant morbidity and mortality remain in patients with PPF [Lancaster et al. 2019, Fisher et al. 2017, Suissa et al. 2023, Maher et al. 2023]. Moreover, nintedanib is associated with side effects, such as gastrointestinal (GI) effects, hepatic toxicity, phototoxicity, cardiovascular effects, and bleeding, that frequently lead to delayed treatment initiation or early treatment discontinuation [Fletcher et al. 2018, Maher et al. 2019, Holtze et al. 2020, Dempsey et al.2021, Ghumman et al. 2021], which in turn minimises the potential to benefit from these treatments. Also, the side effect profile impedes a mutual combination therapy in case of clinical deterioration and need for therapy expansion. Symptomatic treatment with long-term oxygen frequently prescribed in patients with advanced disease and hypoxemia during exertion and/or rest may improve dyspnoea and functional status. However, oxygen use can be associated with a significant financial burden, practical issues and psychosocial challenges as many patients perceive its use in the community as stigmatising [Khor et al. 2017, Graney et al. 2017, Dakkak et al. 2021, Johannso et al. 2017].

Additional expert consultation

Input from a healthcare professionals' organisation, the European respiratory Society (ERS), has been obtained upon request (summarised below):

'Current standards of care for IPF and PPF are limited to two approved antifibrotic drugs. These agents slow disease progression by about 50% overall, though individual responses vary and many patients require dose reduction or discontinuation due to adverse effects. Treatment initiation in IPF is recommended at diagnosis, while in PPF, therapy begins upon documented progression—a strategy that may delay potentially beneficial intervention. There is a clear unmet need for more effective, better-tolerated therapies, ideally with curative potential. Given the complexity of pulmonary fibrosis, combination therapies are likely needed, and improved tolerance and fewer side effects are essential. The disease remains underrecognized by stakeholders and policymakers, resulting in less research funding and fewer standardized care pathways compared to cancer. Early identification of high-risk patients and broader awareness are critical to improving outcomes for this devastating condition.'

Input from the patient organisation 'European Pulmonary Fibrosis Federation' has been obtained upon request as well (summarised):i'IPF and PPF are complex life limiting diseases. Standard of Care slows the progression of the disease in a non-uniform and highly individual manner. Another treatment whether more effective or not will substantially benefit the patient community as it will allow those patients who can neither tolerate either treatment or for whatever reason gain no or limited benefit from them an opportunity to avail of a medicine that may provide benefit as well as one whose adverse effects may for them be more tolerable or even non-existent given the complex nature of the disease and the individual. Whilst awaiting a cure a third treatment will provide hope for both the newly diagnosed patients and those who are already on a treatment that one of three treatments can be of benefit in their individual case. Progression is inevitable in these diseases but every patient should be able to maximise their survival and quality of life by receiving a progression slowing treatment.'

2.2. Aspects of development

Nerandomilast (BI 1015550) is an oral selective inhibitor of PDE4 with preferential inhibition of the PDE4B isoenzyme. Based on the published broad antifibrotic and immunomodulatory activities of pan-PDE4 inhibitors, nerandomilast is expected to be efficacious as a monotherapy and when added to current therapies in IPF or PPF. The clinical development program of Nerandomilast is comprised of two pivotal phase 3 studies, each being a randomised, double-blind, placebo-controlled, and parallel-group design clinical trial. FIBRONEER-IPF and FIBRONEER-ILD were designed to target the proposed indications of nerandomilast, IPF and non-IPF PPF-ILD.

2.3. Description of the product

Mechanism of action

Nerandomilast is an oral selective inhibitor of PDE4 with preferential inhibition of the PDE4B isoenzyme for the treatment of adult patients with IPF and PPF. The PDE4 enzyme hydrolyses and thereby inactivates the second messenger molecule cAMP, which can contribute to fibrotic and inflammatory processes. PDE4B inhibition in the lung is expected to inhibit pro-fibrotic growth factors; to decrease fibroblast proliferation, transformation of fibroblast to myofibroblast, and fibroblast motility; as well as to promote cell death of fibroblasts and to decrease synthesis, release, and function of ECM components. In human, the PDE4B isoenzyme is highly expressed in the lung and plays an important role in fibrosis and inflammation in the lungs.

Proposed Posology and initial wording

The recommended dosage of Nerandomilast is 18 mg twice daily, administered approximately 12 hours apart.

Based on individual patient tolerability, the dosage may be reduced to 9 mg twice daily.

2.4. Inspection issues

2.4.1. Good clinical practice (GCP) inspection(s)

The Applicant provided an overview of relevant information relating to GCP aspects as part of this submission in order to facilitate identification of a need for pre-authorisation GCP inspection if considered necessary and in response to questions raised during the procedure.

IPF pivotal trial 1305-0014 and PPF trial 1305 0023

For the pivotal trials, GCP critical non-compliances were identified at three sites in China, i.e. CHN1, CHN7 and CHN8.

At site CHN1 (China), the delayed submission of CTP version 4.0 and high patient discontinuation rate was investigated. The applicant's Severe Issue Committee (SIC) determined a serious breach due to impact on data completeness and integrity. Although no concerns about patient safety or rights were identified and data used for analyses was deemed by the applicant to be correct. These violations raised initial uncertainty regarding the conduct of the clinical trials at this site.

At site CHN7 (China), a further serious breach of GCP was identified on Oct 10, 2024. A failure to obtain Ethics Committee (EC) approval for documents released between May 2023 and Jul 2024 was identified along with fraudulent activity by the Clinical Research Associate (CRA) who falsely reported EC approvals and fabricated approval dates. Two study participants were involved, one in each study. This violation also raised initial uncertainty regarding the conduct of the clinical trials.

In addition, during the assessment the applicant notified the CHMP of an additional critical non-compliance at site CHN8 (China) which related to discrepancies in timestamps on the e-signature and e-stamps on the HRCT footer.

Upon clarification, the CHMP considered that the identified issues remained isolated and did not impact the study integrity. No GCP inspection was deemed necessary.

3. Quality aspects

3.1. Introduction

The finished product is presented as film-coated tablets containing 9 mg or 18 mg of nerandomilast.

Other ingredients are:

lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, hypromellose 2910, talc, mannitol, macrogol 8000.

9 mg film-coated tablets only: iron oxide yellow (E172).

18 mg film-coated tablets only: iron oxide red (E172), iron oxide black (E172).

The product is available in PVC/Alu (polyvinyl chloride/aluminium) perforated unit dose blisters or HDPE (high density polyethylene) bottle with a child-resistant closure as described in section 6.5 of the SmPC.

3.2. Active substance

3.2.1. General information

The chemical name of nerandomilast is [1-[[(5R)-2-[4-(5-chloropyrimidin-2-yl)-1-piperidyl]-5-oxo-6,7-dihydrothieno[3,2-d]pyrimidin-4-yl]amino]cyclobutyl]methanol corresponding to the molecular formula $C_{20}H_{25}ClN_6O_2S$. It has a relative molecular mass of 448.97 g/mol and the following structure:

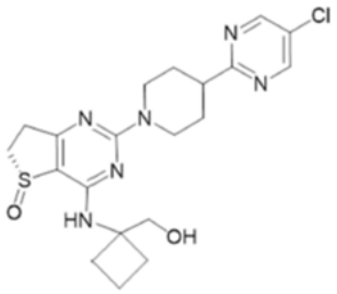


Figure *1*: active substance structure

The chemical structure of nerandomilast was elucidated by a combination of elemental analysis, IR spectroscopy, mass spectrometry, ^{1}H-NMR, ^{13}C-NMR, UV spectroscopy and single crystal X-ray structure analysis. The solid-state properties of the active substance were determined by X-ray powder diffraction (XRPD), polarized light microscopy (PLM), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). For development purposes only, Raman spectroscopy was also used to monitor polymorphic conversion.

The active substance is a white to off-white to light yellow powder. The active substance is poorly soluble in organic solvents, and its aqueous solubility is pH-dependent with slight solubility at very low pH, and solubility decreasing with increasing pH. Nerandomilast is classified as BCS Class IV compound due to its low solubility and low permeability. The active substance is non-hygroscopic.

Nerandomilast exhibits stereoisomerism due to the presence of one chiral centre: the sulfur within the sulfoxide group. Nerandomilast is developed as an enantiopure chiral drug that contains a sulfoxide in the R-orientation. The chiral isomer (S-enantiomer) is considered as an impurity (PD 1420).

Enantiomeric purity is routinely controlled in the active substance specification by chiral HPLC with UV detection. Enantiomeric purity has also been enhanced through targeted manufacturing process improvements.

Polymorphism has been observed for nerandomilast and a suitable solid state form is used for commercial development.

Results from the stability studies performed on the active substance indicate that no change to the polymorphic form occurs during long-term and accelerated conditions. The omission of polymorphism testing from the active substance specification is considered justified in line with ICH Q6A. A conversion from one polymorphic form to another is thermodynamically unfavourable.

The Applicant claimed new active substance (NAS) status for nerandomilast. During the assessment an MO was raised due to insufficient justification, which resulted in an additional MO due to missing information on the therapeutic moiety of nerandomilast molecule, on the limits for which it derives non-similarity, and gaps in the research on relevant databases. This was considered solved during the second assessment by provision of sufficient justification. Based on the review of available data, the CHMP considers that nerandomilast is to be qualified as NAS as it is not a constituent of a medicinal product previously authorised within the European Union. Hence, the administration of nerandomilast does not expose the patient to the same therapeutic moiety as any already authorised active substance.

3.2.2. Manufacture, characterisation, and process controls

The active substance is manufactured at one site. Satisfactory GMP documentation has been provided.

Nerandomilast is synthesized in multiple steps using well defined starting materials with acceptable specifications. Appropriate specifications have been provided for reagents and auxiliary materials.

The active substance is synthesized in a convergent synthesis, using well defined starting materials. Several re-crystallisations take place after the introduction of each starting material. Adequate descriptions of the process and the equipment used have been provided.

Critical process parameters have been identified, which are related to the control of unspecified impurities. The controls of CPPs are acceptable.

Proven acceptable ranges (PARs) have been defined for each manufacturing step. During the assessment an MO was raised due to insufficient discussion and justification of the PARs, which resulted in an additional MO due to missing information in Module S.2.2. This was considered solved during the second assessment; appropriate data has been provided to justify the PARs.

The actual yields and the proposed commercial batch size have been clearly stated. No re-processing outside of GMP as per ICH Q7 is proposed.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

During the procedure, an MO was raised in relation to the control strategy of mutagenic impurities. The MO was resolved by providing sufficient data demonstrating control of potential mutagenic impurities in line with ICH M7 requirements. All relevant impurities are adequately purged when controlled at the proposed levels. A comprehensive review of the active substance’s starting materials, intermediates,

reagents, actual and potential impurities, and degradation products was submitted for an in silico (Q)SAR assessment. All analytical methods responsible for controlling genotoxic impurities and those used in spike and carry-over studies of mutagenic impurities, have undergone appropriate validation.

The potential risk of formation of nitrosamine related impurities has been sufficiently discussed in relation to the active substance in the nitrosamine risk assessment in P.2. The definition of no risk in relation to small molecule and any substance specific nitrosamines is accepted.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. During development the chemical process was adjusted to the requirements of scale-up, the process is largely similar to that used in the earlier development. Changes introduced have been presented in sufficient detail and have been justified.

Overall, sufficient information on the manufacturing process development has been provided.

The active substance is packaged in low-density polyethylene (LDPE) bag which complies with Commission Regulation (EU) 10/2011, as amended. The bag, closed with a suitable closing system, is inserted into an aluminium laminated plastic bag, which is sealed and finally packaged into a fibre drum.

3.2.3. Specification

The active substance specification includes tests for description (visual), identification (IR, HPLC-UV), organic impurities (HPLC-UV), enantiomeric impurity (HPLC-UV), loss on drying (thermogravimetry), elemental impurities (ICP-OES), sulfated ash (gravimetry), assay (HPLC-UV), and calculated content.

The active substance specifications are based on the active substance critical quality attributes (CQA). The proposed tests and related limits are considered acceptable as per ICH guidance.

The manufacturing process bases on thorough impurity carry-over understanding and ensures a consistent high quality of the intermediates. All impurities are supported by adequate carry-over and/or spike and purge studies. *Omission of control of impurities which are controlled appropriately at the intermediate stage is acceptable.*

Class I solvents have been monitored and batch data were consistently below 10% of the ICH Q3C limit for the respective solvents, thus justifying omission of testing.

Microbiological quality testing according to Ph. Eur. 2.6.12 and Ph. Eur. 2.6.13 was performed for batches of nerandomilast manufactured according to the commercial process. Omission of microbial testing has been appropriately justified in line with the relevant decision tree ICH Q6A. No real time release testing is proposed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from three production scale batches of the active substance manufactured at the site of commercial production according to development process variant stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The development process variant is stated to be similar to the proposed commercial process.

Results on stress conditions in the solid and solution state were also provided. The stress conditions included elevated temperature, humidity, and light stress to investigate the intrinsic stability of the active substance. Solution stress conditions investigated include acid, base, neutral pH, oxidative stress, metal ion stress, and light exposure. Based on stress studies, long-term storage of the active substance is in solid state.

Photostability testing following the ICH guideline Q1B was performed. Degradation products are observed when nerandomilast is exposed to light. The data provided justify the storage condition in aluminium outer packaging to protect from light.

The following parameters were tested for temperature and humidity: description, assay, peak homogeneity, organic impurities, enantiomeric impurity, XRPD. The analytical methods are stability indicating. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

The stability results justify the proposed retest period of 36 months in the proposed container in order to protect from light. The post-approval stability protocol is appropriate as per ICH guidance for the ongoing confirmation of the re-test period. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Nerandomilast 9 mg film-coated tablets are presented as light yellow, oval, biconvex film-coated tablets of a size of about 9.5 x 4.6 mm. One side is debossed with the Boehringer Ingelheim company symbol, and the other side is debossed with "F9".

Nerandomilast 18 mg film-coated tablets are presented as light red, oval, biconvex film-coated tablets of a size of about 12 x 5.9 mm. One side is debossed with the Boehringer Ingelheim company symbol, and the other side is debossed with "F18".

The tablets are for oral administration.

Nerandomilast is classified as BCS Class IV drug due to its low solubility and low permeability. Stability studies have proven slight light sensitivity.

The active substance shows polymorphism. The omission of polymorphism testing from the active substance specification is considered justified in line with ICH Q6A. The polymorphic form used for commercial development has shown to be thermodynamically stable.

The omission of PSD testing in the active substance has been adequately justified based on the consistency and reproducibility of the PSD observed during the development of nerandomilast manufacturing process. PSD has no impact on the polymorphic form of the active substance.

The CMAs of the active substance that could impact the CQAs of the finished product have been identified and clearly described in the dossier.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. One excipient (lactose monohydrate) is of animal origin and a TSE declaration has been provided. The CMAs of the excipients have been investigated.

The choice and function of the selected excipients have been adequately described. Compatibility of the selected excipients with the active substance has been adequately demonstrated by compatibility studies. Compendial microbiological controls for relevant excipients are applied.

Pharmaceutical development of the finished product contains QbD elements.

A tablet dosage form was used from Phase I through Phase III pivotal clinical trials (a liquid oral formulation was also used in Phase I clinical trials). The dissolution profiles of the formulations were compared and the results were used to support a claim that a PK effect was not expected from changes made. The composition of the film-coated tablet formulations used in phase III clinical studies and the one developed for commercialisation differ only in the non-functional film coating. This difference does not have a significant effect on the bioavailability of the active substance. Bioequivalence studies were performed showing bioequivalence between the clinical formulation and the proposed commercial formulation (1305-0037, 1305-0051 - for more information reference is made to clinical part of this report). Equivalence between the phase III clinical formulation and the proposed commercial formulation of nerandomilast film-coated tablets has additionally been substantiated by comparative dissolution profiles.

Nerandomilast 9 mg and 18 mg film-coated tablets are manufactured using a wet granulation process. The resulting tablet cores are coated in a perforated drum coater with a non-functional coating using a conventional aqueous coating suspension. Protection against light is required for nerandomilast film-coated tablets since they are sensitive to light. This is ensured by the blister packaging configuration or the HDPE-bottle with closure, which sufficiently protect the film-coated tablets from light.

The formulation and manufacturing development have been evaluated through the use of risk assessments, design of experiments and other modelling techniques to identify the impact of the formulation components and process steps on the finished product quality attributes. Critical process parameters and IPCs have been adequately described.

The proposed QC dissolution method is the following: paddle apparatus (Apparatus II, Ph. Eur., USP, JP, ChP). The selection of dissolution method parameters has been adequately justified and the discriminatory power has been demonstrated.

With a low water activity, nerandomilast film-coated tablets do not carry a significant microbiological risk at the time of manufacture. The microbiological purity of the excipients is adequately controlled.

Nerandomilast film-coated tablets can also be administered by dissolving in water. Compatibility studies confirm no significant loss in purity over 24 hours after dissolving in water, an acceptable dose is delivered after the rinsing step is executed. Dissolution profiles generated on both the whole and dispersed tablets were confirmed as comparable.

The primary packaging is PVC/Alu (polyvinyl chloride/aluminium) perforated unit dose blisters or HDPE (high density polyethylene) bottle with a child-resistant closure. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. For the HDPE bottle closures, conformity to the relevant ISO standards has been confirmed.

3.3.2. Manufacture of the product and process controls

The finished product is manufactured at one site. Satisfactory GMP documentation has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

During the procedure, an MO was raised to include at least one site able to perform microbiological testing on the finished product. The MO was resolved by adding two sites along with the necessary GMP documentation.

The manufacturing process consists of the following stages: pre-blending, granulation and drying, final blending, compression, film-coating and packaging.

The critical process steps and critical process parameters have been defined. The in-process controls are adequate for this type of manufacturing process.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed CPPs. No design space is claimed.

The process is considered to be a standard manufacturing process.

Process validation has been performed on commercial scale batches of each product strength. All IPCs and finished product testing were within acceptance criteria. Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual examination), dissolution (UV, Ph. Eur.), identification (HPLC, UV), degradation products (HPLC), enantiomeric impurity (HPLC), assay (HPLC, UV), uniformity of dosage units by content uniformity (HPLC, UV Ph. Eur.), microbiological quality (Ph. Eur.).

The parameters tested are generally in line with the Ph. Eur. and ICH Q6A guideline for the dosage form.

In line with the clinical pivotal batches, it was requested to the Applicant to tighten the dissolution acceptance criterion. In response to the question, the Applicant provided a significant amount of dissolution data suggesting that the tighter specification may be somewhat overly discriminatory. Differences in dissolution profiles of the distinct formulations used during process development suggest that the method is capable of detecting differences in the formulation not reflected in vivo. Consequently, a tightened dissolution specification has been introduced by the Applicant.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

The active substance, nerandomilast and a number of structurally related impurities include a potentially nitrosatable secondary amine in their structure. Details of the experimentation performed have been provided and are considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The omission of testing for water content and hardness has been adequately justified based on the inclusion of relevant IPC and /or PP controls.
As dissolution is a controlled parameter, a test for disintegration is not considered necessary.
For microbiological quality, an OC was raised to include skip-lot testing in the finished product specification. The OC was resolved by revising the FP specification and proposing an acceptable microbial testing frequency.

Batch analysis results are provided for commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. No degradation products have been observed in nerandomilast film-coated tablets at release or on stability.

3.3.4. Stability of the product

Stability data from twelve batches (three for each strength and packaging) of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, dissolution, degradation products, assay, enantiomeric impurity, disintegration (for information only), loss on drying (for information only), water activity (for information only), resistance to crushing (for information only) and assessment of packaging material (for information only). The analytical procedures used are stability indicating.

The results indicate that the finished product is inherently stable, no trends or significant changes were observed in any of the tested parameters.

The proposed bulk holding time is acceptable.

In addition, finished product batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and results demonstrate slight sensitivity to light. Both primary packaging materials (HDPE bottles and PVC/Alu blisters) have proven to provide sufficient protection for the film-coated tablets.

Heat and humidity stress stability studies have also been performed. Results from stress studies conclude that the finished product is not sensitive to heat or humidity and is stable under in-use conditions.

Based on available stability data, the proposed shelf-life of 2 years at the proposed storage conditions "Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions." as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

3.3.5. Adventitious agents

One excipient of animal origin is used: lactose monohydrate.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Six MOs were raised by CHMP during the evaluation: MO1 on the NAS status claim resulted in an additional MO (MO2) due to missing information, which was resolved by provision of sufficient justification; MO3 for the insufficient discussion and justification on the PARs resulted in an additional MO (MO4) due to missing information in Module S.2.2, which was resolved during the second assessment; MO5 in relation to the control strategy of mutagenic impurities was resolved in line with ICH M7 requirements; MO6 to include in the dossier at least one site able to perform microbiological testing on the finished product was resolved by adding two sites for microbiological quality testing with their respective valid GMP documentation.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

3.6. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The nonclinical testing program of nerandomilast was designed in accordance with the International Council for Harmonization guidelines, M3, M12, M7, S7A, Q3A and Q3B.

In vitro studies and in vivo pharmacology models in mice, rats, and Suncus murinus were conducted to evaluate the anti-inflammatory and antifibrotic activity of nerandomilast. Potential off-target effects of nerandomilast, and PDE-related activity of nerandomilast, minor metabolites PD 1420 and CD 6352, and major metabolite BI 764333 were explored in in vitro studies.

General pharmacology studies (non-GLP) were conducted to assess cardiovascular (in vitro hERG and action potential duration studies and in vivo in rat and minipig studies), CNS (rat study), and respiratory (rat study) effects on nerandomilast. Per ICH M3(R2) and S7A guidance, core battery safety pharmacology assessments in vivo were later conducted under GLP in rats (CNS, respiratory) and minipigs (cardiovascular). Although not required based on ICH guidance or due to observance of a signal in nonclinical species or the clinic, a hERG assay (GLP) was conducted on major human metabolite, BI 764333.

The pharmacokinetic (PK) and drug metabolism profile of nerandomilast was studied in humans and nonclinical species utilized in toxicology studies, including mice (NMRI), rats (Han Wistar), minipigs (Göttingen), and monkeys (cynomolgus). The metabolic profile in humans and nonclinical species was evaluated and contrasted to ensure species suitability. Plasma protein binding was investigated in vitro, in pooled human plasma, in mice, rats, minipigs, monkeys and additionally in New Zealand white rabbits. In toxicology studies in these animal species, the PK profiles of nerandomilast following repeated dosing, i.e., the toxicokinetic profiles, were determined.

A comprehensive package of repeat-dose toxicity (rat, minipig, and non-human primate up to 26, 39, and 39 weeks, respectively), genetic toxicity, and carcinogenicity (transgenic mouse and rat) studies have been completed. Developmental and reproductive toxicology (DART) studies that evaluated fertility and early embryonic development (rat), embryo-fetal development (rat and rabbit), and pre- and postnatal development (rat) were conducted to inform on potential risks relevant to women of childbearing potential. All pivotal studies were performed to GLP. As it is formed in nonclinical species, BI 764333 has been evaluated in repeat-dose, DART, and carcinogenicity studies, and for genotoxicity in in vitro studies. Actual impurities that exceed levels set in ICH Q3A(R2) and Q3B(R2) have been qualified. Potential and actual impurities have been evaluated in silico using Q(SAR) models as recommended in ICH M7(R2) and assessed for mutagenicity per guidelines.

4.2. Analytical methods

LC-MS/MS methods were developed to detect nerandomilast and the major metabolite BI 764333 in the plasma of rats, mice, minipigs, monkeys and rabbits to support nonclinical development of nerandomilast. These methods were validated under GLP conditions in accordance with bioanalytical guidelines (Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009) and are sufficiently sensitive, specific, accurate and precise for the intended analysis.

Bioanalytical methods that were not validated under GLP conditions were also developed for analysis of nerandomilast in non-GLP studies, including enantioselective analysis of nerandomilast (*R*-enantiomer) and PD 1420 (*S*-enantiomer) in non-GLP PK studies and for analysis of the metabolite BI 764333 in GLP studies. All in-study validation resulted demonstrated acceptable accuracy and precision of the method used.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Mechanism of action

Nerandomilast is a potent and selective inhibitor of the PDE4 enzyme intended for oral administration. Nerandomilast inhibited the PDE4B enzyme with an IC_{50} of 10.3 nM, displaying a 9-fold selectivity vs PDE4D, IC_{50} 91 nM. The mean IC_{50} value for PDE4A and PDE4C2 enzymes was determined to be 248 nM and 8.7 μM, respectively (Hermann et al, 2022).

The pharmacological activities of the major human metabolite (BI 764333), CD 6352 and PD 1420 were also investigated. At a concentration of 10 μmol/L, BI 764333 inhibited PDE4A1A, PDE4B1 and PDE4D2 for 51.9%, 77.2%, and 60.4% respectively, with inhibition values ≤15.5% for the other tested enzymes (PDE1B, PDE2A1, PDE3A, PDE3B, PDE5, PDE6, PDE7A1, PDE8A1, PDE10A2 and PDE11A). Therefore, pharmacological contribution of this metabolite is considered to be low. The inhibitory activity of PD 1420 versus the primary target PDE4B is 66-fold lower than that of nerandomilast (IC_{50} 10 nmol/L), the pharmacological contribution of this S-enantiomer is considered to be low. CD 6352 showed only limited inhibition to PDE4B even at a high concentration of 10 μmol/L, the pharmacological contribution of CD 6352 is also considered to be low.

Anti-inflammatory models

In cellular anti-inflammatory assays nerandomilast prevented the LPS induced tumor necrosis factor (TNF)-α release and the phytohemagglutinin (PHA) induced IL-2 release from peripheral blood mononuclear cells (PBMC) with IC_{50} of 35 nM and 9 nM respectively.

The anti-inflammatory ex-vivo activity of nerandomilast was demonstrated in a mouse LPS model. Oral administration of nerandomilast inhibited the increase in TNF-α release in LPS induced whole blood with an ED_{50} of 0.04 mg/kg.

Furthermore, in two anti-inflammatory in-vivo models, nerandomilast also reduced the LPS-induced influx of neutrophils into the bronchoalveolar lavage fluid (BALF) of rats and Suncus murinus in a dose-dependent fashion with ED_{50} of 0.1 mg/kg and 0.6 mg/kg, respectively.

Models of fibrosis

In a study in the inhibition of IPF lung fibroblast transformation, nerandomilast inhibited α-SMA protein expression of TGF-β-stimulated cells with an IC_{50} of 210 nmol/L. A combination of nerandomilast with 10, 30 or 100 nmol/L Nintedanib yielded in IC_{50} values of 250, 180, and 110 nmol/L, respectively. This study also used pirfenidone, though this is not discussed by the applicant. A combination of nerandomilast with 100 μM Pirfenidone resulted in an IC_{50} value of 310 nmol/L. The combination of nerandomilast with Pirfenidone (100 μmol/L) did not yield in additional inhibitory effects regardless of the assay used in this study.

Nerandomilast inhibits fibroblasts-to-myofibroblast transformation (as indicated by α-SMA protein and collagen I, -III, and fibronectin gene expression) of TGF-β stimulated human lung fibroblasts from patients with IPF. There was no effect of nintedanib alone, IC_{50} of nerandomilast alone: 210 nM, IC_{50} of nerandomilast together with 100 nM nintedanib: 110 nM. Furthermore, nerandomilast inhibits FGF plus IL-1β- induced proliferation of IPF-LF. A combination of nerandomilast with Nintedanib (100 nmol/L) resulted in synergistic inhibitory activity on FGF plus IL-1β-induced proliferation and additive effects on TGF-β-induced collagen III mRNA expression. For α-SMA protein and collagen I, or fibronectin gene expression no additional inhibitory effects of a combination were seen.

In the in vivo bleomycin model of lung fibrosis, nerandomilast was safe and well tolerated and associated with reversal of bleomycin-induced changes in pulmonary remodelling, lung function in mice at 12.5 mg/kg bid and rats at 2.5 mg/kg bid.

4.3.1.2. Secondary pharmacodynamics

Selectivity testing of nerandomilast versus 78 receptors and 42 enzymes at the high concentration of 10 µM did not result in any relevant interaction.

In a Suncus murinus emesis model the compound showed no or little emetic potency with doses of 0.5 and 6 mg/kg respectively.

In an LPS-stimulated, high-dose PDE4 inhibitor treated whole blood assay, results in the minipig resembles more the situation in the human than the rat. For minipig WB, the magnitude of TNF-α inhibition and the decrease of IL-6 release with increasing PDE4i concentration were consistent with human WB results, in contrast to rat WB which showed an increase in IL-6 with increased PDE4i concentration.

4.3.1.3. Safety pharmacology

Non-GLP studies also evaluated the effect of nerandomilast on liver, renal and GI systems without findings. Subsequent core battery safety pharmacology studies were conducted under GLP conditions. The GLP studies included FOB to evaluate CNS effects in rats, examinations of cardiovascular and respiratory parameters in minipigs and rats, respectively. CNS-related effects including gnawing, fur scratching, licking were observed in the 1 mg/kg dose group in rats in the non-GLP Irwin test. These behaviours became more pronounced at 3 mg/kg and a reduction in water intake and number of faeces were also noted. However, no CNS effects were noted in the GLP FOB study. No notable cardiovascular effects were reported in the GLP study. In the GLP respiratory study, a mild transient decrease in respiratory rate and minute volume was evident at 2 and 4 h post dose in rats in the highest dose group (12 mg/kg). Given the transient nature and low magnitude of the response, this was not considered biologically significant; no respiratory effects were reported in the repeat-dose toxicity studies. The core battery safety pharmacology studies were in line with ICHS7A.

The effects of nerandomilast on hERG-mediated potassium current and action potential configuration in myocardial tissue were examined *in vitro* in studies that were not GLP compliant. A weak inhibitory effect (24%) on hERG-mediated potassium channel and a slight but significant prolongation of APD90 in myocardial tissue was observed at 10 µM nerandomilast. The concentration of 10 µM is 94-fold higher than steady state C_{max} unbound fraction of nerandomilast at the maximum human dose (18 mg BID). Therefore, these data present no *in vitro* signal for a potential proarrhythmic risk of nerandomilast up to free plasma levels of 10 µM. The major metabolite, BI 764333, was also investigated in hERG assay.

4.3.1.4. Pharmacodynamic drug interactions

No dedicated studies were performed. In one PD study the inhibition of IPF lung fibroblast (IPF-LF) transformation, nerandomilast inhibited α-SMA protein expression of TGF-β-stimulated cells with an IC50 of 210 nmol/L. The combination of nerandomilast with 10, 30 or 100 nmol/L nintedanib yielded in IC50 values of 250, 180, and 110 nmol/L, respectively for concentration–dependent inhibition of TGF-β-stimulated α-SMA protein expression in human lung fibroblasts from patients with IPF. Additive effects of nerandomilast and nintedanib were seen for TGF-β-induced collagen III mRNA expression. A combination of nerandomilast with 100 µM pirfenidone resulted in an IC50 value of 310 nmol/L, nerandomilast alone resulted in an IC50 of 210 nmol/L. Nintedanib and pirfenidone were not used alone.

In addition, nerandomilast inhibits FGF plus IL-1β- induced proliferation of IPF-LF. A combination of nerandomilast with nintedanib (100 nmol/L) resulted in synergistic inhibitory activity on FGF plus IL-1β-induced proliferation. Nerandomilast alone resulted in an IC50 of 255 nmol/L. The combination with 100

nmol/L of nintedanib resulted in a synergistic inhibitory efficacy and shifted the IC50 to 23 nmol/L. Pirfenidone and nerandomilast resulted in an IC50 value of 100 nmol/L, which was not considered a significant change in efficacy.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

The intrinsic permeability of nerandomilast across Caco-2 cell monolayers indicated that active efflux is involved in nerandomilast transport. Nerandomilast is expected to be absorbed well after oral administration based on its intrinsic membrane permeability (P_{app} >20x10^{-6} cm/sec) and oral bioavailability in humans (73%). *In vitro* studies with selective inhibitors in Caco-2 cells demonstrated that nerandomilast is a substrate of P-gp but not BCRP. Studies in HEK293 cells demonstrated that nerandomilast was not a substrate of any of the major SLC uptake transporters in the kidney or liver.

The PK of nerandomilast in nonclinical species was characterised by low clearance, moderate volume of distribution and moderate to high bioavailability, indicating it is well absorbed from the GI tract (48-87% in nonclinical species). Exposure (AUC) was similar following IV and PO dosing in mouse and rat.Nerandomilast and BI 764333 exposure generally increased proportionally with dose. Accumulation of nerandomilast was evident in minipigs and slight accumulation was observed in mice at high doses, while exposure levels following repeated dosing were generally similar to exposure on Day 1 in rats and monkeys. Sex differences in plasma exposure were species dependent as nerandomilast and BI 764333 levels were higher in female rats compared to male, but higher in male mice compared to female. No sex-based differences were evident for minipig or monkey. Plasma exposure of nerandomilast and BI 764333 was measured in pregnant rats in an EFD study and in pregnant and lactating rats in a PPND study. In pups, plasma concentrations of nerandomilast and BI 764333 increased proportionally with the increase in maternal nerandomilast dose. Nerandomilast concentrations were much lower (up to ~30-fold) in the plasma of F1 pups compared to F0 dams , while BI 764333 plasma concentrations in pups were similar or higher than dams. Plasma exposure of nerandomilast was also measured in pregnant rabbits in an EFD study.

4.3.2.2. Distribution

Plasma protein binding and blood cell partitioning were investigated in vitro. The binding of [^{14}C]nerandomilast to plasma proteins was low in all species except rat where binding was moderate (88%) and rabbit where binding was high (96%). Binding was low in humans at 77%. The extent of partitioning in blood cell vs plasma was moderate in rat, minipigs and humans (CB/CP = 0.4-0.8). When evaluated ex vivo, there was a trend of increasing partitioning of nerandomilast into blood cells with increasing time post administration in mouse, monkey and minipig. Distribution of nerandomilast was quantified using QWBA following administration of [^{14}C]nerandomilast to albino and pigmented male rats as well as pregnant female rats. Tissue distribution of radioactivity from whole blood into peripheral tissues appeared to be fast and extensive. In pigmented rats, there was moderate affinity of radioactivity to melanin-containing tissues of the eye, but no discernible affinity to melanin in the skin. Radioactivity was low but still detectable in the CNS with levels up to 7% of levels in the blood at 1 and 8 h post dosing. While radioactivity of up to 4% of in brain tissue is accepted as background levels, the presence of up to 7% may indicate low permeability of the blood-brain-barrier to nerandomilast and/or its metabolites in pigmented and albino rats.

Distribution of radioactivity into the placenta was moderate (~1.2X higher than maternal heart blood). In general, the concentration of radioactivity found in total embryos (GD 12-14) and in foetuses blood (GD 18-20) after oral administration to the dams was considered low in comparison to the concentrations measured in maternal heart blood (approx. 0.3), indicating little transfer through the placenta, but exposure of different foetal tissues varies and could strongly exceed maternal tissues, for instance brain (x5).

4.3.2.3. Metabolism

Nerandomilast was extensively metabolized via multiple pathways, which were generally similar across the species evaluated. The predominant metabolic pathways included oxidation, glucuronidation and *N*-dealkylation. Numerous metabolites were identified in nonclinical species including 24 in mice, 21 in rats, 22 in minipigs and 27 in monkeys. The most abundant circulating metabolite differed among species and included CD 6352 and M464(6) in male and female mice respectively, CD 6352 in rats, M624(1) in minipigs and M640(3) in monkeys. Eighteen metabolites were identified in humans. The only major human metabolite was BI 764333 which represented 12.5% of total circulating drug-related material at steady state. This metabolite is not pharmacologically active at relevant circulating concentrations in humans. The contribution of individual CYP and UGT isoforms to the metabolism of nerandomilast were evaluated *in vitro* using HLMs and rCYPs/rUGTs. CYP3A (mainly 3A4) was identified as the predominant metabolising enzyme and is responsible for the formation of CD 6352 and the only major human metabolite BI 764333 through oxidation. *In vitro* studies using a selective CYP3A inhibitor estimated that this CYP isoform contributes to approximately 70% of nerandomilast metabolism in humans. Clinical DDI trials were conducted with a strong CYP3A inhibitor, itraconazole, and moderate and strong CYP3A inducers. UGT isoforms 1A3, 1A8, 1A9, 2B4 and 2B7 contribute to the glucuronidation of nerandomilast to form M624(1), however this is a minor metabolic pathway in humans and the exposure of M624(1) is less than 25% of nerandomilast exposure, therefore no DDI studies were conducted.

Nerandomilast undergoes *in vivo* enzymatic chiral inversion to form its *S*-enantiomer, PD 1420, following oral administration to humans and all evaluated nonclinical species. Nerandomilast (sulfoxide) undergoes gut microflora-mediated reduction to form BI 764334 (sulfide) which is then oxidized to PD 1420 by CYP3A. PD 1420 accounts for 3.27% of circulating drug-related material in humans and is considered a minor metabolite. It is not active at relevant plasma concentrations in humans. *In vivo* studies were conducted to definitively determine the relative plasma exposures of nerandomilast (*R*-enantiomer) and PD 1420 (*S*-enantiomer) in mice, rats, minipigs, monkeys, pregnant rabbits and humans using chiral bioanalytical methods. Nerandomilast was the predominant enantiomer in all species, but PD 1420 was detectable in plasma indicating chiral inversion occurred. Chiral inversion was very limited in mice (<2%) but occurred to a greater extent in other nonclinical species evaluated ranging from 1.27-6.47% in rats, rabbits and monkeys. Humans experienced ~11% of chiral inversion.

4.3.2.4. Excretion

The major route of excretion in all evaluated species was faeces, representing 49-89% of the dose. In urine 12-36% of the oral radioactive dose was recovered across species. Rodents had a greater extent of radioactivity excreted via faeces when compared to minipigs, monkeys, and humans, which were generally similar. Renal secretion of parent nerandomilast was lower in nonclinical species (1.1-5.2% of dose) than in humans (approximately 12-13%). Based upon the excretion of nerandomilast and metabolites in urine and faeces, the primary route of nerandomilast clearance was via metabolism by CYP3A. Nerandomilast-related radioactivity was measured in the milk of lactating rats administered

[^{14}C]nerandomilast. Radioactivity was measurable 1 h post-dose indicating a rapid transfer and ~2.6% of the administered dose was recovered in milk over 24 h period.

4.3.2.5. Pharmacokinetic drug interactions

The potential for nerandomilast to induce CYPs enzymes 1A2, 2B6, 3A4, 2C8, 2C9, and 2C19 was evaluated *in vitro* in human hepatocytes from 3 individual donors. Nerandomilast did not induce CYP1A2 mRNA up to 60 µM but did induce CYP2B6 and CYP3A4 mRNA in a concentration-dependent manner at ≥30 µM and CYPs 2C8 and 2C9 mRNA at ≥10 µM. Based on unbound $C_{max,ss}$ and calculation methods outlined in ICH M12, it was concluded that nerandomilast could cause clinically relevant induction of CYPs 3A4, 2C8, 2C9 and 2C19. Therefore, a clinical DDI study examining impact of oral nerandomilast on the exposure of a specific CYP3A substrate, midazolam, was conducted (See Clinical Pharmacology). No clinical DDI studies were conducted for CYPs 2C8, 2C9 or 2C19 as these enzymes are regulated through the same transcriptional pathway as CYP3A4 i.e. PXR and are typically less sensitive to induction via nuclear receptor activation.

The potential for nerandomilast to reversibly and irreversibly inhibit the CYP isoforms was investigated in HLMs and no clinically relevant inhibition of CYP enzymes was considered likely, therefore no clinical DDI studies are necessary. Furthermore, the potential of nerandomilast to inhibit UGT isoforms 1A1, 1A3, 1A4, 1A7, 1A8, 1A9, 2B4 and 2B7 was evaluated *in vitro* using HLMs or rUGTs and no clinical DDI study was considered necessary. Nerandomilast was shown to inhibit P-gp, BCRP, OAT3, MATE1 and MATE2-K *in vitro* with IC_{50} values of 26, 30-100, 30-100, 14.2, 11.2 µM. Using basic methods and cutoff values outlined in ICH M12, nerandomilast is not predicted to cause clinically relevant inhibition of any of these evaluated transporters and no clinical DDI study is necessary.

4.4. Toxicology

4.4.1. Single-dose toxicity

No dedicated single-dose toxicity studies have been conducted with nerandomilast, although single dose levels were administered to rats as part of an in vivo micronucleus study.

Observations after the initial dose of 25 mg/kg to mini pigs in the 39-week study resulted in decreased appetite. After the initial dose of 60 mg/kg in the dose escalation/DRF in monkeys, emesis was observed, and at ≥300 mg/kg decreased motor activity was observed.

4.4.2. Repeat-dose toxicity

Repeat-dose toxicity studies with nerandomilast were performed by the oral route of administration in rats, minipigs, and cynomolgus monkeys in studies of up to 26, 39, and 39 weeks, respectively.

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). The rat was considered the most sensitive species to toxicity caused by nerandomilast.

In the 39-week study 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.

An increased IL-6 expression (mRNA and protein) as a consequence of usage of high doses of pan-PDE4 inhibitors has been linked to the development of mesenteric vasculitis in rat [Dietsch 2006].

The objective of a study was to determine if LPS-stimulated, high-dose PDE4 inhibitor treated whole blood assay in the minipig resembles more the situation in the human or the rat (maximum TNF-α inhibition around 80% without induction of IL-6 release for human versus 100% TNF-α inhibition and up to 7-fold increase in IL-6 release for rat), as published.

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. The mesentery, GI tract 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. Vasculopathy was associated with moribundity and mortality at high exposures. At lower exposures vasculopathy was mostly reversible following recovery in rats and minipigs.

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 $\geq$60 mg/kg/day. 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.

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). 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.

Hypertrophic osteopathy, inflammation surrounding the periosteum of the tibia and periosteal new bone formation, has been observed in a few rats following long-term repeat-dosing of nerandomilast, but has not been seen in non-rodent species. These included rats administered 7.5 mg/kg/day for 26 weeks and 2 mg/kg/day for 104 weeks, at exposures 6-fold and 1-fold human exposure at the MRHD, respectively.

In a 4-day rat study, nerandomilast had no relevant effects on body weight, splenic weight, or absolute neutrophil count when administered orally at 6 mg/kg/day. Minimal focal mononuclear cell infiltration was observed microscopically in the mesentery of 1 out of 6 nerandomilast-treated rats, suggesting a marginal effect.

4.4.3. Genotoxicity

Nerandomilast was tested in a standard Ames test, an in vitro chromosome aberration assay and an oral in vivo Micronucleus test in rats. All tests were in line with ICH S2(R1) and according to GLP. There were no indications of genotoxic effects of nerandomilast in any of the test systems. Based on this, nerandomilast can be considered as non-genotoxic.

4.4.4. Carcinogenicity

Nerandomilast showed no evidence of carcinogenic potential when administered for 26 weeks to transgenic mice (Tg.rasH2) or for 104 weeks to rats up to dose levels of 60 (male)/ 100 (female) and 2 mg/kg/day, respectively. Nerandomilast exposure levels corresponded to AUC exposure levels in male/female mice and in rats that were 47/57-fold and 1.6/2.2-fold human exposure at the MRHD, respectively.

Due to mortality at ≥ 4 mg/kg/day in the 26-week rat study, the low incidence of mesenteric changes at 2 and 4 mg/kg/day in the 26-week rat study and the absence of mortality and inflammation in the gastrointestinal tract at 3 and 6 mg/kg/day in the 13-week rat study, a high-dose of 2.0 mg/kg/day was chosen for the 2-year rat carcinogenicity study. The 2 mg/kg dose resulted in a low exposure margin of 1.6 and 2.2 based on AUC in males and females.

4.4.5. Developmental and reproductive toxicity

Non-adverse increases in mean testicular weights were observed in rat repeat-dose toxicity studies of 4 to 26 weeks duration at dose levels between 3 to 6/12 mg/kg/day.

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). Menstrual cycles were not affected at 3 mg/kg/day (equivalent to human AUC exposure at the MRHD).

In the FEED studies, no adverse effects on fertility in male and female rats were noted at the NOAEL, 6 or 3 mg/kg/day (4 or 3-fold human AUC exposure at the MRHD, respectively).

At 9 mg/kg/day in males there were macroscopic findings in the testis and epididymis, and in females there were adverse effects on the maternal performance (increased post-implantation loss (%) and mean number of early resorptions and decreased mean number of live embryos) and on parental reproductive performance (lower mating, fertility and pregnancy indices).

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-fold AUC exposure and 4-fold human AUC, unbound exposure at the MRHD). Embryofoetal 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) or in rabbits at 15 mg/kg/day (4-fold human AUC, unbound exposure at the MRHD).

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. The pivotal 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. Offspring (F1) development, behaviour, and reproductive performance were not affected.

In a single dose milk secretion study in lactating rats dosed with radiolabelled nerandomilast by the oral route, similar concentrations of total radioactivity were observed in the milk and plasma of lactating females at 1 h post-dose. The maximum radioactive concentration in milk was observed at 1 hour post dose and was significantly reduced by 24 hours post dose. The presence of nerandomilast in the plasma of rat pups during the nursing period suggested secretion of nerandomilast into rat milk. This conclusion is supported by the excretion of nerandomilast-associated radioactivity in the milk of lactating rats administered [14C]nerandomilast orally.

A non-GLP dose range-finding (DRF) study was conducted in juvenile rats. to evaluate nerandomilast tolerability and toxicokinetics (TK) and dose level selection for the definitive study. Doses of 1, 3, and 6 mg/kg/day were administered. Animals were dosed by once daily oral gavage from PNDs 14-27, supporting development from 1 year of age in humans. Based on early termination, mortalities, adverse microscopic findings, adverse clinical signs and decreased body weight gain, the no-observed-adverse-effect level (NOAEL) was considered to be 1 mg/kg/day.

4.4.6. Toxicokinetics and exposure margins

Toxicokinetics was performed in all repeat-dose toxicity studies with nerandomilast in rats, minipigs, and monkeys, using the non-chiral method as discussed. As nerandomilast is administered twice per day to humans, AUC0-τ, where τ = 12 hours, was multiplied by 2 to obtain a human AUC0-24 for comparison to nonclinical exposures

Plasma exposure values of nerandomilast and of the major human metabolite BI 764333 (where applicable) were generated after repeated oral administration of nerandomilast during toxicity studies in mice, rats, rabbits, minipigs, and monkeys. The toxicokinetic characteristics of nerandomilast in pregnant rats were determined.

In general, exposures (AUC and Cmax) increased in a dose-proportional to greater than dose-proportional manner.

In rats, plasma levels were higher in females than in males administered the same dose and were relatively similar after single (Day 1) and repeated dosing. In minipigs, there was no apparent sex effect on plasma level, and in monkeys, plasma levels were generally consistent between sexes.

In the 26-week repeat-dose toxicity study in rats, the NOAEL of 2 mg/kg/day resulted in steady state Cmax and AUC0-24 levels that were 1-fold (equivalent) to human levels at the MRHD.

In the 39-week minipig repeat-dose toxicity study, the LOAEL of 3 mg/kg/day resulted in steady state Cmax and AUC0-24 levels that were 1-fold (equivalent) to human levels at the MRHD.

No adverse effects were noted in monkeys at the highest dose tested, 30 mg/kg/day, and was the NOAEL in the 13- and 39-week studies, corresponding in the latter study to 12- and 10-fold human exposure at the Cmax and AUC0-24, respectively.

4.4.7. Local tolerance

Not applicable

4.4.8. Other toxicity studies

Metabolites

BI 764333

The major human metabolite BI 764333 is formed in multiple nonclinical species including mice, rats, minipigs, and monkeys. Plasma exposures reached in repeat-dose toxicity, DART, and carcinogenicity studies were adequate to evaluate its respective effects, with the conclusion that BI 764333 did not contribute to adverse changes. BI 764333 was negative for mutagenicity and clastogenicity in the in vitro bacterial reverse mutation and chromosomal aberration assays. A hERG assay performed with BI 764333 indicated a minimal likelihood of an effect on the potassium channel.

Adverse findings in the nerandomilast oral repeat-dose toxicity and DART studies were attributed to primary or secondary effects of PDE4i, rather than to BI 764333 exposure.

Nerandomilast showed no evidence of carcinogenic potential in oral administration studies in mice or rats. Therefore, BI 764333 was considered adequately characterized for general toxicity, carcinogenicity, and DART based on results of the nerandomilast oral administration studies.

S-enantiomer of nerandomilast (PD 1420)

The S-enantiomer of nerandomilast is a minor metabolite in humans . The S-enantiomer was shown to be 66-fold less potent at inhibition of PDE4B than nerandomilast and is considered to contribute minimally to pharmacological activity.

The S-enantiomer is formed in all nonclinical species with the exception of the mouse, but the extent of chiral inversion varies between species and can differ between sexes and/or nerandomilast dose level. Plasma levels of nerandomilast in all toxicology studies were measured using a non-chiral method, so actual levels of nerandomilast as the R-enantiomer and its S-enantiomer can only be estimated. For most nonclinical species aside from minipig, in vivo chiral inversion of nerandomilast is lower than in humans.

Impurities

The Applicant performed a GLP study to compare the toxicity of nerandomilast without or with three potential impurities/degradants in the rat following at least 13 weeks of oral administration, to determine the general toxicity of impurities for qualification per ICH guidelines Q3A(R2) and Q3B(R2).

Impurities added to nerandomilast were observed PD 1424, CD 6352, and PD 1420 ; S-enantiomer of nerandomilast). Once daily oral (gavage) administration of nerandomilast for at least 13 weeks in the rat at 1 and 3 mg/kg/day either with or without impurities resulted in no nerandomilast-related changes in any of the parameters examined. Therefore, impurities are considered qualified with respect to their exposure at the higher dose level of 3 mg/kg/day.

Calculations resulted in qualification for general toxicity of PD 1420. No similar calculations for PD 1424 and CD 6352 were performed as they are below the ICH Q3A and Q3B qualification thresholds in DS and DP.

In a mutagenicity assessment, PD1420 showed no potential for inducing base pair substitutions nor frameshift mutations.

Other actual and potential impurities or degradation products of nerandomilast were assessed in silico in accordance with ICH M7(R2) guideline. Each impurity was assigned to one of the classes listed in Table 1 of the ICH M7(R2) guideline. All other compounds identified as potential impurities or degradants were assigned Class 4 or Class 5.

Phototoxicity

Nerandomilast tested negative for phototoxic potential in the 3T3 neutral red uptake in vitro assay, suggesting a low potential for phototoxicity. Additionally, no toxicity has been identified by ophthalmoscopy and/or microscopic examination in the non-pigmented eyes or skin of rats, minipigs, or monkeys during repeat dose oral toxicity studies of up to 26, 39, and 39 weeks, respectively.

4.4.9. Ecotoxicity/environmental risk assessment

An environmental risk assessment for nerandomilast has been conducted in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4440/00 Rev.1-Corr*) including a risk assessment and a hazard assessment.

Table 3: Summary of main study results: Phase I

Substance (INN/Invented Name):	Nerandomilast
CAS-number (if available):	1423719-30-5

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PEC_{sw}, default	0.18	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 4: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	***Test protocol***	***Result***	***Remarks***
Adsorption-Desorption Soil 1 = silt loam	OECD 106	KFOC, soil 1 = 637.1 L/kgoc	
Soil 2 = sandy loam		KFOC, soil 2 = 509.8 L/kgoc	
Soil 3 = loamy sand		KFOC, soil 3 = 385.9 L/kgoc	
Sludge 1 = Broadholme		KFOC, sludge 1 = 70.1 L/kgoc	
Sludge 2 = Milton		KFOC, sludge 2 = 87.9 L/kgoc	
Ready Biodegradability Test	OECD 301B	2.6 % (28 d) not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = Calwich Abbey (silt loam)	OECD 308	DT50, water 1 = 6.52 d DT50, whole system 1 = 30.3 d CO2 = <1 %	20 °C
Sediment 2 = Lumsdale (sand)		DT50, water 2 = 9.81d DT50, whole system 2 = 81.5 d CO2 = <1 %	20°C
Transformation products		>10% = N	

Phase II Aquatic effect studies					
Study type	***Test protocol***	***Endpoint***	***Value***	***Unit***	***Remarks***
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC10	4090	µg/L	growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	EC10 NOEC	3300 8830	µg/L µg/L	Reproduction Mortality
Fish, ELS/*Danio rerio*	OECD 210	EC10 EC10	7590 >8870	µg/L µg/L	Dry weight Hatching, survival, length

Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	1^{E+6}	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/Chironomus riparius	OECD 218	EC10	>2314.7	mg/kgdw	Emergence ratio, developmental rat, normalised to 10% o.c.
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	1.8 µg/L	100000 µg/L	0.000018		No risk
Surface water	0.18 µg/L	330 µg/L	0.0005		No risk
Groundwater	0.000045m µg/L	0.033 mg/L	0.0014		No risk
Sediment	0.0120 mg/kgdw	23.15 mg/kgdw	0.0005		No risk

Considering the above data from Phase I and Phase II, Nerandomilast is not expected to pose a risk to surface water, sediment, groundwater, soil or the functioning of STPs. However, no conclusions can currently be drawn on the PBT/vPvB potential of nerandomilast and the potential for secondary poisoning cannot be concluded.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

Mechanism of Action

Nerandomilast is a potent and selective inhibitor of the PDE4 enzyme intended for oral administration. Based on in vitro data, the applicant claims preferential inhibition of the PDE4B isoenzyme over PDE4A, C and D. However, at the proposed clinical dose of 18 mg BID, the observed unbound Cmax was approximately 107 nM. Thus, at these systemic concentrations, significant inhibition of both PDE4B and PDE4D is expected. It is known that inhibition of PDE4D may be responsible for the emetic effects. In this regard, emesis was indeed observed in animal species. Therefore, while the claim of preferential PDE4B inhibition may be supported by in vitro potency data, it is somewhat misleading without acknowledging that the clinical exposure range leads to substantial PDE4D inhibition as well. Section 5.1 of the SmPC reflects available in vitro and clinical data.

The pharmacological activity of the major human metabolite (BI 764333), CD 6352 and PD 1420 were also investigated. Studies demonstrated that pharmacological contribution of BI764333, CD 6352 and S-enantiomer PD 1420 metabolites is considered to be low.

The nonclinical species used in toxicology assessment of nerandomilast are considered pharmacologically relevant for various reasons including data demonstrating similar IC50 values for human and minipig for nerandomilast. Pharmacological activity has also been demonstrated in a variety of species, including mice and rats, and there is high PDE4B2 gene homology between species.

Anti-inflammatory models

In cellular anti-inflammatory assays nerandomilast prevented the LPS induced tumour necrosis factor (TNF)-a release and the phytohemagglutinin (PHA) induced IL-2 release from peripheral blood mononuclear cells (PBMC) with IC50 of 35 nM and 9 nM respectively.

The anti-inflammatory ex-vivo activity of nerandomilast was demonstrated in a mouse LPS model. Oral administration of nerandomilast inhibited the increase in TNF-α release in LPS induced whole blood with an ED50 of 0.04 mg/kg.

Furthermore, in two anti-inflammatory in-vivo models, nerandomilast also reduced the LPS-induced influx of neutrophils into the bronchoalveolar lavage fluid (BALF) of rats and Suncus murinus in a dose-dependent fashion with ED50 of 0.1 mg/kg and 0.6 mg/kg, respectively.

Proof-of-concept in pre-clinical models of inflammation has been demonstrated. These studies also confirm the anti-inflammatory activity of nerandomilast in small animal species used preclinically for toxicology studies.

Models of Fibrosis

In the inhibition of IPF lung fibroblast transformation study, nerandomilast inhibited α-SMA protein expression of TGF-β-stimulated cells with an IC50 of 210 nmol/L. A combination of nerandomilast with 10, 30 or 100 nmol/L nintedanib yielded in IC50 values of 250, 180, and 110 nmol/L, respectively. A combination of nerandomilast with 100 µM pirfenidone resulted in an IC50 value of 310 nmol/L and did not yield in additional inhibitory effects.

Nerandomilast inhibits fibroblasts-to-myofibroblast transformation (as indicated by α-SMA protein and collagen I, -III, and fibronectin gene expression) of TGF-β stimulated human lung fibroblasts from patients with IPF.

In the in vivo bleomycin model of lung fibrosis, nerandomilast was associated with reversal of bleomycin-induced changes in pulmonary remodelling, lung function in mice at 12.5 mg/kg bid and rats at 2.5 mg/kg bid. However, no significant therapeutic improvement in lung volume over the existing therapy with kinase inhibitor (BIBF1000 - structurally-related predecessor compound to nintedanib) has been demonstrated in non-clinical studies. Moreover, there was only little improvement in fibrosis score after treatment with either nerandomilast or BIBF1000., However as single dose bleomycin-induced pulmonary fibrosis disease often transiently resolves in rodents, the relevance of the current in vivo data (i.e. mice/rats treated with nerandomilast 8-10 days after bleomycin challenge) for the clinical situation with progressive pulmonary fibrosis (PPF) is questionable.

Considering the nature of the models and the high doses required for efficacy, the models are not appropriate for determining exposure/efficacy data, and the doses used were not considered as part of the rationale for deciding on the therapeutic dose. The dose of 18 mg BID was assumed to be the human efficacious dose in IPF and PPF based on other preclinical data and target engagement in Phase I.

Secondary Pharmacology

Selectivity testing of nerandomilast versus 78 receptors and 42 enzymes at the high concentration of 10 µM did not result in any relevant interaction.

Gastrointestinal side-effects, including vomiting, are known effects limiting the use of PDE4 inhibitors in humans. Dose-limiting nausea- and emesis-associated effects caused by the inhibition of PDE4 subtypes in the emetic centre in the brain has limited the use of these inhibitors (Kolb 2023).

Nerandomilast showed no significant emetic potential in Suncus murinus at doses of 0.5 mg/kg and only limited emetic potential with 6 mg/kg. However, emesis was observed in toxicity studies in other animal species

In a 4-day rat study, nerandomilast had no relevant effects on body weight, splenic weight, or absolute neutrophil count when administered orally at 6 mg/kg/day. Minimal focal mononuclear cell infiltration was observed microscopically in the mesentery of 1 out of 6 nerandomilast-treated rats, suggesting a marginal effect.

An increased IL-6 expression (mRNA and protein) as a consequence of usage of high doses of pan-PDE4 inhibitors has been linked to the development of mesenteric vasculitis in rat (Dietsch 2006). This finding has not been described with marketed PDE4 inhibitors in humans to date.

Safety Pharmacology

Safety pharmacology *in vivo* studies were conducted under non-GLP conditions in rats and minipigs to assess the impact of single oral dose of nerandomilast on CNS, cardiovascular, respiratory parameters and on GI motility, kidney and liver function, without any findings. No relevant adverse findings were associated with nerandomilast administration in the additional GLP core battery safety pharmacology assessments. A dose-dependent chronotropic effect on heart rate was observed in minipigs but was not considered clinically relevant. *In vitro* studies revealed a weak inhibitory effect on hERG-mediated potassium channel in HEK293 cells and a slight but signification prolongation of APD90 in myocardial tissue at 10 µM nerandomilast. As this is 94-fold higher than steady state Cmax unbound fraction of nerandomilast at the maximum human dose, this is not considered a signal for potential proarrhythmic risk. Several deficiencies were evident in the hERG assay, which was not conducted under GLP conditions as per ICH S7B. However, given that nerandomilast did not show QT prolongation potential in a dedicated clinical QT assessment, the addition of a GLP *in vitro* hERG assay is not warranted.

PD drug interactions

Nintedanib showed additive effects when combined with nerandomilast on inhibition of α-SMA protein expression of TGF-β-stimulated cells and additive effects on TGF-β-induced collagen III mRNA expression. Synergistic inhibitory efficacy on FGF plus IL-1β-induced proliferation was observed.

Pirfenidone had no effect on nerandomilast inhibition of TGF-β-stimulated α-SMA or on nerandomilast inhibition of FGF plus IL-1β-stimulated proliferation of human lung fibroblasts from patients with IPF.

Pharmacokinetics

Nerandomilast is a selective and potent inhibitor of the human PDE4B enzyme. It has been developed as an enantiopure chiral drug that contains a sulfoxide in the R-orientation, while the S-enantiomer (PD 1420) is pharmacologically inactive at relevant exposure in humans.

Absorption

Nerandomilast is expected to be absorbed well after oral administration based on its intrinsic membrane permeability (Papp >20x10-6 cm/sec) and oral bioavailability in humans (73%). Nerandomilast is a substrate of P-gp but not BCRP. Clinical DDI study using itraconazole, (moderate P-gp inhibitor and strong CYP3A inhibitor) showed a moderate increase in nerandomilast exposure in humans.

The PK profile was determined in mouse, rat, minipig and monkey following a single PO or IV dose of nerandomilast. The PK was characterised by low clearance (6.2-15% of hepatic blood flow for species), moderate volume of distribution (0.94-2.95 L/kg) and moderate to high bioavailability (48-87%). Exposure (AUC) of nerandomilast was similar in mouse and rat following PO and IV dosing but different in minipigs; primarily driven by variation in female minipigs. The terminal half-life was similar in all species after IV and oral administration. The rate of absorption (expressed by Tmax) was fastest in mice (T_{max} of 0.5 h) but slower in other species (T_{max} of 2-5 h).

Exposure of nerandomilast and BI 764333 tended to increase with increasing dose. Slight accumulation of nerandomilast was evident in mice at high doses and in minipigs, but not rats or monkeys. Accumulation of BI 764333 was observed following repeated dosing in mice, minipigs and monkeys. Sex differences were evident in mice and rats but not monkeys or minipigs.

Similar PK profiles were evident in pregnant rats and rabbits with nerandomilast exposure increasing proportionally with dose and little or no accumulation of nerandomilast. In the rat PPND study, plasma concentrations of nerandomilast were much lower in pups compared to the dams at 2 h post dose, while BI 764333 plasma concentrations were similar between the pups and dams or higher in pups.

Distribution

Nerandomilast showed low plasma protein binding in mouse (77.3%), minipig (62.5%), monkey (65.4%) and human (76.9%), moderate in rat (88.1%) and high in rabbit (96.0%). The extent of partitioning in blood cell vs plasma was moderate in rat, minipigs and humans (C_B/C_P = 0.4-0.8).

Tissue distribution of [^{14}C]nerandomilast-associated radioactivity was evaluated in albino and pigmented rats using QWBA. Following PO administration, the distribution of nerandomilast into peripheral tissue was fast and extensive with highest levels of radioactivity in the liver, GI tract and kidneys and very similar after oral and IV administration. Radioactivity was detectable in the CNS with concentrations up to 7% of radioactivity measured in the blood indicating that low levels of nerandomilast and/or metabolites can reach the CNS.

Pregnant female rats had a similar distribution pattern as seen in male rats in previous studies. The distribution of nerandomilast into the placenta was considered moderate, with concentrations of radioactivity detected in the placenta being up to 1.2X higher than concentrations detected in maternal heart blood in both the embryonic (GD 12) and foetal (GD 18) stages of development. Concentrations of radioactivity in rat embryos and foetuses were low compared to maternal blood, but exposure in different foetal tissues varied and could strongly exceed maternal tissues, for instance, concentrations of radioactivity in the foetal brain were 5.87X higher than the maternal brain 1 h post dose, then dropped to undetectable levels at 24 and 48 h. Information about placental transfer and embryofoetal exposure in rats is included in SmPC section 5.3.

Metabolism

Nerandomilast was determined to be metabolised via multiple pathways that were generally similar between species. The predominant metabolic pathways were oxidation, glucuronidation, and *N*-dealkylation. No unique human metabolites were identified. Metabolic profiling was only conducted in healthy male subjects and therefore it is unknown if there is a sex effect in metabolism in humans.

In humans, CYP3A was estimated to contribute to 70% of the metabolism of nerandomilast and was determined to be responsible for the formation of the only major human metabolite BI 764333 which represented 12.5% of total drug-related material (TDRM) in human plasma at steady state. This metabolite is not pharmacologically active at the relevant clinical dose. The next most abundant metabolite was CD 6352 (6.6%). All other metabolites each represented ≤2% of total circulating drug-

related material. Results of a clinical DDI study with the CYP3A inhibitor, itraconazole, confirmed that CYP3A contributes to the metabolic clearance of nerandomilast. Clinical studies evaluating the impact of moderate and strong CYP3A inducers were also conducted. No other CYP isoform contributes to >25% of the metabolism of nerandomilast. Multiple UGT isoforms contribute to the glucuronidation of nerandomilast and formation of M624(1), but these account for <25% of metabolism and are considered a minor metabolic pathway.

Plasma samples were analysed for circulating levels of nerandomilast and PD 1420 (inactive *S*-enantiomer of nerandomilast) and the extent of chiral inversion was calculated for each species following oral administration of nerandomilast. Parent nerandomilast was identified as the predominant drug-related component in the plasma of all species. Low levels of circulating PD 1420 were detected in the plasma of all species except mice confirming chiral inversion occurs *in vivo*. The extent of chiral inversion ranged from 1.2-6.8% in rats, rabbits and monkeys, and 8.3% in minipigs, which increased upon repeated administration to 28.6%. In humans the extent of chiral inversion was estimated at ~11%. CYP3A was demonstrated to be responsible for the oxidation of BI 76334 (intermediate metabolite formed *in vivo*) to PD 1420 or the reformation of parent nerandomilast.

Excretion

Excretion of drug-related radioactivity was rapid in mice and rats but slower in minipigs and monkeys. Faecal excretion was identified as the predominant route of nerandomilast excretion (58% in human, 49% in monkey, 60% in minipig, 89% in rat and 73% in mouse), followed by urinary excretion (36% in humans, 12-16% in rodents and 26-37% in minipigs and monkeys). Elimination through bile was also present in all nonclinical species. [^{14}C]nerandomilast was demonstrated to be excreted in the milk of lactating female rats on Day 12 postpartum. Following oral administration of radiolabelled nerandomilast, the mean exposure of drug-related radioactivity in milk was comparable to the mean exposure of plasma radioactivity. Within 24 h, 2.6% of the total radioactive dose administered to dams was secreted into milk.

PK drug interactions

The interaction of nerandomilast with CYP and UGT isoforms was investigated *in vitro* and the potential for nerandomilast to cause DDIs as perpetrator was assessed using calculation methods from ICH M12. It was concluded that nerandomilast could induce CYPs 3A4, 2C8, 2C9 and potentially 2C19. In a clinical DDIstudy, nerandomilast was co-administered orally with a sensitive CYP3A substrate, midazolam, and no clinically relevant changes in midazolam exposure was observed. Based on these results, it is unlikely that nerandomilast would cause clinically relevant changes in exposure of CYP2C substrates as these enzymes are regulated by the same transcriptional pathways as CYP3A i.e. PXR and are less sensitive than CYP3A. Nerandomilast did not inhibit or inactivate CYP or UGT isoforms. Nerandomilast was shown to inhibit P-gp, BCRP, OAT3, MATE1 and MATE2-K *in vitro* with IC_{50} values of 26, 30-100, 30-100, 14.2, 11.2 µM, it is unlikely nerandomilast would cause clinically relevant inhibition of these transporters.

Single-dose toxicity

Observations after the initial dose of 25 mg/kg to mini pigs in the 39-week study resulted in decreased appetite. After the initial dose of 60 mg/kg in the dose escalation/DRF in monkeys, emesis was observed, and at ≥ 300 mg/kg decreased motor activity was observed.

Repeat-dose toxicity

In **rats**, a dose level of 2 mg/kg/day was considered to not result in adverse changes and exposure was equivalent to (1-fold) humans at the MRHD (18 mg twice daily). The rat was considered the most sensitive species to toxicity caused by nerandomilast.

In the 13-week study, effects on seminiferous tubules and rete tubules were observed in a dose-related manner in testes of male rats receiving ≥3 mg/kg/day (full to partial recovery), however, no effect of nerandomilast on fertility was observed in the rat FEED studies. In the 26-week rat study, hindlimb swelling and hypertrophic osteopathy, defined as inflammation adjacent to and within the periosteum with periosteal new bone formation, were observed at ≥4 mg/kg/day. Partial recovery in rats receiving the high-dose of 7.5 mg/kg/day was observed in a 13-week recovery period.

In 4-, 13-, and 26-week rat studies, the NOAEL was considered to be 3, 6, and 2 mg/kg/day, respectively. However, NOAEL of the 13-week study is not agreed with. NOAEL should be <3 mg/kg/day due to liver and testes side effects.

In the 39-week study 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.

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. 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. Vasculopathy was associated with moribundity and mortality at high exposures. At lower exposures vasculopathy was mostly reversible following recovery in rats and minipigs. Vasculopathy is considered a potential risk for humans in the RMP.

Increased TNF-a and subsequent IL-6 release is associated with the development of mesenteric vasculitis in rat (Dietsch 2006). Study [n00269057] showed that for minipig WB, the magnitude of TNF-α inhibition and the decrease of IL-6 release with increasing PDE4i concentration were consistent with human whole blood results, in contrast to rat WB which showed an increase in IL-6 with increased PDE4i concentration.

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].

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 and has been added in SmPC section 5.3.

Hypertrophic osteopathy, inflammation surrounding the periosteum of the tibia and periosteal new bone formation, has been observed in a few rats following long-term repeat-dosing of nerandomilast, but has not been seen in non-rodent species. This included rats administered ≥4 mg/kg/day for 26 weeks and 2 mg/kg/day for 104 weeks, at exposures 4-fold and 2-fold human exposure at the MRHD,

respectively. While this may not be considered of relevance for adults, it may become relevant for any future paediatric development.

In conclusion, NOAELs in rat were determined at exposures which were 0.8 to 2-fold clinical exposure at the MRHD. In pig, NOAEL in the 13-week study was 6-fold the human exposure, but no NOAEL could be established in the 39-week study with cardiotoxic effects seen at exposure 0.9-fold the clinical exposure at the MRHD. NOAELs in monkey were at 7 to 10-fold the clinical exposure. In comparison with apremilast (a pan-PDE4i), where in mouse, rat and monkey, safety margins at NOAEL were of up to 3-fold, less than 0.1-fold and up to 6-fold, respectively, nerandomilast seems to be marginally less toxic to animals. Taking into account that a somewhat larger portion of nerandomilast is unbound in pig and monkey than in humans, the safety margins may be slightly underestimated in these two species. The vasculopathy in rats and minipigs, characterized by inflammation, haemorrhage, and necrosis of blood vessels, is a known class effect of PDE4 inhibitors in non-clinical models, and is thought to be a consequence of vascular tonus 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 and effects. Still, vascular effects seen at higher doses in all species tested do not seem to be avoided by the selectivity of nerandomilast and its 9-fold preferential inhibition of PDE4B to other PDE4 receptors.

Genotoxicity

There were no indications of genotoxic effects of nerandomilast in any of the conducted tests: Ames test, an in vitro chromosome aberration assay and an oral in vivo micronucleus test in rats. Based on this, nerandomilast can be considered as non-genotoxic.

Carcinogenicity

Nerandomilast showed no evidence of carcinogenic potential when administered for 26 weeks to transgenic mice (Tg.rasH2) or for 104 weeks to rats up to dose levels of 60 (male)/ 100 (female) and 2 mg/kg/day, respectively. Nerandomilast exposure levels corresponded to AUC exposure levels in male/female mice and in rats that were 47/57-fold and 1.6/2.2-fold human exposure at the MRHD, respectively. The low exposure margins achieved in rats at the high dose of 2 mg/kg of 1.6 and 2.2 based on AUC in males and females was discussed and considered acceptable in line with ICH S1 (R1) addendum.

Taking the totality of data available, it can be agreed that the carcinogenic risk of nerandomilast is adequately characterised.

Developmental and reproductive toxicity

DART studies were conducted in rats and EFD studies were performed in rats and rabbits, which are both standard species for reproductive toxicology. The rat is the most sensitive species to PDE4i-related effects and the rabbit was less sensitive. Sufficient exposures could be achieved in both. Safety margins in rabbits, 4-fold at the NOAEL, were calculated based on the unbound fraction of nerandomilast due to the large difference in the unbound fraction between human and rabbit.

FEED

Non-adverse increases in mean testicular weights were observed in rat repeat-dose toxicity studies of 4 to 26 weeks duration at dose levels between 3 to 6/12 mg/kg/day.

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). Menstrual cycles were not affected at 3 mg/kg/day (equivalent to human AUC exposure at the MRHD) as mentioned in SmPC section 5.3.

In the FEED studies, no adverse effects on fertility in male and female rats were noted at 3 mg/kg/day (1.5 to 2.5-fold human AUC exposure at the MRHD). Increased testis weight was observed at ≥ 6 mg/kg in FEED1 and marginally increased testis weights at 3 and 6 mg/kg/day in FEED2. At 9 mg/kg/day in males there were macroscopic findings in the testis and epididymis, and in females there were adverse effects on the maternal performance at doses above 6 mg/kg/day (increased post-implantation loss (%) and mean number of early resorptions and decreased mean number of live embryos) and on parental reproductive performance (lower mating, fertility and pregnancy indices).

In the two FEED studies, the Applicant considers the NOAEL for fertility and early embryo-foetal development was to be 6 mg/kg/day, which is not agreed with. The post-implantation loss observed at 3 mg/kg was not taken into account and therefore, it is deemed more appropriate that the NOAEL is considered 6 mg/kg/day for fertility effects in males (Cmax = 4410 nmol/L; AUC(0-24h) = 26700 nmol•hr/L) and 3 mg/kg/day (Cmax = 3280 nmol/L; AUC(0-24h) = 18700 nmol•hr/L) in females and for early embryo-foetal development. NOAEL exposure levels (AUC0-24) in male and female rats were 3-4-fold human exposure at 18 mg bid. The text in SmPC Section 5.3 has been agreed to reflect these data.

EFD

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-fold AUC exposure and 4-fold human AUC,unbound exposure at the MRHD, respectively). Embryofoetal 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) or in rabbits at 15 mg/kg/day (4-fold human AUC,unbound exposure at the MRHD).

Reproductive findings are consistent with findings for other PDE4 inhibitors described in the literature (Losco 2010, [R17-0922]) and appears related to the pharmacology of PDE4 (reviewed by Kolb 2023) as PDE4 is involved in ovulation. Inhibition leads to impaired follicular function and development and disruption of granulosa cell differentiation.

PPND

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. The pivotal 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. Offspring (F1) 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. This conclusion is supported by the excretion of nerandomilast-associated radioactivity in the milk of lactating rats administered [^{14}C]nerandomilast orally.

In compliance with the PIP, (P/0459/2021), a non-GLP dose range-finding (DRF) study was conducted in juvenile rats. The study aimed to evaluate nerandomilast tolerability and toxicokinetics (TK) and enable dose level selection for the definitive study. Doses of 1, 3, and 6 mg/kg/day were administered. Animals were dosed by once daily oral gavage from PNDs 14-27, supporting development from 1 year of age in humans. Based on early termination, mortalities, adverse microscopic findings, adverse clinical signs and decreased body weight gain, the no-observed-adverse-effect level (NOAEL) was

considered to be 1 mg/kg/day, the lowest dose tested. A definitive juvenile toxicity rat study is agreed in the PIP, with the completion of this study deferred to September 2025.

Toxicokinetics and exposure margins

In general, exposures (AUC and Cmax) increased in a dose-proportional to greater than dose-proportional manner.

In rats, plasma levels were higher in females than in males administered the same dose and were relatively similar after single (Day 1) and repeated dosing. In minipigs, there was no apparent sex effect on plasma level, and in monkeys, plasma levels were generally consistent between sexes.

In the 26-week repeat-dose toxicity study in rats, the NOAEL of 2 mg/kg/day resulted in steady state Cmax and AUC0-24 levels that were 1-fold (equivalent) to human levels at the MRHD.

In the 39-week minipig repeat-dose toxicity study, the LOAEL of 3 mg/kg/day resulted in steady state Cmax and AUC0-24 levels that were 1-fold (equivalent) to human levels at the MRHD.

No adverse effects were noted in monkeys at the highest dose tested, 30 mg/kg/day, and was the NOAEL in the 13- and 39-week studies, corresponding in the latter study to 12- and 10-fold human exposure at the Cmax and AUC0-24, respectively.

Metabolites

BI 764333

BI 764333 is formed in multiple nonclinical species including mice, rats, minipigs, and monkeys and did not contribute to adverse changes. Only, a hERG assay performed with BI 764333 indicated a minimal likelihood of an effect on the potassium channel.

S-enantiomer of nerandomilast (PD 1420)

The S-enantiomer of nerandomilast is a minor metabolite in humans . The S-enantiomer was shown to be 66-fold less potent at inhibition of PDE4B than nerandomilast and is considered to contribute minimally to pharmacological activity. Plasma levels of nerandomilast in all toxicology studies were measured using a non-chiral method, so actual levels of nerandomilast as the R-enantiomer and its S-enantiomer can only be estimated. For most nonclinical species aside from minipig, in vivo chiral inversion of nerandomilast is lower than in humans.

Impurities

Impurities added to nerandomilast were PD 1424, CD 6352, and PD 1420 (S-enantiomer of nerandomilast). Once daily oral (gavage) administration of nerandomilast for at least 13 weeks in the rat at 1 and 3 mg/kg/day either with or without impurities resulted in no nerandomilast-related changes in any of the parameters examined. Therefore, impurities are considered qualified with respect to their exposure at the higher dose level of 3 mg/kg/day.mPD1420 showed no potential for mutagenicity.

PD 1412 was present in DS used in repeat-dose toxicology, carcinogenicity, and DART. General toxicity was adequately assessed in repeat-dose toxicity studies in monkeys. Nerandomilast containing 0.55% PD 1412 was orally administered for 13 and 39 weeks, with monkeys receiving up to 0.165 mg/kg/day PD 1412 at the nerandomilast high-dose of 30 mg/kg/day. PD 1412 may be considered qualified up to 7.38% based on the weight of 50kg. Considering high-dose levels of 9 mg/kg/day (pregnant rats) and 60 mg/kg/day (male mice), PD 1412 can be qualified at 1.11% and 3.73%, for DART studies and carcinogenicity respectively, based on the weight of 50kg.

Together with carcinogenicity data from transgenic mice, the impurity can be considered as non-mutagenic. Taken together, PD 1412 is considered qualified.

Other actual and potential impurities or degradation products of nerandomilast were assessed No Class 1 impurities or those belonging to the cohort-of-concern were identified. Class 2 and Class 3 impurities were evaluated. All other compounds identified as potential impurities or degradants were assigned Class 4 or Class 5.

Phototoxicity

Nerandomilast tested negative for phototoxic potential in the 3T3 neutral red uptake in vitro assay, suggesting a low potential for phototoxicity.

ERA

The octanol/water partition coefficient was determined using the HPLC screening method in accordance with OECD 117 which is no longer accepted. The CHMP agreed with a commitment to provide the missing studies by July 2026 and no conclusions can currently be drawn on the PBT/vPvB potential of nerandomilast and the potential for secondary poisoning cannot be concluded. Based on available data on the environmental risk assessment, nerandomilast is not expected to pose a risk to surface water, sediment, groundwater, soil or the functioning of STPs.

4.5.2. Conclusions

The nonclinical package submitted for nerandomilast for MAA is acceptable.

Pharmacology studies demonstrate general anti-inflammatory and antifibrotic activities, which support the proposed indications.

The pharmacokinetics of nerandomilast were well characterised in a series of *in vitro* and *in vivo* studies.

The toxicology program included repeat-dose toxicity in rats, minipigs, and cynomolgus monkeys in studies of up to 26, 39, and 39 weeks, respectively. In the repeat-dose studies, vasculopathy was the primary nerandomilast-related finding observed, and is considered due to PDE4i in nonclinical species.

Adverse vascular effects observed in rats and in minipigs affected various tissues (i.e., mesentery and GI tract in rats, heart and lung in minipigs). In long-term studies, no adverse vascular changes were observed in rats at 2 mg/kg/day, and vascular changes were observed in one minipig at 3 mg/kg/day (both equivalent to human exposure, based on AUC at the MRHD) as stated in SmPc section 5.3.

Changes observed in the menstrual cycles of monkeys are considered of potential relevance to humans. 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. These findings have been adequately mentioned in the SmPC section 4.6.

The Applicant has committed to submitting the water solubility test, the dissociation constants in water test, and the octanol/water coefficient study as a Post-Authorisation Commitment by July 2026.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant also provided details of internal GCP audits and findings upon CHMP request as described earlier in this report. The CHMP concluded that the GCP violation in 3 sites in China for both pivotal trials did not impact the outcome of the trials thus no action was taken during assessment.

5.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 2 Therapeutic exploratory					
1305-0013	RD/DB/PC - 12-week treatment period with day 1-week follow-up period	Product 18 mg bid orally	Adults ≥40 with IPF not on SoC antifibrotic treatment or Adults ≥40 with IPF receiving treatment with antifibrotic SoC of nintedanib or pirfenidone.	Efficacy, safety and tolerability of nerandomilast in patients with IPF. The primary endpoint in this trial was the change from baseline in FVC at 12 weeks [mL].	233 screened, 147 randomised and treated. AF 18 mg oral bid: 49/42 AF placebo oral bid: 25/25 non-AF 18 mg oral bid: 48/44 non-AF placebo oral bid: 25/25
Phase 3 Therapeutic confirmatory					
FIBRONEER-IPF 1305-0014	RD/DB/PC - 52-week treatment period followed by treatment period B in which patients continued randomised blinded treatment for a variable duration. Max total treatment 20.8 months.	Product 9 mg or 18 mg bid orally	Adults ≥40 with IPF not on SoC antifibrotic treatment or Adults ≥40 with IPF receiving treatment with antifibrotic SoC of nintedanib or pirfenidone.	Efficacy and safety of nerandomilast 9 mg and 18 mg bid in patients with IPF in addition to SoC treatment. The primary endpoint was the absolute change from baseline in FVC [mL] at Week 52	1719 screened. 1177 randomised and treated. 9 mg oral bid : 392/383 18 mg oral bid: 392/375 Placebo oral bid: 393/380
FIBRONEER-ILD 1305-0023	Treatment period A: 52-weeks with 1 week follow-up. Treatment period B: Subsequent to A for variable duration	Product 9 mg or 18 mg bid orally	Adults ≥18 with PPF not on SoC antifibrotic treatment or adults ≥40 with IPF receiving treatment with antifibrotic SoC of nintedanib.	Efficacy and safety of nerandomilast 9 mg and 18 mg bid in patients with IPF in addition to SoC treatment. The primary endpoint was the absolute change from baseline in FVC [mL] at Week 52	Participants randomised, treated and analysed: 1,176 9 mg oral bid: 393/371 18 mg oral bid: 391/372 Placebo oral bid: 392/380

RD = randomised; DB = double blind; PC = placebo controlled; bid = bis in die (Twice daily); IPF = Idiopathic pulmonary fibrosis; SOC = Standard of Care

5.2. Clinical pharmacology

5.2.1. Methods

The bioanalytical assays showed good overall performance, and the results obtained were of the required quality and integrity.

5.2.2. Pharmacokinetics

5.2.1.1. Introduction

The clinical development program for nerandomilast encompasses 20 Phase I studies, one Phase II study, and two Phase III studies. The Phase I studies included four single rising dose (SRD) / multiple rising dose (MRD) studies, three drug-drug interaction (DDI) studies, three regional PK studies, three relative bioavailability (BA)/bioequivalence (BE) studies, two food effect (FE) studies, two special population studies, one thorough QT study, one absolute BA study and one hADME study. Sparse PK samples were collected in the Phase II and Phase III studies in the target patient population.

5.2.1.2. Population PK

The final population PK analysis built on work conducted in a previous population PK analysis focused on subjects with IPF, by including new data from patients with PPF. The dataset included data from six Phase 1 studies in healthy subjects and two Phase III studies in patients with IPF and PPF.

The base model was a three-compartment disposition model with sequential zero- and first-order absorption, and linear elimination. The base model included the effect of body weight on all clearance (CL/F, Q3/F, and Q4/F) and volume (V2/F, V3/F, and V4/F) parameters using the fixed allometric exponents of 0.75 and 1, respectively. The reduced covariate nerandomilast model included the effects of Chinese and Japanese ethnicity, eGFR, bilirubin, concomitant use of nintedanib or pirfenidone, and diagnosis of IPF or PPF on CL/F, and the effects of Chinese and Japanese ethnicity, sex, and diagnosis of IPF or PPF on V2/F.

The reduced covariate nerandomilast model (within the combined enantiomer model) was used for simulations. Parameter estimates of this model are presented in **Table *6*** (fixed effects) and **Table 7** (random effects), respectively. Fixed and random effect parameters were estimated with reasonable precision as judged by the width of the asymptotic and SIR CIs. No model misspecification was evident in plots of nerandomilast concentration observations versus population and individual predictions in the overall population.

Table 6: Reduced Covariate Nerandomilast Model (Run 550B): Fixed effect parameter estimates

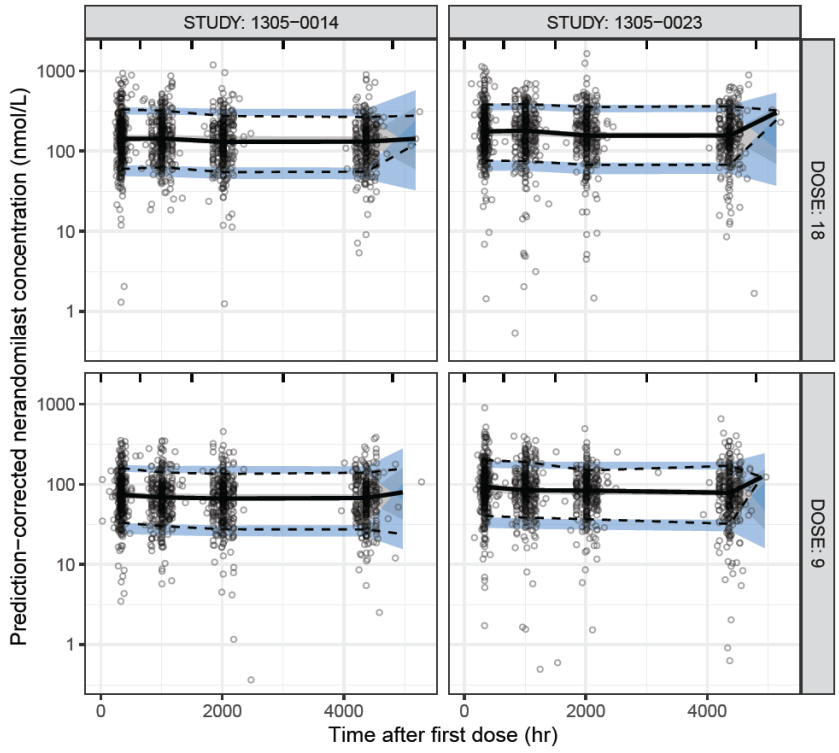
			Model		SIR	
			Estimate	95% CI	Median	95% CI
Structural model parameters						
CL/F (L/h)	$\exp(\theta_1)$	Apparent clearance	15.1	14.1, 16.2	15.2	14.3, 16.3
V2/F (L)	$\exp(\theta_2)$	Apparent central volume	90.8	83.7, 98.5	91.7	83.4, 98.5
V3/F (L)	$\exp(\theta_3)$	First apparent peripheral volume	17.8	13.0, 24.5	17.5	14.2, 20.7
D1 (h)	$\exp(\theta_4)$	Duration of zero-order absorption	0.672	0.591, 0.764	0.672	0.564, 0.796
KA (1/h)	$\exp(\theta_5)$	First-order absorption rate constant	4.86	3.68, 6.42	4.84	3.74, 6.41
Q3/F (L/h)	$\exp(\theta_6)$	Apparent V2/F-V3/F intercompartmental clearance	0.545	0.373, 0.798	0.530	0.323, 0.723
V4/F (L)	$\exp(\theta_7)$	Second apparent peripheral volume	29.4	25.1, 34.3	29.6	25.7, 32.9
Q4/F (L/h)	$\exp(\theta_8)$	Apparent V2/F-V4/F intercompartmental clearance	4.88	4.11, 5.78	4.94	4.16, 5.65
Covariate effect parameters						
CL/F ~ Chinese	$\exp(\theta_9)$	Chinese effect on CL/F	0.900	0.834, 0.971	0.900	0.827, 0.963
CL/F ~ Japanese	$\exp(\theta_{10})$	Japanese effect on CL/F	0.857	0.783, 0.938	0.849	0.789, 0.937
CL/F ~ eGFR	$\exp(\theta_{13})$	eGFR effect on CL/F	1.35	1.25, 1.45	1.34	1.24, 1.45
CL/F ~ bilirubin	$\exp(\theta_{16})$	Bilirubin effect on CL/F	0.914	0.879, 0.951	0.916	0.883, 0.965
CL/F ~ nintedanib	$\exp(\theta_{17})$	Nintedanib effect on CL/F	1.03	0.998, 1.07	1.04	0.999, 1.07
CL/F ~ pirfenidone	$\exp(\theta_{18})$	Pirfenidone effect on CL/F	1.48	1.40, 1.56	1.49	1.42, 1.58
CL/F ~ population	$\exp(\theta_{19})$	Patient effect on CL/F	0.752	0.693, 0.816	0.749	0.694, 0.819
V2/F ~ population	$\exp(\theta_{20})$	Patient effect on V2/F	1.60	1.37, 1.87	1.60	1.41, 1.82
V2/F ~ sex	$\exp(\theta_{21})$	Female effect on V2/F	0.848	0.783, 0.919	0.853	0.796, 0.940
V2/F ~ Chinese	$\exp(\theta_{22})$	Chinese effect on V2/F	0.892	0.755, 1.05	0.891	0.754, 1.04
V2/F ~ Japanese	$\exp(\theta_{23})$	Japanese effect on V2/F	0.699	0.539, 0.907	0.676	0.566, 0.828

Table 7: Reduced Covariate Nerandomilast Model (Run 550b): Random effect parameter estimates

		Model			SIR	
		Estimate	95% CI	Shrinkage (%)	Median	95% CI
Interindividual variance parameters						
IIV-CL/F	$\Omega_{(1,1)}$	0.123 [CV%=36.1]	0.102, 0.144	20.5	0.122	0.109, 0.141
IIV-V2/F	$\Omega_{(2,2)}$	0.133 [CV%=37.7]	0.0429, 0.223	69.1	0.140	0.107, 0.185
IIV-D1 (Phase 1)	$\Omega_{(3,3)}$	0.520 [CV%=82.6]	0.250, 0.789	61.6	0.541	0.377, 0.999
Interindividual covariance parameters						
CL/F-V2/F	$\Omega_{(2,1)}$	0.0608 [Corr=0.476]	0.0235, 0.0981	-	0.0617	0.0437, 0.0874
Residual variance						
Proportional residual error (Phase 1)	$\Sigma_{(1,1)}$	0.0590 [CV%=24.3]	0.0474, 0.0705	4.70	0.0590	0.0548, 0.0629
Additive residual error (Phase 1)	$\Sigma_{(2,2)}$	0.374 [SD=0.611]	0.239, 0.508	4.70	0.384	0.299, 0.480
Proportional residual error (Phase 3)	$\Sigma_{(3,3)}$	0.153 [CV%=39.1]	0.143, 0.163	9.02	0.153	0.145, 0.160

Parameters estimated in the log-domain were back-transformed for clarity
CI: confidence interval; Corr: correlation coefficient; CV: coefficient of variation; SD: standard deviation; SE: standard error; SIR: sampling importance resampling
Model CIs = estimate ± 1.96 · SE
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100
CV% of sigmas = sqrt(estimate) · 100
The model CIs were determined from the asymptotic standard errors of the estimates.
The SIR CIs were determined from the 2.5th and 97.5th percentiles of the SIR resamples.
Source code: pk-reduced-cov-R-table.R
Source file: pk-param-reduced-cov-R-random-550b.tex

Figure* 2** shows the longitudinal VPC, generated using the reduced covariate nerandomilast model, of nerandomilast concentrations from the Phase III trials stratified by study and dose. ***Figure 2 shows the longitudinal VPC, generated using the reduced covariate combined enantiomer model, of S-enantiomer concentrations. These show that simulated nerandomilast and S-enantiomer concentrations were similar to observed concentrations at the 10th, 50th, and 90th percentiles across most of the concentration-time profiles, indicating that the respective PK models described the data well.

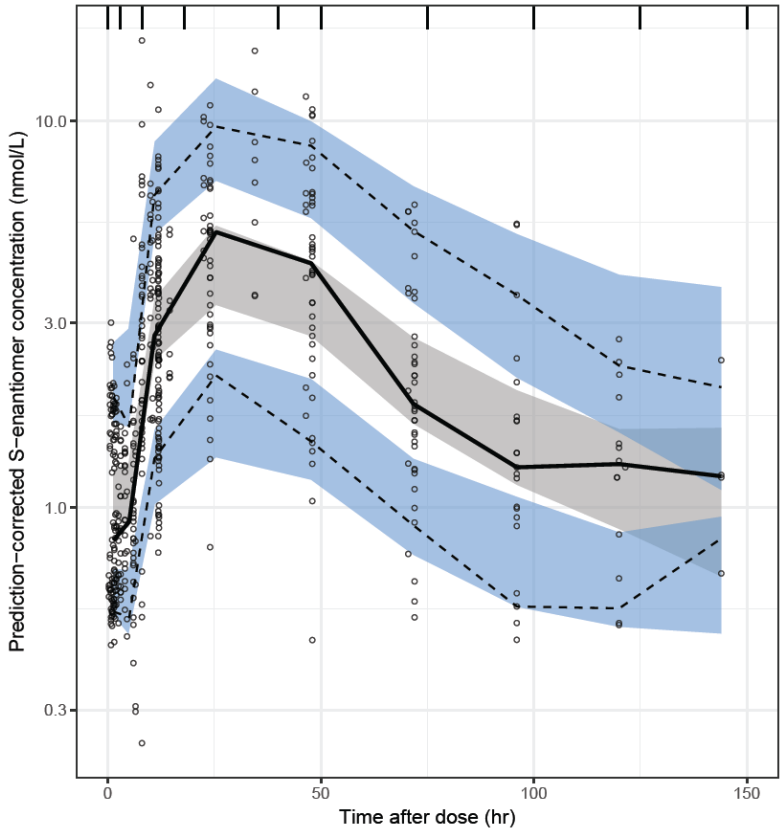


Source code: pk−vpc−R−final.R
Source graphic: deliv/figure/pk/vpc/550b/pcvpc−550b−RBI−phase−3−study−dose.pdf

Figure 4: Reduced Covariate Nerandomilast Model: Visual predictive check (VPC) of nerandomilast concentration from Studies 1305-0014 and 1305-0023 versus time after first dose stratified by study and nerandomilast dose.

The black lines represent the median (solid) or 10th / 90th percentiles of the observed data. The shaded areas represent the 95% confidence interval for median (gray) or 10th / 90th (blue) percentiles of simulated data. Open circles represent prediction-corrected observed concentration data. Black tick marks represent bin locations.

Figure *2*: Reduced Covariate Nerandomilast Model: Visual predictive check (VPC) of nerandomilast concentration from Studies 1305-0014 and 1305-0023 versus time after first dose stratified by study and nerandomilast dose.



Source code: pk−vpc−S−final.R
Source graphic: deliv/figure/pk/vpc/923b/longitudinal−vpc−923b−combined.pdf page: 1

Figure S163: Reduced Covariate Combined Enantiomer Model: Visual predictive check (VPC) of S-enantiomer concentration versus time after dose with observed data points.

The black lines represent the median (solid) or 10th / 90th percentiles of the observed data. The shaded areas represent the 95% confidence interval for median (gray) or 10th / 90th (blue) percentiles of simulated data. Open circles represent prediction-corrected observed concentration data. Black tick marks represent bin locations.

Figure 3: Reduced Covariate Combined Enantiomer Model: Visual predictive check (VPC) of S-enantiomer concentration versus time after dose with observed data points.

5.2.1.3. Absorption

After single oral doses of 9 mg and 18 mg, nerandomilast was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.00 – 1.25 hours post-dose (range 0.5-4 hours) (Trials 1305-0037 and 1305-0051).

Absolute bioavailability (Trial 1305-0030)

This was an open-label, non-randomised, single period, single arm trial in 8 healthy male volunteers. Study treatments were as follows:

- Treatment T: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C1, fasting
- Treatment R: 10 µg (10 mL) of nerandomilast (C-14) as IV solution given as 15-min IV infusion at 1.5 hour after the administration of oral dose

Based on the ANOVA statistical model of adjusted gMean ratios of dose-normalised AUC0-∞ values, the absolute oral bioavailability of nerandomilast administered as an 18 mg oral tablet was 73.15% (90% CI: 67.32%, 79.48%).

Food effects

The effect of food on different tablet formulations was assessed in trials 1305-0020 for TF I, 1305-0028 for Formulation C1, and 1305-0039 for Formulation C2 (marketed formulation).

Food effect with TF I (1305-0020)

This was an open-label, randomised, single dose, two-period, two-sequence crossover trial in 12 healthy male volunteers. Study treatments were as follows:

- Treatment T: 4 x 6 mg tablets of nerandomilast as trial formulation I (TF I), after a high-fat, high-caloric breakfast
- Treatment R: 4 x 6 mg tablets of nerandomilast as trial formulation I (TF I), after an overnight fast of at least 10 hours (fasted)

The statistical evaluation showed that the adjusted gMean for AUC0-tz and AUC0-∞ were comparable under fed conditions compared to fasted conditions, while the gMean for Cmax was reduced by 20.9% under fed condition. The 90% CI of the gMean ratio of test/reference for AUCs were within the bioequivalence range suggesting food does not impact the overall exposure of nerandomilast when administered as TF I.

Food effect with Formulation C1 (Trial 1305-0028)

This was an open-label, randomised, single-dose, two-way crossover trial in 24 healthy subjects. Study treatments were as follows:

- Treatment T1: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C1, after an overnight fast of at least 10 hours (fasted)
- Treatment T2: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C1, after a high-fat, high-caloric breakfast (fed)

The statistical evaluation showed that the adjusted gMean for Cmax, AUC0-tz and AUC0-∞ were comparable under fed conditions compared to fasted conditions. The 90% CI of the gMean ratio of test/reference for AUCs were within 80.00% to 125.00%, suggesting food does not impact nerandomilast exposure when administered as Formulation C1.

Food effect with Formulation C2 (Trial 1305-0039)

This was an open-label, randomised, single dose, two-period, two-sequence crossover design in 18 healthy subjects. Study treatments were as follows:

- Treatment T: 1 x 18 mg tablet of nerandomilast as Formulation C2, after a high-fat, high-caloric breakfast (fed)
- Treatment R: 1 x 18 mg tablet of nerandomilast as Formulation C2, after an overnight fast of at least 10 hours (fasted)

Statistical evaluation indicated the gMean for Cmax was decreased by 14% when it was administered in the fed state compared to the fasted state, while the gMean nerandomilast total exposure (AUC0-tz and AUC0-∞) was increased by 15% when administered with food. The 90% CI of the gMean ratio of test/reference for AUCs were both within bioequivalence range of 80.00-125.00% suggesting food had no impact on the total exposure of nerandomilast when administered as Formulation C2.

5.2.1.4. Bioequivalence

Formulation development for oral nerandomilast comprises a liquid oral formulation (powder for oral solution [PfOS]) for initial clinical trials with wide dose ranges, and four different immediate release (IR) tablet formulations (TF I, TF II, Formulation C1 and Formulation C2) with multiple dosage strengths that were used in different phases of clinical development. TF I (uncoated tab) was used in early Phase I trials. TF II (film-coated tab) was developed for Phase II trials. Formulation C1 (film-coated tablet) was developed for Phase III trials and late Phase 1 trials. The final commercial formulation is Formulation C2 (film-coated tablet).

Relative bioavailability of Formulation C1 vs TF II (Trial 1305-0028)

This was assessed with an open-label, randomised, single-dose, two-way crossover trial in 24 healthy subjects. Study treatments were as follows:

- Treatment T1: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C1, fasted
- Treatment R: 3 x 6 mg film-coated tablets of nerandomilast as TF II formulation, fasted

Based on the statistical evaluation, Formulation C1 had 15.6% and 22.0% higher Cmax and AUC0-tz, respectively, compared to TF II formulation. However, Formulation C1 had 4.99% lower AUC0-∞. The 90% CI of the ratios were within 80.00% to 125.00% for AUC0-∞, but not for Cmax and AUC0-tz. This is likely due to one subject with inexplicably low exposure under TF II formulation treatment and AUC0-∞ could not be estimated. Sensitivity analysis without this subject resulted in adjusted gMean ratios of 94.47% and 92.85% for AUC0-tz and Cmax, respectively, where 90% CIs for both AUC0-tz and Cmax were within 80% to 125%.

Pivotal bioequivalence of high dose (18 mg) Formulation C2 vs C1 (Trial 1305-0037)

This was an open-label, randomised, single-dose, two-period, two-sequence crossover study in 64 healthy subjects. Study treatments were as follows:

- Treatment T: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C2, fasted
- Treatment R: 1 x 18 mg film-coated tablet of nerandomilast as Formulation C1, fasted

Statistical evaluation indicated that nerandomilast Cmax was comparable between Formulation C1 and Formulation C2 with a gMean ratio of 113.32% (90% CIs 102.70 - 125.05%). Nerandomilast AUC was within bioequivalence range between Formulation C1 and C2.

Pivotal bioequivalence of low dose (9 mg) Formulation C2 vs C1 (Trial 1305-0051)

This was an open-label, randomised, single-dose, two-period, two-sequence crossover study in 64 healthy subjects. Study treatments were as follows:

- Treatment T: 1 x 9 mg film-coated tablet of nerandomilast as Formulation C2, fasted
- Treatment R: 1 x 9 mg film-coated tablet of nerandomilast as Formulation C1, fasted

Statistical evaluation indicated that bioequivalence was established between Formulation C1 and Formulation C2 after oral administration of 9 mg nerandomilast, as the 90% CI of the gMean ratios for Cmax, AUC0-tz, and AUC0-∞ were all within 80.00% to 125.00% range.

Nerandomilast administration as dispersion: Dissolution data using standard conditions at pH 1.2, 4.5 and 6.8 showed comparable dissolution between the tablet as a dispersion vs. the whole tablet. Stability of the dispersion was demonstrated for up to 24 hours. The data indicate that there is no significant impact expected on bioavailability in case the tablet is administered as a dispersion.

5.2.1.5. Distribution

Nerandomilast disposition is described as biphasic: a rapid distribution phase and a slower elimination phase (Trials 1305-0001 and 1305-0011). The volume of distribution was 93.9 L (Vss after IV dose) and the apparent volume of distribution was similar after single or multiple oral administrations. In the final popPK model, the apparent central, first peripheral and second peripheral volumes were 90.8 L, 17.8 L and 29.4L, respectively.

Plasma protein binding of nerandomilast was 76.9% with no evidence of saturation over the concentration range tested *in vitro* (100 – 3000 nM). Nerandomilast is primarily bound to human serum albumin in human plasma.

Nerandomilast shows preferential distribution into plasma. In the human ADME (mass balance) study, the radioactivity concentration in whole blood was ~0.6 to 0.8 of the concentrations in plasma (Trial 1305-0016).

5.2.1.6. Metabolism

Nerandomilast is mainly metabolised by CYP3A; oxidation by CYP3A was estimated to contribute to ~70% of hepatic metabolic clearance. Multiple UGT isoforms, including UGTs 1A3, 1A8, 1A9, 2B4, and 2B7, were also found to contribute to the direct glucuronidation of nerandomilast.

Metabolite profiling after single dose

Metabolic patterns in plasma, urine and faeces were investigated in the human ADME trial after a single dose oral administration of 18 mg [^{14}C]-nerandomilast in 6 healthy male subjects (Trial 1305-0016). Eighteen metabolites were identified across all matrices, 12 of which were detected in plasma.

In plasma, nerandomilast was the most abundant circulating drug-related component, representing 51.3% of total plasma radioactivity (AUC0-36). The most abundant metabolites in plasma were glucuronide metabolite M624(1) and di-oxidative metabolite BI 764333, which represented 15.6% and 7.1% of total plasma radioactivity (AUC0-36), respectively.

Metabolite profiling after multiple dose

In trial 1305-0011, metabolites were measured in the 12 mg bid nerandomilast treatment group. At steady state, nerandomilast was the predominant compound circulating in human plasma, accounting for ~72% of the total drug-related material (TDRM). 11 metabolites were identified in human plasma at steady state, however, BI 764333 (di-oxidation metabolite) was the only major human metabolite as it represented 12% of TDRM (AUC0-24). The next most abundant metabolite identified was CD 6352, a product of mono-oxidation, which represented only 6.6% of TDRM in these plasma samples.

Interconversion

As nerandomilast molecule contains a chiral sulfur within the sulfoxide group, there is potential for *in vivo* chiral inversion of administered nerandomilast (as the chirally pure R-enantiomer) to the S-enantiomer (PD 1420).

Following oral administration of nerandomilast, the R-enantiomer was identified as the predominant enantiomer present in human plasma. Although chiral inversion of the sulfoxide to S-enantiomer was identified in human plasma, the S-enantiomer was determined to be a minor metabolite (PD 1420), representing 2.7%, 3.95%, and 3.3% of total plasma radioactivity exposure based on AUC0-36, AUC0-96 and AUC0-inf, respectively (Trial 1305-0016).

5.2.1.7. Elimination

The terminal half-life of nerandomilast was observed to be around 10 – 17 h and was similar after a single dose and multiple bid doses. Based on this, it can be expected that steady state would be reached in ~3 – 4 days. The clearance of nerandomilast was comparable after single dose (285 mL/min, 1305-0028) and multiple doses at steady state (274 mL/min, 1305-0033). In the final popPK model, apparent clearance was 15.1 L/h (251.7 mL/min).

Human ADME (mass balance) study (Trial 1305-0016)

This was a phase I, open-label, non-randomized, single-dose, single-arm, single-period study in 6 healthy male subjects. Each subject received a single dose administration of 18 mg nerandomilast (C-14) oral solution.

The gMean total cumulative recovery of [^{14}C]nerandomilast-EQ in urine and faeces was 95.0%, and individual values ranged from 89.9% to 98.0% of the administered dose. The contribution of urinary excretion was 36.4%, whereas 58.0% was excreted in faeces. 11.9% of the administered dose was excreted as unchanged parent drug in urine.

5.2.1.8. Dose proportionality and time dependency

Dose proportionality

Trial 1305-0001 was a single rising dose study in 70 healthy male subjects. The doses tested ranged from 0.02 – 24 mg nerandomilast. Nerandomilast exposure (Cmax and AUC0-∞) increased proportionally with dose over the dose range of 0.06 to 24 mg. Time to peak (tmax), t1/2, CL/F, Vz/F of nerandomilast, when evaluable, were dose independent.

Trial 1305-0011 was a single and multiple rising dose trial in 42 healthy males with doses. Overall, the total exposure appeared to increase dose-proportionally over the ranges of evaluated doses: single doses of 6 mg to 48 mg in the SRD and MRD part combined, and multiple doses of 6 mg and 12 mg bid in the MRD part.

Across trials 1305-0002, 1305-0011, and 1305-0033, based on the non-chiral bioanalytical assay, nerandomilast exposure after multiple doses was deemed dose-proportional between 1 mg to 18 mg bid dosing, since the dose-normalized Cmax,ss and AUCτ,ss were similar across these evaluated dose groups.

Time dependency

The clearance of nerandomilast is comparable after single dose (285 mL/min, Trial 1305-0028) and multiple doses at steady state (274 mL/min, Trial 1305-0033).

In trial 1305-0002, healthy male subjects received 1 mg or 6 mg nerandomilast bid for 14 days. The gMean accumulation ratio for AUC was 1.60 and 1.69 for 1 mg and 6 mg bid, respectively. The gMean accumulation ratio Cmax was 1.19 and 1.45 for 1 mg and 6 mg bid, respectively.

In the multiple dose part of trial 1305-0011, healthy male subjects received 6 mg or 12 mg bid over 14 days. The gMean accumulation ratio for AUC was 1.85 and 1.68 for 6 mg and 12 mg bid, respectively. The gMean accumulation ratio for Cmax was 1.60 and 1.52 for 6 mg and 12 mg bid, respectively.

In trial 1305-033, healthy male subjects received 18 mg nerandomilast bid for 14 days. Accumulation ratios were 1.38 and 1.30 for AUCτ and Cmax, respectively as stated in SmPC. The shape of PK profiles of nerandomilast and tmax were similar after the first dose and last dose at steady state, consistent with time-invariant plasma kinetics.

5.2.1.9. Pharmacokinetics in the target population

Phase II study in IPF patients with and without antifibrotic background treatment (Trial 1305-0013)

This was a randomized, double-blind, placebo-controlled, parallel-group study over 12 weeks. Patients with IPF were randomized in a 2:1 ratio to nerandomilast 18 mg bid or placebo. The randomization of patients was stratified by baseline antifibrotic treatment (non-AF stratum: patients not on background antifibrotic treatment at baseline [for at least 8 weeks]; AF stratum: stable antifibrotic treatment with nintedanib or pirfenidone at baseline).

Nerandomilast exposure (pre-dose and post-dose) was similar between patients on nintedanib background treatment and those without any background antifibrotic treatment (**Table 8**). A 35-50% lower exposure was observed for patients on pirfenidone background therapy compared to patients without antifibrotic background treatment. The trend was slightly more pronounced for the predose concentrations compared with post-dose concentrations.

Table 8: Comparison of geometric mean predose and postdose plasma concentrations (nmol/L) of BI 1015550 at Week 4 and Week 12 after multiple oral administration of 18 mg BI 1015550 bid - PKS

	Week 4						Week 12					
	Predose			Postdose			Predose			Postdose		
	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)
Overall	82	162	93.6	78	431	57.2	78	165	71.5	74	446	49.9
Non-AF	40	200	107	39	493	46.9	40	198	57.0	37	497	48.6
AF	42	132	73.9	39	377	63.3	38	136	79.5	37	401	49.1
Nintedanib	20	178	68.0	17	494	49.8	18	171	109	18	507	48.8
Pirfenidone	22	101	64.3	22	305	63.1	20	111	41.9	19	321	36.0

Source data: Tables 15.6.1.1: 1 to 15.6.1.1: 3

Phase III study in IPF patients with and without antifibrotic background treatment (Trial 1305-0014)

This was a Phase III, randomised, double-blind, placebo-controlled, parallel-group study in multiple nations and multiple centers over at least 52 weeks. Patients with IPF were randomized in a 1:1:1 ratio to receive nerandomilast 9 mg bid, nerandomilast 18 mg bid, or placebo bid. The randomization of patients was stratified by baseline antifibrotic treatment (non-AF group: patients not on background antifibrotic treatment for at least 8 weeks at baseline; AF group: stable antifibrotic treatment with nintedanib or pirfenidone for at least 12 weeks at baseline).

The overall steady state Mean pre-dose concentrations of nerandomilast were 62.2 and 131 nmol for 9 and 18 mg bid treatment groups, respectively. Inter-individual variability of nerandomilast pre-dose concentrations was high (gCV range 80.0% to 98.5%).

A 55% (9 mg bid) and 48% (18 mg bid) lower nerandomilast trough exposure was observed in patients on pirfenidone background therapy compared to patients who were not on any antifibrotic background therapy (**Table *9***). Nerandomilast pre-dose plasma concentrations in patients with nintedanib background treatment were comparable to those in non-AF patients.

Table 9: Comparison of predose plasma concentrations (nmol/L) of nerandomilast at Weeks 2, 6, 12, and 26 and overall trough concentration across four PK visits after multiple oral administration of 9 mg or 18 mg bid nerandomilast across different antifibrotic treatment groups

	Week 2			Week 6			Week 12			Week 26			Overall		
	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)
Nera 9 mg bid															
Non-AF	65	85.6	68.8	62	90.1	57.2	57	85.6	66.3	56	74.7	63.0	73	87.6	49.4
AF	202	57.3	93.3	209	52.4	85.8	191	52.5	78.5	194	53.1	86.1	262	56.5	75.4
Nintedanib	116	76.2	68.4	116	70.7	68.1	104	67.7	64.1	111	68.0	75.7	151	73.7	55.6
Pirfenidone	86	39.0	101	93	36.1	82.3	87	38.7	78.2	83	38.2	80.9	111	39.3	77.7
Nera 18 mg bid															
Non-AF	61	161	78.1	66	160	71.2	60	165	78.4	58	151	69.3	76	167	60.3
AF	203	114	92.7	208	116	85.3	179	103	99.8	185	108	88.1	274	122	75.4
Nintedanib	115	152	69.2	117	157	60.1	91	143	70.7	95	139	62.7	156	158	56.1
Pirfenidone	88	77.6	97.3	91	77.6	88.1	88	73.0	107	90	83.0	100	118	86.7	78.4

Source data: Tables 15.6.1.1.1: 2 and 15.6.1.1.1: 3

The reduced nerandomilast plasma exposure in the 9 mg bid group with pirfenidone background therapy may have contributed to a lack of observed treatment effect for the 9 mg bid dose in this subgroup (see Clinical Efficacy for further information).

Phase III study in PPF patients with and without antifibrotic background treatment (Trial 1305-0023)

This was a Phase III, randomized, double-blind, placebo-controlled, parallel-group study in multiple nations and multiple centers over at least 52 weeks. Patients with PPF were randomized in a 1:1:1 ratio to nerandomilast 9 mg bid, nerandomilast 18 mg bid, or placebo bid. The randomization of patients was stratified by baseline antifibrotic treatment (non-AF group: patients not on background treatment with nintedanib for at least 8 weeks at baseline; AF group: stable background treatment with nintedanib for at least 12 weeks at baseline) and by the HRCT pattern ("UIP or UIP-like fibrotic pattern" vs "other fibrotic patterns").

The overall steady state gMean pre-dose concentrations of nerandomilast were 84.8 and 172 nmol for 9 and 18 mg bid treatment groups, respectively. Inter-individual variability of nerandomilast pre-dose concentrations at steady state was generally high (gCV range 73.3% to 105%) in PPF patients.

Nerandomilast pre-dose plasma concentrations in PPF patients with nintedanib background treatment were comparable (11-19% lower) to those not on nintedanib background treatment (**Table 10**).

Table 10: Comparison of predose plasma concentrations (nmol/L) of nerandomilast at Weeks 2, 6, 12, and 26 and overall trough concentration across four PK visits after multiple oral administration of 9 or 18 mg bid neramdomilast across different antifibrotic treatment groups

	Week 2			Week 6			Week 12			Week 26			Overall		
	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)	N	gMean	gCV (%)
Nera 9 mg bid															
Non-nintedanib	172	96.0	85.2	166	91.2	82.6	165	81.7	80.5	145	79.3	85.8	199	92.9	67.5
Nintedanib	110	74.6	89.6	108	73.8	72.6	95	69.4	58.8	84	64.2	136	150	75.2	66.5
Nera 18 mg bid															
Non-nintedanib	164	187	74.3	163	172	69.4	150	157	94.1	142	150	71.9	200	180	59.7
Nintedanib	107	166	76.5	101	135	113	87	137	99.8	93	153	99.0	143	161	68.8

Source data: Tables 15.6.1.1.1: 2 to 15.6.1.1.1: 3

Model-based simulations

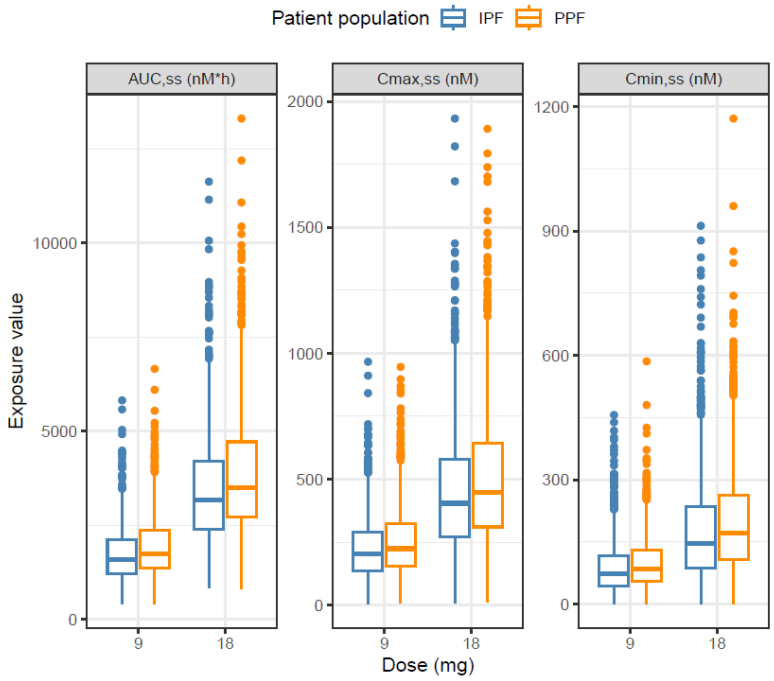
Population-level simulations assessing the distribution of nerandomilast exposures across the IPF and PPF patient population were performed. A summary of predicted nerandomilast exposure metrics at steady state are presented in **Table 11**.

Table 11: Population Level Simulations: Nerandomilast exposure summary statistics stratified by exposure metric and nerandomilast dose.

Summary Metric	9 mg	18 mg
AUC,ss (nM*h)	1660 (811, 3310)	3320 (1620, 6620)
Cmax,ss (nM)	206 (68.2, 521)	413 (136, 1040)
Cmin,ss (nM)	78.0 (21.9, 223)	156 (43.7, 447)

Summary is median (90% distribution interval).
AUC,ss: area under the concentration-time curve for a dosing interval at steady state.
Cmax,ss: maximum concentration in the dosing interval at steady state.
Cmin,ss: minimum concentration in the dosing interval at steady state.
Source code: pk-population-sims.R
Source file: pop-sim-overall.tex

Numerically higher exposures were predicted in the PPF patient population compared to the IPF population with 10.1%, 10.9%, and 17.2% increases in the median nerandomilast AUC,ss, Cmax,ss, and Cmin,ss, respectively (**Figure 4**). These differences were likely attributable to differences in the distributions of other covariates impacting nerandomilast PK, such as sex, bodyweight, Japanese ethnicity, and concomitant pirfenidone use in the IPF population.



Source code: pk−population−sims.R
Source graphic: deliv/figure/pk/popsims/pat−pop−bp.pdf

Figure 10: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and patient population (IPF and PPF).

Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5 × IQR. Points are values beyond 1.5 × IQR. IPF: idiopathic pulmonary fibrosis; PPF: progressive pulmonary fibrosis; AUC,ss: area under the concentration-time curve for a dosing interval at steady state; Cmax,ss: maximum concentration in the dosing interval at steady state; Cmin,ss: minimum concentration in the dosing interval at steady state.

Figure 4: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and patient population (IPF and PPF)

5.2.1.10. Special populations

Renal impairment

Dedicated renal impairment study (Trial 1305-0025)

This was an open-label, non-randomised, individual-matched study to investigate the effect of severe and moderate renal impairment on the PK of nerandomilast. 16 subjects with renal impairment (8 subjects in each moderate and severe renal impairment groups) and 10 subjects with normal renal function as controls (6 subjects were matched to each renal impairment group) were administered a single dose of nerandomilast 18 mg.

Results of the statistical comparison when the renal function of participants was calculated based on BSA-normalised GFR (ml/min/1.73 m^2):

Participants with moderate renal impairment had 3% lower Cmax and 36-37% higher overall exposure (AUC0-tz and AUC0-∞) compared with matched controls with normal renal function. Participants with severe renal impairment had 14% lower Cmax and 29% higher overall exposure compared with matched controls with normal renal function (***Table 12***).

Table 12: Statistical comparison of nerandomilast exposure in subjects with renal impairment to subjects with normal renal function in trial 1305-0025

PK parameter	Renal impairment		Matched control		gMean ratio (T/R; %)	gSE	90% CI	
	n	adjusted gMean	n	adjusted gMean			Lower (%)	Upper (%)
Moderate vs. Normal								
C_{max} [nmol/L]	8	367.36	8	380.43	96.57	1.35	56.80	164.16
AUC_{0-tz} [nmol·h/L]	8	3141.86	8	2285.92	137.44	1.28	89.06	212.12
$AUC_{0-\infty}$ [nmol·h/L]	8	3177.31	8	2333.59	136.16	1.28	88.41	209.69
Severe vs. Normal								
C_{max} [nmol/L]	8	399.46	8	464.19	86.06	1.16	64.88	114.15
AUC_{0-tz} [nmol·h/L]	8	3347.73	8	2590.32	129.24	1.20	91.62	182.31
$AUC_{0-\infty}$ [nmol·h/L]	7	3391.98	8	2638.63	128.55	1.23	87.42	189.02

Source data: [c43226517, Tables 15.5.1: 1 and 15.5.1: 3]

Results of the statistical comparison when the renal function of participants was calculated based on absolute GFR (ml/min):

Participants with moderate renal impairment had 19% lower Cmax and 37-39% higher overall exposure (AUC0-tz and AUC0-∞) compared with matched controls with normal renal function. Participants with severe renal impairment had 21% lower Cmax and 10-14% higher overall exposure compared with matched controls with normal renal function (**Table 13**).

Table 13: Statistical comparison of nerandomilast exposure in subjects with renal impairment to subjects with normal renal function based on absolute GFR (mL/min) in trial 1305-0025

PK parameter	Renal impairment		Matched control		gMean ratio (T/R; %)	gSE	90% CI	
	n	adjusted gMean	n	adjusted gMean			Lower (%)	Upper (%)
Moderate vs. Normal								
C_{max} [nmol/L]	6	382.65	6	469.92	81.43	1.26	53.61	123.67
AUC_{0-tz} [nmol·h/L]	6	3589.79	6	2582.41	139.01	1.25	93.07	207.62
$AUC_{0-\infty}$ [nmol·h/L]	6	3626.30	6	2649.52	136.87	1.24	92.14	203.30
Severe vs. Normal								
C_{max} [nmol/L]	7	385.87	6	487.67	79.13	1.18	56.54	110.74
AUC_{0-tz} [nmol·h/L]	7	3110.18	6	2740.17	113.50	1.17	82.70	155.78
$AUC_{0-\infty}$ [nmol·h/L]	6	3069.45	6	2798.20	109.69	1.20	74.69	161.11

Phase II and III studies (1305-0013, 1305-0014 and 1305-0023)

In Phase II trial 1305-0013, only IPF patients with GFR > 45 mL/min/1.73 m2 (according to CDK-EPI) were included in the study and ~76% of the patients receiving nerandomilast treatment had chronic kidney disease (eGFR value <90 ml/min/1.73m2); the majority with mild renal impairment (65 participants) and 9 participants with moderate renal impairment. Compared with patients with normal renal function, gMean steady state trough levels were 20% and 28% higher in the groups with mild and moderate renal impairment, respectively.

In the Phase III studies 1305-0014 and 1305-0023, patients with eGFR > 30 ml/min/1.73 m^2 (according to the CKD-EPI formula) were allowed to be enrolled. Exploratory subgroup analysis of steady state trough concentrations suggested that IPF or PPF patients with moderate renal impairment had 24-36% and 35-56% higher trough concentrations at 9 mg bid and 18 mg bid dose groups, respectively, compared with IPF/PPF patients with normal renal function, while nerandomilast trough concentrations

were comparable between IPF/PPF patients with mild renal impairment and IPF/PPF patients with normal renal function.

Hepatic impairment

Dedicated hepatic impairment study (Trial 1305-0027)

Trial 1305-0027 was an open-label, non-randomised, parallel, individual-matched study to investigate the effect of mild (Child-Pugh A, C-P A) and moderate (Child-Pugh B, C-P B) hepatic impairment on the PK of nerandomilast. 16 subjects with hepatic impairment (8 subjects in each hepatic impairment group) and 12 subjects with normal hepatic function (4 subjects with normal hepatic function were matched with both subjects with C-P A and C-P B groups) were administered a single oral dose of nerandomilast 18 mg.

Based on the statistical comparison, participants with mild hepatic impairment (C-P A) had 5% higher AUC while Cmax was 17% lower compared with the matched control group (control C-P A) (**Table 14**). In the moderate hepatic impairment group (C-P B), AUC of nerandomilast was 31% higher while Cmax was 31% lower compared with the control group (control C-P B). The higher percentage increase of AUC in moderate hepatic impairment group was likely driven by the relatively low exposure of the corresponding control group (control C-P B), as the observed AUC values were similar among the other three groups.

Table 14: Statistical Comparison of nerandomilast exposure with subjects with hepatic impairment to subjects with normal hepatic function in trial 1305-0027

PK parameter	Hepatic impairment		Matched control		gMean ratio (T/R; %)	gSE	90% CI	
	n	adjusted gMean	n	adjusted gMean			Lower (%)	Upper (%)
Mild (C-P A) vs. Normal (control C-P A)								
C_{max} [nmol/L]	8	409.35	8	491.48	83.29	1.18	60.47	114.71
AUC_{0-tz} [nmol·h/L]	8	2913.55	8	2786.43	104.56	1.07	91.89	118.98
$AUC_{0-\infty}$ [nmol·h/L]	8	2964.46	8	2811.48	105.44	1.07	92.36	120.38
Moderate (C-P B) vs. Normal (control C-P B)								
C_{max} [nmol/L]	8	277.67	8	404.46	68.65	1.23	46.48	101.41
AUC_{0-tz} [nmol·h/L]	8	2837.74	8	2168.11	130.89	1.22	89.34	191.75
$AUC_{0-\infty}$ [nmol·h/L]	8	2866.58	8	2186.53	131.10	1.22	89.96	191.05

Source data: [c42811255, Tables 15.5.1: 1 and 15.5.1: 3]

Gender

In exploratory subgroup analyses in the Phase III trials (1305-0014 and 1305-0023), comparable nerandomilast trough concentrations were observed between male and females. Sex was included as a covariate in the popPK model, impacting V2/F of nerandomilast. Overall, nerandomilast Cmax,ss was predicted to be slightly higher in female versus male subjects, whereas Cmin,ss was slightly lower but the difference is not considered clinically relevant.

Ethnic factors

The PK of nerandomilast following a single dose of 18 mg in Chinese (Trial 1305-0024) and Japanese (Trial 1305-0038) healthy volunteers was compared to that of Caucasian healthy volunteers (Trial 1305-0028). AUC0-∞ and Cmax in Chinese subjects were 1.4-fold and 1.7-fold higher, respectively, compared

to Caucasian subjects (**Table 15**). Similarly, nerandomilast AUC0-∞ and Cmax in Japanese subjects were 1.6 and 1.8-fold higher, respectively, compared to Caucasian healthy volunteers.

Table 15: Summary of PK parameters of nerandomilast after a single oral dose administration of 18 mg nerandomilast (Formulation C1) in healthy Caucasian (Trial 1305-0028) and Asian subjects (trials 1305-0024 and 1305-0038)

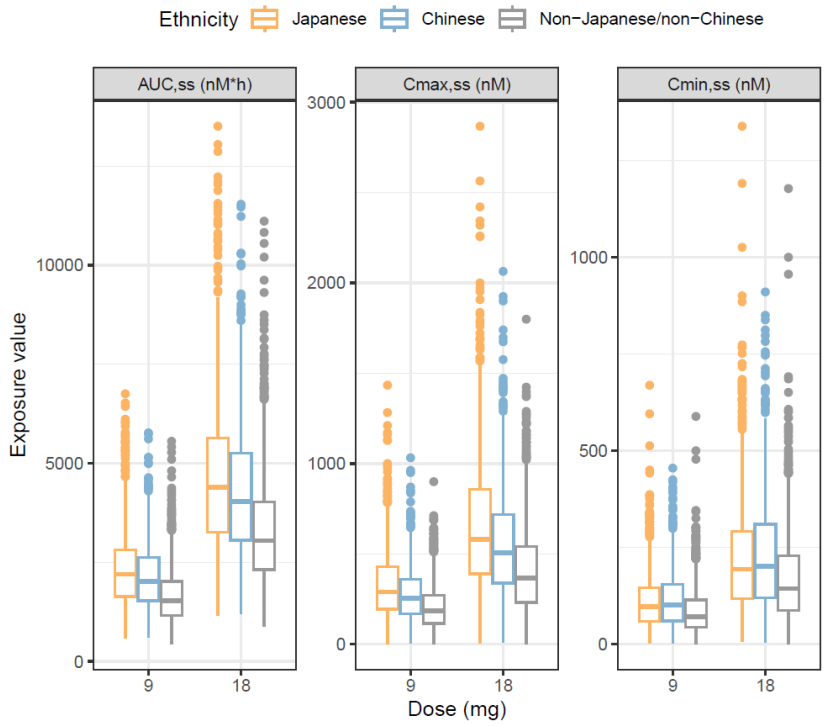
	Trial 1305-0028 Caucasian (N=23)		Trial 1305-0024 Chinese (N=12)		Trial 1305-0038 Japanese (N=6)	
	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)
AUC_{0-tz} [nmol·h/L]	2310	29.6	3240	34.0	3730	53.0
$AUC_{0-\infty}$ [nmol·h/L]	2340	30.0	3270	33.9	3740	52.8
C_{max} [nmol/L]	352	35.4	587	40.1	628	138
t_{max} [h][1]	1.25	(0.75, 3.00)	1.25	(0.500, 2.50)	0.750	(0.500, 4.00)
$t_{1/2}$ [h]	16.7	124	11.4	75.7	10.2	24.0
CL/F [mL/min]	285	30.0	204	33.9	179	52.8
V_z/F [L]	413	112	201	70.6	157	53.1

[1] For t_{max}, median and range (Min – Max) are provided

Source data: [c40013550-02, Table 15.6.2: 2], [c41893590, Tables 15.6.3: 2 and 15.6.3: 8], [c43837553, Tables 15.6.3: 1 and 15.6.3: 7]

In exploratory subgroup analysis in the Phase III trial 1305-0014, nerandomilast pre-dose plasma concentrations in IPF patients were approximately 47% and 41% higher in Asian patients for the 9 mg bid and 18 mg bid dose groups, respectively, compared with those observed in White patients. In PPF patients (trial 1305-0023), nerandomilast pre-dose plasma concentrations were approximately 43% higher in Asian patients in 9 mg bid dose group and 10% higher in 18 mg bid dose group when compared to White patients.

In the population PK analysis, most subjects were White (62.6%) or Asian (35.1%) and 39 subjects (2.4%) had a race categorized as Other. Across all subjects, there were 186 (11.3%) Chinese subjects and 208 (12.6%) Japanese subjects. Chinese and Japanese ethnicities were identified as covariates impacting both CL/F and V2/F. Model-based simulations predicted Japanese patients to have 44.7%, 57.9%, and 34.7% higher median nerandomilast AUC,ss, Cmax,ss, and Cmin,ss, respectively, compared to the non-Japanese/non-Chinese population (**Figure 5**). Increases in exposure were also predicted in the Chinese population with 32.9%, 37.7%, and 40.3% increases in the median nerandomilast AUC,ss, Cmax,ss, and Cmin,ss, respectively, relative to the non-Japanese/non-Chinese population (**Figure 5**).



Source code: pk−population−sims.R
Source graphic: deliv/figure/pk/popsims/jpnchn−bp.pdf

Figure 8: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and ethnicity (Japanese, Chinese, and non-Japanese/non-Chinese).

Median values are designated by a solid line in the center of the box. Boxes indicate the inter-quartile range (IQR) with whiskers extending to 1.5 × IQR. Points are values beyond 1.5 × IQR. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; Cmax,ss: maximum concentration in the dosing interval at steady state; Cmin,ss: minimum concentration in the dosing interval at steady state.

Figure 5: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and ethnicity (Japanese, Chinese, and non-Japanese/non-Chinese).

Additional simulations in the safety exposure-response models for diarrhoea and weight loss >=5% showed that although the exposures are higher in Asian patients with low body weight (40 kg), the predicted diarrhoea rate is lower than non-Japanese and non-Chinese patients with normal body weight (70 kg). This phenomenon is attributed to an Asian race covariate effect identified in the diarrhoea exposure-response model and is consistent with observed safety events that Asian patients had an overall lower incidence of diarrhoea compared to non-Asian patients at 18 mg, despite a generally higher exposure. Similarly, the incidence of weight loss (≥ 5%) in Asian patients with low body weight are comparable to non-Asian patients with normal body weight when administered nerandomilast 18 mg bid.

Weight

Exploratory subgroup analysis in the phase III trial in IPF patients (1305-0014) indicated that patients with lower body weight (< 65 kg) have slightly higher (16- 20%) nerandomilast trough concentrations at steady state compared with those with higher body weight (≥ 65 kg). A similar trend was observed in PPF trial 1305-0023 in the 9 mg dose group, where patients with lower body weight (< 65 kg) had approximately 26% higher nerandomilast trough concentrations compared to patients with body weight ≥65 kg. However, comparable (0.96 fold) nerandomilast predose concentrations were observed between the two weight groups in the 18 mg bid treatment group.

In terms of safety, patients with low body weight (40 kg) are not expected to have a significant increase in exposure-related safety events (diarrhoea and weight loss ≥5%) compared to patients with normal body weight (70 kg). In terms of efficacy, subjects with a body weight of 150 kg who are administered 18 mg bid are predicted to have a median Cmin,ss of 106 nM. In the efficacy ER model, Cmin,ss was identified as the exposure metric to describe changes in FVC. As the predicted median Cmin,ss of 106 nM is above the observed values of Cmin,ss for 9 mg bid in both IPF or PPF patients without background antifibrotic treatment (gMean of 87.6 nM and 92.9 nM, respectively), which is efficacious, it is therefore expected that subjects with high body weights will still remain efficacious on 18 mg bid.

Elderly

In IPF patients (Trial 1305-0014), comparable nerandomilast trough concentrations were observed between older patients (≥65 years) and younger patients (<65 years) for both 9 mg bid and 18 mg bid dose groups in the exploratory subgroup analysis. In PPF patients (1305-0023), nerandomilast exposures were comparable between older patients (≥65 years) and younger patients (<65 years) in the 9 mg bid group, while a slightly higher (around 1.31-fold) exposure was observed in older patients (≥65 years) compared with younger patients (<65 years) in the 18 mg bid group.

In the popPK analysis dataset, the median age of IPF patients receiving nerandomilast was 71 years (range 44 to 90 years), and the median age of PPF patients receiving nerandomilast was 68 years (range 27 to 88 years). Age was not identified as a significant covariate on nerandomilast PK.

The number of elderly patients in different age ranges included in the clinical studies is provided in the table below.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
All PK Trials	30/544	10/544	0/544
1305-0012	6/15	5/15	0/15
1305-0025	11/26	5/26	0/26
1305-0027	13/28	0/28	0/28

5.2.1.11. Pharmacokinetic interaction studies

***In vitro* studies**

Several *in vitro* studies were conducted to determine the DDI potential of nerandomilast. The results are summarised below:

- CYP3A was identified as the primary enzyme involved in nerandomilast metabolism.
- UGTs contribute to nerandomilast metabolism but no single UGT isoform contributes to ≥ 25% of metabolism.
- Nerandomilast is a substrate of P-gp. Nerandomilast is not a substrate of BCRP or the other uptake transporters (OATP1B1, OATP1B3, OAT1, OAT3, and OCT2).
- Nerandomilast is not expected to inhibit CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4,

both reversibly or in a time-dependent manner.

- Nerandomilast is not an inducer of CYP1A2 in vitro. Clinically relevant induction of CYP2B6 by nerandomilast is unlikely. Potential clinical DDIs due to induction of CYPs 3A4, 2C8, 2C9, and 2C19 by nerandomilast are considered possible.
- Nerandomilast is not anticipated to cause clinically relevant inhibition of any UGT isoforms.
- Nerandomilast is not predicted to cause clinically relevant inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K transporters.
- The results of an in vitro study (206893_11043006) to evaluate the potential for pirfenidone to induce human CYP3A4 suggested that clinically relevant induction of CYP3A4 by pirfenidone is likely. In vitro induction of P-gp by pirfenidone was not observed.

***In vivo* studies**

Effects of other drugs on nerandomilast

CYP3A inducers

Effect of a strong CYP3A inducer (carbamazepine)

Trial 1305-0119 was an open-label, two-period, fixed sequence trial to evaluate the effect of multiple oral doses of carbamazepine on the single oral dose PK of nerandomilast in 16 healthy male subjects. Each subject received the fixed sequence of Reference Treatment (R) followed by Test Treatment (T). There was a washout period of at least 5 days between treatments.

- Period 1 [Reference (R)]: Single dose of nerandomilast 18 mg in the fasting state on Day 1.
- Period 2 [Test (T)]: Up-titration of carbamazepine (after dinner) from 200 mg QD for 4 days, to 400 mg QD for 7 days, to 600 mg QD for 12 days (Day -18 to Day 5). A single dose of nerandomilast 18 mg in the fasting state on Day 1 (after 7th carbamazepine 600 mg dose).

After co-administration of a single dose of nerandomilast with multiple doses of carbamazepine, the adjusted gMean AUC0-tz and AUC0-∞ of nerandomilast decreased by approximately 51%, and the adjusted gMean Cmax decreased by approximately 31%, as compared with when nerandomilast was administered alone.

The Cmax and AUC0-tz of metabolite BI 764333 and the metabolite/parent ratios parameters increased with carbamazepine coadministration compared with nerandomilast was given alone.

The urinary 6β-OH-cortisol/cortisol ratio increased over time during carbamazepine treatment, confirming progressive CYP3A induction. At Day -5 of the test period, the percent change from baseline in the urinary 6β-OH-cortisol/cortisol ratio was close to the maximum observed effect. Furthermore, all participants had measurable carbamazepine trough concentrations from Day -12 until Day 5 (gMean range: 4950 to 6280 ng/mL), with steady state attained well before nerandomilast was dosed in the test period.

Effect of a moderate CYP3A inducer (bosentan)

Trial 1305-0113 was an open-label, two-period, fixed sequence trial to evaluate the effect of multiple oral doses of bosentan on the single oral dose PK of nerandomilast in 16 healthy male subjects. Each subject received the fixed sequence of Reference Treatment (R) followed by Test Treatment (T). There was a washout period of at least 5 days between treatments.

- Period 1 [Reference (R)]: Single dose of nerandomilast 18 mg in the fasting state on Day 1.

- Period 2 [Test (T)]: Bosentan 125 mg bid for 17 days (Day -14 to Day 3). Single dose of nerandomilast 18 mg in the fasting state on Day 1 (after 14 days of bosentan treatment).

After co-administration of a single dose of nerandomilast with multiple doses of bosentan, the adjusted gMean AUC0-tz and AUC0-∞ of nerandomilast decreased by approximately 41%, and the adjusted gMean Cmax decreased by approximately 15%, as compared with when nerandomilast was administered alone.

The Cmax of metabolite BI 764333 was higher when nerandomilast was coadministered with bosentan, while AUC0-tz did not change substantially. The metabolite/parent ratios for exposure parameters increased following coadministration of bosentan.

The urinary 6β-OH-cortisol/cortisol ratio increased over time during bosentan treatment, confirming CYP3A induction. After 11 days of bosentan treatment (Day -3), the percent change from baseline in the urinary 6β-OH-cortisol/cortisol ratio remained relatively stable, indicating that CYP3A induction had reached its maximum before nerandomilast dosing in the test period. Furthermore, all participants had measurable bosentan trough concentrations, which were stable from Day -7 through Day 4 (gMean range: 69.4 to 107 ng/mL), suggesting attainment of steady state well before nerandomilast dosing in the test period.

CYP3A inhibitors

Effect of a strong CYP3A inhibitor (itraconazole)

Trial 1305-0015 was an open-label, fixed-sequence trial to compare the relative bioavailability of nerandomilast given alone (reference treatment, R) to the relative bioavailability of nerandomilast given on the fourth day of a 12-day-treatment with itraconazole (test treatment, T) in 16 healthy male subjects. Study treatments were as follows:

Treatment R: Single dose of 6 mg nerandomilast on Day 1

Treatment T: 12 days of itraconazole treatment (200 mg qd) combined with a single dose of 6 mg nerandomilast on the 4th day of the itraconazole treatment (1 h after itraconazole administration).

After coadministration of nerandomilast and itraconazole the adjusted gMean ratio of AUC0-119 (222.13%) and AUC0-∞ (229.26%) were higher than that of Cmax (127.96%). The plasma concentrations of the metabolite BI 764333 were BLQ at all time points when BI 1015550 was co-administrated with itraconazole.

P-gp inhibitors

Since itraconazole is recognized as an inhibitor of P-gp (in addition to being a strong CYP3A inhibitor) and nerandomilast is a substrate of P-gp, the change in nerandomilast plasma exposure in the itraconazole DDI study could potentially be due to inhibition of P-gp in addition to inhibition of CYP3A. However, the contribution from P-gp inhibition is not expected to be significant as Cmax was only increased by 30% in this trial. The potential increase in nerandomilast exposure with P-gp inhibitors is limited due to the high absolute bioavailability of nerandomilast of 73% (Trial 1305-0030). Exposure change due to P-gp inhibition only is expected to be less prominent than the combination of CYP3A and P-gp inhibition. Hence. no dose adjustment is needed for P-gp inhibitors.

Acid reducing agents

The solubility of nerandomilast is pH dependent. At or below pH 3 the solubility of nerandomilast is very slightly to slightly soluble, and above pH 3 it is practically insoluble. The potential influence of concomitant medication that could potentially elevate gastric pH (i.e., acid reducing agents [ARAs]) on

nerandomilast exposure was explored by conducting a subgroup analysis of nerandomilast trough concentrations in Phase III trials in IPF and PPF patients (1305-0014 and 1305-0023, respectively).

In both studies, comparable nerandomilast trough concentrations were observed between patients with ARA treatment and patients without ARA treatment. Among different ARA types, PPIs were most frequently used. Similarly, comparable nerandomilast trough concentrations were observed between patients with PPI treatment and patients without PPI treatment. Overall, there was no clear trend that ARA use would influence nerandomilast exposure.

Nintedanib and pirfenidone

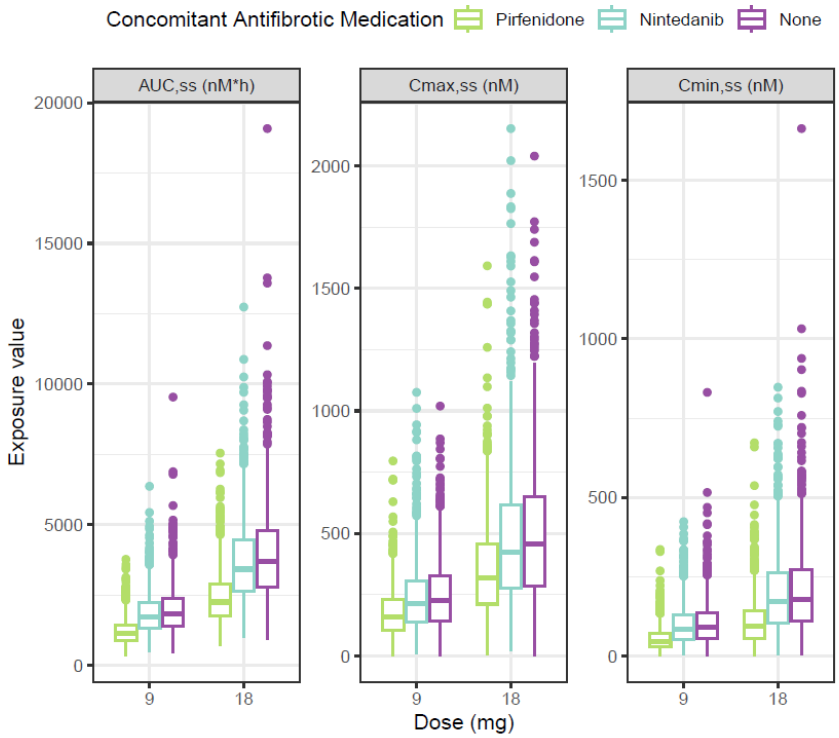
Based on the known ADME characteristics of nintedanib and pirfenidone, neither nintedanib nor pirfenidone were expected to have an impact on nerandomilast exposure. Their potential impact on nerandomilast exposure with co-medications was explored by subgroup analyses of PK data from the Phase II trial and Phase III trial 1305-0014 and in the popPK covariate analysis.

Results of exploratory subgroup analysis from the Phase II trial in patients with IPF (1305-0013) showed that pre- and post-dose concentrations of nerandomilast were similar between IPF patients on nintedanib background therapy and those who were not on any antifibrotic background treatment (non-AF). However, IPF patients on pirfenidone background therapy had a 35-50% lower nerandomilast exposure compared to non-AF patients.

Results from Phase III trials subgroup analyses of trough concentrations were consistent with those of Phase II. Nerandomilast trough plasma concentrations in patients with nintedanib background treatment were comparable to those non-AF patients in both IPF (1305-0014) and PPF patient populations (1305-0023). However, patients on pirfenidone background treatment showed 55% and 48% lower nerandomilast trough concentrations in the 9 mg bid dose group and the 18 mg bid dose group, respectively, compared to non-AF patients.

These findings were further confirmed by popPK analysis, where background treatment with pirfenidone was identified to increase nerandomilast CL/F by 48%. Model-based simulations predicted lower median nerandomilast AUC,ss, Cmax,ss, and Cmin,ss in patients with concomitant pirfenidone use (38.9%, 30.3%, and 47.8%, respectively) and concomitant nintedanib use (7.6%, 7.0%, and 4.8%, respectively) compared to the non-AF population (**Figure 6**).

This drug-drug interaction between pirfenidone and nerandomilast resulted in the lack of treatment effect of the 9 mg bid dose in patients with pirfenidone background therapy.



Source code: pk−population−sims.R
Source graphic: deliv/figure/pk/popsims/ninpir−bp.pdf

Figure 9: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and concomitant antifibrotic medication.

Figure 6: Population Level Simulations: Boxplots of nerandomilast exposure versus dose stratified by exposure metric and concomitant antifibrotic medication

Effects of nerandomilast on other drugs

CYP3A substrates

Trial 1305-0033 was an open-label, crossover, two-period, fixed sequence study to investigate the effect of multiple oral doses of nerandomilast on the metabolism of midazolam administered in healthy male subjects. Study treatments were as follows:

Treatment Reference (R): 2 mg single oral dose of midazolam on Day 1 of the reference period.

Treatment Test (T): 18 mg oral nerandomilast bid for 13 days (Day -13 to Day -1) and only the morning dose on Day 1 of test period together with a 2 mg single oral dose of midazolam.

Midazolam

The adjusted gMean ratios for AUC0-tz and AUC0-∞ were 92.3% and 89.8%, the corresponding lower bound 90% CIs were close to 80%, and the upper bound 90% CIs were below 125%. The adjusted gMean ratio for Cmax was 78.0% and the entire 90% CIs were below 100%. The slight decreases in systemic exposure and maximal plasma concentration of midazolam in the presence of nerandomilast were not considered clinically meaningful.

1-OH-midazolam

The gMean ratios of test/reference for Cmax, AUC0-tz, and AUC0-∞ were 82.3%, 93.3%, and 93.2% respectively. AUC0-12, AUC0-∞ and Cmax metabolite to parent ratios were similar between the two treatment periods.

Nerandomilast

Steady state analysis indicated that steady state for nerandomilast had been reached by Day 4 following 18 mg bid dosing.

Urinary 6β-hydroxycortisol to cortisol ratio

No relevant increase in the 6β-OH-cortisol to cortisol ratio over time was observed during nerandomilast dosing.

CYP2C substrates

In vitro data indicated that nerandomilast has the potential to induce CYP28 and CYP2C9 in vivo, in addition to CYP3A. However, the negative result for CYP3A induction from the midazolam DDI study (1305-0033) can be used to rule out CYP2C induction potential by nerandomilast because both CYP3A and CYP2C enzymes are induced via activation of the same PXR pathway.

Nintedanib and pirfenidone

Trial 1305-0034 was an open-label, two-period, fixed-sequence, crossover study to investigate the effect of multiple doses of nerandomilast on the PK of nintedanib and pirfenidone in healthy male subjects. Study treatments were as follows:

Treatment Reference (R): 267 mg pirfenidone (single dose) administered on Day 1 and 100 mg nintedanib (single dose) on Day 2.

Treatment Test (T): 18 mg bid nerandomilast for 10 days (Day -6 to Day 4). 267 mg pirfenidone (single dose) administered on Day 1 and 100 mg nintedanib (single dose) on Day 2.

Pirfenidone

The PK parameters for pirfenidone alone were similar to those for pirfenidone with nerandomilast. Estimates for exposure, based on test/reference ratio, were 101.97% for AUC0-tz; 101.31% for AUC0-∞; and 101.11% for Cmax.

Nintedanib

The PK parameters for nintedanib alone were similar to those for nintedanib with nerandomilast. Based on the statistical evaluation, estimates for exposure, based on test/reference ratio for 108.37% AUC0-tz, 108.82% for AUC0-∞, and 87.24% for Cmax.

5.2.2. Pharmacodynamics

5.2.2.1. Primary and secondary pharmacology

Primary pharmacology

The pharmacodynamic (PD) effect of nerandomilast was evaluated in 4 clinical studies; 3 studies in healthy volunteers and 1 study in patients with IPF.

Trial1305-001 was a single rising dose study in 70 healthy male subjects. Nerandomilast doses ranged from 0.02 – 24 mg nerandomilast. As a measure of PDE4 target engagement with nerandomilast, two exploratory biomarkers [tumor necrosis factor (TNF)-α and leukotriene B4 (LTB4)] were analysed in *ex-vivo* assays based on whole blood samples of treated subjects.

The inhibitory effect of nerandomilast on TNF-α release increased with increasing dose and was observed at doses > 4 mg. A dose-dependent inhibition of TNF-α release was observed beginning at 8 mg and the median inhibition was up to 60% at the 24 mg dose. No significant effect of nerandomilast was observed on LTB4 release.

Trial 1305-0002 was a multiple rising dose study in healthy male subjects. Subjects received 1 mg or 6 mg nerandomilast bid for 14 days. As a measure of PDE4 target engagement with nerandomilast, TNF-α was analysed in *ex-vivo* assays based on whole blood samples of treated subjects.

Nerandomilast 6 mg twice daily inhibited TNF-α release with a maximum mean inhibitory effect size between 35% vs. predose (Day 1 after single dose) and 56% vs. predose (Day 12 at steady state). A clear discrimination from placebo was observed throughout most of the dosing intervals for 6mg nerandomilast twice daily. No relevant inhibition was seen with 1 mg BI 1015550 twice daily.

Trial 1305-0011 was a single and multiple rising dose study in healthy male subjects. Indirect target engagement of nerandomilast was evaluated using an *ex vivo* whole blood stimulation assay. LPS-stimulated TNF-α, IFN-γ, and MCP-1 were considered exploratory biomarkers in this context.

LPS-induced TNF-α

The Emax values of 36 mg and 48 mg nerandomilast were 60.8% and 66.2%, respectively, which are higher than that of placebo (42.1%).

The Emax and Emax,0-4h values of 12 mg bid nerandomilast are numerically higher than placebo (8% to 12%), but the difference is small considering the variability.

LPS-induced IFN-γ

The Emax values of 36 mg and 48 mg nerandomilast were 89.3% to 93.7%, while that of placebo was 62.8%.

No increase of Emax,0-4h values from placebo was observed after the first dose of 6 mg nerandomilast, while a slight increase was observed after the first dose of 12 mg nerandomilast. At steady state, the Emax,ss and Emax,ss,0-4h values of 6 mg and 12 mg bid nerandomilast were much higher than those of placebo.

PK-PD evaluation

In general, a concentration-dependent increase of %inhibition of TNF-α and IFN-γ was observed. Higher %inhibition for TNF-α and IFN-γ was seen with plasma concentrations ≥400 nM.

Trial 1305-0012 was a multiple rising dose study in patients with IPF on no background antifibrotic therapy. Indirect target engagement of nerandomilast was evaluated using an *ex vivo* whole blood stimulation assay. LPS-stimulated TNF-α, IFN-γ, and MCP-1 were considered exploratory biomarkers in this context.

TNF-α inhibition

Due to high variability, no conclusive effect can be assumed. Unexpectedly, the placebo group also showed a reduction in LPS-stimulated TNF-α release with a high variability. The mean value for placebo at steady state (51%) was similar to the value of the nerandomilast group (51%).

IFN-γ *inhibition*

Due to the high variability no conclusive effect can be assumed. Unexpectedly, the placebo group showed a reduction in LPS-stimulated IFN-γ release with a high variability. The mean value at steady state (84%) was similar to the mean value of the nerandomilast group (56%).

PK-PD evaluation

Generally, no clear relationship between concentrations of nerandomilast and %inhibition of TNF-α and IFN-γ from baseline was observed. However, despite the high variability, there is a trend towards exposure-related inhibition of TNF-α release and also of INF-γ release in the nerandomilast group.

Secondary pharmacology

Thorough QT study (Trial 1305-0026)

This was randomised, placebo-controlled, double-blind (moxifloxacin: open-label), five-period, crossover study to evaluate the effects of a single therapeutic and supratherapeutic dose of nerandomilast on the QT/QTc interval as measured by QTcF changes from baseline in healthy volunteers.

The treatments were as follows: 30 mg nerandomilast [L], 48 mg nerandomilast [H], 400 mg moxifloxacin (positive control; [M]) and 2 periods with placebo [P1 and P2]. Each treatment period was separated by a washout period of at least 7 days.

The primary endpoint was the maximum mean difference between each single dose of either 30 mg or 48 mg of nerandomilast and placebo in QTcF changes from baseline between 20 minutes (min) to 24 h after drug administration. The secondary endpoint was the maximum mean difference between moxifloxacin and placebo in QTcF changes from baseline between 20 min to 24 h after drug administration (the formal test for assay sensitivity was based on the results for the pre-selected time points 2, 3, and 4 h post dosing).

ECG exposure-response relationship

The exposure-response analysis revealed that the predicted values of mean ΔΔQTcF and their corresponding upper limits of the 90% CI at gMean Cmax of nerandomilast (0.8 msec with upper limit of the 90% CI of 1.9 msec at 30 mg and 1.1 msec with upper limit of the 90% CI of 2.5 msec at 48 mg) did not exceed the threshold of 10 msec and did not demonstrate a clinically relevant prolongation of the QTcF intervals at gMean Cmax of nerandomilast at either of the tested doses. The estimated slope (SE) was 0.0059 (0.002) msec/(nmol/L) with the corresponding 90% CI including 0, further supporting no relationship between nerandomilast plasma concentrations and ΔΔQTcF and supporting the result of the primary analysis. A scatterplot depicting all individual data pairs of nerandomilast plasma concentrations and corresponding ΔΔQTcF with regression line and confidence limits is displayed in **Figure 7**.

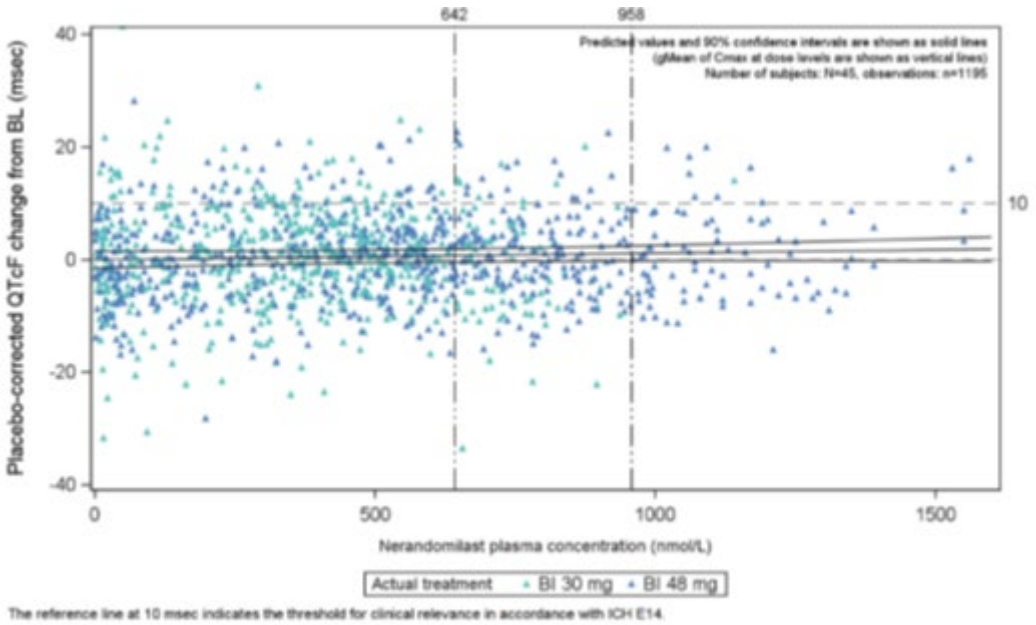


Figure 7: Scatterplot of the relationship between nerandomilast plasma concentrations and placebo-corrected QTcF changes from baseline following the administration of single oral doses of 30 mg and 48 mg nerandomilast - ECGPCS

Primary ECG endpoint

Adjusted means and upper limits of the 90% 2-sided CI of the differences between nerandomilast and placebo in QTcF changes from baseline remained below the threshold of 10 milliseconds (msec) for all pre-selected post-dose time points with the therapeutic and with the supratherapeutic dose of nerandomilast. **Figure 8** displays the time profiles of the adjusted mean differences between nerandomilast and placebo in changes QTcF from baseline over 24 h and their 90% CI for both nerandomilast dose levels, based on the MMRM.

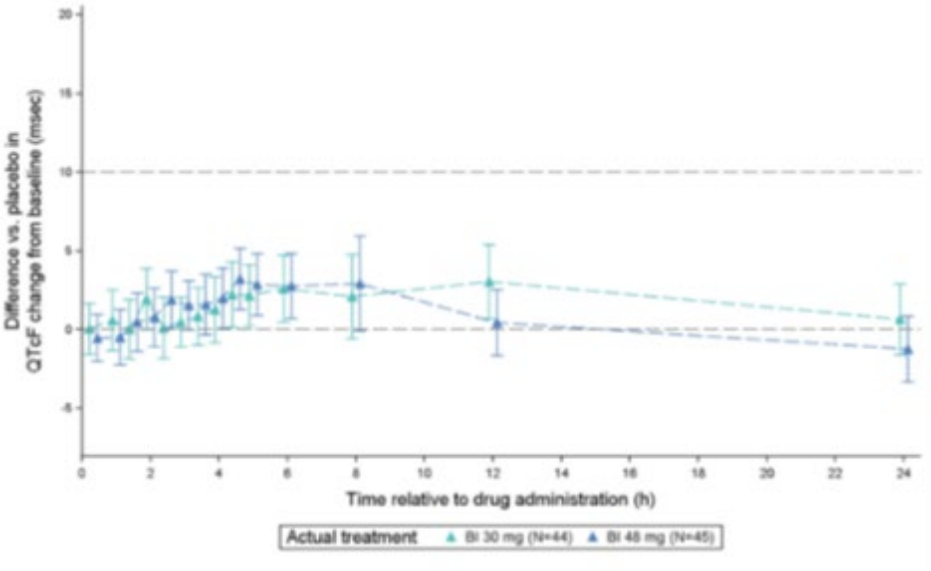


Figure 8: Time profile of QTcF change from baseline over 24 hours, placebo-corrected adjusted means and 90% CI for 30 mg and 48 mg nerandomilast - ECGS

With 30 mg nerandomilast, the maximum adjusted mean difference vs. placebo in QTcF changes from baseline was 3.0 msec (90% CI: 0.7, 5.4), observed at 12 h after dosing. With 48 mg nerandomilast, the corresponding QTcF endpoint was 3.2 msec (90% CI: 1.2, 5.2), observed at 4.5 h after dosing.

Further ECG analyses

The analysis of QT, PR, RR intervals, of heart rate, and of QRS taking into account all time points between 20 min and 24 h after dosing, did not indicate clinically relevant effects associated with the administration of nerandomilast.

Analysis of categorical ECG endpoints, assessment of notable findings and morphological ECG analyses indicated no relevant effect of nerandomilast on cardiac safety.

5.2.2.2. Pharmacodynamic interactions with other medicinal products or substances

No information was provided on the potential for PD interactions of nerandomilast with other medicines or substances.

5.2.2.3. Genetic differences in PD response

No information was provided on the potential for genetic differences in the PD response of nerandomilast.

5.2.3. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-response analysis for efficacy

The aim of this analysis was to evaluate the relationship between nerandomilast exposure and the efficacy endpoint of absolute change in forced vital capacity (FVC) in patients with IPF and PPF. The analysis population included 2353 patients contributing 20,937 FVC observations.

A linear disease progression model best described the decline (i.e., placebo response) in FVC over the 52-week course in IPF and PPF patients. The relationship between nerandomilast exposure (represented by Cmin,ss) and absolute FVC response was incorporated by an offset effect (BETA) and a disease-modifying effect of nerandomilast on the slope (ALPHA) of disease progression as measured by FVC decline. Covariates of age, height, sex, diagnosis (IPF vs. PPF) and antifibrotic background treatment (nintedanib or pirfenidone as separate covariate effects) had an impact on baseline FVC. Covariates of height and antifibrotic background treatment had an impact on FVC slope (disease progression rate).

Fixed and random effect parameter estimates for the final model are presented in **Table 16** and **Table 17**, respectively. Longitudinal VPCs of the change from baseline FVC stratified by dose and underlying disease are presented in **Figure 9**, respectively.

Table 16: FVC Final Model (Run 441): Fixed effects parameter estimates

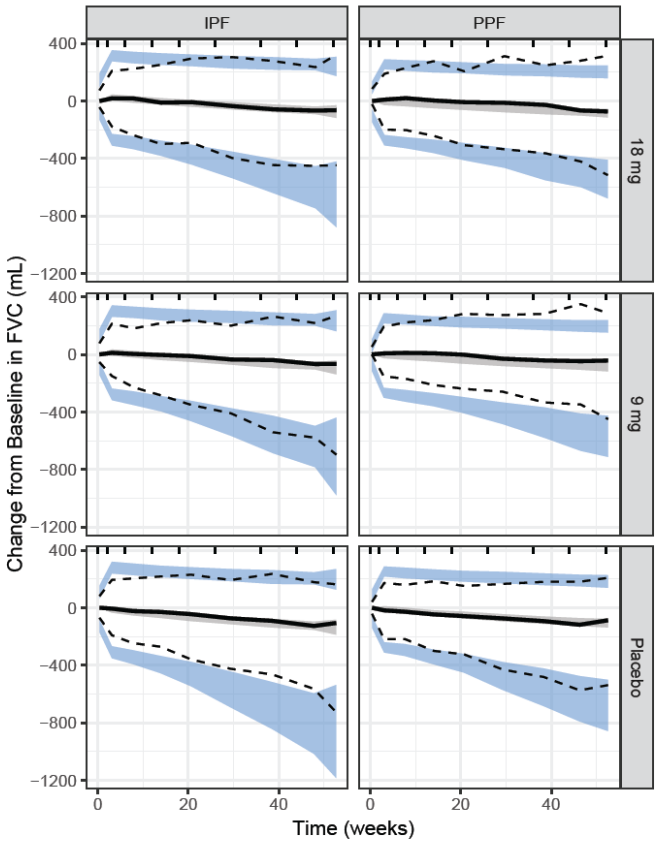
				SIR	
			Estimate	Median	95% CI
Structural model parameters					
ALPHA (mL/week)	$\exp(\theta_2)$	Disease progression rate	1.27	1.30	1.14, 1.53
BASE (mL)	$\exp(\theta_1)$	Baseline FVC	2800	2800	2750, 2850
BETA (mL/sqrt(nM))	$\exp(\theta_3)$	Nerandomilast offset drug effect	2.39	2.42	1.72, 3.24
Covariate effect parameters					
ALPHA~HGT	θ_9	Effect of height on disease progression rate	3.44	3.40	1.90, 4.82
ALPHA~NER	$\exp(\theta_{12})$	Effect of nerandomilast on disease progression rate	0.976	0.976	0.964, 0.988
ALPHA~NINT	$\exp(\theta_{10})$	Effect of background nintedanib treatment on disease progression rate	1.22	1.21	1.03, 1.47
ALPHA~PIRF	$\exp(\theta_{11})$	Effect of background pirfenidone treatment on disease progression rate	1.48	1.47	1.14, 1.87
BASE~AGE	θ_4	Effect of age on baseline FVC	-0.208	-0.209	-0.270, -0.147
BASE~DIAG	$\exp(\theta_{13})$	Effect of PPF underlying diagnosis on baseline FVC	0.889	0.889	0.874, 0.907
BASE~HGT	θ_6	Effect of height on baseline FVC	2.65	2.65	2.46, 2.81
BASE~NINT	$\exp(\theta_7)$	Effect of background nintedanib treatment on baseline FVC	0.980	0.980	0.964, 0.996
BASE~PIRF	$\exp(\theta_8)$	Effect of background pirfenidone treatment on baseline FVC	0.945	0.944	0.919, 0.969
BASE~SEX	$\exp(\theta_5)$	Effect of female sex on baseline FVC	0.859	0.859	0.837, 0.880

Parameters estimated in the log-domain were back-transformed for clarity
CI: confidence interval; SIR: sampling importance resampling
The CI was determined from the 2.5th and 97.5th percentiles of the SIR (n=1000) resamples.
Run number: 441
Source code: script/efficacy/fvc-model-table-sir.R
Source file: fvc-param-fixed-sir.tex

Table 17: FVC Final Model (Run 441): Random effects parameter estimates

		Estimate	Shrinkage (%)	SIR Median	SIR 95% CI
Interindividual variance parameters					
IIV-BASE	$\Omega_{(1,1)}$	0.0482 [CV%=22.2]	0.533	0.0483	0.0449, 0.0514
IIV-ALPHA	$\Omega_{(2,2)}$	1.77 [CV%=221]	30.4	1.72	1.52, 1.91
IIV-BETA	$\Omega_{(3,3)}$	0.208 [CV%=48.1]	91.5	0.210	0.00818, 0.740
Residual variance					
Proportional residual error	$\Sigma_{(1,1)}$	0.00109 [CV%=3.30]	7.89	0.00109	0.00106, 0.00112
Additive residual error (mL)	$\Sigma_{(2,2)}$	6010 [SD=77.5]	7.89	6010	5820, 6190

CI: confidence interval; CV: coefficient of variation; SD: standard deviation; SIR: sampling importance resampling
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100
CV% of sigma = sqrt(estimate) · 100
The CI was determined from the 2.5th and 97.5th percentiles of the SIR (n=1000) resamples.
Run number: 441
Source code: script/efficacy/fvc-model-table-sir.R
Source file: fvc-param-random-sir.tex



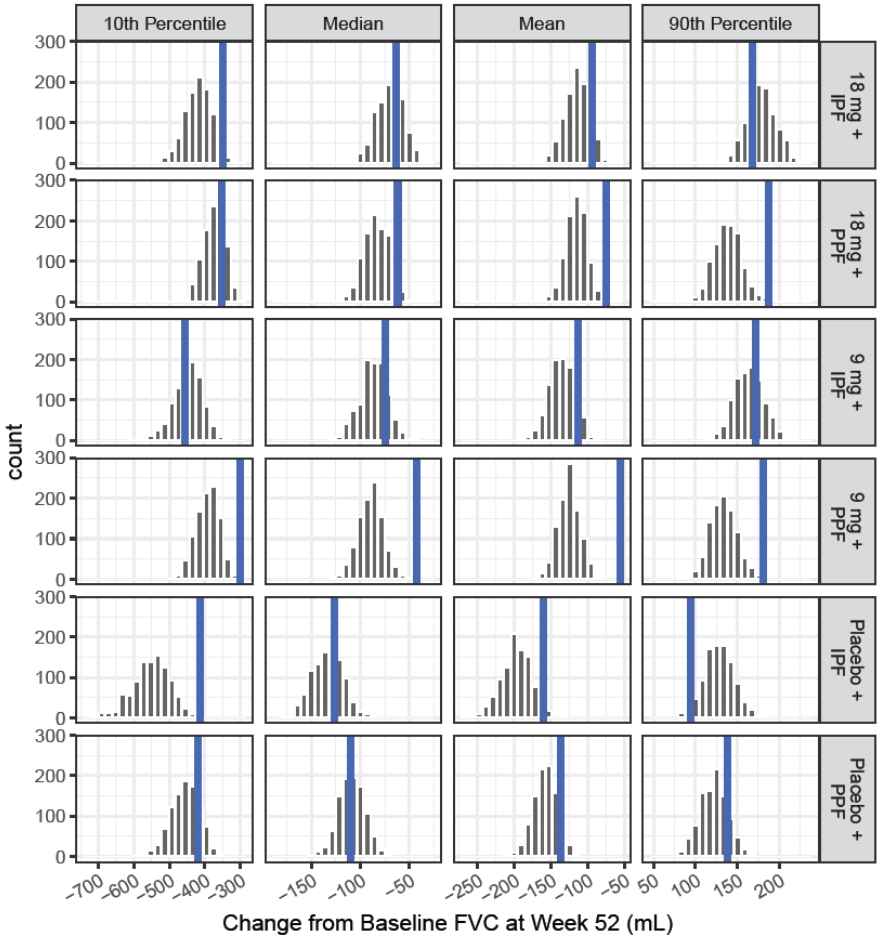
Source code: script/efficacy/fvc−vpc.R
Source graphic: deliv/figure/efficacy/vpc/fvccfb−441−vpc−study.pdf

Figure S264: FVC Final Model (Run 441): Forced vital capacity (FVC) change from baseline visual predictive check (VPC) stratified by nerandomilast dose and underlying disease diagnosis.

The black lines represent the median (solid) or 10th / 90th percentiles (dashed) of the observed data. The shaded areas represent the 95% confidence interval for median (gray) or 10th / 90th (blue) percentiles of simulated data. Black tick marks represent bin locations. IPF: idiopathic pulmonary fibrosis; PPF: progressive pulmonary fibrosis.

Figure 9: FVC Final Model (Run 441): Forced vital capacity (FVC) change from baseline visual predictive check (VPC) stratified by nerandomilast dose and underlying disease diagnosis.

The ability of the model to describe the effect of nerandomilast at Week 52, the primary efficacy endpoint of Studies 1305-0014 and 1305-0023, was assessed using landmark VPCs. These showed that the observed change from baseline FVC at Week 52 was for the most part contained within the simulated distribution in the placebo group and the 18 mg dose group. However, the change from baseline was not as well described in the 9 mg nerandomilast arm. This can be attributed to the monotonic relationship between nerandomilast exposure and change in FVC estimated in the final model based on data from Studies 1305-0014 and 1305-0023 combined, while the observed data showed a similar or even better response in FVC at 52 weeks for 9mg compared to 18mg nerandomilast in Study 1305-0023, but not in Study 1305-0014. Stratifying Week 52 change from baseline FVC by both dose level and IPF versus PPF diagnosis showed that the median change from baseline at Week 52 was well described in all groups except for PPF patients receiving 9 mg nerandomilast (**Figure 10**).



Source code: script/efficacy/fvc−landmark−vpc.R
Source graphic: deliv/figure/efficacy/vpc/fvc−441−landmark−week52−ipf−ppf.pdf

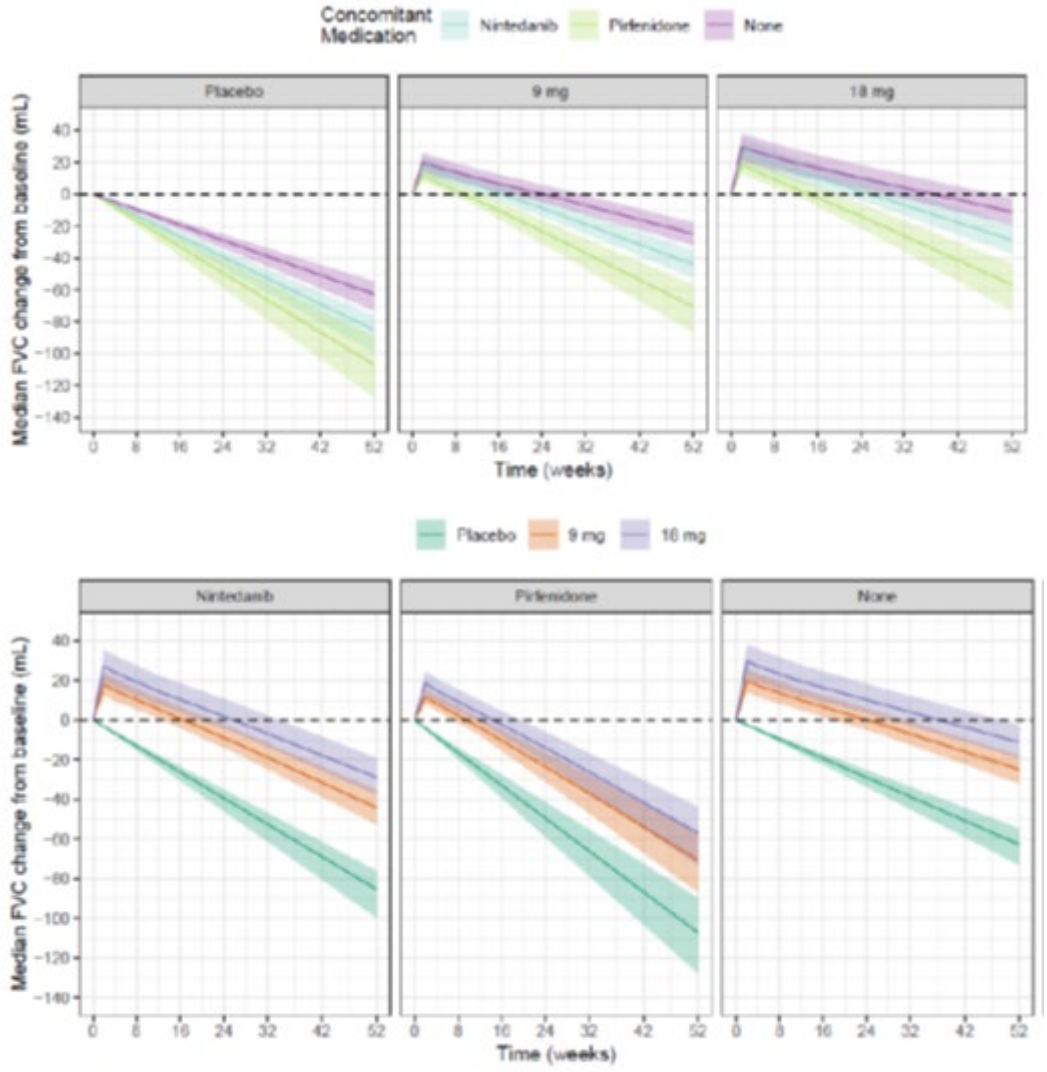
Figure S266: FVC Final Model (Run 441): Forced vital capacity (FVC) landmark visual predictive check (VPC) at Week 52 stratified by nerandomilast dose and underlying disease diagnosis.

The vertical blue lines represent the median, mean, or 10th / 90th percentiles of the observed data. The gray bars represent the distribution of the median, mean, or 10th / 90th percentiles of simulated data.

Figure 10: FVC Final Model (Run 441): Forced vital capacity (FVC) landmark visual predictive check (VPC) at Week 52 stratified by nerandomilast dose and underlying disease diagnosis.

Model-based simulations

Figure 11 shows the differences in FVC change from baseline over time amongst the various combinations of nerandomilast dose and concomitant antifibrotic medication. Baseline FVC did not vary amongst the different nerandomilast treatment arms; however, there was a difference in the nerandomilast-induced initial offset effect, which increased with dose level and was not seen in the placebo group. The disease progression rate, assessed FVC decline over time, was less rapid in subjects taking nerandomilast relative to placebo subjects. Patients taking a concomitant antifibrotic at baseline had more rapid disease progression than patients not on an antifibrotic at baseline (and even more rapid in those on pirfenidone (**Figure 11**). This is likely due to those patients presenting with more advanced disease and a longer disease duration.



Source data: [206893_11097684_1.0, Figure 12 and S272]

Solid line represents median across 300 simulation replicates. Shaded region represents 90% CI. Dashed line included as reference at y=0 to represent no change from baseline.

Figure 11: Typical value simulations for median FVC change from baseline versus time, stratified by nerandomilast dose and anti-fibrotic background treatment

The relationship between median annual FVC change from baseline (the primary efficacy endpoint) and Cmin,ss, stratified by concomitant antifibrotic medication, is shown in **Figure 12**. Regardless of antifibrotic medication, median annual FVC change from baseline appears to be reduced as nerandomilast trough concentrations increase. The smallest FVC decrease from baseline, without any nerandomilast (e.g., Cmin,ss = 0), is seen in the group not taking any concomitant antifibrotic medication, which likely reflects the differences in disease characteristics noted between patients with and without antifibrotic background treatment.

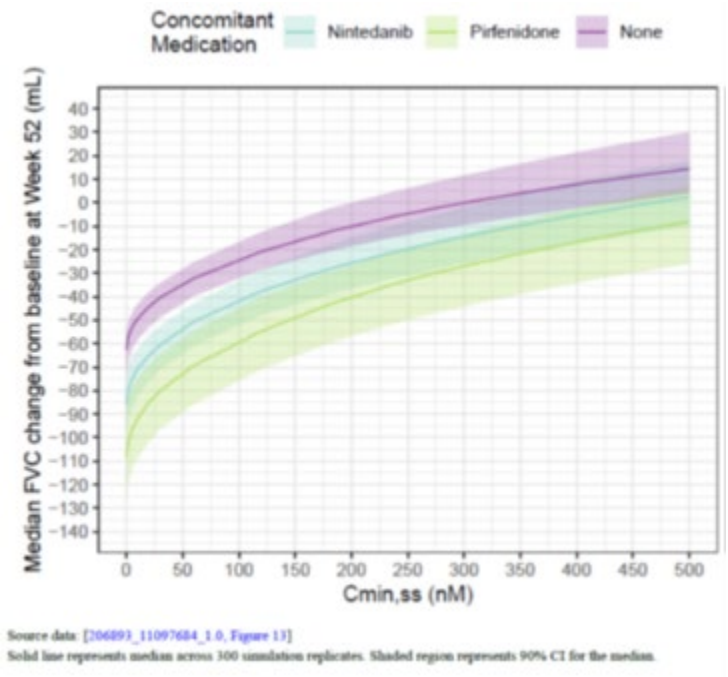
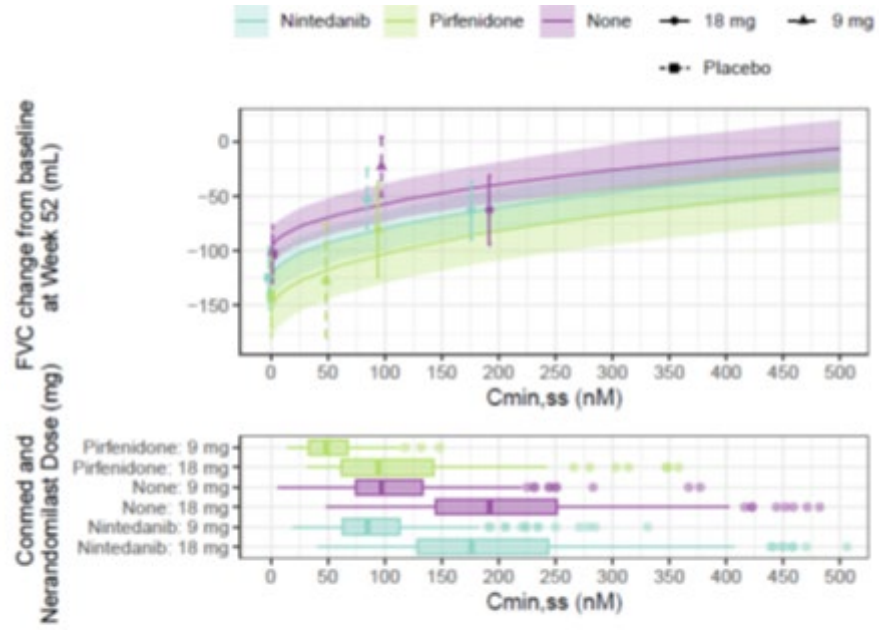


Figure 12: Typical value simulations for FVC change from baseline at week 52 versus simulated nerandomilast Cmin,ss, stratified by anti-fibrotic background treatment

Population simulations (with inclusion of IIV) were generated with the range of observed FVC change from baseline at Week 52 overlaid separately for each dose and concomitant antifibrotic group, centered at the median Cmin,ss for that group (**Figure 13**). The range of exposures shown in these plots, conditional on concomitant antifibrotic medication, suggests that the differences in change from baseline FVC at Week 52 may be mediated by differences in exposure, since patients taking concomitant pirfenidone had lower exposures relative to the other concomitant antifibrotic groups.

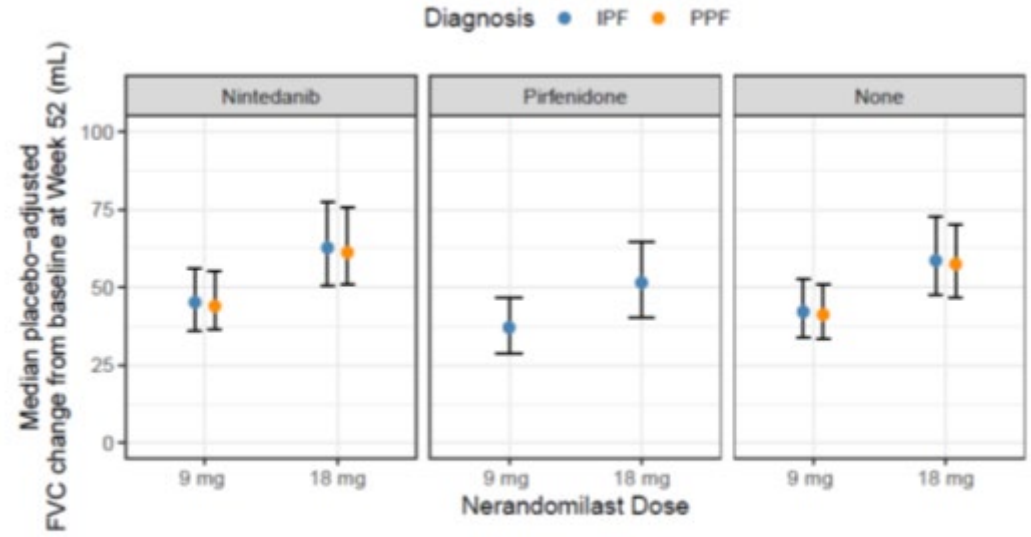


Source data: [206893_11097684_1.0, Figure 14]

Solid horizontal line represents median FVC across 300 simulation replicates. Shaded region represents 95% CIs. Vertical lines represent the observed 95% CI for the median FVC response in each concomitant antifibrotic medication and dose group, centered at the median Cmin,ss for that group (solid line: 18 mg; long dashes: 9 mg; short dashes: placebo; green: nintedanib; orange: pirfenadone, blue: none).

Figure 13: Top panel: Simulations including residual unexplained variability for FVC change from baseline at week 52 versus simulated nerandomilast Cmin,ss, stratified by anti-fibrotic background treatment. Bottom panel: Observed nerandomilast Cmin,ss, stratified by dose and antifibrotic background treatment

Figure 14 shows the impact of an underlying disease diagnosis of IPF versus PPF on FVC change from baseline at Week 52, stratified by background antifibrotic medication. There is large overlap between IPF and PPF patients for 9 mg nerandomilast, and 18 mg nerandomilast groups across the different antifibrotic therapies (**Figure 14**). Note that the simulations did not include any PPF patients taking pirfenidone as a concomitant antifibrotic therapy.



Source data: [206893_11097684_1.0, Figure 15]

Points represent median across 300 simulation replicates. Error bars represent the 90% prediction intervals.

Figure 14: Typical value simulations for FVC change from baseline at week 52 versus nerandomilast dose in IPF and PPF patients, stratified by anti-fibrotic background treatment

Exposure-response analysis for safety

The aim of this analysis was to apply modelling and simulation to characterise the relationship between nerandomilast exposure and five safety endpoints of interest (diarrhoea, nausea, infection, and weight loss) based on data from the Phase III studies in patients with IPF and PPF.

Diarrhoea

A log-linear model parameterized in terms of Cmin,ss provided the best and most parsimonious fit to the data. As shown in the visual PPC (**Figure 15**), the base model provided a reasonable description of the data and demonstrated an increasing ER relationship.

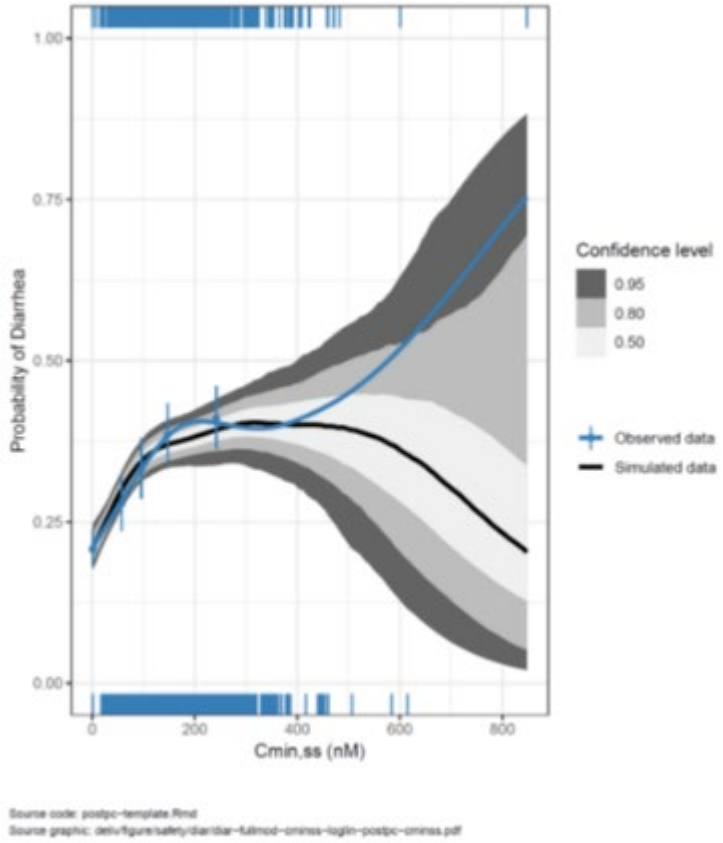


Figure 15: Diarrhea Full Model: Posterior predictive check for diarrhea versus minimum concentration in the dosing interval at steady state (Cmin, ss) assuming an log-linear ER relationship

Model-based simulations indicated that the predicted probability of diarrhoea increased as a function of nerandomilast exposure, and this was observed across all covariate subgroups of sex, race, and background antifibrotic concomitant medication use.

For race subgroups, the probability of diarrhoea was higher for White subjects than Asian subjects and this difference was statistically significant at the 95% credible level.

For concomitant antifibrotic use, the probability of diarrhoea for patients on background nintedanib was higher than for subjects on pirfenidone or on no concomitant antifibrotic. This difference was statistically significant at the 95% credible level.

Infection

A linear ER model parameterized in terms of Cmin,ss provided the best and most parsimonious fit to the data. The base model provided a reasonable description of the data and showed an almost flat ER relationship. No covariate subgroup differences were found to be predictive for infection.

Nausea

A linear ER model parameterized in terms of Cmax,ss provided the best and most parsimonious fit to the data. The base model provided a reasonable description of the data and showed an almost flat ER relationship.

Simulations showed that the probability of nausea did not increase as a function of nerandomilast exposure, but differences were observed across subgroups of background nintedanib use, race and sex. The probability of nausea was higher in White subjects than Asian subjects, higher in females, and higher for concomitant nintedanib.

Weight decrease of ≥5%

A linear model parameterized in terms of Cmin,ss provided the best and most parsimonious fit to the data. As shown in the visual PPC (**Figure 16**), the base model provided a reasonable description of the data and demonstrated an increasing ER relationship.

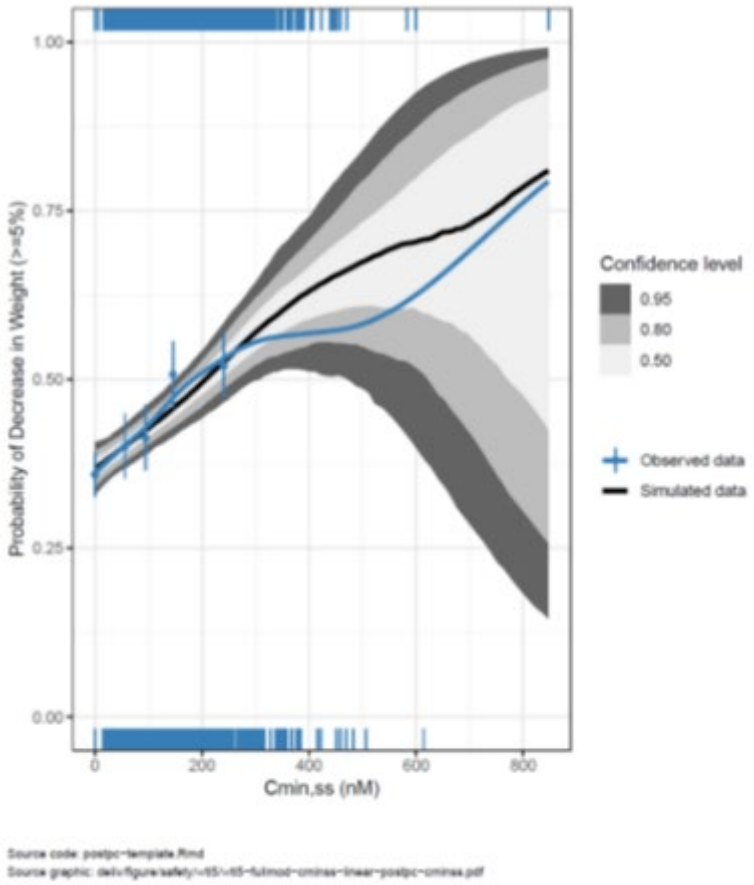


Figure 16: Decrease in Weight (›=5%) Full Model: Posterior predictive check for decrease in weight (≥5%) versus minimum concentration in the dosing interval at steady state (Cmin,ss) assuming a linear ER relationship.

Model-based simulations indicated that the probability of a decrease in weight (≥5%) increased as a function of exposure, and this was observed in multiple covariate subgroups including sex, race, background antifibrotic use, concomitant weight loss medication use and BMI.

For background antifibrotic medication use, the predicted probability of a decrease in weight (≥5%) for the background nintedanib subgroup was higher than the no background treatment and the pirfenidone treatment subgroups, but the credible intervals overlapped.

Weight decrease of ≥10%

A linear ER model parameterized in terms of AUC,ss provided the best and most parsimonious fit to the data. As shown in the visual PPC (**Figure 17**), the base model provided a reasonable description of the data and showed an ER relationship.

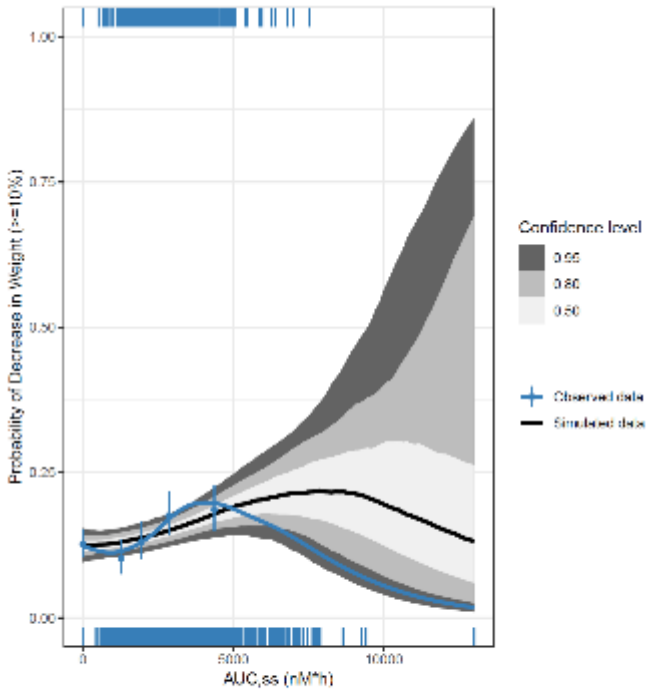


Figure 20: Decrease in Weight (>=10%) Full Model: Posterior predictive check for decrease in weight (≥10%) versus area under the concentration-time curve for a dosing interval at steady state (AUC,ss) and linear ER relationship.

Figure 17: Decrease in Weight (›=10%) Full Model: Posterior predictive check for decrease in weight (≥10%) versus area under the concentration-time curve for a dosing interval at steady state (AUC,ss), and linear ER relationship.

Model-based simulations indicated that the predicted probability of a decrease in weight (≥10%) increased as a function of exposure, and this was observed in multiple covariate subgroups including sex, race, background antifibrotic medication, concomitant weight loss medication and BMI.

The probability of weight decrease ≥10% was higher for patients with background nintedanib than those receiving pirfenidone or no background antifibrotic medication, but this was only statistically different at the highest quartile of exposure.

5.2.4. Dose selection and therapeutic window

The precise therapeutic window for nerandomilast has not been defined. However, the lower bound is likely the plasma exposure corresponding to a 4.5-9 mg bid dose and the upper bound is likely above the plasma exposure corresponding to an 18 mg bid dose, which was the highest multiple dose tested. However, single doses up to 48 mg have been evaluated with no safety concerns.

Both 18 mg bid and 9 mg bid nerandomilast doses are safe and efficacious in patients with IPF not on background treatment with pirfenidone. Based on an integrated assessment (including data from trial 1305-0023 in PPF patients), 18 mg bid is considered to offer optimisation of benefit beyond lung function with a trend in reducing the risk of death compared with 9 mg bid in these patients. The recommended maximum daily dose of 18 mg bid should not be exceeded as it was the highest daily dose investigated in multiple-dose trials. Diarrhoea and weight decrease (both ADRs) were more frequent under 18 mg bid nerandomilast than under 9 mg bid nerandomilast. To avoid treatment discontinuation, 9 mg bid can be considered for patients who cannot tolerate 18 mg bid.

Pharmacokinetic investigations

Pirfenidone reduced nerandomilast exposure by ~50% in Phase II and Phase III trials. This drug-drug interaction was accompanied by a lack of observed treatment effect on the primary endpoint for the 9 mg bid dose in patients with pirfenidone background treatment. The strong CYP3A inhibitor itraconazole increased nerandomilast Cmax by 1.3-fold and AUC by 2.2-fold. Therefore, the expected exposure when nerandomilast 9 mg is co-administered with strong CYP3A inhibitors is approximately equivalent to that of 18 mg nerandomilast alone.

Although nerandomilast exposure was increased in Asian patients and in patients with lower body weight, no relevant differences in the treatment effect were seen on the primary endpoint by race. No relevant impact of race or body weight was observed in the safety analyses as well. Thus, dose adjustment based on race or body weight is not considered necessary.

No relevant impact on nerandomilast exposure was observed for other intrinsic or extrinsic factors including age, sex, or renal (mild, moderate, and severe) or hepatic (mild and moderate) impairment, in line with no relevant differences in the available subgroup analyses of efficacy or safety.

Exposure-response analyses

Exposure-response modelling of absolute FVC demonstrated incrementally less FVC decline with increasing nerandomilast exposure. Model-based simulations suggested a numerical difference in Week 52 FVC change from baseline with a nerandomilast dosing regimen of 18 mg bid compared with 9 mg bid. Exposure-response modelling of AEs of interest demonstrated an increase in the rates of diarrhoea and weight loss of ≥5% with increasing nerandomilast Cmin,ss. Model-based simulations suggested a modest contribution of nerandomilast to these AE rates, with clinically relevant increases possibly at the highest quartile of nerandomilast exposure.

5.2.5. Overall discussion and conclusions on clinical pharmacology

5.2.5.1. Discussion

The clinical development program for nerandomilast to date comprises of 20 Phase I studies, one Phase II study, and two Phase III studies.

All reviewed bioanalytical method validation packages and associated bioanalytical study reports were acceptable and compliant with the applicable requirements of ICH M10, with no critical deficiencies identified.

Population PK Analysis

The respective PK models described the data adequately as judged by visual inspection of model diagnostic plots and VPCs. Fixed and random effect parameters were estimated with reasonable precision. Importantly, stratification of the VPCs, generated using the reduced covariate nerandomilast model, supported its predictive ability in the target population and across nerandomilast dose levels. Overall, the reduced covariate nerandomilast model is deemed fit for performing simulations.

Bioavailability

Trial 1305-0030 investigated the PK of nerandomilast administered as an oral dose with an IV microtracer dose of [14C]-nerandomilast. The absolute oral bioavailability of nerandomilast was 73%.

In conclusion, there are no clinically relevant effects of food on nerandomilast exposure regardless of formulation. Therefore, nerandomilast can be administered irrespective of food.

Elimination

Overall, renal excretion and hepatic metabolism were shown to be important elimination pathways for nerandomilast. Therefore, dedicated studies in patients with renal and hepatic impairment are warranted.

Metabolite profiling after single dose

In the human ADME study, the predominant metabolic pathways of nerandomilast were oxidation and glucuronidation. Following a single dose administration of 18 mg nerandomilast (C-14), nerandomilast was the most abundant circulating drug-related component, representing 51.3% of total plasma radioactivity (AUC0-36h). The most abundant metabolites in plasma after a single dose administration were the glucuronide metabolite M624(1) and the di-oxidative metabolite BI 764333, which represented 15.6% and 7.1% of total plasma radioactivity, respectively.

Metabolite profiling after multiple doses at steady state

At steady state, nerandomilast accounted for ~72% of the total drug-related material in plasma. Of the 11 metabolites identified, BI 764333 represented 12.5% of total drug-related material in plasma and was defined as the only major human metabolite, as its abundance was >10% of total circulating drug-related material at steady-state. BI 764333 is not pharmacologically active at relevant circulating concentrations in humans. No metabolites were characterized as having plasma exposure >25% of parent exposure at steady state. Therefore, in vitro evaluation of any nerandomilast metabolite as a potential inhibitor of CYPs, UGTs, or transporters is not required.

Interconversion

Nerandomilast has been developed as an enantiopure chiral drug that contains a sulfoxide group in the *R*-orientation. Following oral administration, nerandomilast undergoes minor metabolic chiral inversion to the pharmacologically inactive *S*-enantiomer. The half-life of the S-enantiomer is slightly longer than nerandomilast.

Dose proportionality and time dependency

Across multiple studies in healthy volunteers, nerandomilast was shown to exhibit approximately dose proportional PK over the single dose range of 0.06 mg to 48 mg. Similarly, across several studies in healthy volunteers, nerandomilast PK was approximately dose-proportional following multiple doses between 1 mg to 18 mg bid.Nerandomilast does not display time-dependent PK.

Pharmacokinetics in the target population

In the Phase II trial 1305-0013, nerandomilast PK was characterized in IPF patients with and without antifibrotic background treatment (i.e. nintedanib or pirfenidone). Nerandomilast exposure was similar between patients on nintedanib and those on no background antifibrotic. However, patients on pirfenidone had 35-50% lower nerandomilast exposure compared to patients on no antifibrotic.

Similarly, in the Phase III trial 1305-0014, IPF patients treated with pirfenidone had 48-55% lower nerandomilast trough concentrations compared to patients who were not on any antifibrotic, yet trough concentrations were comparable between patients on nintedanib and those not on any antifibrotic. A lack of treatment benefit was observed for the 9 mg dose group in patients with pirfenidone background therapy, which is thought to be driven by reduced nerandomilast exposure resulting from a suspected drug-drug interaction between nerandomilast and pirfenidone. See Drug Interactions for further information.

In Phase III trial 1305-0023 in patients with PPF, nerandomilast trough concentrations were similar between patients on nintedanib and those not on any antifibrotic. No patients took pirfenidone concomitantly. Nerandomilast trough concentrations in PPF patients were comparable to those in IPF patients who were not on pirfenidone background therapy (1305-0014). The impact of intrinsic and extrinsic factors on nerandomilast exposure, based on exploratory sub-group analyses of pre-dose concentrations, were comparable in patients with PPF and IPF.

Special populations

Renal impairment

In the dedicated renal impairment study, the impact of renal impairment (based on BSA-normalised eGFR according to CKD-EPI) on the PK of nerandomilast was evaluated following 18 mg nerandomilast single administration. Subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) had comparable Cmax (3% lower) but 37% higher AUC compared to matched healthy subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). Subjects with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) had 14% lower Cmax but 29% higher AUC compared to matched healthy subjects. The impact of renal impairment on nerandomilast exposure in subjects with end stage renal disease (eGFR value <15 mL/min/1.73m^2) was not evaluated.

Based on absolute GFR values (in mL/min), the overall exposure (AUC) of nerandomilast was ~10-39% higher and Cmax was ~20% lower in subjects with moderate/severe renal impairment, which is comparable to those based on BSA normalised GFR (ml/min/1.73m^2).

In the Phase III studies (1305-0014 and 1305-0023), exploratory subgroup analyses of steady state trough concentrations suggested that IPF or PPF patients with moderate renal impairment had 24-36% and 35-56% higher trough concentrations at 9 mg bid and 18 mg bid dose groups, respectively, compared with IPF/PPF patients with normal renal function. Despite this higher exposure, there were no safety concerns associated with nerandomilast treatment in patients with impaired renal function.

Overall, the applicant's conclusion that a dose adjustment is not warranted in patients with mild, moderate and severe renal impairment is agreed. The SmPC section 4.2 adequately mentions this information. As the impact of end stage renal disease on nerandomilast PK has not been studied, it is not recommended to be used in these patients, as stated in the SmPC.

Hepatic impairment

Trial 1305-0027 investigated the impact of hepatic impairment on the PK of nerandomilast following a single dose of 18 mg. Subjects with mild hepatic impairment (Child-Pugh A) had comparable AUC (5% higher) and ~17% lower Cmax compared to healthy subjects with normal hepatic function. Subjects with moderate hepatic impairment (Child-Pugh B) had ~31% higher AUC but 31% lower Cmax compared to healthy subjects with normal hepatic function. The impact of severe hepatic impairment (Child-Pugh C) on nerandomilast exposure was not evaluated.

The safety profile of nerandomilast was comparable between subjects with moderate hepatic impairment and subjects with normal hepatic function in the present study. Thus, it is agreed that a dose adjustment in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment is not warranted.

As the impact of severe hepatic impairment on nerandomilast PK has not been studied, it is not recommended to be used in these patients as stated in the SmPC section 4.2.

Ethnic factors

Higher nerandomilast exposure was observed in Asian patients in subgroup analyses in the Phase III trials compared to Caucasian patients. Results showed up to 47% higher nerandomilast pre-dose concentrations in Asian IPF and PPF patients compared to those observed in White patients. These differences in nerandomilast exposure may be partially explained by body weight.

Simulations predicted Chinese patients to have around 33%, 38%, and 40%, higher median AUC,ss, Cmax,ss, and Cmin,ss, respectively, and Japanese patients to have around 45%, 58%, and 35% higher median AUC,ss, Cmax,ss, and Cmin,ss, respectively, compared to non-Chinese/non-Japanese patients.

Despite the higher nerandomilast exposures, the applicant has justified that the safety profile for Asian patients is favourable and similar to the overall population, for the following reasons: 1) exposure-response models do not indicate an increased risk attributable to higher exposures in Asian patients; 2) Asian patients showed comparable trends for frequencies of AEs, SAEs, and fatal AEs as White patients; and 3) Relative frequencies of weight loss and diarrhoea events across treatment groups are similar between East Asian and non-East Asian patients. Therefore, it is agreed that a dose adjustment of nerandomilast based on weight is not necessary.

Weight

An inverse correlation between nerandomilast exposures (trough concentrations) and body weight was observed in patients with IPF and PPF in the Phase III trials. In the population pharmacokinetic analysis, bodyweight was a significant covariate impacting clearance and volume of distribution parameters. Compared to reference patient of 70 kg, individuals with low bodyweight (e.g. 40 kg) are predicted have a 53% increase in the AUCss and a 60% increase in Cmax,ss, whilst individuals with high bodyweight (e.g. 150 kg) are predicted to have a 42% decrease in the AUCss and a 38% decrease in Cmin,ss. The applicant has adequately justified that nerandomilast exposures in low and high body weight patients are not expected to be of concern in terms of safety or efficacy, respectively. Therefore, a dose adjustment based on body weight is not considered necessary.

Gender and age

There are no clinically relevant effects of gender or age on nerandomilast PK in the studied patient population. Nerandomilast is not indicated in paediatric patients.

Pharmacokinetic drug interactions

In vitro

Effects of other drugs on nerandomilast

Nerandomilast is mainly metabolized by CYP3A, with contributions also from UGTs. Therefore, coadministration of nerandomilast with concomitantly administered medications that modulate CYP3A activity, such as CYP3A inhibitors and/or inducers, may have an impact on clinical nerandomilast exposure. Nerandomilast is also a substrate of P-gp. Therefore, a dedicated DDI study with a strong CYP3A and P-gp inhibitor (itraconazole) was performed. Dedicated DDI studies were also performed with strong and moderate CYP3A inducers, carbamazepine and bosentan, respectively (see *In vivo* drug interactions for details).

Nerandomilast exposure is considered less likely to be affected by coadministration of drugs that modulate UGT activity because multiple UGTs contribute to the glucuronidation of nerandomilast and the direct glucuronide metabolite, M624(1), is a minor metabolic clearance pathway in humans. Therefore, it is agreed that a clinical DDI study with a UGT modulator is not warranted.

Effects of nerandomilast on other drugs

In vitro studies suggested that nerandomilast may cause clinically relevant induction of CYP3A and CYP2Cs. Therefore, a dedicated DDI study with a sensitive CYP3A substrate, midazolam, was conducted (Trial 1305-0033). Based on the results of this study, a dedicated study with a sensitive CYP2C substrate is not warranted (see *In vivo* drug interactions for details).

Since no metabolite of nerandomilast has an AUCmetabolite ≥25% of AUCparent at steady state, *in vitro* evaluations of CYP, UGT, or transporter inhibition potential of any metabolites are not required.

In vivo

Effects of other drugs on nerandomilast

CYP3A inducers

Two clinical DDI studies evaluating the effects of strong and moderate CYP3A induction on the PK of nerandomilast were performed. Both studies were adequately designed and conducted in line with the principles outlined in ICH M12. The findings are considered sufficiently robust to inform dose recommendations when nerandomilast is coadministered with moderate or strong CYP3A inducers.

As both strong and moderate CYP3A inducers reduced nerandomilast exposure to a similar extent (~40-50%) and given the lack of treatment effect with the 9 mg bid regimen in IPF patients receiving pirfenidone due to reduced nerandomilast exposure, a recommended dose of 18 mg bid in the presence of moderate or strong CYP3A inducers is appropriate. It is also agreed that the dose should not be reduced to 9 mg bid when such inducers are coadministered, as this carries a risk of reduced efficacy. The proposed updates to Sections 4.2 and 4.5 of the SmPC based on these data are acceptable.

The impact of mild CYP3A inducers on nerandomilast PK is expected to be modest compared to moderate and strong inducers. In addition, weak CYP3A inducers (e.g. corticosteroids) were commonly used in the Phase 3 trials. Therefore, it is agreed that it is not necessary to restrict the use of mild CYP3A inducers with nerandomilast.

CYP3A inhibitors

Trial 1305-0015 investigated the effect of a strong CYP3A4 inhibitor itraconazole on the PK of nerandomilast in healthy volunteers. The design and methodology are in line with relevant guidelines. Itraconazole was shown to increase nerandomilast Cmax by 1.3-fold and AUC by 2.2-fold. CL/F and Vz/F of nerandomilast decreased by approximately 50% with the co-administration of itraconazole.

Based on these results, strong CYP3A inhibitors were restricted in Phase II and III studies. The recommended of nerandomilast dose when coadministered with strong CYP3A inhibitors is 9 mg. This is agreed because the safety and efficacy of nerandomilast was established at both 9 mg and 18 mg bid doses in the Phase III trials, and the expected exposure when nerandomilast 9 mg is administered with strong CYP3A inhibitors is approximately equivalent to that of 18 mg nerandomilast alone.

P-gp inhibitors

Since itraconazole is known to inhibit both CYP3A and P-glycoprotein (P-gp), and nerandomilast is a substrate of P-gp, the observed increase in nerandomilast exposure in the itraconazole study may be attributed to dual inhibition of these pathways. However, the impact of P-gp inhibition alone is likely small, as evidenced by a modest 30% increase in Cmax. Given nerandomilast's high absolute bioavailability (approximately 73%), the potential for further increases in exposure via P-gp inhibition is limited. Therefore, the contribution of P-gp inhibition is expected to be less significant than the

combined effect of CYP3A and P-gp inhibition. Based on these findings, dose adjustment for coadministration with P-gp inhibitors is not considered necessary.

Acid reducing agents

Nerandomilast displays a pH-dependant solubility profile, with higher solubility at acidic pH (<3). Therefore, acid reducing agents (ARAs) such as PPIs could potentially impact the absorption of nerandomilast.

A dedicated DDI study to evaluate the effects of ARAs on nerandomilast PK was not conducted. Instead, the applicant conducted a post hoc subgroup analysis comparing sparsely collected nerandomilast predose concentrations in patients taking an ARA with patients not taking an ARA in the Phase III studies. The results showed that trough concentrations were generally comparable between patient groups. Furthermore, efficacy of nerandomilast (FVC decline in week 52 compared to placebo) was comparable between ARA users and non-ARA users in the phase III trials. Overall, it is agreed that a dose adjustment of nerandomilast in patients taking ARAs is not necessary.

Nintedanib and pirfenidone

Nintedanib had no relevant impact on nerandomilast trough concentrations in the exploratory subgroup analyses of Phase II and Phase III data, as well as in the popPK covariate analysis. Based on these data, a dose adjustment of nerandomilast is not warranted in patients taking nintedanib concomitantly and a dedicated DDI study to further investigate the effect of nintedanib on nerandomilast PK is not considered necessary.

By contrast, in exploratory subgroup analyses of data from the Phase II and Phase III trials, IPF patients with pirfenidone background treatment were observed to have 35-50% and 48-55% lower nerandomilast exposure, respectively, compared with patients without antifibrotic background treatment. Further, model-based simulations predicted 30-48% lower median nerandomilast exposure in patients with concomitant pirfenidone use. Based on these findings, the lack of treatment benefit of 9 mg bid nerandomilast observed in patients with pirfenidone background therapy is driven by reduced nerandomilast exposure via a drug-drug interaction between nerandomilast and pirfenidone. The likely mechanism of this interaction, based on an *in vitro* study, is a CYP3A4 induction by pirfenidone.

Therefore, CHPM agreed that the recommended dosage of nerandomilast is 18 mg twice daily. Based on individual patient tolerability, the dosage may be reduced to 9 mg twice daily.

However, in patients using pirfenidone, the recommended dosage is 18 mg twice daily and must not be reduced to 9 mg twice daily. If used concomitantly with strong CYP3A inhibitors, the recommended dosage is 9 mg twice daily. If used concomitantly with strong or moderate CYP3A inducers, the recommended dosage is 18 mg twice daily and must not be reduced to 9 mg twice daily.As a post approval commitment, the Applicant will submit the results of the clinical DDI study (1305-0035), evaluating the impact of pirfenidone on nerandomilast PK by 30 June 2027.

Effects of nerandomilast on other drugs

CYP3A substrates

Trial 1305-0033 was a dedicated DDI study with a CYP3A4 sensitive substrate (midazolam) to evaluate the potential for induction of CYP3A4 by nerandomilast. The design and methodology are acceptable.

Coadministration of 18 mg nerandomilast bid with 2 mg midazolam reduced the midazolam Cmax by 22% and AUC by 8-10% compared with administration of midazolam alone but not considered to be

clinically relevant. Further, no relevant increase in the biomarker for CYP3A induction was observed during nerandomilast treatment.

Taken together, these results show that nerandomilast does not cause clinically relevant induction of CYP3A. As such, a dose adjustment of CYP3A substrates is not warranted when taken concomitantly with nerandomilast.

CYP2C substrates

As nerandomilast did not induce CYP3A4, it can be assumed that nerandomilast will not induce CYP2C enzymes because CYP3A and CYP2C enzymes are induced via activation of the same transcriptional pathway. As such, lack of a dedicated study with a sensitive CYP2C substrate is acceptable.

Nintedanib and pirfenidone

Trial 1305-0034 was a DDI study to investigate the effect of steady state nerandomilast on the PK of pirfenidone and nintedanib. The design and methodology of this study are acceptable. Steady state of nerandomilast was observed to have been reached before pirfenidone and nintedanib test doses were administered.

Coadministration of 18 mg nerandomilast twice daily did not affect pirfenidone exposure (both Cmax and AUC). Similarly, coadministration of 18 mg nerandomilast twice daily did not affect nintedanib AUC but reduced Cmax slightly by 13%. Taken together, co-administration of nerandomilast did not change pirfenidone or nintedanib exposure to a clinically relevant extent.

Pharmacodynamics

Primary pharmacology

The applicant evaluated LTB4, TNF-α and IFN-γ inhibition in the clinical studies in an exploratory manner. Overall, the results of the pharmacodynamic evaluations were inconclusive. Two of the selected exploratory biomarkers (LPS-induced MCP-1 and MLP-induced LTB4) did not demonstrate that nerandomilast had any inhibitory effect. Nerandomilast showed some inhibitory effect on LPS-induced TNF-α and IFN-γ, however, in the majority of the studies with PD data the results were overall inconclusive due to high variability. This could have been the result of low patient numbers or the suitability of the assay.

The results regarding TNF-α and IFN-γ were also inconclusive due to high variability. It is understood that there were technical problems with assay handling at some sites and low numbers of participants, which could contribute to the variability seen.

Secondary pharmacology

The design and methodology of the thorough QT trial are in line with the ICH E14 Guideline. The 30 mg dose adequately accounts for accumulation at steady state following 18 mg bid dosing. The supratherapeutic dose of 48 mg, which is expected to result in exposure ~2.2 times the Cmax,ss at the 18 mg bid dose, is also considered adequate to account for a high clinical exposure scenario due to intrinsic or extrinsic factors. Assay sensitivity of the trial was sufficiently demonstrated with moxifloxacin.

The results showed that nerandomilast is not associated with a relevant prolongation of the QTcF interval. Following the single oral administration of 30 mg nerandomilast, accounting for the expected clinical therapeutic exposure at steady state, as well as 48 mg as the supratherapeutic dose, the maximum adjusted mean differences between nerandomilast and placebo in QTcF changes from baseline were 3.0 msec with 30 mg (90% CI: 0.7, 5.4) and 3.2 msec with 48 mg (90% CI: 1.2, 5.2),

and the corresponding upper limits of the 2-sided 90% CI remained well below the threshold of 10 msec.

Pharmacokinetics-Pharmacodynamics (PK/PD)

Exposure-response analyses for efficacy

The main goal of the ER analysis for efficacy was to characterize the relationship between nerandomilast exposure and absolute change in FVC for patients with IPF and patients with PPF. The final model consisted of a linear disease progression component (FVC decline) based on placebo data only and a nerandomilast treatment effect component based on data from the active treatment arms. The effect of nerandomilast included a combined initial off-set effect on FVC and a modifying effect on disease progression (measured as FVC slope).

A key consideration of this analysis was to ensure the model could reliably predict change from baseline in FVC at Week 52, the primary endpoint in both Phase III trials. This was evaluated using landmark VPCs, which demonstrated that the final model adequately predicted the observed annual change in FVC for the placebo and 18 mg dose groups. However, for the 9 mg dose group, the observed median and mean values fell outside the predicted distributions. Consequently, simulation results should be interpreted with caution.

Based on simulations, the effect of nerandomilast was reasonably consistent between IPF and PPF patients. Modelled annual decline in FVC from baseline was predicted to decrease with increasing nerandomilast exposure; however, the observed difference between the two dose groups was minimal (~16 mL) and not considered clinically meaningful.

Patients on no antifibrotic background treatment appeared to have less decline than patients on nintedanib or pirfenidone, which likely reflects the difference in disease characteristics between patients with and without antifibrotic background treatment. Poorer outcomes were predicted for patients on pirfenidone compared to those on nintedanib or no antifibrotic, which was probably due to reduced nerandomilast exposure. Simulations suggested comparable nerandomilast exposure and similar response between patients on 9 mg without pirfenidone and those on 18 mg with concomitant pirfenidone. These findings support the contention of a drug-drug interaction between nerandomilast and pirfenidone.

Exposure-response analyses for safety

The exposure-safety analysis was based on data from the Phase III studies in patients with IPF and PPF. The aim was to characterise relationships between nerandomilast exposure and multiple AEs (diarrhoea, nausea, infection, and weight loss [≥5% and ≥10%]), and to evaluate the predictive effect of the covariates of interest. There are no notable issues with the methodology for model development. As judged by visual inspection of model PPCs, the developed logistic regression models described the observed AE data reasonably well.

Population simulations were performed to quantify the probability of AEs across the IPF and PPF patient population stratified by levels of nerandomilast exposure and influential covariate subgroups. Of the five safety endpoints evaluated, a statistically significant increase in the incidence of diarrhoea and weight loss was observed with escalating nerandomilast exposure, indicating a dose-limiting toxicity profile.

Of the covariate subgroups evaluated, White subjects were predicted to be more likely to have diarrhoea or nausea than Asian subjects. Subjects on nintedanib background therapy were more likely to experience nausea and weight loss. The probability of weight loss was also higher for patients on

weight loss medication concomitantly. No covariate subgroup differences were found to be predictive for infection.

Dose justification

Nerandomilast doses of 9 mg bid and 18 mg bid were the only doses evaluated in the Phase III trials, and both were considered to be safe and effective.

In the ER analysis for efficacy, modelled annual decline in FVC from baseline was predicted to decrease with increasing nerandomilast exposure; however, the observed difference between the two dose groups was minimal and not considered clinically meaningful. In the ER analyses for safety, a statistically significant increase in the incidence of diarrhoea and weight loss was observed with escalating nerandomilast exposure, suggesting a dose-limiting toxicity profile.

The justification for recommending the higher dose of 18 mg, even though this dose was associated with more frequent AEs and treatment discontinuations, is based on an observed trend for a mortality benefit with the 18 mg dose and is agreed.

5.2.5.2. Conclusions

An extensive clinical pharmacology package for nerandomilast was submitted, providing adequate characterisation of its pharmacokinetic and pharmacodynamic properties. There is an outstanding clinical DDI study (1305-0035) to evaluate the effect of pirfenidone on nerandomilast PK. The Applicant has committed to submitting the results of this study by June 2027.

5.3. Clinical efficacy

5.3.1. Dose response study

No formal dose response study has been investigated.

Based on population PK/PD analysis of Phase II study 1305-0013 in IPF patients, the FVC response did not change as a function of exposure within the exposure range observed for the nerandomilast 18 mg bid dose given over 12 weeks. This suggested that the maximum effect of nerandomilast on FVC had been reached with the 18 mg bid dose consistent with the observed clinical stabilization of FVC over the treatment period.

Based on the simulated exposure, 9 mg bid dose provided a sufficient differentiation in the distribution of exposure compared with 18 mg bid dose, supporting that 9 mg and 18 mg bid doses provided wide ranges of plasma exposure to explore dose-response and exposure response relationship.

Further dose response was assessed in the pivotal FIBRONEER-ILD study to investigate the efficacy and safety of nerandomilast at a dose of 9 mg twice daily or 18 mg twice daily in participants with ILD-PPF over at least 52 weeks. The applicant did not conduct a formal dose response study in participants with non-IPF ILD-PPF or using the 9 mg nerandomilast twice daily dose before initiating the Phase III FIBRONEER-ILD clinical trial. The rationale for the 9 mg dose of nerandomilast twice daily was based on preclinical data on target engagement and simulated exposure assessments, so that both efficacy and safety with this lower dose can be investigated according to the applicant.

5.3.2. Main studies

5.3.2.1. FIBRONEER-IPF (1305-0014) (EU-CT 2)022-001091-34

Study title/design

This Phase III trial was a multi-centre, multi-national, prospective, randomised, placebo controlled double-blind clinical trial to investigate the efficacy and safety of nerandomilast at a dose of 9 mg bid and 18 mg bid in patients with IPF over at least 52 weeks. A total of approximately 963 patients were to be randomised into the trial, of which 321 patients were to be in each active treatment group and in the placebo group. The trial consisted of a screening period of up to 8 weeks, a randomised treatment period of at least 52 weeks, and a follow-up period of 7 days. Randomisation was stratified by the absence vs. presence of baseline antifibrotic treatment (nintedanib or pirfenidone).

Patient randomisation was stratified by the presence of background treatment with antifibrotics (AF group vs. non-AF group) expected to be 70% vs 30%, respectively, based on prescription practices in host countries:

- Non-AF group: patients not treated with an approved antifibrotic medication (nintedanib or pirfenidone) in the last 8 weeks prior to enrolment, (e.g. patients previously treated with antifibrotics but who discontinued that treatment, or patients never treated with antifibrotics before).
- AF group: patients on a stable treatment with an approved antifibrotic drug (e.g. nintedanib or pirfenidone) for at least 12 weeks at study entry, and who were planning to stay on this background treatment after randomisation.

The trial was conducted in 2 parts, as shown below. Treatment Period A of the trial consisted of Visits 2 through 10, until one year after randomisation. Treatment Period B began following completion of the Week 52 visit (Visit 10); patients continued treatment with blinded trial medication in Treatment Period B and had trial visits every 12 weeks. Assuming a respective recruitment period (about 18 months), it was estimated that the first randomised patients could be on trial treatment for up to 130 weeks.

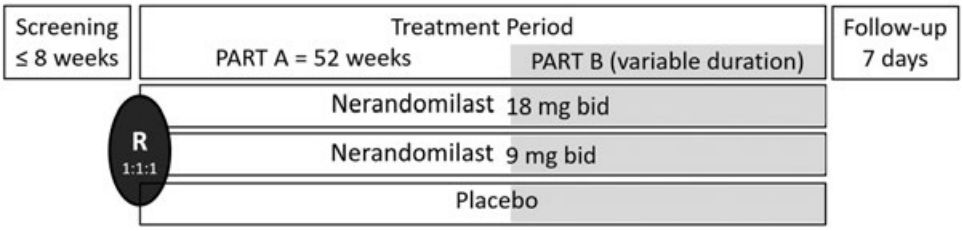


Figure 18: Overview of study 1305-0014 Trial design (Figure 9: 1)

Treatment

After randomisation patients began treatment for at least 52 weeks. Patients received either active treatment at a dose of 9 mg, 18 mg, or placebo to be orally taken twice daily (morning and evening).

There were no specific requirements regarding the timing of doses in relation to meals.

If taken around the same time (approximately within an hour), patients on nintedanib or pirfenidone background should have taken trial medication first, followed by the antifibrotic background medication. A

missed dose was to be skipped if the time window to the next dose was less than 8 h. The next dose was to be taken as scheduled. If an episode of vomiting happened after medication intake, re-dose with trial medication was not advised. After a temporary interruption, trial treatment could be restarted.

Randomisation

After the assessment of all inclusion and exclusion criteria, each eligible patient was randomised in 1:1:1 ratio to either 9 mg bid nerandomilast, 18 mg bid nerandomilast, or placebo at Visit 2. Patients were then stratified based on their background use of anti-fibrotic therapy or not.

Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in the double-blind trial remained blinded regarding the randomised treatment assignments until the database was declared ready for analysis.

Patient population

- Patients ≥40 years old at the time of signed informed consent.
- Diagnosis of IPF

Main criteria for trial entry

The 2022 ATS/ERS/JRS/ALAT Guideline as confirmed by the investigator based on chest HRCT scan taken within 12 months of Visit 1 and, if available, surgical lung biopsy or transbronchial lung cryobiopsy, and

"UIP" or "Probable UIP" HRCT pattern consistent with the clinical diagnosis of IPF, as confirmed by central review prior to Visit 2. Patients with an "Indeterminate" HRCT finding were eligible if a clinical diagnosis of IPF could be confirmed locally based on (historical) surgical lung biopsy or cryobiopsy demonstrating a "UIP" or "Probable UIP" histopathology pattern. (See table below)

Patients with an "Alternative diagnosis" HRCT finding were eligible if a clinical diagnosis of IPF could be confirmed locally based on (historical) surgical lung biopsy or cryobiopsy demonstrating a "UIP" histopathology pattern. (See table below)

• **IPF suspected**[1]		Histopathology pattern			
		UIP	**Probable UIP**	**Indeterminate for UIP or biopsy not performed**	**Alternative diagnosis**
HRCT pattern	**UIP**	**IPF**	**IPF**	**IPF**	**Non-IPF dx**
	Probable UIP	**IPF**	**IPF**	**IPF (Likely)**[2]	**Non-IPF dx**
	Indeterminate	**IPF**	**IPF (Likely)**[2]	**Indeterminate**[3]	**Non-IPF dx**
	Alternative diagnosis	**IPF(Likely)**[2]	**Indeterminate**[3]	**Non-IPF dx**	**Non-IPF dx**

dx = diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia

(CSR 1305-0014, Table 10.6: 1, Appendix 16.1.1.2)

- Patients could be either:
    - AF-Group: On a stable therapy with nintedanib or pirfenidone for at least 12 weeks prior to Visit 1 and during screening and were planning to stay on this background treatment

after randomisation. Combination of nintedanib plus pirfenidone was not allowed. Stable therapy was defined as the individually and general tolerated regimen of either nintedanib or pirfenidone (no dose changes) for at least 12 weeks.

  - Non-AF: Not on a treatment with nintedanib or pirfenidone for at least 8 weeks prior to Visit 1 and during the screening period (e.g. either AF-treatment naïve or previously discontinued) and did not plan to start or re-start antifibrotic treatment.

- Forced Vital Capacity (FVC) ≥45% of predicted normal at Visit 1.
- DLCO ≥25% of predicted normal corrected for haemoglobin (Hb) at Visit 1

Exclusion Criteria

- Prebronchodilator of FEV1/FVC <0.7 at Visit 1.
- In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
- Acute IPF exacerbation within 3 months prior to Visit 1 and/or during the screening period (investigator-determined).
- Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis.
- Confirmed infection with SARS-CoV-2 not fully recovered, according to investigator judgement, within the 4 weeks prior to randomisation (Visit 2).
- Major surgery (major according to the investigators assessment) performed within 6 weeks prior to Visit 2 or planned during the trial period, e.g. hip replacement.
  - Registration on lung transplantation list was not considered as planned major surgery.
- 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.
- AST or ALT >2.5x ULN or total bilirubin >1.5x ULN at Visit 1.
- eGFR ≤30 mL/min/1.73 m2 at Visit 1.
- Patients with underlying liver cirrhosis (Child Pugh A, B or C hepatic impairment).
- 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 ischemic attack within 6 months of Visit 1.
  - Unstable cardiac angina within 6 months of Visit 1.
- Patients who were treated with immunomodulatory medications (other than oral corticosteroids) or prednisone >15 mg/day or equivalent for respiratory or pulmonary reasons.
- Active vasculitis, unstable or uncontrolled within 8 weeks prior to Visit 1 or during the screening period.
- Any suicidal behaviour in the 2 years preceding the study (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).

- Any suicidal ideation of type 4 or 5 on the C-SSRS in the 3 months preceding the trial or at Visit 1 and/or Visit 2 (i.e. active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan).

- Acute or chronic severe depression defined as HADS subscore >14 at Visit 1 and/or Visit 2.
- Patients who must or wished to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. Please note: potent CYP3A4 inhibitors were not to be taken 5 half-life times prior to Visit 1.
- Patients treated with PDE1, PDE3, PDE4, PDE10 inhibitors, and non-selective PDE inhibitors within 30 days before Visit 1.
- Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, made the patient an unreliable trial participant).
- Inability to refrain from smoking on trial visit days.
- History of allergy or hypersensitivity or contraindications to the class of drugs under study including known hypersensitivity to the drug or its excipients.
- Patients with a significant disease or condition other than the ILD under study, which in the opinion of the investigator, could have put the patient at risk because of participation, interfered with study procedures, or caused concern regarding the patient's ability to participate in the study.
- Patients with active tuberculosis (TB).
- Previous randomisation in this trial or in trial 1305-0023.
- Patients who were enrolled in another investigational device or drug trial, or that had less than 30 days since ending another investigational device or drug trial(s) or from receiving other investigational treatment(s).
- History of stem cell therapy for the treatment of pulmonary fibrosis.

5.3.2.1.1. Objectives and estimands

Primary objective

The trial evaluated the efficacy and safety of 9 mg and 18 mg bid nerandomilast compared with placebo in patients with IPF in addition to the patient's standard of care treatment. The **primary objective** was a superiority objective to demonstrate a reduction in lung function decline as measured by the change from baseline in FVC for nerandomilast when compared with placebo in patients with IPF.

The primary endpoint was tested at an initial 4% significance level for the comparison of nerandomilast 18 mg versus placebo and at a 1% significance level for the comparison of nerandomilast 9 mg versus placebo. If at least one of the two hypotheses was rejected, the retained significance level from the successful hypothesis would be propagated according to the weights pre-specified in the graphical testing procedure. Each time a hypothesis was rejected, the graph would be updated to reflect the reallocation of the significance level.

Estimands for the primary objective

Table 18: Estimands for primary objective

Population	Patients with idiopathic pulmonary fibrosis who encountered the Intercurrent Events of change of background antifibrotic therapy, started of a restricted medication, treatment discontinuation, death, and lung transplant if assigned to nerandomilast or placebo.
Treatment condition	Assignment to nerandomilast, regardless of discontinuation and use of additional medications, compared to assignment to placebo, regardless of discontinuation and use of additional medications.
Endpoint (variable)	Absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52.
Population-level summary	Difference in mean change from baseline of FVC at Week 52 between nerandomilast and placebo
Intercurrent events and strategy to handle them	
Change in background antifibrotic therapy after baseline	Treatment policy – All available data up to Week 52 was included in the primary analyses
Start of a restricted medication	Treatment policy – All available data up to Week 52 was included in the primary analyses
Treatment discontinuation or interruption (anycause)	Treatment policy – All available data up to Week 52 was included in the primary analyses
Death	Hypothetical/Composite – Death events were considered a treatment failure and missing FVC change from baseline after death event was imputed based on 10th percentile of observed values across all treatment arms at each visit
Lung transplant	Hypothetical – Data collected after lung transplant was excluded

Statistical methods for estimation and sensitivity analysis on primary estimands

Analysis Sets

The following analysis sets were defined for statistical analyses:

- Entered Set (ES) – All patients who signed informed consent; used for analysis of participant disposition
- Randomised Set (RS) – All patients who were entered and randomised; used for analysis of participant disposition
- Full Analysis Set (FAS) – All randomised patients who received at least one dose of study drug; patients will be analysed based on the trial drug they actually received; used for baseline demographics, protocol deviations, and all efficacy analyses
- Treated Set (TS) – All randomised patients who received at least one dose of study drug; used for all safety analyses
- PK Parameter Analysis Set (PKS) – All patients in TS who provide at least one valid plasma concentration

Main analysis methods / statistical tests and estimation methods

Primary endpoint

The primary endpoint analysis followed a restricted maximum likelihood (REML)approach using a Mixed Model for Repeated Measures (MMRM) to compare change from baseline in FVC at Week 52 between the treatment groups. The model included the fixed categorical effects of treatment and baseline AF treatment, the fixed continuous effects of baseline FVC value, with visit being treated as the repeated measure with an unstructured covariance matrix.

Statistical testing was based on a comparison of least-square means of change from baseline between BI 1015550 and placebo using a significance level based upon a graphical testing procedure.

Handling of missing data

Primary endpoint

Missing data for non-death reasons were not imputed. Missing data due to death was to be assigned the 10^{th} percentile change from baseline of observed Week 52 FVC values from all observed values across all treatment arms at each visit. This is based on having a poor treatment outcome under the composite strategy for intercurrent events.

Sensitivity and supplementary analysis methods

Sensitivity analyses – Primary endpoint

There were two sensitivity analyses for the impact of missing data on the primary analysis, for these analyses missing data was classified into four subsets depending on the level and reason for missingness. These subsets were:

- Subset 1 – Patients with a Week 52 FVC value and received trial drug until Week 52
- Subset 2 – Patients with a Week 52 FVC value who prematurely discontinue trial drug before Week 52
- Subset 3 – Patients without a Week 52 FVC value who were alive at Week 52
- Subset 4 – Patients without a Week 52 FVC value who had died before Week 52

For both sensitivity analyses, patients who were in subset 4 had missing data imputed from the 10^{th} percentile change from baseline of all observed Week 52 FVC values across all treatment arms at each visit.

For the first sensitivity analysis, patients who were in subset 3 had missing data imputed using a follow reference approach. For the second sensitivity analysis, patients who were in this same subset had this missing data imputed using a retrieved dropout approach.

A tipping point analysis was conducted using the Multiple Delta Adjustment method to assess how extreme departures, from the missing at random (MAR) assumption in the primary analysis model, would have to be in order to reverse the conclusions of the primary analysis. This analysis was performed under different assumptions regarding a declining continuation of efficacy following withdrawal of treatment. A ranked ANCOVA analysis was conducted on the ranked change from baseline at Week 52. For patients with missing data at Week 52, for non-death reasons, the FVC change from baseline at Week 52 was imputed using multiple imputation. For patients who died before Week 52 ranking worse than those who remained alive at Week 52. Among the patients who died before Week 52, the rank was based on time to death from first trial drug intake date with shortest time to death as the worst rank.

A sensitivity analysis using the same model as the primary analysis was conducted where baseline AF treatment was replaced with the values used during the randomisation process as a covariate for adjustment.

A sensitivity analysis using the same model as the primary analysis with the additional covariates of sex, age, and height was conducted.

A sensitivity analysis using the same model as the primary analysis where records with FVC change from baseline values greater than +1000 mL or less than -1000 mL were excluded.

Supplementary analyses – Primary endpoint

The following supplementary analyses were conducted to utilise different strategies in handling ICEs:

- Treatment discontinuation – Hypothetical: Analysis including only data while on-treatment, this includes any off-treatment period due to treatment interruption
- Initiation in background antifibrotic therapy – Hypothetical: Data after initiation of antifibrotic therapy was excluded from analysis
- Initiation in background antifibrotic therapy – Composite: Data after initiation of antifibrotic therapy was assigned a poor outcome following the same rule as for the ICE of death in the primary analysis
- Important protocol deviation – Hypothetical: Data after different categories of important protocol deviations was excluded from analysis
- Death – Composite: Following the same strategy as the primary analysis but instead data was replaced based on the 0.1^{st}, 0.5^{th}, 1^{st}, 2.5^{th}, and 5^{th} percentile of observed values across all treatment arms at each visit
- Death – Hypothetical: Missing data after death was assumed to be MAR and analysis was only use observed data before death event
- Lung transplant – Composite: Data after lung transplant was assigned a poor outcome following the same rule as for the ICE of death in the primary analysis.

Secondary objectives

The main secondary objective of the trial was a superiority objective to demonstrate nerandomilast's ability in reducing the occurrence of clinically meaningful events of any acute IPF exacerbation, hospitalisation for respiratory cause, or death, over the duration of the trial when compared with placebo in patients with IPF. An additional superiority secondary objective of the trial was to show an effect of nerandomilast on symptoms and lung function.

Further objectives of the trial were:

- To assess additional measures of efficacy, safety, and tolerability of nerandomilast compared with placebo, including Quality-of-Life questionnaires, time to progression, acute IPF exacerbations, hospitalisations (for respiratory cause), mortality, and additional lung function assessments.
- To explore PK of nerandomilast in IPF patients with or without antifibrotic treatment
- To assess PK/PD and exploratory IPF biomarkers

Key Secondary endpoint

The key secondary endpoint in this trial was time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalisation for respiratory cause, or death (whichever occurred first) over the duration of the trial. Acute IPF exacerbations and hospitalisations for respiratory cause were not independently adjudicated.

Other secondary endpoints:

• Time to first acute IPF exacerbation or death over the duration of the trial

• Time to hospitalisation for respiratory cause or death over the duration of the trial

• Time to death over the duration of the trial

• Absolute change from baseline in FVC % predicted at Week 52

• Time to absolute decline in FVC % predicted of >10% from baseline or death over the duration of the trial

• Absolute change from baseline in DLCO % predicted (corrected for haemoglobin) at Week 52

• Time to absolute decline in DLCO % predicted of >15% from baseline or death over the duration of the trial

• Absolute change from baseline in L-PF Symptoms Dyspnoea domain score at Week 52

• Absolute change from baseline in L-PF Symptoms Cough domain score at Week 52

• Absolute change from baseline in L-PF Symptoms Fatigue domain score at Week 52

Estimands for the secondary objectives

Table 19: Estimands for secondary objectives

Population	Patients with idiopathic pulmonary fibrosis who would encounter the Intercurrent Events of change of background antifibrotic therapy, started of a restricted medication, treatment discontinuation, and lung transplant if assigned to BI 1015550 or placebo.
Treatment condition	Assignment to BI 1015550, regardless of discontinuation and use of additional medications, compared to assignment to placebo, regardless of discontinuation and use of additional medications.
Endpoint (variable)	Time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalisation for respiratory cause, or death (whichever occurs first) over the duration of the trial.
Population-level summary	Difference in hazard rates over the whole trial between BI 1015550 and placebo
Intercurrent events and strategy to handle them	
Change in background antifibrotic therapy after baseline	Treatment policy – All available data was included in the key secondary analyses
Start of a restricted medication	Treatment policy – All available data was included in the key secondary analyses
Treatment discontinuation or interruption (any cause)	Treatment policy – All available data was included in the key secondary analyses
Death	Composite – Death was treated as an event in the analysis
Lung transplant	Hypothetical – Data collected after lung transplant was censored

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The key secondary endpoint analysis was a time-to-event analysis for time to first acute IPF exacerbation, first hospitalisation for respiratory cause or death using a Cox proportional hazards model. The model used data across the whole trial and included the covariates of treatment, baseline AF treatment, age, FVC %predicted, and DLCO %predicted.

Statistical testing was carried out on the equality of hazard rates by the Wald test for BI 1015550 versus placebo using a significance level based upon a graphical testing procedure.

Handling of missing data for key secondary endpoint

Patients who did not have an event during the trial were censored at the last day the patient was known to be free of any event.

Sensitivity and supplementary analysis method*s for key secondary endpoint*

The following sensitivity analyses were conducted:

- Cox proportional hazards model but with only treatment as a covariate and not adjusting for other variables
- Cox proportional hazards model but with additional covariates of sex, and height
- Cox proportional hazards model with only confirmed acute exacerbations as events

Supplementary analyses – Key secondary endpoint

The following supplementary analyses were conducted to utilise different strategies in handling ICEs:

- Treatment discontinuation – Hypothetical: Same analysis as the key secondary analysis, but with the observation period set up to days after discontinuation of treatment
- Important protocol deviations – Hypothetical: Same analysis as the key secondary analysis, with the observation period set up as while patients are compliant with the protocol
- Initiation in background antifibrotic therapy – Hypothetical: Same analysis as the key secondary analysis, with data censored at the time of initiation of background antifibrotic therapy
- Initiation in background antifibrotic therapy – Composite: Same analysis as the key secondary analysis, with initiation of background antifibrotic therapy considered as an event
- Lung transplant – Composite: Same analysis as the key secondary analysis, with occurrence of lung transplant considered as an event

5.3.2.1.2. Results

Participant flow and numbers analysed

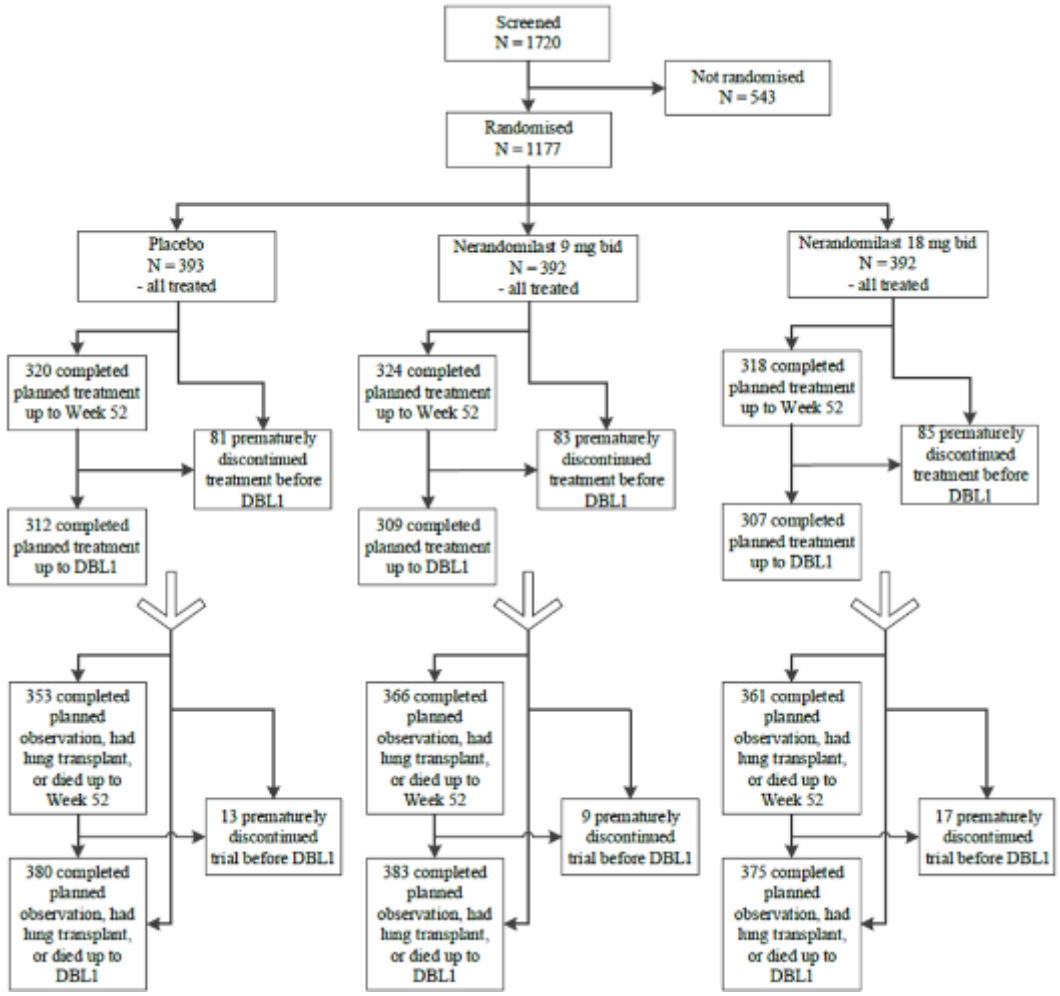


Figure 19: Participant flow - Disposition of patients up to DBL1 (CSR 1305-0014)

The trial ran from 06 Oct 2022 – 17 Dec 2024. The main analysis at DBL1 was performed with data collected up to 16 Aug 2024 and the final analysis at DBL2 was 17 Dec 2024. Patients were followed for a median time of 14.6 months at the time of main analysis and 17.0 months at the end-of-trial analysis. A total of 1720 patients were screened and 1177 randomised. Randomisation was stratified by the presence of background treatment with antifibrotics (AF group vs. non-AF group). There were 214 (22.2%) more randomised patients than planned (963 in CTP) in this trial due to faster than expected recruitment and a large number of patients in screening at the time recruitment was stopped. Randomisation of all eligible screened patients was allowed as per CTP. A total of 31.6% of the screened patients were not randomised, with the most common reason being a failure to meet the eligibility criteria (28.8% of screened patients). The most common eligibility criteria not met were the diagnosis of IPF, the DLCO inclusion criterion, and prebronchodilator FEV1/FVC exclusion criterion. All 1177 randomised patients were treated with study medication.

Up to Week 52, 962 patients (81.7% of the treated patients) completed planned treatment and a total of 1080 patients (91.8%) completed planned observation for the primary endpoint assessment. A total of 1138 patients (96.7%) completed the planned observation in trial (up to DBL1 cut-off date): 1046 patients (88.9%) were ongoing, 17 (1.4%) had lung transplant, and 75 (6.4%) died.

The disposition of patients was balanced across the treatment groups, except for more treatment discontinuations due to AEs, fewer treatment discontinuations due to withdrawal by patients, and fewer deaths in the 18 mg bid nerandomilast group. Treatment was prematurely discontinued in 20.6% of patients in the placebo group, 21.2% of patients in the 9 mg bid nerandomilast group, and 21.7% of patients in the 18 mg bid nerandomilast group. On average, premature treatment discontinuation occurred earlier with the 18 mg bid nerandomilast dose (median for patients who discontinued: 151 days) than with the 9 mg bid nerandomilast dose (219 days) or placebo (186 days), mainly due to more discontinuations within the first month of treatment. However, there was a dose-dependent increase in treatment discontinuation rate was observed in females (placebo: 5.4%, 9 mg bid nerandomilast: 18.7%, 18 mg bid nerandomilast: 27.5%), but not in males, mainly due to AEs.

In both non-AF and AF strata, the rate of treatment discontinuation (mainly due to AEs) was similar in the placebo group and 9 mg bid nerandomilast group (ranging from 19.3% to 21.8%). However, the 18 mg bid nerandomilast group showed differential trends between the strata: fewer discontinuations in the non-AF stratum (11.5%) while more discontinuations in the AF stratum (24.6%) were observed. When further broken down by the type of AF therapy, differential trends were seen between nintedanib and pirfenidone background treatments: more treatment discontinuations were observed on nerandomilast (25.0% for 9 mg bid and 29.8% for 18 mg bid) than placebo (19.7%) in patients with nintedanib background treatment, while fewer discontinuations were observed on nerandomilast (16.7% for 9 mg bid and 17.3% for 18 mg bid) than placebo (21.1%) in patients with pirfenidone background treatment.

Table 20: Treatment completion by background AF therapy up to DBL1 – TS

Placebo			Nera 9 mg bid		Nera 18 mg bid		Total	
N	%		N	%	N	%	N	%
Patients without background AF therapy								
Treated (treatment assigned as randomised)	87	100.0	88	100.0	87	100.0	262	100.0
Completed planned treatment up to Week 52[1]	70	80.5	73	83.0	78	89.7	221	84.4
Completed planned treatment up to DBL1 (ongoing at DBL1)	68	78.2	71	80.7	77	88.5	216	82.4
Prematurely discontinued treatment before DBL1	19	21.8	17	19.3	10	11.5	46	17.6
Adverse event	7	8.0	6	6.8	6	6.9	19	7.3
Protocol deviation	1	1.1	0		0		1	0.4
Withdrawal by patient	6	6.9	8	9.1	1	1.1	15	5.7
Lost to follow-up	0		0		0		0	
Other	4	4.6	3	3.4	3	3.4	10	3.8
Patients with background AF therapy								
Treated (treatment assigned as randomised)	306	100.0	304	100.0	305	100.0	915	100.0
Completed planned treatment up to Week 52[1]	250	81.7	251	82.6	240	78.7	741	81.0
Completed planned treatment up to DBL1 (ongoing at DBL1)	244	79.7	238	78.3	230	75.4	712	77.8
Prematurely discontinued treatment before DBL1	62	20.3	66	21.7	75	24.6	203	22.2
Adverse event	36	11.8	43	14.1	53	17.4	132	14.4
Protocol deviation	0		0		0		0	
Withdrawal by patient	13	4.2	8	2.6	9	3.0	30	3.3
Lost to follow-up	1	0.3	0		0		1	0.1
Other	12	3.9	15	4.9	12	3.9	39	4.3
Patients with nintedanib background therapy								
Treated (treatment assigned as randomised)	173	100.0	184	100.0	178	100.0	535	100.0
Completed planned treatment up to Week 52[1]	141	81.5	147	79.9	130	73.0	418	78.1
Completed planned treatment up to DBL1 (ongoing at DBL1)	139	80.3	138	75.0	125	70.2	402	75.1
Prematurely discontinued treatment before DBL1	34	19.7	46	25.0	53	29.8	133	24.9
Adverse event	23	13.3	34	18.5	40	22.5	97	18.1
Protocol deviation	0		0		0		0	
Withdrawal by patient	6	3.5	5	2.7	5	2.8	16	3.0
Lost to follow-up	0		0		0		0	
Other	5	2.9	7	3.8	7	3.9	19	3.6
Patients with pirfenidone background therapy								
Treated (treatment assigned as randomised)	133	100.0	120	100.0	127	100.0	380	100.0
Completed planned treatment up to Week 52[1]	109	82.0	104	86.7	110	86.6	323	85.0
Completed planned treatment up to DBL1 (ongoing at DBL1)	105	78.9	100	83.3	105	82.7	310	81.6
Prematurely discontinued treatment before DBL1	28	21.1	20	16.7	22	17.3	70	18.4
Adverse event	13	9.8	9	7.5	13	10.2	35	9.2
Protocol deviation	0		0		0		0	
Withdrawal by patient	7	5.3	3	2.5	4	3.1	14	3.7
Lost to follow-up	1	0.8	0		0		1	0.3
Other	7	5.3	8	6.7	5	3.9	20	5.3

Post DBL2, the total number of patients screened was corrected from 1720 to 1719 because 1 patient had been rescreened and randomised under a different patient number. Up to DBL2, 889 patients (75.5%) completed planned treatment. Of these 889 eligible patients, 852 patients (95.8%) continued or switched to nerandomilast 18 mg bid treatment in the open-label extension trial 1305-0031.

The most common reasons for premature discontinuation of study medication before DBL2 (a total of 24.5% of 1177 treated patients) were similar to those before DBL1: occurrence of an AE (14.3%), followed by "other" (5.2%), and withdrawal by patient (4.5%).

A total of 1129 patients (95.9%) completed the trial: 1003 patients (85.2%) completed the planned observation at DBL2, 22 (1.9%) had lung transplant, and 104 (8.8%) died. Similar to what was observed for DBL1, the disposition of patients up to DBL2 was balanced across the treatment groups, except for more treatment discontinuations due to AEs, fewer treatment discontinuations due to withdrawal by patients, and fewer deaths in the 18 mg bid nerandomilast group.

Treatment was prematurely discontinued before DBL2 in 25.7% of patients in the placebo group, 24.0% of patients in the 9 mg bid nerandomilast group, and 23.7% of patients in the 18 mg bid nerandomilast group. Premature treatment discontinuation was confirmed to occur earlier, on average, with the 18 mg bid nerandomilast dose (median for patients who discontinued: 182.0 days) than with the 9 mg bid nerandomilast dose (231.5 days) or placebo (228.0 days), mainly due to more discontinuations within the first month of treatment.

Deviations from study plan

A total of 3 global amendments and 9 local amendments to the CTP were issued. Global Amendment 1 (dated 26 July 2022) referred to minor changes and was implemented without approval from the IEC/IRBs. Global Amendment 2 (dated 10 May 2023) and Global Amendment 3 (dated 20 September 2023) introduced major changes and were both implemented after approval from the IEC/IRBs.

Major changes from Global Amendment 2 (dated 10 May 2023) Eligibility criteria were updated to include patients with an "alternative diagnosis" HRCT finding.

- The upper limit for DLCO was deleted since it was not relevant as an exclusion criterion.
- Any FEV/FVC ratio <0.7 was to be avoided as the risk of emphysema and obstruction would be high and would influence efficacy endpoint measurements.
- Management and handling of patients and data in case the dose of 9 mg bid was considered as futile were clarified where needed, based on blinding and unblinding concerns, randomisation, and on interim analysis details.
- Restrictions regarding prednisone prior to the study were updated from not permitted to permitted, referring to historical episodes of intake and introduction in case of exacerbations.
- Patients were to be analysed as randomised in the efficacy analysis, and as treated in the safety analysis. The PPS was deleted as post-randomisation events were to be handled via estimands (based on ICH E9 addendum), as described in the TSAP. For this reason, the FAS was added as the primary population for the efficacy analysis, and the definition of the TS was modified, as this was to be the primary population for the safety analysis (but not the efficacy analysis).
- Since there could be a few days gap between the randomisation date and the first drug intake date, for the purpose of time to event analyses, the actual time at risk should start with the first drug intake. For this reason, for all time-to-event endpoints, the start date considered when calculating the time to event of interest (and the time to censoring) was changed from 'randomisation date' to 'first drug intake date'.

Major changes from Global Amendment 3 (dated 20 September 2023)

- The efficacy interim analysis was not to be conducted, and the main analysis and the final analysis were specified. This decision was made by the sponsor before the futility analysis based on Health Authority feedback and shifting trial timelines with fast recruitment, which made the time advantage in conducting the interim analysis limited.
- The overall trial design section that was revised to specify the main and final analyses.
- Unblinding of the sponsor at the main analysis (DBL1) was clarified, as well as the use of unblinded PK data before DBL1 by personnel involved in the PK analyses to front-load.
- An explanation that the hypothesis testing of the key secondary endpoint was to be done at the main analysis, and a high-level description of what would be analysed at the main and the final analysis.
- On restrictions regarding concomitant treatment, restricted PDE inhibitors were narrowed down to those that specifically interfere with PDE4.
- AE reporting based on HADS was clarified.

Important protocol deviations

Up to DBL1, the proportions of patients with iPDs were low and similar between the treatment groups. The most common iPD was the use of potent CYP3A4 inhibitors as concomitant medications between randomisation and EOT (2.8% of patients). The use of potent CYP3A4 inhibitors tended to be less frequent under 18 mg bid nerandomilast treatment than under 9 mg bid nerandomilast treatment or placebo. All other iPDs were reported in no more than 2% of patients overall.

Between DBL1 and DBL2, the proportions of patients with iPDs increased (14.9% overall) but remained similar between the treatment groups (16.0% under placebo, 15.6% under 9 mg bid nerandomilast, and 13.0% under 18 mg bid nerandomilast) Up to DBL2, the trends regarding iPDs were consistent with those described for DBL1. The most common iPD remained the use of potent CYP3A4 inhibitors as concomitant medications between randomisation and EOT (4.6% of patients), with a less frequent use under 18 mg bid nerandomilast treatment (2.8%) than under 9 mg bid nerandomilast treatment (5.1%) or placebo (5.9%).

Baseline data

A total of 1720 patients were screened and 1177 randomised. The majority of randomised patients were from Europe (37.6%) and Asia (30.4%), followed by the United States (16.7%). The majority of the trial patients were men (83.0%). Almost all patients were either White (67.7%) or Asian (31.6%), 6 patients were Black or African American (0.5%), and 2 patients (0.2%) were multiple race respondents. Most were elderly (mean age 70.2 years, SD 7.7) and the majority of the population (47.9%) was between 65≤ to <75 years old. These data were generally balanced across the treatment groups. Most participants in this trial are former smokers 68.8% and 2.2% are current smokers, however 29% of the patients in this trial are never smokers.

Table 21: Demographic data at baseline – FAS (CSR 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Number of patients (N %)	393	100.0	392	100.0	392	100.0	1177	100.0
Sex (N %)								
Male	337	85.8	317	80.9	323	82.4	977	83.0
Female	56	14.2	75	19.1	69	17.6	200	17.0
Race (subgroup) (N %)[1]								
White	273	69.5	266	67.9	258	65.8	797	67.7
Asian	117	29.8	123	31.4	132	33.7	372	31.6
Black/African American	2	0.5	3	0.8	1	0.3	6	0.5
Ethnicity (N %)								
Not Hispanic/Latino	365	92.9	369	94.1	348	88.8	1082	91.9
Hispanic/Latino	28	7.1	23	5.9	44	11.2	95	8.1
Age [years] (mean, SD)	69.9	7.5	70.5	7.8	70.3	7.8	70.2	7.7
<65 (N %)	86	21.9	78	19.9	83	21.2	247	21.0
≥65 (N %)	307	78.1	314	80.1	309	78.8	930	79.0
≥65 to <75 (N %)	192	48.9	189	48.2	183	46.7	564	47.9
≥75 (N %)	115	29.3	125	31.9	126	32.1	366	31.1
Body weight [kg] (mean, SD)	77.5	14.5	76.1	15.8	76.3	14.0	76.6	14.8
Height [cm] (mean, SD)	171	9.3	169	9.6	169	9.1	170	9.4
BMI [kg/m^2] (mean, SD)	26.5	3.8	26.4	4.1	26.5	3.8	26.5	3.9
Smoking status (N %)								
Never	113	28.8	119	30.4	109	27.8	341	29.0
Former	275	70.0	263	67.1	272	69.4	810	68.8
Current	5	1.3	10	2.6	11	2.8	26	2.2

1 Multiple race respondents are not shown; see source table for the data.

Baseline AF therapy

A total of 915 patients (77.7%) had been on background treatment with approved antifibrotics (AF) at baseline with an average treatment duration of 28 months for nintedanib (45.5% of randomised patients) and 33 months for pirfenidone (32.3% of randomised patients). A total of 262 (22.3%) patients had no AF therapy at baseline; among these patients, the majority (172 patients, 14.6% of overall population) were naïve to AF therapy. The mean time since IPF diagnosis was 3.5 years (SD 2.7) before the trial, and about half of the patients had been diagnosed for more than 3 years. These data were generally balanced across the treatment groups.

Patients with background AF therapy had longer time since diagnosis (3.4 years with nintedanib and 4.1 years with pirfenidone, vs. 2.8 years in patients without background AF therapy) lower FVC % predicted, lower DLCO % predicted than those without and more frequent use of supplemental oxygen (22.4% of patients with nintedanib and 22.6% with pirfenidone, vs. 16.0% without background AF therapy). Between patients with nintedanib and pirfenidone background treatments, these characteristics were comparable.

Table 22: Trial indication and baseline AF therapy – FAS (CSR 1305-0014, Table 10:9)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Number of patients (N %)	393	100.0	392	100.0	392	100.0	1177	100.0
Time since first IPF diagnosis [years] (mean, SD)	3.53	2.75	3.46	2.63	3.60	2.79	3.53	2.72
≤1 (N %)	66	16.8	61	15.6	58	14.8	185	15.7
>1 to ≤3 (N %)	134	34.1	140	35.7	135	34.4	409	34.7
>3 to ≤5 (N %)	98	24.9	104	26.5	105	26.8	307	26.1
>5 (N %)	95	24.2	87	22.2	94	24.0	276	23.4
Baseline AF therapy (N %)	306	77.9	304	77.6	305	77.8	915	77.7
Nintedanib	173	44.0	184	46.9	178	45.4	535	45.5
Duration on current AF treatment [months] (mean, SD)	28.9	22.9	27.7	22.5	27.4	21.0	28.0	22.1
Pirfenidone	133	33.8	120	30.6	127	32.4	380	32.3
Duration on current AF treatment [months] (mean, SD)	35.0	24.6	32.6	22.9	30.9	21.8	32.8	23.2
No baseline AF therapy (N %)	87	22.1	88	22.4	87	22.2	262	22.3
Previous AF use	32	8.1	31	7.9	27	6.9	90	7.6
AF naïve	55	14.0	57	14.5	60	15.3	172	14.6
Baseline supplemental oxygen use (N %)	90	22.9	68	17.3	90	23.0	248	21.1

Baseline disease characteristics

The mean predicted FVC for patients in this trial was 78.2%, DLCO was 50.9%, and mean L-PF score was 25.24 which would indicate a mild-moderate level of disease severity.

Patients with background AF therapy had lower FVC % predicted (78.1% in patients with nintedanib and 75.7% with pirfenidone, vs. 82.2% in patients without background AF therapy) and lower DLCO % predicted (49.6% in patients with nintedanib and 49.7% with pirfenidone, vs. 55.2% without background AF therapy). No major differences were observed between nintedanib and pirfenidone AF subgroups. In the patients without background AF therapy, DLCO % predicted was higher in patients in the 9 mg bid nerandomilast group (57.4%) and 18 mg bid nerandomilast group (57.1%) than in patients in the placebo group (51.0%).

Table 23: Baseline lung function variables by background AF therapy – FAS (CSR 1305-0014, Table 10: 12)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Patients without background AF therapy								
Number of patients (N %)	87	100.0	88	100.0	87	100.0	262	100.0
Time since first IPF diagnosis [years] (mean, SD)	2.78	3.17	2.78	2.49	2.93	3.14	2.83	2.94
Baseline supplemental oxygen use (N %)	17	19.5	11	12.5	14	16.1	42	16.0
FVC [mL] (mean, SD)	2833	886	2764	739	2761	778	2786	801
FVC [% predicted] (mean, SD)	82.2	19.5	82.3	15.7	82.1	18.7	82.2	17.9
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	51.0	17.5	57.4	18.5	57.1	18.4	55.2	18.3
Patients with background AF therapy								
Number of patients (N %)	306	100.0	304	100.0	305	100.0	915	100.0
Time since first IPF diagnosis [years] (mean, SD)	3.74	2.59	3.65	2.64	3.79	2.65	3.73	2.62
Baseline supplemental oxygen use (N %)	73	23.9	57	18.8	76	24.9	206	22.5
FVC [mL] (mean, SD)	2873	781	2859	793	2846	752	2859	775
FVC [% predicted] (mean, SD)	75.9	17.8	78.0	16.9	77.4	16.2	77.1	17.0
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	49.0	15.3	50.0	14.1	49.9	17.0	49.6	15.5
Patients with nintedanib background therapy								
Number of patients (N %)	173	100.0	184	100.0	178	100.0	535	100.0
Time since first IPF diagnosis [years] (mean, SD)	3.36	2.34	3.40	2.61	3.55	2.68	3.44	2.55
Baseline supplemental oxygen use (N %)	37	21.4	33	17.9	50	28.1	120	22.4
FVC [mL] (mean, SD)	2971	802	2937	829	2863	805	2924	812
FVC [% predicted] (mean, SD)	76.9	17.4	79.9	17.7	77.5	17.4	78.1	17.5
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	48.9	15.7	51.1	14.3	48.6	17.1	49.6	15.7
Patients with pirfenidone background therapy								
Number of patients (N %)	133	100.0	120	100.0	127	100.0	380	100.0
Time since first IPF diagnosis [years] (mean, SD)	4.24	2.80	4.03	2.64	4.12	2.59	4.13	2.68
Baseline supplemental oxygen use (N %)	36	27.1	24	20.0	26	20.5	86	22.6
FVC [mL] (mean, SD)	2744	737	2738	722	2822	674	2768	711
FVC [% predicted] (mean, SD)	74.6	18.2	75.1	15.4	77.3	14.3	75.7	16.1
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	49.1	14.8	48.4	13.7	51.7	16.7	49.7	15.2

Outcomes and estimation

The adjusted mean (95% CI) change from baseline in FVC [mL] at Week 52 was -183.5 (-210.9, -156.1) in the placebo group, -138.6 (-165.6, -111.6) in the 9 mg bid nerandomilast group, and -114.7 (-141.8, -87.5) in the 18 mg bid nerandomilast group. The differences of nerandomilast 9mg and 18 mg bid to placebo were both statistically significant (see below). The adjusted mean difference (95% CI, p-value) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 44.9 (6.4, 83.3, p = 0.0222) and between 18 mg bid nerandomilast and placebo groups was 68.8 (30.3, 107.4, p = 0.0005).

Based on a graphical testing procedure that maintained an overall type I error rate of 5% both nerandomilast doses were superior to placebo for the primary endpoint: p = 0.0005 for 18 mg bid dose was below the initially assigned alpha level of 0.04; p = 0.0222 for 9 mg bid dose was below the updated alpha level of 0.03.

The adjusted mean of absolute change from baseline in FVC in both nerandomilast dose groups started to separate from the placebo group shortly after randomisation at Week 2 and continued to diverge up to Week 52. The primary endpoint was analysed at DBL1 as prespecified, once the last randomised patient had reached the Week 52 visit and was not re-analysed at DBL2.

Table 24: Absolute change from baseline in FVC [mL] at week 52 – FAS (study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in FAS	393		392		392	
Number of patients analysed[1]	391		390		392	
Baseline (mean, SD)	2863.9	804.6	2837.2	781.4	2827.3	758.0
Week 52 change from baseline						
Adjusted mean	-183.5		-138.6		-114.7	
95% CI	-210.9	-156.1	-165.6	-111.6	-141.8	-87.5
Comparison vs. placebo						
Adjusted mean	--		44.9		68.8	
95% CI	--		6.4	83.3	30.3	107.4
p-value[2]	--		0.0222		0.0005	

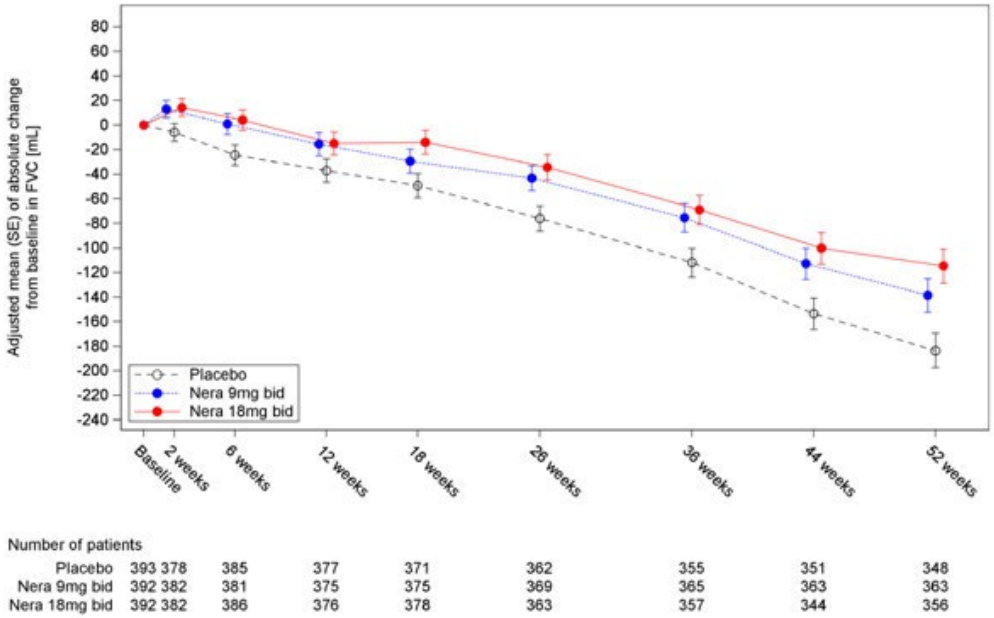


Figure 20: Adjusted mean (SE) of absolute change from baseline in FVC [mL] over 52 weeks – FAS (Study 1305-0014)

Secondary endpoints

Primary analysis of key secondary endpoint

The confirmatory key secondary endpoint was the time to the first occurrence of any of the components of the composite endpoint: first acute IPF exacerbation (events clinically considered to meet the definition of acute IPF exacerbation, either confirmed with CT data or suspected events without CT data), first hospitalisation for respiratory cause, or death over the duration of the trial. Acute IPF exacerbations and hospitalisations for respiratory cause were not independently adjudicated. Hospitalisations for respiratory cause were the most common events contributing to the key secondary endpoint (about half of the first events).

The hypothesis testing of the key secondary endpoint was based on data over the whole trial up to DBL1. The primary estimand followed the treatment policy approach and data over the whole trial up to DBL1 (including data beyond 52 weeks) were included. Key secondary endpoint events occurred in 80 patients (20.4%) in the placebo group, 79 patients (20.2%) in the 9 mg bid nerandomilast group, 85 patients (21.7%) in the 18 mg bid nerandomilast group. There was no statistically significant treatment difference

to placebo for either nerandomilast dose. HR vs. placebo for 9 mg bid 1.03, 95% CI 0.75, 1.41, p = 0.8568; for 18 mg bid 1.17, 95% CI 0.86, 1.59, p = 0.3102; p-value for both doses above the alpha level of 0.05. The probability of an event was similar in all treatment groups throughout the trial up to DBL1.

Table 25: Time to the first event in the key secondary composite endpoint (acute IPF exacerbation, first hospitalisation for respiratory cause, or death) over the duration of the trial up to DBL1 – FAS (study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	393	100.0	392	100.0	392	100.0
Patients with event (N %)	80	20.4	79	20.2	85	21.7
Acute IPF exacerbation as the 1 st event	27	6.9	28	7.1	36	9.2
Hospitalisation for respiratory cause as the 1 st event	41	10.4	40	10.2	42	10.7
Death as the 1 st event	12	3.1	11	2.8	7	1.8
HR vs. placebo[1]	--		1.03		1.17	
95% CI			0.75	1.41	0.86	1.59
p-value[2]			0.8568		0.3102	
Estimated percentage of patients with event at Week 52	18.32		17.58		19.34	
95% CI	14.81	22.55	14.13	21.76	15.74	23.64
Difference in probability vs. placebo	--		-0.95		0.99	
95% CI			-6.34	4.45	-4.51	6.49

1 Based on Cox proportional hazards model including treatment, baseline antifibrotic therapy, age, baseline FVC % predicted, and baseline DL_{CO} % predicted (corrected for haemoglobin) as covariates

2 p-value using a Wald test; as per a pre-defined graphical testing procedure, the p-value was not statistically significant for either nerandomilast dose

The p-values presented in DBL2 results were considered exploratory in nature and no adjustment for multiplicity was made. With additional treatment exposure and observation time up to DBL2, the event rate for the key secondary endpoint increased across treatment groups up to DBL2, with the largest increase in the placebo group. No difference in the risk of having a key secondary endpoint event was observed between the treatment groups. However, the HRs for both nerandomilast groups vs. placebo were numerically lower than those for DBL1 and were <1, after about 1.5 months of additional mean treatment exposure and 2 months of additional mean observation time.

Between DBL1 and DBL2, 42 additional events contributing to the key secondary endpoint occurred, representing an increase of approximately 17% of the total number of key secondary endpoint events reported at DBL1. There were more events reported in the placebo group (+23 events) than in the 9 mg and 18 mg bid nerandomilast groups (+11 and +8 events, respectively). Over the duration of the trial, up to DBL2, key secondary endpoint events occurred in 103 patients (26.2%) in the placebo group, 90 patients (23.0%) in the 9 mg bid nerandomilast group, 93 patients (23.7%) in the 18 mg bid nerandomilast group. Compared with placebo, the HR (95% CI) was 0.92 (0.69, 1.22) for 9 mg bid nerandomilast (p = 0.5443) and 0.99 (0.75, 1.31) for 18 mg bid nerandomilast (p = 0.9512). Hospitalisations for respiratory cause remained the most common events contributing to the key secondary endpoint (about half of the first events).

Secondary and further endpoints related to the key secondary endpoint

No treatment difference to placebo for either nerandomilast dose was observed for any of the 3 components of the key secondary endpoint as stand-alone endpoints. While a numerical difference in favour of 18 mg bid nerandomilast was observed for death, numerical differences in disfavour were observed for acute IPF exacerbation and hospitalisation for respiratory cause. In the 9 mg bid nerandomilast group, these component events occurred at a similar rate as in placebo.

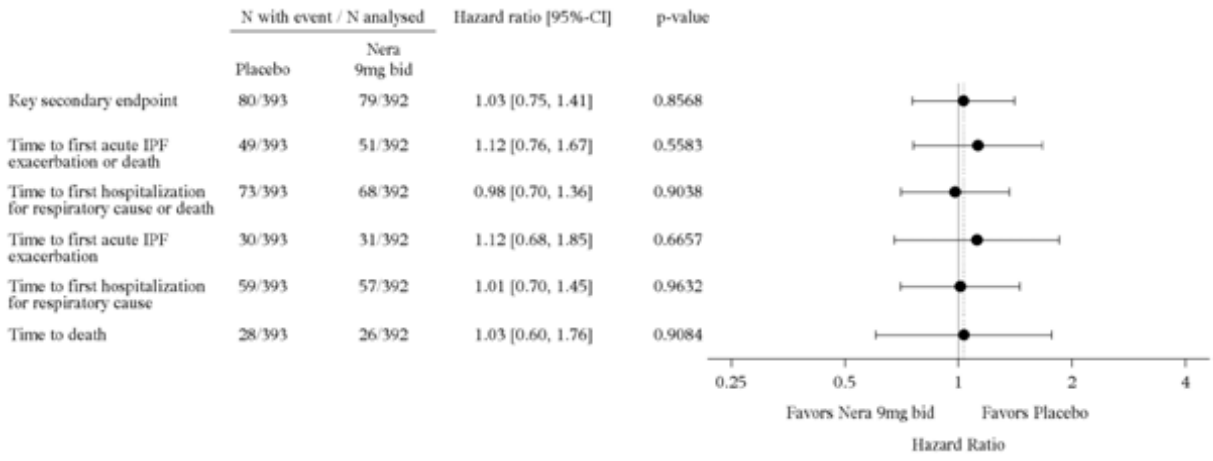
Table 26: Endpoints based on the time to the first clinical event over the duration of the trial up to DBL1 – FAS (Study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	393	100.0	392	100.0	392	100.0
Patients with acute IPF exacerbation or death (N %)	49	12.5	51	13.0	50	12.8
HR vs. placebo	--		1.12		1.11	
95% CI			0.76	1.67	0.75	1.65
p-value			0.5583		0.5896	
Acute IPF exacerbation (N %)	30	7.6	31	7.9	38	9.7
HR vs. placebo	--		1.12		1.36	
95% CI			0.68	1.85	0.84	2.20
p-value			0.6657		0.2040	
Patients with hospitalisation for respiratory cause or death (N %)	73	18.6	68	17.3	75	19.1
HR vs. placebo	--		0.98		1.13	
95% CI			0.70	1.36	0.82	1.56
p-value			0.9038		0.4687	
Hospitalisation for respiratory cause (N %)	59	15.0	57	14.5	68	17.3
HR vs. placebo	--		1.01		1.26	
95% CI			0.70	1.45	0.89	1.78
p-value			0.9632		0.1982	
Death (N %)	28	7.1	26	6.6	21	5.4
HR vs. placebo	--		1.03		0.81	
95% CI			0.60	1.76	0.46	1.43
p-value			0.9084		0.4682	
Patients with non-elective hospitalisation for any cause or death (N %)	108	27.5	101	25.8	106	27.0
HR vs. placebo	--		0.93		1.01	
95% CI			0.71	1.22	0.78	1.33
p-value			0.5808		0.9174	

Cox proportional hazards model including treatment, baseline antifibrotic therapy, age, baseline FVC % predicted, and baseline DL_{CO} % predicted (corrected for haemoglobin) as covariates

p-values not adjusted for multiplicity

Nerandomilast 9 mg bid vs. placebo



Nerandomilast 18 mg bid vs. placebo

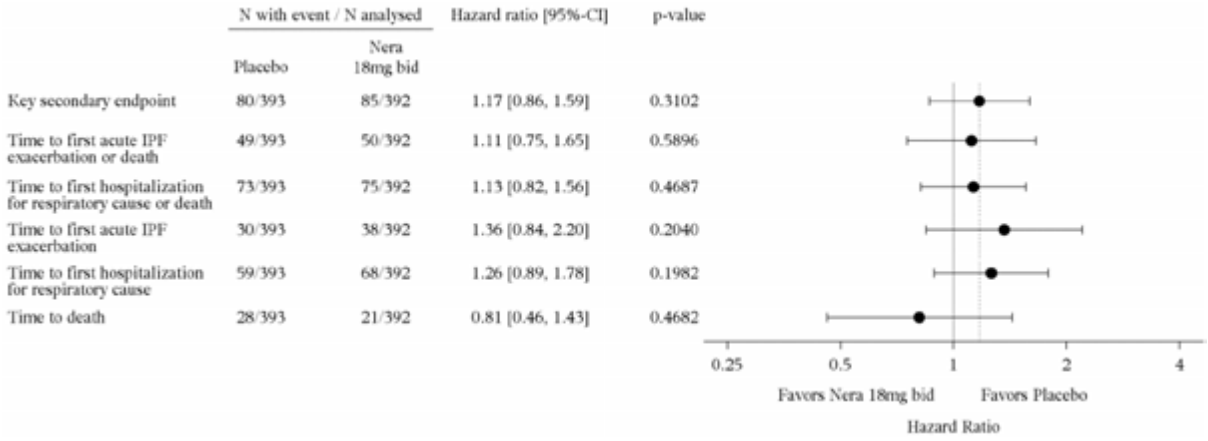


Figure 21: Components of the key secondary endpoint over the duration of the trial up to DBL1 – FAS (Study 1305-0014) - *Updated data from DBL2*

Up to DBL2, all HRs vs. placebo were numerically lower than those for DBL1. All HRs were <1, except the HRs for time to acute IPF exacerbations and time to hospitalisation for respiratory cause in the 18 mg bid nerandomilast arm. For all components of the key secondary endpoint, either alone or in combination with death, the largest increase in the number of events between DBL1 and DBL2 was observed in the placebo group and the lowest increase in the 18 mg bid nerandomilast group. The numerical difference that was observed in favour of 18 mg bid nerandomilast (vs. placebo) for death at DBL1 further increased at DBL2, and the numerical differences observed in disfavour of 18 mg (vs. placebo) for acute IPF exacerbation and hospitalisation for respiratory cause at DBL1 were no longer observed at DBL2.

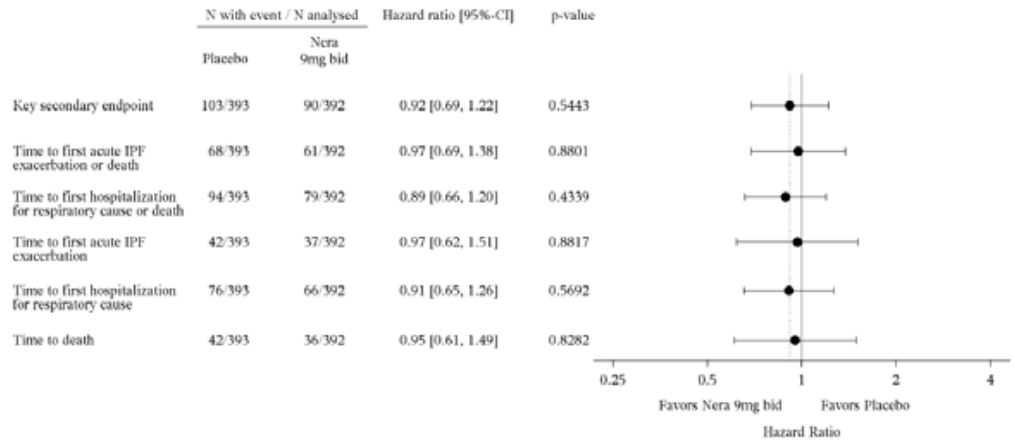
Table 27: Endpoints based on the time to the first clinical event over the duration of the trial up to DBL2 – FAS (Study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	393	100.0	392	100.0	392	100.0
Patients with acute IPF exacerbation or death (N %)	68	17.3	61	15.6	54	13.8
HR vs. placebo	--		0.97		0.87	
95% CI			0.69	1.38	0.61	1.24
p-value			0.8801		0.4369	
Acute IPF exacerbation (N %)	42	10.7	37	9.4	40	10.2
HR vs. placebo	--		0.97		1.05	
95% CI			0.62	1.51	0.68	1.62
p-value			0.8817		0.8308	
Patients with hospitalisation for respiratory cause or death (N %)	94	23.9	79	20.2	84	21.4
HR vs. placebo	--		0.89		0.97	
95% CI			0.66	1.2	0.73	1.31
p-value			0.4339		0.8596	
Hospitalisation for respiratory cause (N %)	76	19.3	66	16.8	75	19.1
HR vs. placebo	--		0.91		1.07	
95% CI			0.65	1.26	0.78	1.47
p-value			0.5692		0.6889	
Death (N %)	42	10.7	36	9.2	26	6.6
HR vs. placebo	--		0.95		0.66	
95% CI			0.61	1.49	0.41	1.08
p-value			0.8282		0.0973	
Patients with non-elective hospitalisation for any cause or death (N %)	128	32.6	117	29.8	118	30.1
HR vs. placebo	--		0.91		0.95	
95% CI			0.71	1.17	0.74	1.23
p-value			0.4501		0.7150	

Cox proportional hazards model including treatment, baseline antifibrotic therapy, age, baseline FVC % predicted, and baseline DL_{CO} % predicted (corrected for haemoglobin) as covariates

p-values not adjusted for multiplicity

Nerandomilast 9 mg bid vs. placebo



Nerandomilast 18 mg bid vs. placebo

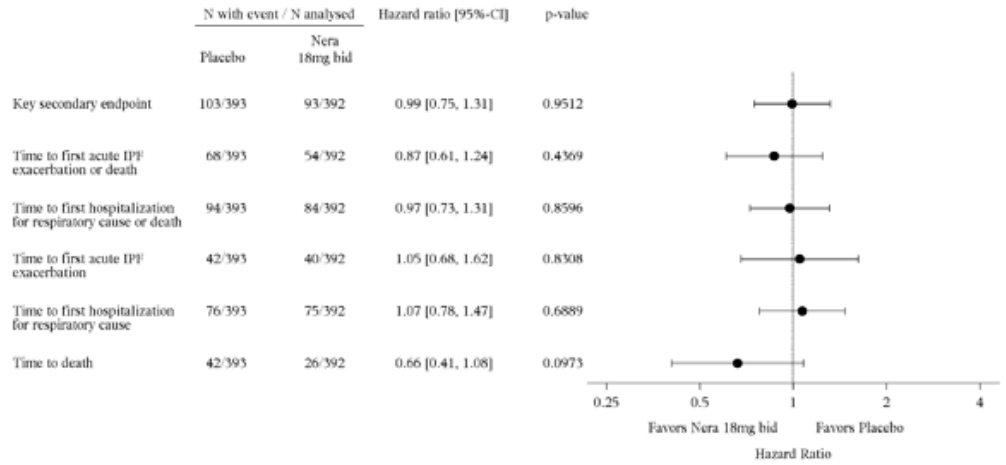


Figure 22: Components of the key secondary endpoint over the duration of the trial up to DBL2 – FAS (Study 1305-0014)

Acute IPF exacerbation alone (further endpoint) or combined with death (secondary endpoint)

Up to DBL1, acute IPF exacerbations (confirmed or suspected) or deaths over the duration of the trial occurred in 12.5% of the patients in the placebo group, 13.0% in the 9 mg bid nerandomilast group, and 12.8% in the 18 mg bid nerandomilast group. Compared with placebo, the HR (95% CI) was 1.12 (0.76, 1.67) for 9 mg bid nerandomilast and 1.11 (0.75, 1.65) for 18 mg bid nerandomilast.

Additional information collected on specific IPF exacerbations eCRF pages up to DBL1. The number (%) of patients with at least one acute IPF exacerbation reported on the AE page by the investigator was lower in the 9 mg bid nerandomilast group (33 patients, 8.4%) and similar in the 18 mg bid nerandomilast group (42 patients, 10.7%) compared with the placebo group (39 patients, 9.9%).

As derived from TSAP definition, the large majority of events in all treatment groups were confirmed or suspected exacerbations (placebo: 75.9%, 9 mg bid nerandomilast: 94.9%, 18 mg bid nerandomilast: 90.3%). More events were categorised as suspected events (due to no CT data) in 18 mg bid nerandomilast group (27.4%) compared with the placebo group (13.0%) or the 9 mg bid nerandomilast group (12.8%). For the remaining events, exacerbations were neither confirmed nor suspected based on TSAP definition, or the derivation from TSAP definition could not be performed due to missing information on the specific eCRF page.

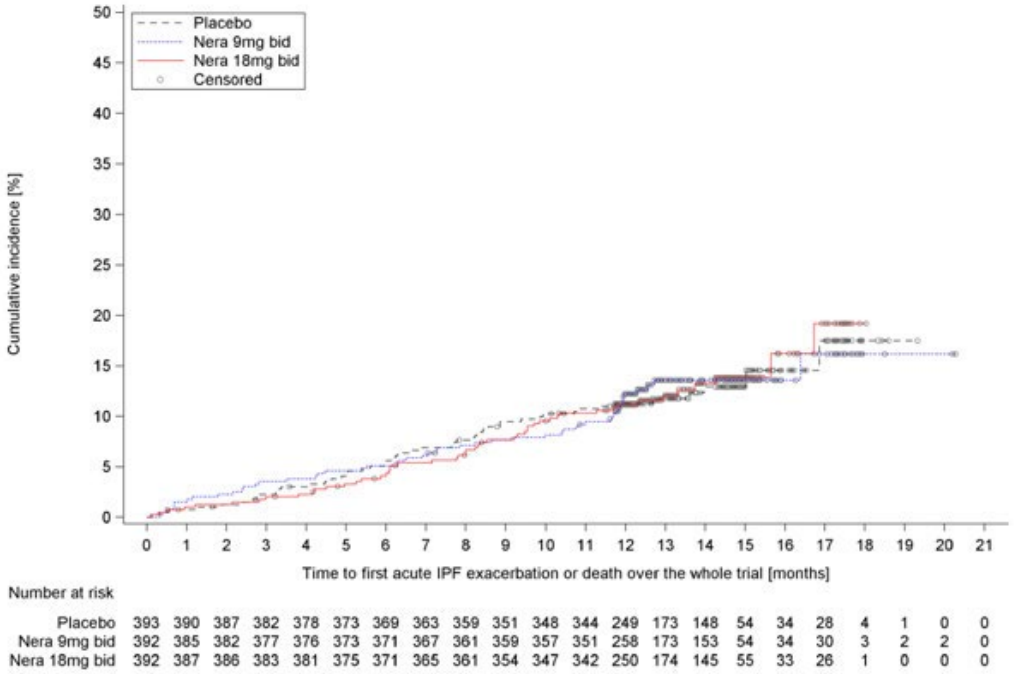


Figure 23: Time to the first acute IPF exacerbation or death over the duration of the trial up to DBL1, estimated cumulative incidence function – FAS (Study 1305-0014)

Table 28: Summary of acute IPF exacerbations with additional information collection on eCRF over the whole trial up to DBL1 – FAS (CSR 1305-0014, Table 11: 10)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	393	100.0	392	100.0	392	100.0
Patients with at least one IPF exacerbation adverse event	39	9.9	33	8.4	42	10.7
Patients with additional information completed on specific IPF eCRF pages	39	9.9	33	8.4	42	10.7
Patients with acute IPF exacerbations (confirmed or suspected)	30	7.6	31	7.9	38	9.7
Number of events						
Number of specific IPF exacerbation eCRF pages completed	54	100.0	39	100.0	62	100.0
Meets protocol definition of acute/suspected IPF exacerbation, based on site response on eCRF page						
Yes	40	74.1	37	94.9	56	90.3
No	14	25.9	2	5.1	6	9.7
Confirmed vs. suspected exacerbation, derived from the TSAP definition[1]						
Confirmed or suspected events[2]	41	75.9	37	94.9	56	90.3
Confirmed events	34	63.0	32	82.1	39	62.9
Suspected events	7	13.0	5	12.8	17	27.4
Neither confirmed nor suspected events[3]	2	3.7	0	0	0	0
Derivation not feasible[4]	11	20.4	2	5.1	6	9.7

Updated data from DBL2

Between DBL1 and DBL2, 33 additional acute IPF exacerbations (confirmed or suspected) or deaths occurred, with more events reported in the placebo group (+19 events) than in the 9 mg and 18 mg bid nerandomilast groups (+10 and +4 events, respectively).

Over the duration of the trial up to DBL2, acute IPF exacerbations (confirmed or suspected) or deaths occurred in 17.3% of the patients in the placebo group, 15.6% in the 9 mg bid nerandomilast group, and 13.8% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were numerically lower compared with DBL1: 0.97 (0.69, 1.38) for 9 mg bid nerandomilast and 0.87 (0.61, 1.24) for 18 mg bid nerandomilast.

Between DBL1 and DBL2, 20 additional acute IPF exacerbations (confirmed or suspected) occurred, with more events in the placebo group (+12 events) than in the 9 mg and 18 mg bid nerandomilast groups (+6 and +2 events, respectively).

Over the duration of the trial up to DBL2, acute IPF exacerbations (confirmed or suspected) occurred in 10.7% of the patients in the placebo group, 9.4% in the 9 mg bid nerandomilast. group, and 10.2% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were numerically lower compared with DBL1: 0.97 (0.62, 1.51) for 9 mg bid nerandomilast and 1.05 (0.68, 1.62) for 18 mg bid nerandomilast.

Additional information collected on specific IPF exacerbations eCRF pages up to DBL2 Up to DBL2, the trends in IPF exacerbations were consistent with those described for DBL1. The number (%) of patients with at least one acute IPF exacerbation reported on the AE page by the investigator was lower in the 9 mg bid nerandomilast group (39 patients, 9.9%) and similar in the 18 mg bid nerandomilast group (45 patients, 11.5%) compared with the placebo group (50 patients, 12.7%).

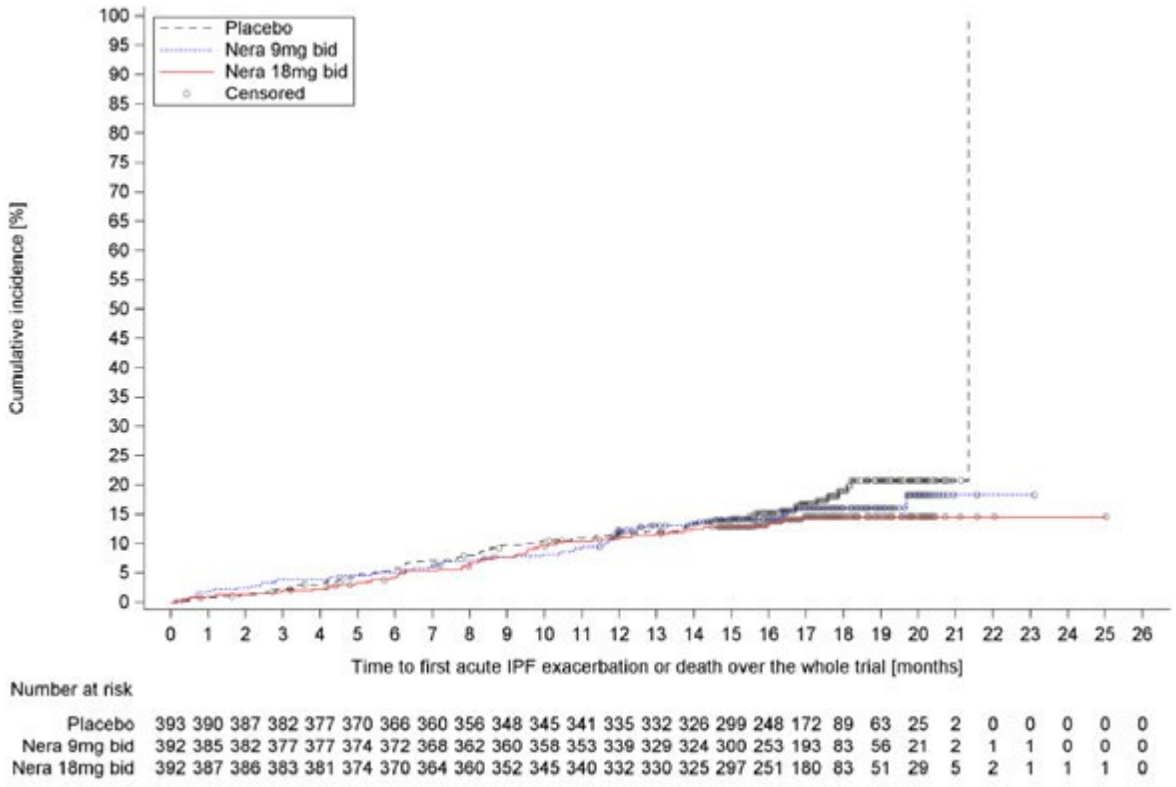


Figure 24: Time to the first acute IPF exacerbation or death over the duration of the trial up to DBL2, estimated cumulative incidence function – FAS (Study 1305-0014)

Table 29: Summary of acute IPF exacerbations with additional information collection on eCRF over the whole trial up to DBL2 – FAS (Study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	393	100.0	392	100.0	392	100.0
Patients with at least one IPF exacerbation adverse event	50	12.7	39	9.9	45	11.5
Patients with additional information completed on specific IPF eCRF pages	50	12.7	39	9.9	45	11.5
Patients with acute IPF exacerbations (confirmed or suspected)	42	10.7	37	9.4	40	10.2
Number of events						
Number of specific IPF exacerbation eCRF pages completed	70	100.0	51	100.0	73	100.0
Meets protocol definition of acute/suspected IPF exacerbation, based on site response on eCRF page						
Yes	60	85.7	49	96.1	67	91.8
No	10	14.3	2	3.9	6	8.2
Confirmed vs. suspected exacerbation, derived from the TSAP definition[1]						
Confirmed or suspected events[2]	58	82.9	49	96.1	66	90.4
Confirmed events	47	67.1	39	76.5	46	63.0
Suspected events	11	15.7	10	19.6	20	27.4
Neither confirmed nor suspected events[3]	12	17.1	2	3.9	4	5.5
Derivation not feasible[4]	0	0	0	0	3	4.1

Hospitalisation for respiratory cause alone (further endpoint) or combined with death (secondary endpoint)

Up to DBL1, hospitalisations for respiratory cause or deaths over the duration of the trial occurred in 18.6% of the patients in the placebo group, 17.3% in the 9 mg bid nerandomilast group, and 19.1% in the 18 mg bid nerandomilast group. Compared with placebo, the HR (95% CI) was 0.98 (0.70, 1.36) for 9 mg bid nerandomilast and 1.13 (0.82, 1.56) for 18 mg bid nerandomilast.

The further analysis of hospitalisation events contributing to the key secondary endpoints suggests that some of them were not due to respiratory cause but were reported on the AE page as other underlying diseases (such as neoplasms, cardiovascular disorders, or gastrointestinal disorders), with secondary respiratory symptoms noted during the event course. Events contributing to the key secondary endpoint were most commonly reported in the SOC infections and infestations, and pneumonia was the most common PT, being reported in 12 of 41 patients with an event in the placebo group, 10 of 40 patients with an event in the 9 mg bid nerandomilast group, and 9 of 42 patients with an event in the 18 mg bid nerandomilast group.

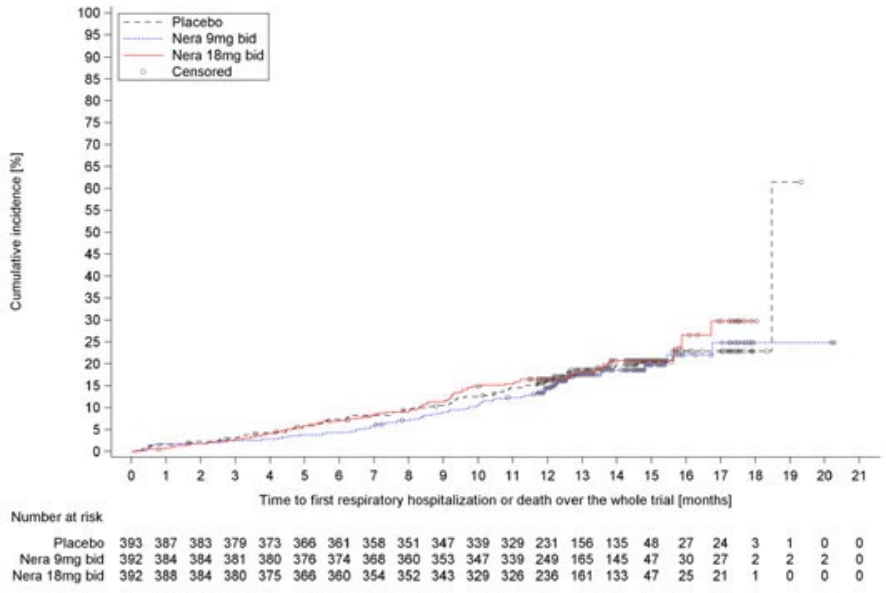


Figure 25: Time to the first hospitalisation for respiratory cause or death over the duration of the trial up to DBL1, estimated cumulative incidence function – FAS (Study 1305-0014)

Updated data from DBL2

Between DBL1 and DBL2, 41 additional hospitalisations for respiratory cause or deaths occurred, with more events in the placebo group (+21 events) than in the 9 mg and 18 mg bid nerandomilast groups (+11 and +9 events, respectively).

Over the duration of the trial up to DBL2, hospitalisations for respiratory cause or deaths occurred in 23.9% of the patients in the placebo group, 20.2% in the 9 mg bid nerandomilast group, and 21.4% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were numerically lower compared with DBL1: 0.89 (0.66, 1.20) for 9 mg bid nerandomilast and 0.97 (0.73, 1.31) for 18 mg bid nerandomilast. Between DBL1 and DBL2, 33 additional hospitalisations for respiratory cause occurred, with more events in the placebo group (+17 events) than in the 9 mg and 18 mg bid nerandomilast groups (+9 and +7 events, respectively).

Over the duration of the trial up to DBL2, hospitalisations for respiratory cause occurred in 19.3% of the patients in the placebo group, 16.8% in the 9 mg bid nerandomilast group, and 19.1% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were numerically lower compared with DBL1: 0.91 (0.65, 1.26) for 9 mg bid nerandomilast and 1.07 (0.78, 1.47) for 18 mg bid nerandomilast.

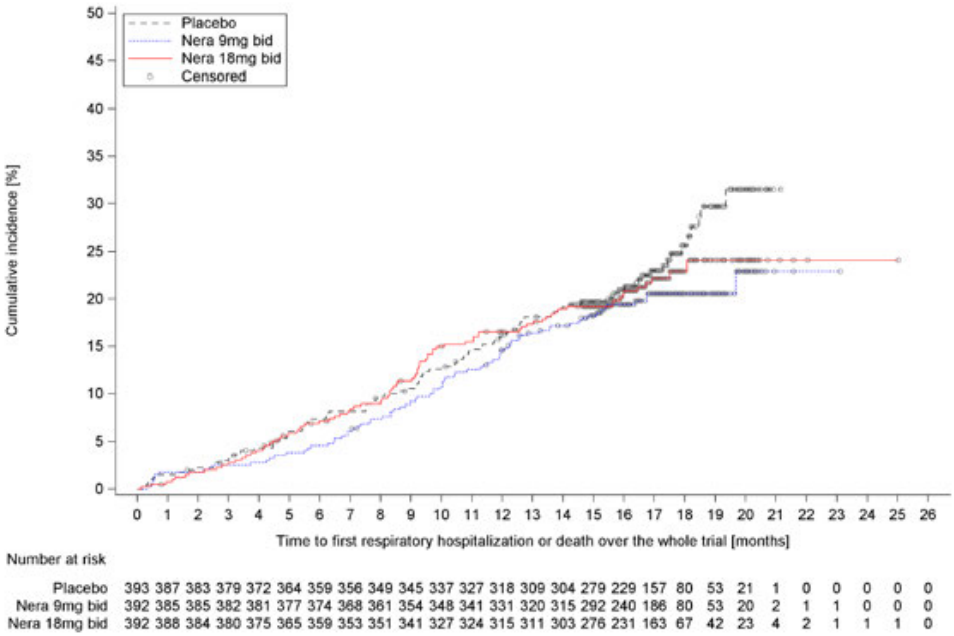


Figure 26: Time to the first hospitalisation for respiratory cause or death over the duration of the trial up to DBL2, estimated cumulative incidence function – FAS (Study 1305-0014*)*

Death (secondary endpoint)

Up to DBL1, deaths over the duration of the trial occurred in 28 patients in the placebo group (7.1%), 26 patients in the 9 mg bid nerandomilast group (6.6%), and 21 patients in the 18 mg bid nerandomilast group (5.4%). Compared with placebo, the HR (95% CI) was 1.03 (0.60, 1.76) for 9 mg bid nerandomilast and 0.81 (0.46, 1.43) for 18 mg bid nerandomilast.

An independent adjudication committee reviewed all fatal cases to determine the primary cause of death. In all treatment groups, respiratory causes were the most frequent primary causes of death (accounting for 40 of 68 adjudicated deaths in total). Underlying interstitial lung disease was the most frequent adjudicated cause of death within respiratory causes.

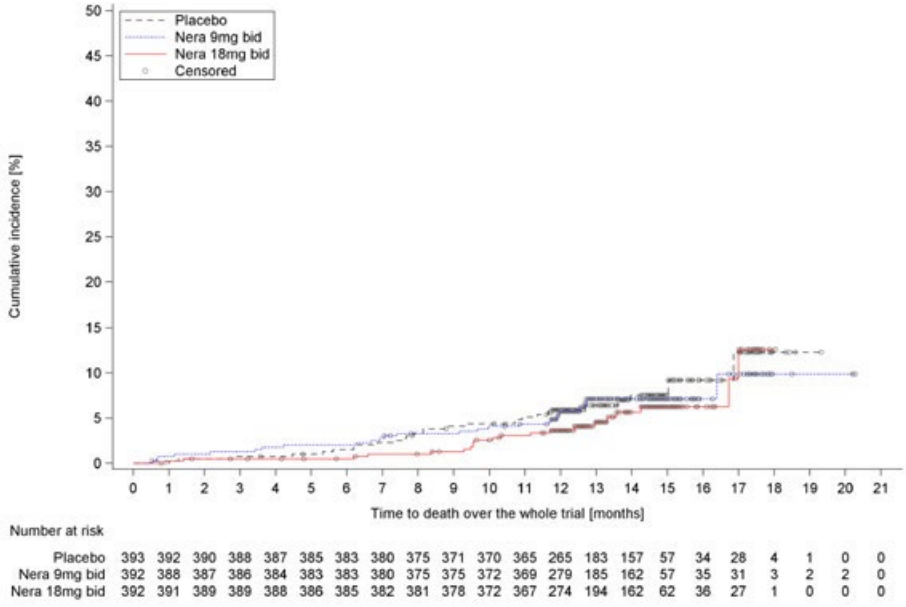


Figure 27: Time to death over the duration of the trial up to DBL1, estimated cumulative incidence function – FAS (Study 1305-0014)

Adjudicated cause of death Specific cause of death	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	393	100.0	392	100.0	392	100.0
All deaths (N %)	28	7.1	26	6.6	21	5.4
Adjudicated deaths (N %)	26	6.6	26	6.6	16	4.1
Respiratory cause	14	3.6	14	3.6	12	3.1
Underlying interstitial lung disease	10	2.5	9	2.3	9	2.3
Pneumonia	2	0.5	5	1.3	3	0.8
Other	2	0.5	0	0	0	0
Cardiovascular (CV) cause (fatal MACE)	5	1.3	6	1.5	2	0.5
Sudden cardiac death	5	1.3	4	1.0	2	0.5
Acute myocardial infarction	0	0	1	0.3	0	0
Hemorrhagic stroke	0	0	1	0.3	0	0
Non-CV, non-respiratory cause	4	1.0	2	0.5	2	0.5
Malignancy (new or worsening)	4	1.0	1	0.3	1	0.3
Infection (including sepsis)	0	0	0	0	1	0.3
Suicide[1]	0	0	1	0.3	0	0
Cause undetermined	3	0.8	4	1.0	0	0

Only the adverse events of death which were entered into CRF pages by sites before 31 Jul 2024 were adjudicated before DBL1 data snapshot. Therefore, 2 events in the placebo group and 5 events in the 18 mg bid nerandomilast group had not been adjudicated by DBL1.

1 The patient (#[redacted]) died by an SAE of physician-assisted suicide (see Section 12.1.4.2).

Figure 28: Adjudicated cause of death over the duration of the trial up to DBL1 – FAS

Updated data from DBL2. At DBL2, 29 additional deaths were reported, representing an increase of almost 40% of the number of deaths reported at DBL1 (75 deaths in total). Of these 29 new deaths, 14 occurred in the placebo group, 10 occurred in the 9 mg bid nerandomilast group, and 5 in the 18 mg bid nerandomilast group.

Over the whole trial up to DBL2, deaths occurred in 42 patients in the placebo group (10.7%), 36 patients in the 9 mg bid nerandomilast group (9.2%), and 26 patients in the 18 mg bid nerandomilast group (6.6%). The HRs (95% CI) vs. placebo were numerically lower compared with DBL1: 0.95 (0.61, 1.49) for 9 mg bid nerandomilast and 0.66 (0.41, 1.08) for 18 mg bid nerandomilast. The cumulative incidence of deaths was numerically lower in the 18 mg bid nerandomilast group than the placebo group as early as month 5 and continued to diverge from the placebo group until the end of the trial.

Pre-defined and post-hoc subgroup analyses

Primary endpoint-subgroup analysis

In the placebo group, patients with background AF therapy (nintedanib or pirfenidone) had a numerically greater loss of FVC over 52 weeks (about -200 mL) than patients without background AF therapy (about -150 mL).

The treatment effect of nerandomilast (9 and 18 mg bid) was observed in both strata by background AF therapy. However, a numerically smaller treatment effect in the 9 mg bid nerandomilast group vs. placebo was observed in the AF stratum compared with the non-AF stratum. This was driven by a lack of observed treatment effect in the subgroup with pirfenidone background treatment.

A decrease in nerandomilast plasma exposure by 55% in the 9 mg bid group with pirfenidone background therapy compared with non-AF patients was observed, which may contribute to a lack of observed treatment effect for the 9 mg bid dose in this subgroup. In the 18 mg bid group, there was a decrease in nerandomilast plasma exposure by 48% with pirfenidone background therapy compared with non-AF patients.

The relative reduction in FVC decline for 9 mg and 18 mg nerandomilast is greater in non-AF patients than either the nintedanib or pirfenidone AF group. In patients without AF therapy the adjusted mean difference in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 78.4 (-3.2, 160.0) and between 18 mg bid nerandomilast and placebo groups was 69.6 (-12.2, 151.4). In patients with nintedanib AF therapy the change from baseline to placebo was 60.9 (4.3, 117.5) and 73.0 (15.3, 130.8) for 9 mg and 18 mg, respectively. In patients with pirfenidone background AF therapy the change from baseline to placebo was -4.8 (-73.2, 63.5) and 63.4 (-3.6, 130.3) for 9 mg and 18 mg, respectively.

Table 30: Absolute change from baseline in FVC (in mL) at Week 52 by background AF therapy – FAS (Study 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients without background antifibrotic therapy[1], N analysed	87		86		87	
Baseline (mean, SD)	2833.3	885.7	2763.6	739.3	2761.5	778.4
Week 52 change from baseline						
Adjusted mean	-148.7		-70.2		-79.1	
95% CI	-206.8	-90.5	-127.5	-13.0	-136.6	-21.5
Comparison vs. placebo						
Adjusted mean	--		78.4		69.6	
95% CI	--		-3.2	160.0	-12.2	151.4
Patients with background antifibrotic therapy[1], N analysed	304		304		305	
Baseline (mean, SD)	2872.6	781.4	2858.5	793.1	2846.1	752.3
Week 52 change from baseline						
Adjusted mean	-193.7		-158.6		-124.9	
95% CI	-224.8	-162.7	-189.2	-127.92	-155.7	-94.1
Comparison vs. placebo						
Adjusted mean	--		35.2		68.8	
95% CI	--		-8.4	78.8	25.1	112.6
Patients with nintedanib background therapy[2], N analysed	172		184		178	
Baseline (mean, SD)	2971.3	802.5	2937.2	828.6	2863.3	805.1
Week 52 change from baseline						
Adjusted mean	-191.6		-130.7		-118.5	
95% CI	-232.6	-150.6	-169.9	-91.5	-159.3	-77.8
Comparison vs. placebo						
Adjusted mean	--		60.9		73.0	
95% CI	--		4.3	117.5	15.3	130.8
Patients with pirfenidone background therapy[2], N analysed	132		120		127	
Baseline (mean, SD)	2744.2	736.5	2737.9	722.2	2821.9	673.7
Week 52 change from baseline						
Adjusted mean	-197.0		-201.8		-133.7	
95% CI	-244.7	-149.4	-250.9	-152.8	-180.7	-86.6
Comparison vs. placebo						
Adjusted mean	--		-4.8		63.4	
95% CI	--		-73.2	63.5	-3.6	130.3

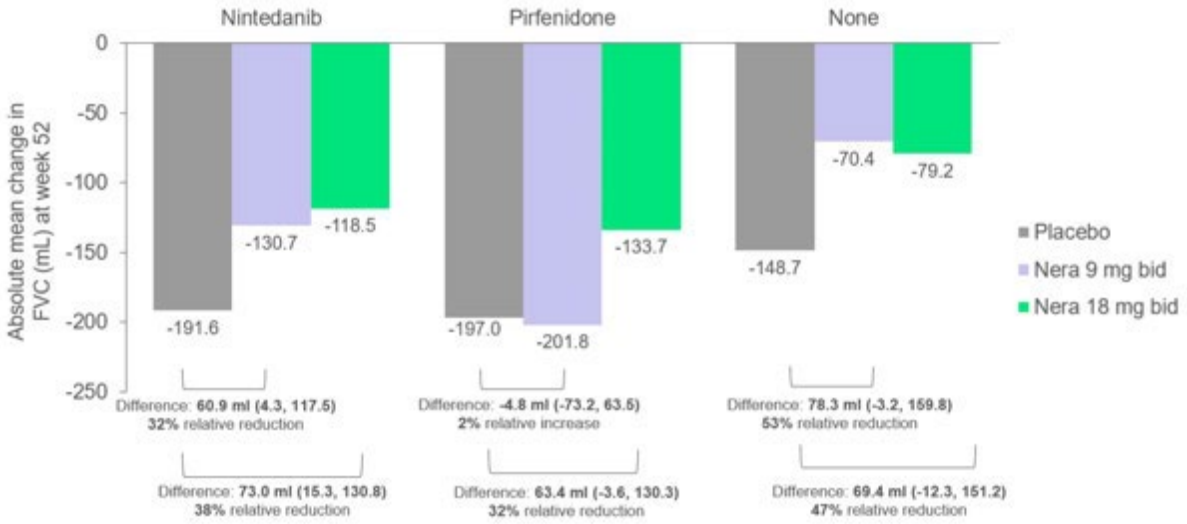


Figure 29: Absolute change from baseline in FVC (in mL) at Week 52 by background AF therapy – FAS (CSR 1305-0014)

Pre-defined and post-hoc sensitivity analyses

The robustness of the primary analysis was investigated in exploratory sensitivity analyses and supplementary analyses. The results of all sensitivity and supplementary analyses were consistent with the primary analysis of the **primary endpoint**. The sensitivity analysis excluding outliers (patients with FVC increase or decrease from baseline at Week 52 of >1000 mL) also confirmed the primary analysis.

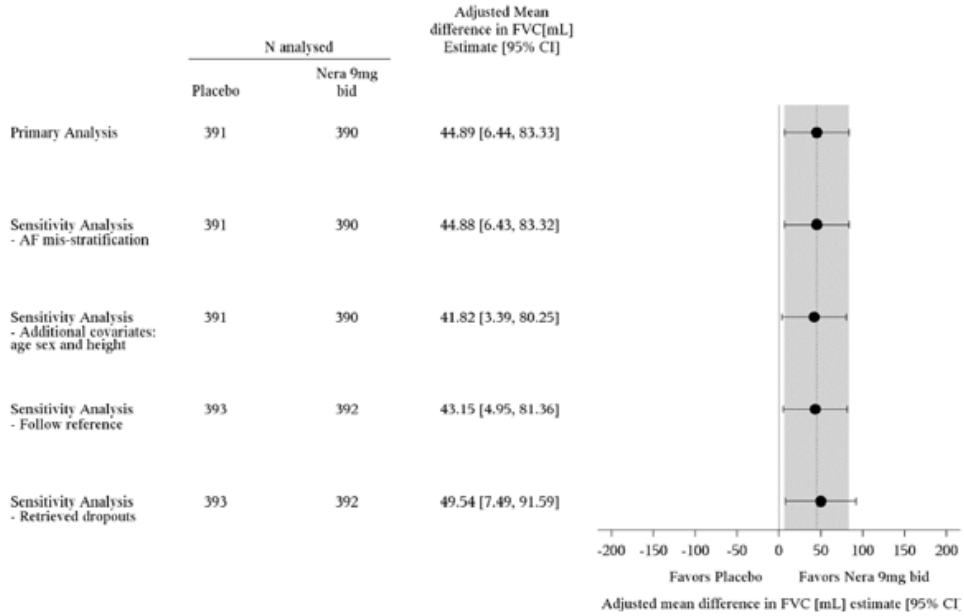


Figure 30: Nerandomilast 9 mg bid vs. placebo (CSR 1305-0014)

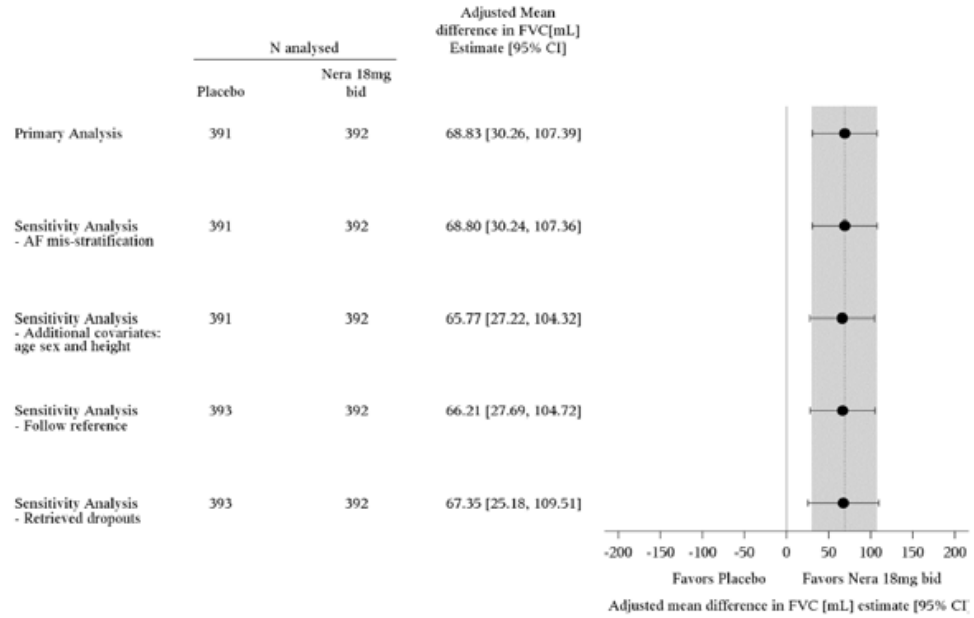


Figure 31: Nerandomilast 18 mg bid vs. placebo (CSR 1305-0014*)*

Ancillary analyses

Primary endpoint post hoc analysis (excluding patients with pirfenidone background therapy)

Based on the decrease in nerandomilast plasma exposure in patients with pirfenidone background therapy (by 55% in the 9 mg bid group and 48% in the 18 mg bid group), a post hoc analysis excluding patients with pirfenidone background therapy was performed.

The adjusted mean difference (95% CI) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 66.4 (19.8, 112.9), similar to that between 18 mg bid nerandomilast and placebo groups of 71.6 (24.4, 118.8) (Table 31).

Table 31: Absolute change from baseline in FVC [mL] at Week 52, excluding patients with pirfenidone background therapy – FAS (CSR 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in FAS	260		272		265	
Number of patients analysed	259		270		265	
Baseline (mean, SD)	2925.1	832.1	2881.0	803.6	2829.9	796.4
Week 52 change from baseline						
Adjusted mean	-178.2		-111.8		-106.6	
95% CI	-211.6	-144.7	-144.1	-79.5	-139.8	-73.3
Comparison vs. placebo						
Adjusted mean	--		66.4		71.6	
95% CI	--		19.8	112.9	24.4	118.8
p-value	--		0.0053		0.0030	

Based on MMRM, with fixed, categorical effects of treatment at each visit, baseline antifibrotic therapy at each visit, and the fixed continuous effects of baseline FVC [mL] at each visit

p-values not adjusted for multiplicity

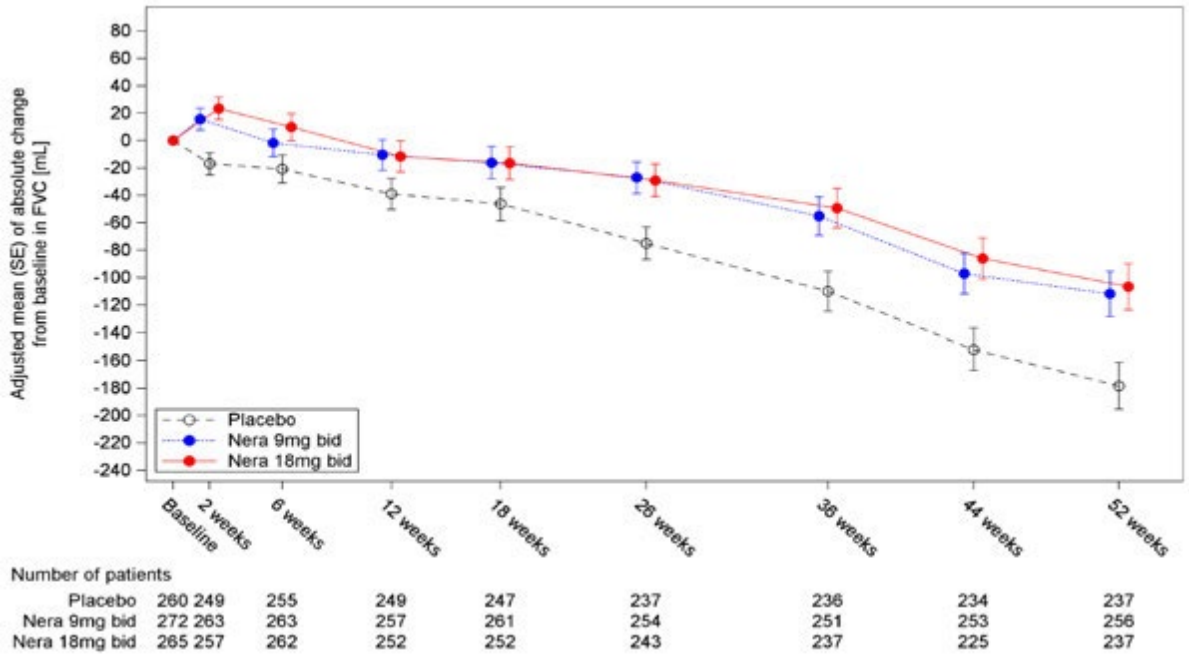


Figure 32: Adjusted mean (SE) of absolute change from baseline in FVC [mL] over 52 weeks, excluding patients with pirfenidone background therapy – FAS (CSR 1305-0014)

Key secondary endpoint- subgroup analysis

Subgroup analyses

Up to DBL1, the results were consistent across most subgroups, as the point estimate of each subgroup was close to the overall estimate and contained within the 95% CI of the overall estimate.

Patients with baseline FVC predicted ≤70% (32% of the population) had a higher frequency of events than patients with baseline FVC predicted >70%, in all 3 treatment groups. Notably, in patients with baseline FVC predicted ≤70%, the frequency of events was higher with 18 mg bid nerandomilast (36.6%) compared with 9 mg bid nerandomilast (28.2%) or placebo (27.1%), with corresponding HR for the 9 mg 1.11 (95% CI 0.70, 1.77), and HR 18 mg 1.57 (95% CI 1.02, 2.41).

Females (17.0% of total patients had a lower frequency of events than males in all 3 treatment groups. The placebo group reported a low number of events i.e.5 females under placebo (8.9%), 11 females under 9 mg bid nerandomilast (14.7%), and 13 females under 18 mg bid nerandomilast (18.8%). The point estimate of the HR was > 1 with a very wide confidence interval.

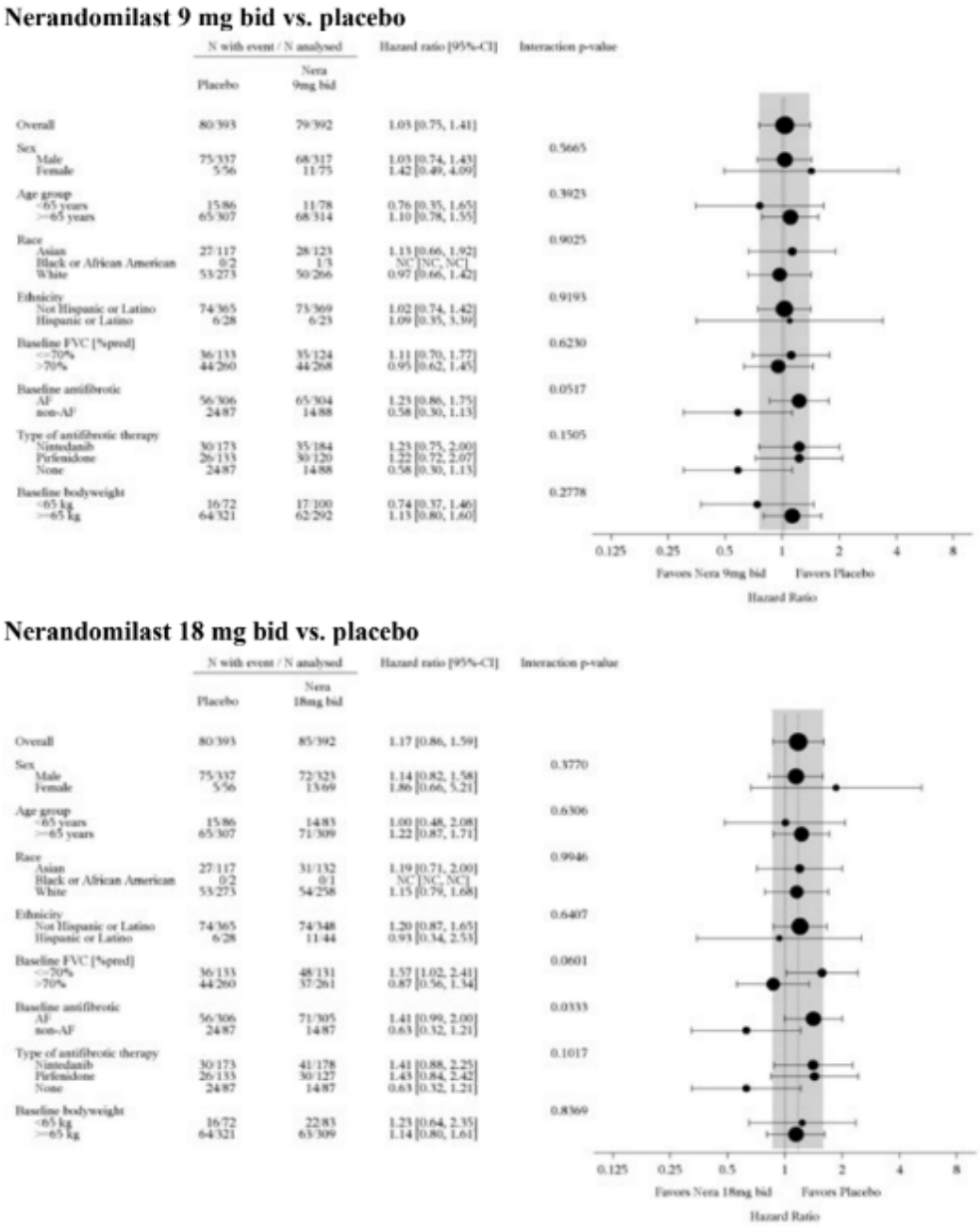


Figure 33: Subgroup analyses of the key secondary endpoint up to DBL1 – FAS (CSR 1305-0014)

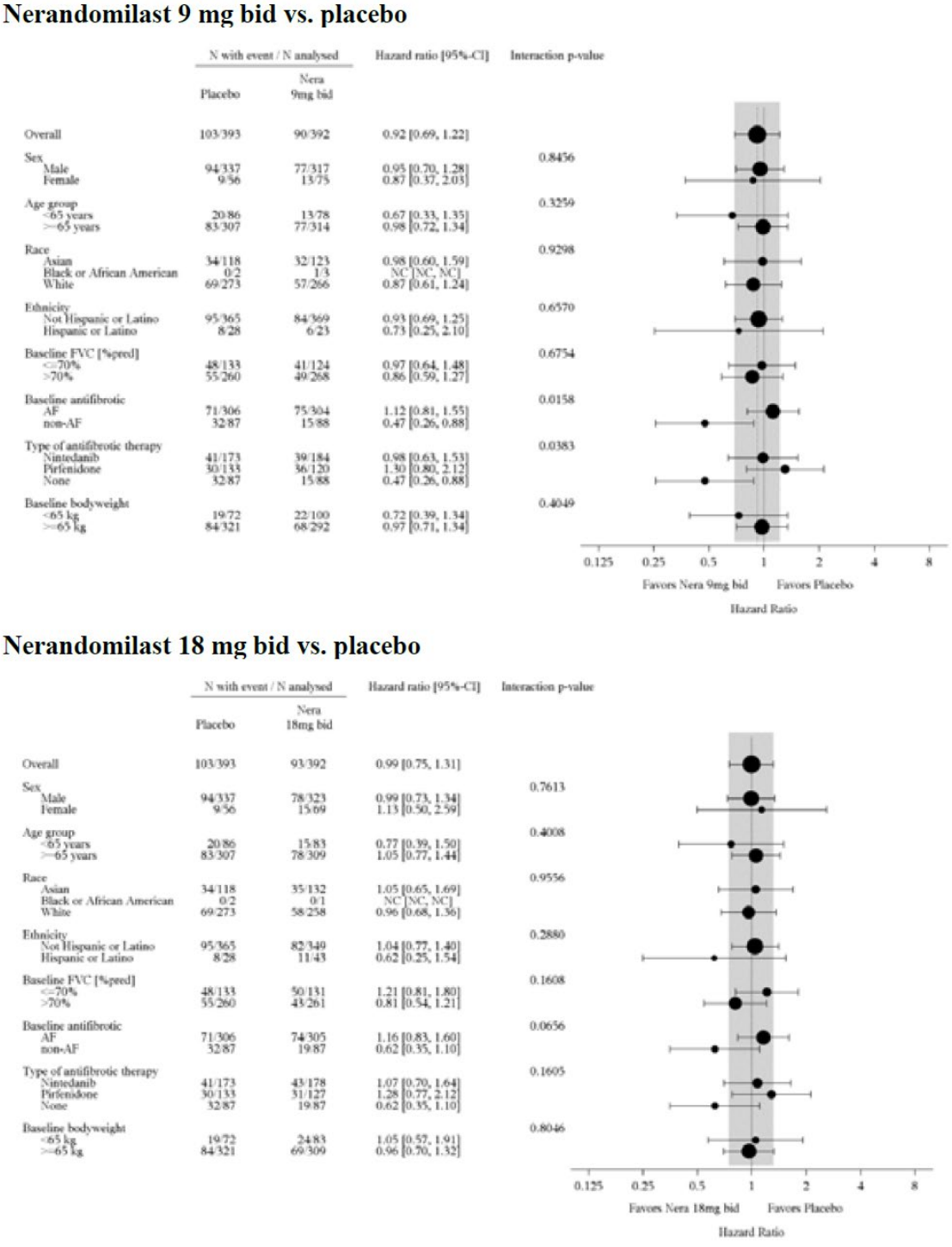


Figure 34: Subgroup analyses of the key secondary endpoint up to DBL2 – FAS (CSR 1305-014)

Up to DBL1 and DBL2, the results of all sensitivity and supplementary analyses were consistent with the primary analysis of the key secondary endpoint.

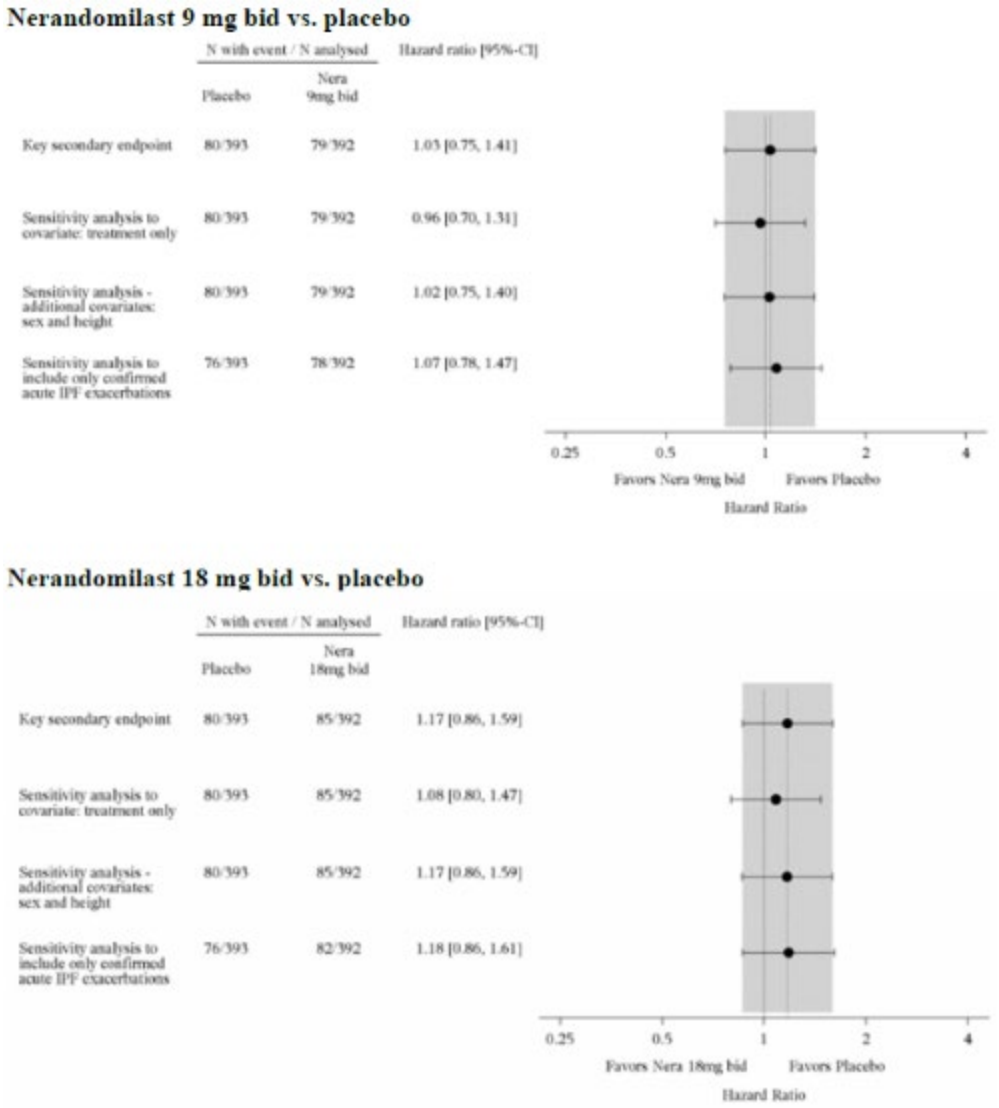


Figure 35: Sensitivity analyses of the key secondary endpoint up to DBL1 - FAS (1305-0014)

Key secondary endpoint by background AF therapy

Table 32: The key secondary endpoint up to DBL1 by background AF therapy –FAS (1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients without background antifibrotic therapy[1] (N %)	87	100.0	88	100.0	87	100.0
Patients with event (N %)	24	27.6	14	15.9	14	16.1
HR vs. placebo	--		0.58		0.63	
95% CI			0.30	1.13	0.32	1.21
Patients with background antifibrotic therapy[1] (N %)	306	100.0	304	100.0	305	100.0
Patients with event (N %)	56	18.3	65	21.4	71	23.3
HR vs. placebo	--		1.23		1.41	
95% CI			0.86	1.75	0.99	2.00
Patients with nintedanib background therapy[2] (N %)	173	100.0	184	100.0	178	100.0
Patients with event (N %)	30	17.3	35	19.0	41	23.0
HR vs. placebo	--		1.23		1.41	
95% CI			0.75	2.00	0.88	2.25
Patients with pirfenidone background therapy[2] (N %)	133	100.0	120	100.0	127	100.0
Patients with event (N %)	26	19.5	30	25.0	30	23.6
HR vs. placebo	--		1.22		1.43	
95% CI			0.72	2.07	0.84	2.42

1 For subgroups by AF background therapy (yes/no): treatment-by-subgroup interaction p = 0.0517 (9 mg bid nerandomilast vs. placebo across 2 subgroups) and 0.0333 (18 mg bid nerandomilast vs. placebo across 2 subgroups)

2 For subgroups by AF background therapy (nintedanib/pirfenidone/none): see source data for the subgroup of patients without background antifibrotic therapy; treatment-by-subgroup interaction p = 0.1505 (9 mg bid nerandomilast vs. placebo across 3 subgroups) and 0.1017 (18 mg bid nerandomilast vs. placebo across 3 subgroups)

Table 33: Cox model for time to first acute IPF exacerbation, first hospitalization for respiratory cause or death over the whole trial – FAS (CSR 1305-0014)

Type of antifibrotic therapy: Nintedanib

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	173	100.0	184	100.0	178	100.0
Number of patients with event (N, %)	41	23.7	39	21.2	43	24.2
Number of patients with components contributing to the first event [1] (N, %)						
Acute IPF exacerbation	16	9.2	16	8.7	14	7.9
Hospitalization for respiratory cause	20	11.6	18	9.8	24	13.5
Death	5	2.9	5	2.7	5	2.8
Number of patients censored (N, %)	132	76.3	145	78.8	135	75.8
Time at risk for event [patient-years]	217.5		231.4		214.6	
Comparison vs Placebo [2]						
Hazard ratio			0.98		1.07	
95% confidence interval			(0.63, 1.53)		(0.70, 1.64)	
Treatment-by-subgroup interaction p-value			0.0383		0.1605	

Type of antifibrotic therapy: Pirfenidone

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	133	100.0	120	100.0	127	100.0
Number of patients with event (N, %)	30	22.6	36	30.0	31	24.4
Number of patients with components contributing to the first event [1] (N, %)						
Acute IPF exacerbation	11	8.3	14	11.7	13	10.2
Hospitalization for respiratory cause	15	11.3	16	13.3	16	12.6
Death	4	3.0	6	5.0	2	1.6
Number of patients censored (N, %)	103	77.4	84	70.0	96	75.6
Time at risk for event [patient-years]	165.6		151.5		157.5	
Comparison vs Placebo [2]						
Hazard ratio			1.30		1.28	
95% confidence interval			(0.80, 2.12)		(0.77, 2.12)	
Treatment-by-subgroup interaction p-value			0.0383		0.1605	

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	87	100.0	88	100.0	87	100.0
Number of patients with event (N, %)	32	36.8	15	17.0	19	21.8
Number of patients with components contributing to the first event [1] (N, %)						
Acute IPF exacerbation	11	12.6	2	2.3	11	12.6
Hospitalization for respiratory cause	14	16.1	11	12.5	7	8.0
Death	7	8.0	2	2.3	1	1.1
Number of patients censored (N, %)	55	63.2	73	83.0	68	78.2
Time at risk for event [patient-years]	101.0		114.0		108.8	
Comparison vs Placebo [2]						
Hazard ratio			0.47		0.62	
95% confidence interval			(0.26, 0.88)		(0.35, 1.10)	
Treatment-by-subgroup interaction p-value			0.0383		0.1605	

Mortality by background AF therapy

Table 34: Cox model for time to death over the whole trial – FAS (CSR 1305-0014)

Type of antifibrotic therapy: Nintedanib

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	173	100.0	184	100.0	178	100.0
Number of patients with event (N, %)	17	9.8	15	8.2	11	6.2
Number of patients censored (N, %)	156	90.2	169	91.8	167	93.8
Time at risk for event [patient-years]	236.2		251.8		240.1	
Comparison vs Placebo [1]						
Hazard ratio			1.02		0.64	
95% confidence interval			(0.51, 2.04)		(0.30, 1.37)	
Treatment-by-subgroup interaction p-value			0.4442		0.1467	

Type of antifibrotic therapy: Pirfenidone

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	133	100.0	120	100.0	127	100.0
Number of patients with event (N, %)	13	9.8	15	12.5	12	9.4
Number of patients censored (N, %)	120	90.2	105	87.5	115	90.6
Time at risk for event [patient-years]	183.2		166.2		175.1	
Comparison vs Placebo [1]						
Hazard ratio			1.23		1.12	
95% confidence interval			(0.58, 2.59)		(0.51, 2.47)	
Treatment-by-subgroup interaction p-value			0.4442		0.1467	

Type of antifibrotic therapy: None

	Placebo		Nera 9mg bid		Nera 18mg bid	
Number of patients (N, %)	87	100.0	88	100.0	87	100.0
Number of patients with event (N, %)	12	13.8	6	6.8	3	3.4
Number of patients censored (N, %)	75	86.2	82	93.2	84	96.6
Time at risk for event [patient-years]	113.9		118.9		120.8	
Comparison vs Placebo [1]						
Hazard ratio			0.56		0.26	
95% confidence interval			(0.21, 1.49)		(0.07, 0.91)	
Treatment-by-subgroup interaction p-value			0.4442		0.1467	

Tables with missing efficacy data

Table 35: Summary of the Key secondary outcome – time-to first clinical event (pulmonary exacerbation, hospitalization due to respiratory disease or death) – FAS and by background treatment - study 1305-0014- IPF at database lock 1

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
FAS	**393 (100.0)**	**392 (100.0)**	**392 (100.0)**		
Key secondary endpoint	**80 (20.4)**	**79 (20.2)**	**85 (21.7)**	**1.03 (0.75, 1.41)**	**1.17 (0.86, 1.59)**
Pulmonary exacerbation[1]	49 (12.5)	51 (13.0)	50 (12.8)	1.12 (0.76, 1.67)	1.11 (0.75, 1.65)
Hosp. Resp. Cause[1]	73 (18.6)	68 (17.3)	75 (19.1)	0.98 (0.70, 1.36)	1.13 (0.82, 1.56)
Death	28 (7.1)	26 (6.6)	21 (5.4)	1.03 (0.60, 1.76)	0.81 (0.46, 1.43)
Without AF background (n=262, 22%)					
Key secondary endpoint[2]	**24 (27.6)**	**14 (15.9)**	**14 (16.1)**	**0.58 (0.30, 1.13)**	**0.63 (0.32, 1.21)**
Pulmonary exacerbation[1, 3]	16 (18.4)	7 (8.0)	10 (11.5)	0.46 (0.19, 1.12)	0.71 (0.32, 1.56)
Hosp. Resp. Cause[1, 4]	21 (24.1)	14 (15.9)	10 (11.5)	0.69 (0.35, 1.36)	0.49 (0.23, 1.05)
Death[5]	9 (10.3)	6 (6.8)	1 (1.1)	0.75 (0.27, 2.10)	0.12 (0.02, 0.96)
Patients naïve to AF therapy (n=172, 15%)					
Key secondary endpoint	12 (21.8)	8 (14.0)	9 (15.0)	0.59 (0.24, 1.48)	0.76 (0.32, 1.82)
Pulmonary exacerbation[1]	8 (14.5)	3 (5.3)	5 (8.3)	0.44 (0.12, 1.67)	0.66 (0.22, 2.04)
Hosp. Resp. Cause[1]	10 (18.2)	8 (14.0)	7 (11.7)	0.74 (0.28, 1.91)	0.72 (0.27, 1.90)
Death	4 (7.3)	3 (5.3)	0	NC	NC
WITH AF BACKGROUND THERAPY (n=915, 78%) *					
Key secondary outcome	56 (18.3)	65 (21.4)	71 (23.3)	1.23 (0.86, 1.775)	1.41 (0.88, 2.25)
Pulmonary exacerbation	33	44	40	1.45 (0.93, 2.29)	1.31 (0.83, 2.08)
Hosp. Resp. Cause[1]	52	54	65	1.10 (0.75, 1.61)	1.39 (0.97, 2.01)
Death	19 (6.2)	20 (6.6)	20 (6.6)	1.17 (0.62, 2.20)	1.14 (0.61, 2.14)
Background nintedanib (n=535, 46%)					
Key secondary endpoint[2]	**30 (17.3)**	**35 (19.0)**	**41 (23.0)**	**1.23 (0.75, 2.00)**	**1.41 (0.88, 2.25)**
Pulmonary exacerbation[1, 3]	18 (10.4)	26 (14.1)	19 (10.7)	1.58 (0.87, 2.89)	1.05 (0.55, 2.00)
Hosp. Resp. Cause[1, 4]	29 (16.8)	29 (15.8)	39 (21.9)	1.08 (0.64, 1.80)	1.39 (0.86, 2.25)
Death[5]	12 (6.9)	13 (7.1)	9 (5.1)	1.26 (0.57, 2.77)	0.74 (0.31, 1.76)
Background pirfenidone (n=380, 32%)					
Key secondary endpoint[2]	**26 (19.5)**	**30 (25.0)**	**30 (23.6)**	**1.22 (0.72, 2.07)**	**1.43 (0.84, 2.42)**
Pulmonary exacerbation[1, 3]	15 (11.3)	18 (15.0)	21 (16.5)	1.31 (0.66, 2.60)	1.70 (0.88, 3.31)
Hosp. Resp. Cause[1, 4]	23 (17.3)	25 (20.8)	26 (20.5)	1.13 (0.64, 1.99)	1.40 (0.80, 2.46)
Death[5]	7 (5.3)	7 (5.8)	11 (8.7)	1.07 (0.37, 3.05)	1.92 (0.74, 4.99)

NC, not calculated (if fewer than 10 patients within subgroup experienced an event, only frequencies of events are presented)
1 Death was considered as an event in a composite strategy
2 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.1505 for 9 mg bid and 0.1017 for 18 mg bid vs. placebo
3 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.0704 for 9 mg bid and 0.2432 for 18 mg bid vs. placebo
4 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.4977 for 9 mg bid and 0.0534 for 18 mg bid vs. placebo
5 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.7338 for 9 mg bid and 0.0451 for 18 mg bid vs. placebo

Table 36: Summary of the key secondary endpoint and components – FAS, and stratified subgroups and subgroups according background nintedanib or pirfenidone treatment 1305-0014 DBL2

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
FAS	**393 (100.0)**	**392 (100.0)**	**392 (100.0)**		
Key secondary endpoint	**103 (26.2)**	**90 (23.0)**	**93 (23.7)**	**0.92 (0.69, 1.22)**	**0.99 (0.75, 1.31)**
Pulmonary exacerbation[1]	68 (17.3)	61 (15.6)	54 (13.8)	0.97 (0.69, 1.38)	0.87 (0.61, 1.24)
Hosp. Resp. Cause[1]	94 (23.9)	79 (20.2)	84 (21.4)	0.89 (0.66, 1.20)	0.97 (0.73, 1.31)
Death	42 (10.7)	36 (9.2)	26 (6.6)	0.95 (0.61, 1.49)	0.66 (0.41, 1.08)
Stratified subgroups					
Without AF background (n= 262, 22%)					
Key secondary endpoint[2]	**32 (36.8)**	**15 (17.0)**	**19 (21.8)**	**0.47 (0.26, 0.88)**	**0.62 (0.35, 1.10)**
Pulmonary exacerbation[1, 3]	21 (24.1)	7 (8.0)	12 (13.8)	0.35 (0.15, 0.83)	0.66 (0.32, 1.35)
Hosp. Resp. Cause[1, 4]	28 (32.2)	15 (17.0)	16 (18.4)	0.56 (0.30, 1.06)	0.57 (0.31, 1.06)
Death[5]	12 (13.8)	6 (6.8)	3 (3.4)	0.56 (0.21, 1.49)	0.26 (0.07, 0.91)
With AF background (n=915, 78%)					
Key secondary endpoint[2]	**71 (23.2)**	**75 (24.7)**	**74 (24.3)**	**1.12 (0.81, 1.55)**	**1.16 (0.83, 1.60)**
Pulmonary exacerbation[1, 3]	47 (15.4)	54 (17.8)	42 (13.8)	1.25 (0.85, 1.85)	0.96 (0.63, 1.45)
Hosp. Resp. Cause[1, 4]	66 (21.6)	64 (21.1)	68 (22.3)	1.03 (0.73, 1.45)	1.15 (0.82, 1.62)
Death[5]	30 (9.8)	30 (9.9)	23 (7.5)	1.11 (0.67, 1.85)	0.83 (0.48, 1.43)
Subgroup of stratified subgroup with AF background therapy					
Background nintedanib (n=535, 46%)					
Key secondary endpoint[6]	**41 (23.7)**	**39 (21.2)**	**43 (24.2)**	**0.98 (0.63, 1.53)**	**1.07 (0.70, 1.64)**
Pulmonary exacerbation[1, 7]	27 (15.6)	29 (15.8)	20 (11.2)	1.16 (0.69, 1.96)	0.73 (0.41, 1.30)
Hosp. Resp. Cause[1, 8]	37 (21.4)	33 (17.9)	41 (23.0)	0.94 (0.59, 1.51)	1.15 (0.73, 1.79)
Death[9]	17 (9.8)	15 (8.2)	11 (6.2)	1.02 (0.51, 2.04)	0.64 (0.30, 1.37)
Background pirfenidone (n=380, 32%)					
Key secondary endpoint[6]	**30 (22.6)**	**36 (30.0)**	**31 (24.4)**	**1.30 (0.80, 2.12)**	**1.28 (0.77, 2.12)**
Pulmonary exacerbation[1, 7]	20 (15.0)	25 (20.8)	22 (17.3)	1.38 (0.77, 2.50)	1.33 (0.72, 2.44)
Hosp. Resp. Cause[1, 8]	29 (21.8)	31 (25.8)	27 (21.3)	1.13 (0.68, 1.88)	1.16 (0.69, 1.96)
Death[9]	13 (9.8)	15 (12.5)	12 (9.4)	1.23 (0.58, 2.59)	1.12 (0.51, 2.47)
Subgroup by baseline FVC % predicted					

1 Death was considered as an event in a composite strategy
2 Treatment-by-subgroup interaction p = 0.0158 for 9 mg bid and 0.0656 for 18 mg bid vs. placebo
3 Treatment-by-subgroup interaction p = 0.0081 for 9 mg bid and 0.3758 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.1008 for 9 mg bid and 0.0512 for 18 mg bid vs. placebo
5 Treatment-by-subgroup interaction p = 0.2233 for 9 mg bid and 0.0951 for 18 mg bid vs. placebo
6 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.0383 for 9 mg bid and 0.1605 for 18 mg bid vs. placebo
7 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.0272 for 9 mg bid and 0.2435 for 18 mg bid vs. placebo
8 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.2266 for 9 mg bid and 0.1500 for 18 mg bid vs. placebo
9 Treatment-by-subgroup (nintedanib/pirfenidone/none) interaction p = 0.4442 for 9 mg bid and 0.1467 for 18 mg bid vs. placebo
10 Treatment-by-subgroup interaction p = 0.6754 for 9 mg bid and 0.1608 for 18 mg bid vs. placebo

5.3.2.2. FIBRONEER-ILD (1305-0023) (EU CT 2022-001134-11)

5.3.2.2.1. Study title/design

FIBRONEER-ILD (1305-0023): A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nerandomilast over at least 52 weeks in patients with Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)

FIBRONEER-ILD was a confirmatory, multicentre, multinational, prospective, randomised, placebo-controlled, double-blind, parrel-design clinical trial to investigate the efficacy and safety of of nerandomilast at a dose of 9 mg twice daily and 18 mg twice daily in patients with PPF over at least 52 weeks. The minimum treatment period of 52 weeks was selected based on guidance from the American

and European Clinicians organizations on the investigation of treatment effects on FVC in IPF and ILD. Data for the FIBRONEER-ILD-ILD trial was provided up until Data Base Lock 1 (DBL1) (Data cut-off for analysis occurred on 18 Dec 2024), the main analysis of the trial was performed after the last randomised participant had completed the Week-52 assessment. As the trial is ongoing, further data past DBL1 is not available until all participants complete the end of treatment visit and the end of study visit as applicable.

The trial consisted of 3 periods, a screening period of up to 8 weeks, a randomised treatment period of at least 52 weeks (part A: 52 weeks and part B: variable duration), and a follow-up period of 7 days. Treatment part A was done sequentially for enrolled subjects, but treatment part B is still ongoing and will stop at the same time for all subjects with a total of trial treatment of up to 130 weeks for the first enrolled subjects. Patients receiving trial medication until the end of Part B will be eligible for open-label treatment with nerandomilast in a separate extension trial. The main analysis of trial 1305-0023 had been performed after DBL1. Following trial completion and final DBL2, a final analysis was performed using all data available at the time of DBL2. The confirmatory testing for the key secondary endpoint was performed at DBL1 and the p-values at DBL2 were not adjusted for multiple testing (i.e. nominal p-values).

The trial population was planned to be stratified based on the presence of background antifibrotic therapy (non-antifibrotic or antifibrotic group) and HCRT pattern (Usual interstitial pneumonia (UIP)/UIP-like fibrotic pattern or Other fibrotic patterns). Presence of background treatment was either no treatment with nintedanib in the last 8 weeks prior to enrolment or with nintedanib treatment for at least 12 weeks at study entry and through the study duration. The expected proportion of participants in the non-antifibrotic or antifibrotic subgroup was planned to correspond to the current treatment/prescription practices across the participating countries (30% vs. 70% respectively).

A historical HRCT can be used to determine eligibility, providing the scan was performed within the 12 months prior to screening. All HRCT scans will be assessed to confirm the presence of relevant fibrotic ILD (>10% extent), prior to randomization. Confirmation of eligibility must be available prior to randomization Visit 2. "UIP or UIP-like fibrotic pattern" is defined by criteria A, B and C, criteria A and C, or criteria B and C.

- Criteria A = Definite honeycomb lung destruction with basal and peripheral predominance
- Criteria B = Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
- Criteria C = Atypical features are absent, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Participants with PF-ILD who do not meet these criteria will be stratified into the group of participants with "Other fibrotic patterns". The following co-existing features will be accepted as other fibrotic patterns:

- Ground glass opacity
- Upper lung or peribronchovascular predominance
- Mosaic attenuation
- Air trapping
- Centrilobular nodules

Widespread consolidation and progressive massive fibrosis will not be considered as other fibrotic patterns and therefore did not qualify for the trial.

Treatments

Participants were randomised in a 1:1:1 ratio of 9mg nerandomilast, 18mg nerandomilast, or placebo matched control to be taken orally twice daily.

Treatment arms were stratified into antifibrotic and non-antifibrotic treatments, for participants being treated with stable nintedanib for at least 12 weeks prior to Visit 1, and during screening, and are planning to stay on this background treatment after randomization. Interruption and/or dose reductions of nintedanib were left at the discretion of the investigator, e.g. to manage side effects in line with the respective prescribing information.

As ILDs encompass a multitude of diseases, background medication for these non-IPF ILDs was permitted for the duration of the trial, with restrictions to antifibrotic medications due to participant stratification. Participants treated with certain immunosuppressive medication for the underlying condition (e.g. connective tissue diseases) can continue this treatment during the trial. Prednisone, up to a maximum of 15 mg, was allowed for the duration of the trial. Equivalency is shown in the table below.

Concomitant and rescue therapies

Treatment interruption

The applicant stated that there were no special emergency procedures to be followed in relation to rescue medication, emergency procedures, and other treatments. Temporary treatment interruptions were allowed to manage adverse events. The applicant states that all efforts were made to re-start the nerandomilast after resolution of the adverse event.

The applicant used the following management guidance regarding treatment interruption for the specific adverse events below:

Diarrhoea:

Depending on the intensity of the events,

For patients on nintedanib medication, management strategies (e.g. dose reduction and/or temporary interruption) as described in the respective prescribing information were to be followed. Temporary interruption of trial treatment could be considered, and trial treatment could be restarted when the patient had recovered according to investigator's assessment.

Severe infections (CTCAE >2), serious infections, opportunistic or *mycobacterium tuberculosis (M. tuberculosis)* infections

No further trial medication should be administered until the active infection had resolved and trial treatment could be restarted when the patient had recovered according to investigator's assessment.

Malignancies

In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma, or *in situ* squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix, the investigator was to permanently discontinue the trial treatment.

Vasculitis

- In case of events suspicious for vasculitis, trial treatment was to be discontinued.

If thorough evaluation did not confirm a causal relationship between trial medication and the event, trial treatment could be restarted based on the investigator's medical judgement.

New onset of severe depression or suicidality

- In case of new onset of severe depression defined as HADS >14 or the patient exhibited any

suicidal behaviour or serious suicidality ideation defined as type 4 or 5 in the C-SSRS

interview, trial treatment had to be discontinued.

In case of severe depression: If thorough evaluation did not confirm a causal relationship between trial medication and the event, and the patient had recovered, trial treatment could be restarted based on the investigator's medical judgement (in case of new onset of suicidality treatment it had to be permanently discontinued)

Rescue therapy

As the treatment arms were stratified into antifibrotic and non-antifibrotic treatments, for participants not receiving the antifibrotic medication nintedanib in the 8 weeks prior to study entry, nintedanib was a restricted medication during the full duration of the blinded treatment period. Nintedanib should not have been initiated in the first 12 weeks of trial treatment. After that timeframe, initiation of nintedanib was only allowed as rescue medication in case of disease worsening, defined as disease under study progression and/or ILD exacerbation. Pirfenidone was not permitted to be used for either arm of the antifibrotic group for the duration of the trial. However, as this medication is currently not approved for non-IPF PPF-ILDs, there was a low risk of this medication having to be halted for access to the trial.

Table 37: Restrictions regarding concomitant treatment (apart from nintedanib medication) (CSR 1305-0023)

Medication	Prior to Study[1]	Screening Period	Treatment Period A and B	Follow up period[6]
Potent CYP3A inhibitors	Not permitted	Not permitted	Not permitted[2]	Permitted
Stem cell therapy for the treatment of pulmonary fibrosis	Not permitted	Not permitted	Not permitted	Not permitted
PDE4 and non-selective PDE inhibitors, pirfenidone	Not permitted	Not permitted	Not permitted	Not permitted
Prednisone >15 mg/day or equivalent[3]	Not Permitted	Not permitted	Not permitted[4,5]	Permitted
Cyclophosphamide, tocilizumab, rituximab, mycophenolate	Not permitted	Not permitted	Not permitted[5]	Permitted

1 For duration of restriction before screening, please see exclusion criteria Section 9.3.2
2 If any short-term treatment with potent CYP3A4 inhibitor was needed, IMP should have been temporarily discontinued.
3 Inhaled, intra-nasal, and topical corticosteroids were allowed.
4 Prednisone >15mg/day or equivalent can be prescribed during the treatment period in case of (suspected) acute ILD exacerbation.
5 After 6 months from randomization, changes are allowed for the management of worsening of the underlying disease as medically indicated.
6 Follow-up period started whenever a patient permanently discontinued trial medication.

Randomisation

After the assessment of all inclusion and exclusion criteria during the screening period (≤12-weeks), each eligible participant was randomized in a 1:1:1 ratio to either 9mg nerandomilast, 18mg nerandomilast, or placebo matched control at Visit 2. Participants were parallel randomized in blocks to double-blind treatment. The randomization was stratified by the presence of background treatment with antifibrotics (AF group vs. non-AF group) and by HRCT pattern ("UIP or UIP-like fibrotic pattern" vs. "Other fibrotic

patterns") using an Interactive Response Technology (IRT) system. All HRCT scans will be sent to a vendor for central review and confirmation of and the presence of relevant fibrotic ILD (>10% extent), prior to randomization. Confirmation of eligibility must be available prior to randomization Visit 2.

Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial were blinded regarding the randomized treatment assignments until the main analysis (DBL1), the sponsor was unblinded to assess the benefit-risk of both doses of nerandomilast vs placebo and select the dose with the more favorable benefit-risk profile for the open-label extension trial. Patients, investigators, and other site personnel remained blinded to the randomized treatment assignment until the end of the trial.

Patient population

Key Inclusion Criteria

- Patients ≥18 years old at the time of signed informed consent.
- Diagnosis of progressive fibrosing ILD other than IPF (physician confirmed) *****.
- Patients could be either:
  a) on a stable therapy (defined as the individually and general tolerated regimen mof nintedanib (no dose changes) for at least 12 weeks) with nintedanib for at least 12 weeks prior to Visit 1 and during screening and were planning to stay on this background treatment after randomisation.
  b) not on a treatment with nintedanib for at least 8 weeks prior to Visit 1 and during the screening period (e.g. either AF-treatment naïve or previously discontinued) and did not plan to start or re-start antifibrotic treatment.
- Forced Vital Capacity (FVC) ≥45% of predicted normal at Visit 1.
- DLCO ≥25% of predicted normal corrected for haemoglobin (Hb) at Visit 1.
- Patients treated with permitted immunosuppressive agents (other than corticosteroids) for an underlying systemic disease (e.g. MTX, AZA) need to be on a stable treatment for at least 12 weeks prior to Visit 1 and during the screening period.

*****Patients diagnosed with progressive fibrosing ILDs who complied with trial requirements qualified to participate in the trial. The diagnosis was based on:

- Presence of fibrotic lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent >10% on HRCT performed within 12 months of Visit 1 as confirmed by central review prior to Visit 2 (for details see Section 9.5.6.2) and
- Patients fulfilled at least one of the following criteria for PF-ILD within 24 months of Visit 1, as assessed by the investigator:
  a. Clinically significant decline in FVC % predicted based on a relative decline of ≥10%
  b. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms

c. Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging

d. Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging

Exclusion Criteria

- Prebronchodilator FEV1/FVC <0.7 at Visit 1.
- In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
- Acute ILD exacerbation within 3 months prior to Visit 1 and/or during the screening period (investigator-determined).
- Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis.
- Patients having developed ILD due to SARS-CoV-2 infection/COVID-19 within 12 months of screening (based on investigators judgement).
- 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 was not considered as planned major surgery.
- 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.
- AST or ALT >2.5x ULN or total bilirubin >1.5x ULN at Visit 1. eGFR ≤30 mL/min/1.73 m2 at Visit 1. (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI)
- Initially described as patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment), was revised to patients with underlying liver cirrhosis (Child Pugh A, B or C hepatic impairment).
- 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 ischemic attack within 6 months of Visit 1.
    - Unstable cardiac angina within 6 months of Visit 1.
- Use of any of the following medications: prednisone >15mg/day or equivalent within 4 weeks of Visit 1; cyclophosphamide, tocilizumab, mycophenolate, pirfenidone within 8 weeks of Visit 1; rituximab within 6 months of Visit 1.
- Active vasculitis, unstable or uncontrolled within 8 weeks prior to Visit 1 or during the screening period.
- Patients who must or wished to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. Please note: potent CYP3A4 inhibitors were not to be taken 5 half-life times prior to Visit 1.
- Patients treated with PDE1, PDE3, PDE4, PDE10 inhibitors, and non-selective PDE inhibitors within 30 days before Visit 1.

- Patients who were enrolled in another investigational device or drug trial, or that had less than 30 days since ending another investigational device or drug trial(s) or from receiving other investigational treatment(s).
- History of stem cell therapy for the treatment of pulmonary fibrosis.

Table 38: Criteria for progressive disease behaviour in fibrosing ILD, comparing FIBRONEER-PPF clinical trial and 2022 ATS/ERS/JRS/ALAT recommendations

1305-0023 and INBUILD	2022 ATS/ERS/JRS/ALAT [P22-03204]
At least 1 of the following measure of progression within 24 months before screening, despite management: • Relative decline in FVC ≥10% predicted • Relative decline in FVC ≥5 to <10% predicted and worsening respiratory symptoms • Relative decline in FVC ≥5 to <10% predicted and increased extent of fibrosis on chest imaging • Worsening of respiratory symptoms and increased extent of fibrosis on chest imaging	At least 2 of the following clinical, physiological, and radiological criteria within the past year, with no alternative explanation: • Worsening respiratory symptoms • Physiological evidence of disease progression (either of the following) o Absolute decline in FVC ≥5% predicted within 1 year of follow-up o Absolute decline in DL_{CO} (corrected for Hb) ≥10% predicted within 1 year of follow-up • Radiological evidence of disease progression

Comparing criteria for disease progression in three different trials (INBUILD, RELIEF, and uILD trials) prior to the clinical guideline update in 2022 showed that the identified participant populations were largely overlapping. Since the publication of the guideline update in May 2022, further evidence has been published describing highly overlapping participant characteristics and disease behaviour based on different criteria used. In FIBRONEER-ILD, 87.2% of the randomised participants were documented by the investigators to also meet the criteria for PPF as proposed by the 2022 ATS/ERS/JRS/ALAT guideline.

5.3.2.2.2. Objectives and estimands

FIBRONEER-ILD is a superiority trial of nerandomilast over placebo with a single key primary endpoint and a single key composite secondary endpoint.

The primary objective of the trial was to demonstrate superiority of at least one dose of nerandomilast to placebo in reducing lung function decline as measured by the change from baseline in FVC [mL] at Week 52.

Estimands for the primary objective

Table 39 : Estimands for primary objective 1305-0023

Population	Patients with progressive fibrosing interstitial lung diseases who would encounter the Intercurrent Events of change of background antifibrotic therapy, start of a restricted medication, treatment discontinuation, death, and lung transplant if assigned to nerandomilast or placebo.
Treatment condition	Assignment to nerandomilast, regardless of discontinuation and use of additional medications, compared to assignment to placebo, regardless of discontinuation and use of additional medications.
Endpoint (variable)	Absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52.
Population-level summary	Difference in mean change from baseline of FVC at Week 52 between nerandomilast and placebo
Intercurrent events and strategy to handle them	
Change in background antifibrotic therapy after baseline	Treatment policy – All available data up to Week 52 was included in the primary analyses
Start of a restricted medication	Treatment policy – All available data up to Week 52 was included in the primary analyses
Treatment discontinuation or interruption (any cause)	Treatment policy – All available data up to Week 52 was included in the primary analyses
Death	Hypothetical/Composite – Death events were considered a treatment failure and missing FVC change from baseline after death event was imputed based on 10th percentile of observed values across all treatment arms at each visit
Lung transplant	Hypothetical – Data collected after lung transplant was excluded

Statistical methods for estimation and sensitivity analysis on primary estimands

Analysis Sets

The following analysis sets were defined for statistical analyses:

- Entered Set (ES) – All patients who signed informed consent; used for analysis of protocol deviations
- Randomised Set (RS) – All patients who were entered and randomised; used for analysis of participant disposition
- Full Analysis Set (FAS) – All randomised patients who received at least one dose of study drug; patients were analysed based on the trial drug they actually received; used for baseline demographics, protocol deviations, and all efficacy analyses
- Treated Set (TS) – All randomised patients who received at least one dose of study drug; patients were analysed based on the trial drug they actually received; used for all safety analyses

- PK Parameter Analysis Set (PKS) – All patients in TS who provide at least one valid plasma concentration

Main analysis methods / statistical tests and estimation methods

Primary endpoint

The primary endpoint analysis followed a REML approach using a Mixed Model for Repeated Measures (MMRM) to compare change from baseline in FVC at Week 52 between the treatment groups. The model included the fixed categorical effects of treatment, baseline AF treatment, and baseline HRCT pattern, the fixed continuous effects of baseline FVC value, with visit being treated as the repeated measure with an unstructured covariance matrix.

Statistical testing was based on a comparison of least-square means of change from baseline between BI 1015550 18 mg / BI 1015550 9 mg and placebo using a significance level based upon a graphical testing procedure.

Handling of missing data

Primary endpoint

Missing data for non-death reasons were not imputed. Missing data due to death was to be assigned the 10th percentile change from baseline of observed Week 52 FVC values from all observed values across all treatment arms at each visit. This is based on having a poor treatment outcome under the composite strategy for intercurrent events.

Sensitivity and supplementary analysis methods

Sensitivity analyses – Primary endpoint

There were two sensitivity analyses for the impact of missing data on the primary analysis, for these analyses missing data was classified into four subsets depending on the level and reason for missingness. These subsets were:

- Subset 1 – Patients with a Week 52 FVC value and received trial drug until Week 52
- Subset 2 – Patients with a Week 52 FVC value who prematurely discontinue trial drug before Week 52
- Subset 3 – Patients without a Week 52 FVC value who were alive at Week 52
- Subset 4 – Patients without a Week 52 FVC value who had died before Week 52

For both sensitivity analyses, patients who were in subset 4 had missing data imputed from the 10th percentile change from baseline of all observed Week 52 FVC values across all treatment arms at each visit.

For the first sensitivity analysis, patients who were in subset 3 had missing data imputed using a follow reference approach. For the second sensitivity analysis, patients who were in this same subset will have this missing data imputed using a retrieved dropout approach.

A tipping point analysis was conducted using the Multiple Delta Adjustment method to assess how extreme departures, from the missing at random (MAR) assumption in the primary analysis model, would have to be in order to reverse the conclusions of the primary analysis. This analysis was performed under different assumptions regarding a declining continuation of efficacy following withdrawal of treatment. A ranked ANCOVA analysis was conducted on the ranked change from baseline at Week 52. For patients with missing data at Week 52, for non-death reasons, the FVC change from baseline at Week 52 was

imputed using multiple imputation. For patients who died before Week 52 ranking worse than those who remained alive at Week 52. Among the patients who died before Week 52, the rank was based on time to death from first trial drug intake date with shortest time to death as the worst rank.

A sensitivity analysis using the same model as the primary analysis was conducted where baseline AF treatment was replaced with the values used during the randomisation process as a covariate for adjustment.

A sensitivity analysis using the same model as the primary analysis with the additional covariates of sex, age, and height was conducted.

A sensitivity analysis using the same model as the primary analysis where records with FVC change from baseline values greater than +1000 mL or less than -1000 mL will be excluded.

Supplementary analyses – Primary endpoint

The following supplementary analyses were conducted to utilise different strategies in handling ICEs:

- Treatment discontinuation – Hypothetical: Analysis including only data while on-treatment, this includes any off-treatment period due to treatment interruption
- Initiation in background antifibrotic therapy – Hypothetical: Data after initiation of antifibrotic therapy was excluded from analysis
- Initiation in background antifibrotic therapy – Composite: Data after initiation of antifibrotic therapy will be assigned a poor outcome following the same rule as for the ICE of death in the primary analysis
- Important protocol deviation – Hypothetical: Data after different categories of important protocol deviations was excluded from analysis
- Death – Composite: Following the same strategy as the primary analysis but instead data will be replaced based on the 0.1st, 0.5th, 1st, 2.5th, and 5th percentile of observed values across all treatment arms at each visit
- Death – Hypothetical: Missing data after death was assumed to be MAR and analysis and only used observed data before death event
- Lung transplant – Composite: Data after lung transplant was assigned a poor outcome following the same rule as for the ICE of death in the primary analysis

Secondary objectives

The key secondary objective was to provide supportive evidence on a clinically meaningful outcome of nerandomilast vs. placebo for the primary endpoint, i.e. in reducing the risk of clinically meaningful events (acute ILD exacerbation, hospitalisation for respiratory cause, or death) over the duration of the trial.

An additional secondary objective of the FIBRONEER-ILD clinical trial was to show an effect of nerandomilast on symptoms and lung function.

Further objectives of the trial were to assess additional measures of efficacy, safety, and tolerability of nerandomilast compared with placebo, including Quality-of-Life questionnaires, time to progression, acute

ILD exacerbations, hospitalisations (for respiratory cause), mortality, and additional lung function assessments.

Key Secondary endpoint

The key secondary endpoint in this trial was time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalisation for respiratory cause, or death (whichever occurred first) over the duration of the trial.

Estimands for the secondary objectives

Table 40: Estimand for the secondary objectives 1305-0023

Population	Patients with progressive fibrosing interstitial lung diseases who would encounter the Intercurrent Events of change of background antifibrotic therapy, start of a restricted medication, treatment discontinuation, death, and lung transplant if assigned to nerandomilast or placebo.
Treatment condition	Assignment to nerandomilast, regardless of discontinuation and use of additional medications, compared to assignment to placebo, regardless of discontinuation and use of additional medications.
Endpoint (variable)	Time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalisation for respiratory cause, or death (whichever occurs first) over the duration of the trial.
Population-level summary	Difference in hazard rates over the whole trial between nerandomilast and placebo
Intercurrent events and strategy to handle them	
Change in background antifibrotic therapy after baseline	Treatment policy – All available data was included in the key secondary analyses
Start of a restricted medication	Treatment policy – All available data was included in the key secondary analyses
Treatment discontinuation or interruption (any cause)	Treatment policy – All available data was included in the key secondary analyses
Death	Composite – Death is treated as an event in the analysis
Lung transplant	Hypothetical – Data collected after lung transplant will be censored

All other and further endpoints were analysed in an exploratory manner and no adjustment for multiplicity was planned beyond primary and key secondary objective analyses.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Key secondary endpoint

The key secondary endpoint analysis was a time-to-event analysis for time to first acute ILD exacerbation, first hospitalisation for respiratory cause or death using a Cox proportional hazards model.

The model used data across the whole trial and included the covariates of treatment, baseline AF treatment, age, FVC %predicted, and DLCO %predicted.

Statistical testing was carried out on the equality of hazard rates by the Wald test for BI 1015550 18 mg / BI 1015550 9 mg versus placebo using a significance level based upon a graphical testing procedure.

Handling of missing data

Key secondary endpoint

Patients who did not have an event during the trial were censored at the last day the patient was known to be free of any event.

Sensitivity and supplementary analysis methods

Sensitivity analyses – Key secondary endpoint

The following sensitivity analyses were conducted:

- Cox proportional hazards model but with only treatment as a covariate and not adjusting for other variables
- Cox proportional hazards model but with additional covariates of sex, and height

Cox proportional hazards model with only confirmed acute exacerbations as events

Supplementary analyses – Key secondary endpoint

The following supplementary analyses were conducted to utilise different strategies in handling ICEs:

- Treatment discontinuation – Hypothetical: Same analysis as the key secondary analysis, but with the observation period set up to days after discontinuation of treatment
- Important protocol deviations – Hypothetical: Same analysis as the key secondary analysis, with the observation period set up as while patients are compliant with the protocol
- Initiation in background antifibrotic therapy – Hypothetical: Same analysis as the key secondary analysis, with data censored at the time of initiation of background antifibrotic therapy
- Initiation in background antifibrotic therapy – Composite: Same analysis as the key secondary analysis, with initiation of background antifibrotic therapy considered as an event
- Lung transplant – Composite: Same analysis as the key secondary analysis, with occurrence of lung transplant considered as an event

5.3.2.2.3. Results

Participant flow and numbers analysed

A total of 1178 patients were randomised as follows: placebo (393 patients), 9 mg bid nerandomilast (393 patients), or 18 mg bid nerandomilast (392 patients). The majority of randomised patients were from Asia (37.1%) and Europe (32.5%), the USA (11.8%) and Western hemisphere excluding the USA (15.4%).

Randomisation was stratified by the presence of background therapy with nintedanib (nintedanib group vs. non-nintedanib group) and by the HRCT pattern ("UIP or UIP-like fibrotic pattern" vs. "other fibrotic patterns").

Table 41: Treatment completion by background nintedanib therapy (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Patients without background nintedanib therapy								
Treated (treatment assigned as randomised)	222	100.0	220	100.0	220	100.0	662	100.0
Completed planned treatment up to Week 52[1]	173	77.9	182	82.7	183	83.2	538	81.3
Completed planned treatment up to DBL1 (ongoing at DBL1)	153	68.9	168	76.4	169	76.8	490	74.0
Prematurely discontinued treatment before DBL1	69	31.1	52	23.6	51	23.2	172	26.0
Lack of efficacy	2	0.9	0		1	0.5	3	0.5
Adverse event	29	13.1	24	10.9	21	9.5	74	11.2
Protocol deviation	0		0		1	0.5	1	0.2
Withdrawal by patient	21	9.5	18	8.2	23	10.5	62	9.4
Other	17	7.7	9	4.1	5	2.3	31	4.7
Completed planned observation for the primary endpoint assessment at Week 52	204	91.9	194	88.2	197	89.5	595	89.9
Completed planned observation	180	81.1	179	81.4	187	85.0	546	82.5
Had lung transplant	2	0.9	0		0		2	0.3
Death	23	10.4	16	7.3	10	4.5	49	7.4
Completed planned observation in trial up to DBL1	211	95.0	204	92.7	211	95.9	626	94.6
Ongoing at DBL1	179	80.6	183	83.2	200	90.9	562	84.9
Had lung transplant	2	0.9	0		0		2	0.3
Death	30	13.5	21	9.5	11	5.0	62	9.4
Patients with background nintedanib therapy[2]								
Treated (treatment assigned as randomised)	170	100.0	173	100.0	171	100.0	514	100.0
Completed planned treatment up to Week 52[1]	145	85.3	140	80.9	129	75.4	414	80.5
Completed planned treatment up to DBL1 (ongoing at DBL1)	128	75.3	134	77.5	115	67.3	377	73.3
Prematurely discontinued treatment before DBL1	42	24.7	39	22.5	56	32.7	137	26.7
Adverse event	18	10.6	18	10.4	23	13.5	59	11.5
Withdrawal by patient	6	3.5	11	6.4	16	9.4	33	6.4
Other	17	10.0	10	5.8	17	9.9	44	8.6
Completed planned observation for the primary endpoint assessment at Week 52	160	94.1	156	90.2	153	89.5	469	91.2
Completed planned observation	146	85.9	146	84.4	137	80.1	429	83.5
Had lung transplant	4	2.4	2	1.2	7	4.1	13	2.5
Death	12	7.1	8	4.6	11	6.4	31	6.0
Completed planned observation in trial up to DBL1	169	99.4	167	96.5	161	94.2	497	96.7
Ongoing at DBL1	141	82.9	152	87.9	140	81.9	433	84.2
Had lung transplant	8	4.7	3	1.7	8	4.7	19	3.7
Death	20	11.8	12	6.9	13	7.6	45	8.8

Table 42: Treatment completion by HRCT pattern (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Patients with UIP or UIP-like fibrotic pattern								
Treated (treatment assigned as randomised)	275	100.0	290	100.0	275	100.0	840	100.0
Completed planned treatment up to Week 52[1]	219	79.6	243	83.8	218	79.3	680	81.0
Completed planned treatment up to DBL1 (ongoing at DBL1)	197	71.6	225	77.6	199	72.4	621	73.9
Prematurely discontinued treatment before DBL1	78	28.4	65	22.4	76	27.6	219	26.1
Adverse event	37	13.5	33	11.4	33	12.0	103	12.3
Protocol deviation	0		0		1	0.4	1	0.1
Withdrawal by patient	16	5.8	18	6.2	25	9.1	59	7.0
Lack of efficacy	1	0.4	0		0		1	0.1
Other	24	8.7	13	4.5	17	6.2	54	6.4
Completed planned observation for the primary endpoint assessment at Week 52	256	93.1	265	91.4	246	89.5	767	91.3
Completed planned observation	227	82.5	248	85.5	226	82.2	701	83.5
Had lung transplant	3	1.1	2	0.7	5	1.8	10	1.2
Death	28	10.2	15	5.2	16	5.8	59	7.0
Completed planned observation in trial up to DBL1	267	97.1	277	95.5	264	96.0	808	96.2
Ongoing at DBL1	226	82.2	250	86.2	240	87.3	716	85.2
Had lung transplant	5	1.8	3	1.0	5	1.8	13	1.5
Death	36	13.1	24	8.3	19	6.9	79	9.4
Patients with other fibrotic pattern								
Treated (treatment assigned as randomised)	117	100.0	103	100.0	116	100.0	336	100.0
Completed planned treatment up to Week 52[1]	99	84.6	79	76.7	94	81.0	272	81.0
Completed planned treatment up to DBL1 (ongoing at DBL1)	84	71.8	77	74.8	85	73.3	246	73.2
Prematurely discontinued treatment before DBL1	33	28.2	26	25.2	31	26.7	90	26.8
Adverse event	10	8.5	9	8.7	11	9.5	30	8.9
Withdrawal by patient	11	9.4	11	10.7	14	12.1	36	10.7
Lack of efficacy	1	0.9	0		1	0.9	2	0.6
Other	10	8.5	6	5.8	5	4.3	21	6.3
Completed planned observation for the primary endpoint assessment at Week 52	108	92.3	85	82.5	104	89.7	297	88.4
Completed planned observation	99	84.6	77	74.8	98	84.5	274	81.5
Had lung transplant	3	2.6	0		2	1.7	5	1.5
Death	7	6.0	9	8.7	5	4.3	21	6.3
Completed planned observation in trial up to DBL1	113	96.6	94	91.3	108	93.1	315	93.8
Ongoing at DBL1	94	80.3	85	82.5	100	86.2	279	83.0
Had lung transplant	5	4.3	0		3	2.6	8	2.4
Death	14	12.0	9	8.7	5	4.3	28	8.3

The main reason for participants not being randomised was failure to meet the eligibility criteria (549 participants, 30.8% of screened participants). The most common eligibility criteria not met were diagnosis of ILD (103 participants), FVC % predicted (98 participants), and DLCO % predicted (corrected for haemoglobin) (57 participants) inclusion criteria.

Up to Week 52, 952 patients (81.0% of the treated patients) completed planned treatment and a total of 1064 patients (90.5%) completed planned observation for the primary endpoint assessment (975 patients with FVC assessment available at the Week 52 visit, 15 patients had lung transplant, and 80 patients died; Table 10: 2).

Up to DBL1 (data snapshot), 867 patients (73.7%) completed planned treatment (i.e. treatment was ongoing for these patients). The most common reason for premature discontinuation of study medication before DBL1 (a total of 26.3% of treated patients) was an AE (11.3%), followed by withdrawal by patient (8.1%), and "other" (6.4%). A total of 1123 patients (95.5%) completed the planned observation in trial up to DBL1: 995 patients (84.6%) were ongoing, 21 (1.8%) had lung transplant, and 107 (9.1%) died.

Table 43: Disposition of patients up to DBL1 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Entered							1780	
Randomised	393		393		392		1178	
Treated (treatment assigned as randomised)	392	100.0	393	100.0	391	100.0	1176	100.0
Completed planned treatment up to Week 52[1]	318	81.1	322	81.9	312	79.8	952	81.0
Completed planned treatment up to DBL1 (ongoing at DBL1)	281	71.7	302	76.8	284	72.6	867	73.7
Prematurely discontinued treatment before DBL1	111	28.3	91	23.2	107	27.4	309	26.3
Lack of efficacy	2	0.5	0		1	0.3	3	0.3
Adverse event	47	12.0	42	10.7	44	11.3	133	11.3
Protocol deviation	0		0		1	0.3	1	0.1
Withdrawal by patient[2]	27	6.9	29	7.4	39	10.0	95	8.1
Other	34	8.7	19	4.8	22	5.6	75	6.4
Completed planned observation for the primary endpoint assessment at Week 52[3]	364	92.9	350	89.1	350	89.5	1064	90.5
Completed planned observation[4]	326	83.2	325	82.7	324	82.9	975	82.9
Had lung transplant	6	1.5	2	0.5	7	1.8	15	1.3
Death	35	8.9	24	6.1	21	5.4	80	6.8
Completed planned observation in trial up to DBL1	380	96.9	371	94.4	372	95.1	1123	95.5
Ongoing at DBL1	320	81.6	335	85.2	340	87.0	995	84.6
Had lung transplant	10	2.6	3	0.8	8	2.0	21	1.8
Death	50	12.8	33	8.4	24	6.1	107	9.1
Prematurely discontinued trial before DBL1	12	3.1	22	5.6	19	4.9	53	4.5
Lost to follow-up	0		1	0.3	1	0.3	2	0.2
Withdrawal by patient	2	0.5	11	2.8	9	2.3	22	1.9
Other	10	2.6	10	2.5	8	2.0	28	2.4

Up to DBL2, 826 patients (70.2%) completed planned treatment. Of these 826 eligible patients, 792 patients (95.9%) continued or switched to nerandomilast treatment in the open-label extension trial 1305-0031. Three more patients who did not complete the planned treatment period but met the requirements to participate in the extension trial (maximum treatment interruption of 12 weeks between the respective parent trial and the extension trial) rolled over to trial 1305-0031. The most common reasons for premature discontinuation of study medication before DBL2 (a total of 29.8% of 1176 treated patients) were similar to those before DBL1: occurrence of an AE (12.4%), followed by withdrawal of treatment by patient (9.0%), and 'other' (7.9%).

In patients without background nintedanib therapy, the rate of treatment discontinuation was higher with placebo compared with the nerandomilast groups (33.8%, vs. 28.2% with 9 mg bid and 25.9% with 18 mg bid), whereas in patients with background nintedanib therapy, the discontinuation rate was higher

with 18 mg bid nerandomilast (36.3%) compared with 9 mg bid nerandomilast (27.7%) or placebo (27.1%).

In patients with baseline "UIP or UIP-like fibrotic pattern", the rate of treatment discontinuation was lower with 9 mg bid nerandomilast (26.6%) compared with placebo or 18 mg bid nerandomilast (each 30.9%), whereas in patients with "other fibrotic pattern", the discontinuation rate was similar across treatment groups (ranging from 29.3% to 32.0%.

Table 44: Disposition of patients up to DBL2 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Entered							1780	
Randomised	393		393		392		1178	
Treated (treatment assigned as randomised)	392	100.0	393	100.0	391	100.0	1176	100.0
Completed planned treatment up to DBL2[1]	271	69.1	283	72.0	272	69.6	826	70.2
Rolled over to trial 1305-0031[2]	261	66.6	273	69.5	261	66.8	795	67.6
Prematurely discontinued treatment before DBL2	121	30.9	110	28.0	119	30.4	350	29.8
Lack of efficacy	2	0.5	0		1	0.3	3	0.3
Adverse event	49	12.5	49	12.5	48	12.3	146	12.4
Protocol deviation	0		0		1	0.3	1	0.1
Withdrawal by patient[3]	30	7.7	34	8.7	42	10.7	106	9.0
Lost to follow-up	0		1	0.3	0		1	0.1
Other	40	10.2	26	6.6	27	6.9	93	7.9
Completed planned observation, had lung transplant, or died up to DBL2	381	97.2	374	95.2	372	95.1	1127	95.8
Completed planned observation	307	78.3	335	85.2	328	83.9	970	82.5
Had lung transplant	10	2.6	3	0.8	10	2.6	23	2.0
Death	64	16.3	36	9.2	34	8.7	134	11.4
Prematurely discontinued trial before DBL2	11	2.8	19	4.8	19	4.9	49	4.2
Lost to follow-up	3	0.8	5	1.3	4	1.0	12	1.0
Withdrawal by patient	5	1.3	10	2.5	12	3.1	27	2.3
Other[4]	0		1	0.3	0		1	0.1
Unknown[5]	3	0.8	3	0.8	3	0.8	9	0.8

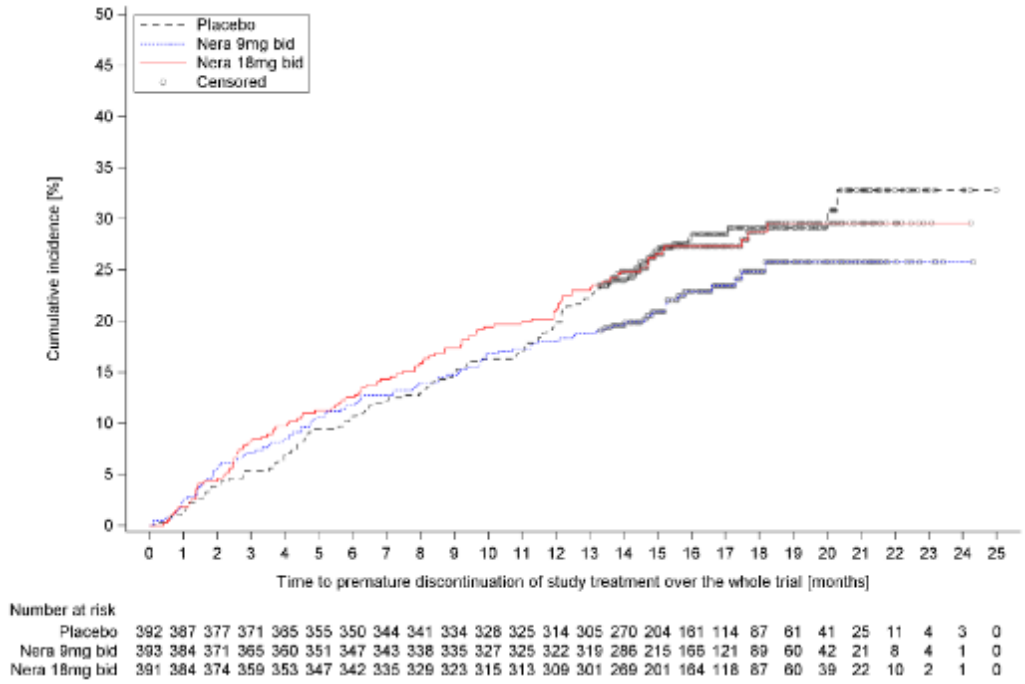


Figure 36: Estimated cumulative incidence function for time to permanent treatment discontinuation by treatment (CSR 1305-0023)

Participants with at least one treatment interruption was increased in the 9mg and 18mg nerandomilast groups with 105 and 98 participants respectively, compared to placebo with 81 participants. This trend remained for 1, 2, and >2 interruptions along with the number of treatment interruptions total. The primary reason for treatment interruptions was due to unrelated adverse events followed by related adverse events accounting for 70 and 13 participants placebo, 68 and 44 participants 9mg nerandomilast, and 68 and 41 participants 18mg nerandomilast respectively.

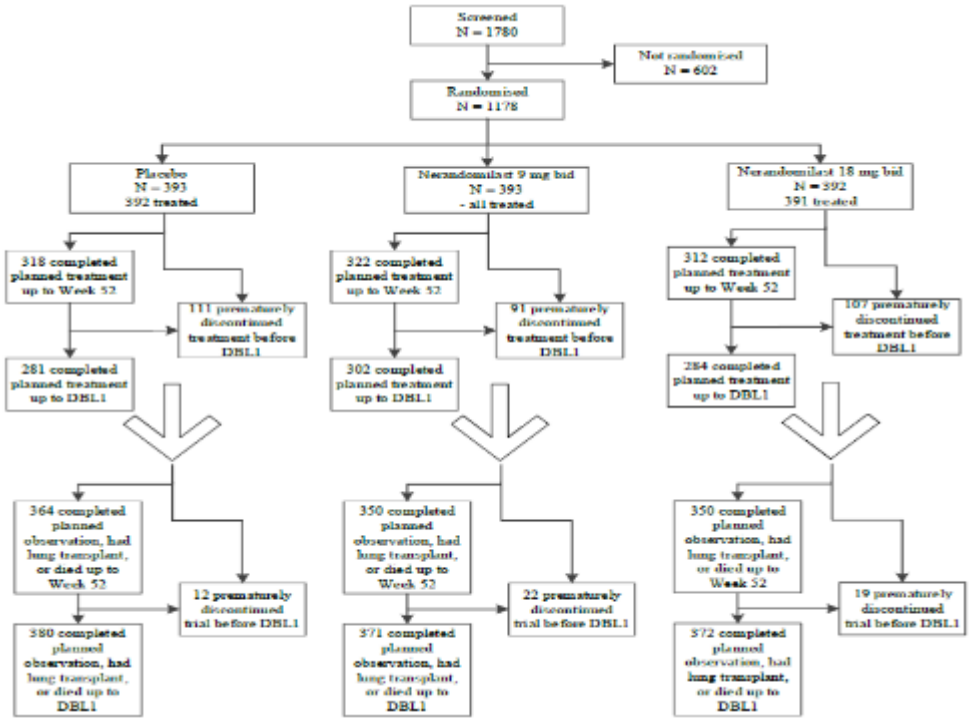


Figure 37: Disposition of participants up to end of DBL1 (CSR 1305-0023)

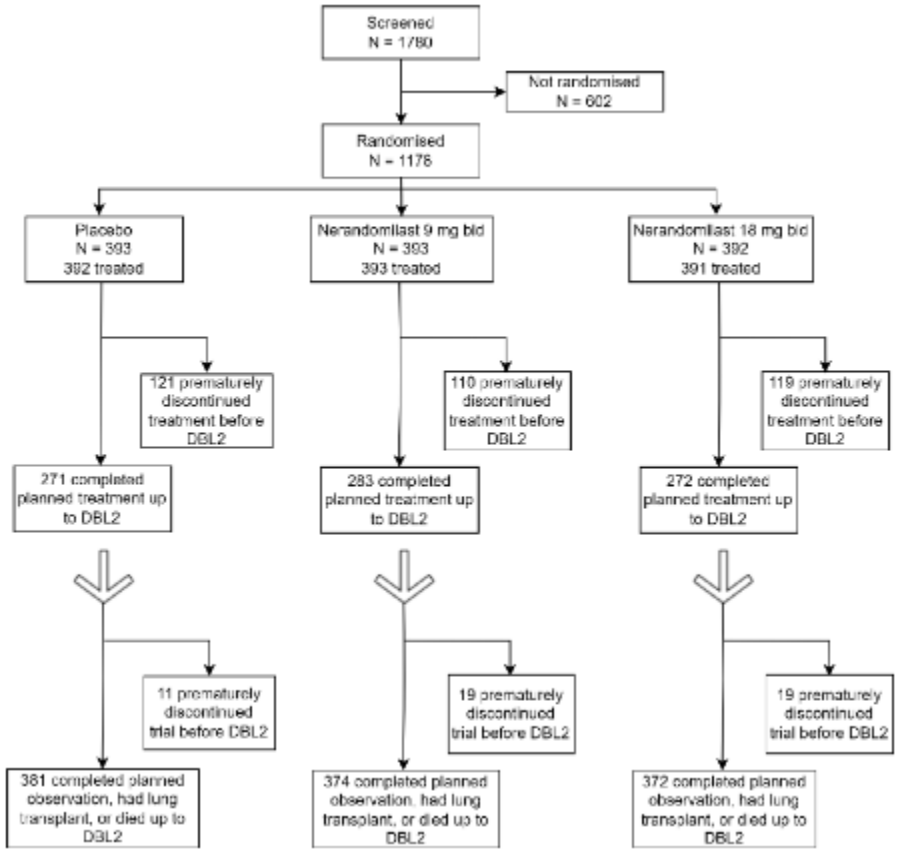


Figure 38: Disposition of participants up to end of DBL2 (CSR 1305-0023)

The primary analysis was performed on the full analysis set (FAS), which included all randomised participants who received at least one dose of study medication. All available data from the FAS within the first 52 weeks were used, regardless of premature treatment discontinuation or the use of nintedaib (rescue) therapy in the non-antifibrotic group. Data after lung transplants were excluded, assuming lung transplants to be random events. Missing data were not imputed except for death, where a poor value was assigned.

Table 45: Participant analysis sets (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Entered Set							1780	
Randomised set (RS)	393	100.0	393	100.0	392	100.0	1178	100.0
Full analysis set (FAS)	392	99.7	393	100.0	391	99.7	1176	99.8
Treated set (TS)	392	99.7	393	100.0	391	99.7	1176	99.8
PK parameter analysis set (PKS)	389	99.0	388	98.7	386	98.5	1163	98.7

Deviations from study plan

A total of 3 global amendments and 9 local amendments to the CTP were issued. Global Amendment 1 (dated 26 July 2022) introduced minor changes and was implemented without approval from the IEC/IRBs. Global Amendment 2 (dated 10 May 2023) and Global Amendment 3 (dated 20 September

2023) introduced major changes and both implemented after approval from the IEC/IRBs. Local amendments were also introduced in selected countries.

Major changes Global Amendment 2 (dated 10 May 2023)

- The sentence about participant eligibility was modified to clarify that participants with PF-ILD could still be eligible if all the fibrotic patterns were not met (except if they met these two patterns: widespread consolidation or progressive massive fibrosis).
- The upper limit for DLCO was deleted since it was not relevant as an exclusion criterion.
- Inclusion criteria (IC7) was updated to reflect that, based on the results of a drug-drug interaction trial on the PK of midazolam, oral contraceptives (OCs) were allowed as highly effective measure of contraception in WOCBP, associated with one barrier method to prevent the risk of potentially reduced efficacy of the OCs in case of severe vomiting and diarrhoea.
- Inclusion criteria (IC8) was updated to clarify that the criterion for permitted immunosuppressive agents did not concern corticosteroids.
- Any FEV/FVC ratio <0.7 was to be avoided as the risk of emphysema and obstruction would be high and would influence efficacy endpoint measurements.
- Exclusion criteria (EC10) was clarified following a question from a site, (as Child Pugh only refers to liver cirrhosis, not chronic liver disease).
- Exclusion criterion (EC23) was updated to reflect that no negative effect of nerandomilast on latent tuberculosis was expected based on preclinical data (immunophenotype in a 39-week monkey study). The TB diagnosis was simplified, relying on the site's expertise.
- A new exclusion criterion, history of stem cell therapy for the treatment of pulmonary fibrosis, was added (EC27) to reflect the fact that the effect of such treatment on the lung in the longer term was unknown. In light of this concern, stem cell therapy for the treatment of pulmonary fibrosis was not allowed in the section on restrictions regarding concomitant treatment.
- Management and handling of participants and data in case the dose of 9 mg bid was considered as futile were clarified where needed, based on blinding and unblinding concerns, randomisation, and on interim analysis details.
- Restrictions regarding immunomodulatory treatment were clarified, to indicate that dose adjustments of prednisone below 15 mg were allowed and that prednisone >15 mg/day or equivalent could be prescribed during the treatment period in case of (suspected) acute ILD exacerbation.
- The restrictions regarding pirfenidone during the follow-up period were updated from permitted to not permitted.
- Participants were to be analysed as randomised in the efficacy analysis, and as treated in the safety analysis. The PPS was deleted as post-randomisation events were to be handled via estimands (based on ICH E9 addendum), as described in the TSAP. For this reason, the Full Analysis Set (FAS) was added as the primary population for the efficacy analysis, and the definition of the Treated Set (TS) was modified, as this was to be the primary population for the safety analysis (but not the efficacy analysis).
- Since there could be a few days gap between the randomisation date and the first drug intake date, for the purpose of time to event analyses, the actual time at risk should start with the first drug intake. For this reason, for all time-to-event endpoints, the start date considered when

calculating the time to event of interest (and the time to censoring) was changed from 'randomisation date' to 'first drug intake date'.

Major changes Global Amendment 3 (dated 20 September 2023)

- The efficacy interim analysis was not to be conducted, and the main analysis and the final analysis were specified. This decision was made by the sponsor before the futility analysis based on Health Authority feedback and shifting trial timelines with fast recruitment, which made the time advantage in conducting the interim analysis limited.
- The futility analysis was not to be conducted due to the following reasons: it was defined as non-binding in the DMC charter - recruitment for this trial would be completed by the time of the previously planned futility analysis, and outliers observed from trial 1305-0014 in FVC changes from baseline among early recruited participant cohort increased the concern that the point estimate for the futility decision might have not been robust; 9 mg was deemed not futile in the parallel trial 1305-0014 by the DMC; no safety concern was observed by the DMC in either 1305-0014 or 1305-0023; consistency of treatment groups and analyses between trial 1305-0014 and 1305-0023 facilitated the interpretation of results across different participant populations.
- The overall trial design section that was revised to specify the main and final analyses.
- Unblinding of the sponsor at the main analysis (DBL1) was clarified, as well as the use of unblinded PK data before DBL1 by personnel involved in the PK analyses to front-load.
- An explanation that the hypothesis testing of the key secondary endpoint was to be done at the main analysis, and a high-level description of what would be analysed at the main and the final analysis.
- On restrictions regarding concomitant treatment, restricted PDE inhibitors were narrowed down to those that specifically interfere with PDE4.
- AE reporting based on HADS was clarified.

Other changes to the CTP

• On November 09, 2023, a note to file documenting the removal of the plan to perform an interim analysis to rule out futility of the 9mg twice daily dose was created.

• On December 21, 2023, a letter was created to describe the steps that lead to an early end of screening and over recruitment in the current trial due to an unexpected fast enrolment speed.

Changes introduced in the trial statistical analysis plan

Added further endpoints for absolute change from baseline in FVC [mL], FVC % predicted, DLCO % predicted and L-PF scores over the whole trial, and for absolute change from baseline in L-PF scores at Week 26. Time to deterioration in L-PF symptoms (dyspnoea, cough, and fatigue) were added as further endpoints. Time to first oxygen use, to increase of supplemental oxygen, change from baseline in supplemental oxygen flow rate over the whole trial, and time to absolute decline in FVC % predicted of >15% from baseline or death over the whole trial were also added as further endpoints.

GCP Violations

For Site CHN1 (China), there was delayed submission of CTP version 4.0 and high participant discontinuation rate observed at the site. The site was audited, and the following issues were detected:

- multiple instances of retrospectively documenting subject visits and associated procedures

- multiple instances of inadequate AE documentation and reporting
- significant delay in data entry/missing data
- lack of PI oversight or inadequate resources
- inadequate monitoring process

the discontinuation reason was documented based on medical notes without further details

The site randomised 13 participants, and 6 participants discontinued treatment. The Severe Issue Committee of the applicant determined a serious breach at the site due to significant impact on data completeness and integrity. They concluded that there were no outstanding concerns regarding the safety and rights of the participants remaining in the trial. Upon review of the final audit report, the applicant states that there was no indication that data used for the analyses was incorrect and so the data collected at the site was used for analyses.

Site CHN7 (China) had a serious breach due to a failure to obtain Ethics Committee's (EC) approval for documents released between May 2023 and Jul 2024. The supplier's Clinical Research Associate (CRA) committed fraud by falsely reporting document approval by the EC and fabricating false EC approval dates. As a result, the trial was conducted at the site under CTP version 2.0 until 2 Sep 2024. Upon review of the changes implemented with the updated CTP versions, the changes were not related to safety. It was concluded by the applicant that there was no impact on participant safety and no impact on data integrity.

Protocol deviations

Up to DBL1, the proportions of participants with important protocol deviations (iPDs) were similar across the treatment groups (≤2% difference between groups) with 70, 70, and 64 participants in placebo, 9mg nerandomilast, and 18mg nerandomilast respectively (204 participants in total). The most common iPD was the use of prednisone >15 mg/day or equivalent between randomisation and EOT (60 participants, 5.1%), followed by the use of PDE4 and non-selective PDE inhibitors, or pirfenidone between randomisation and EOT (38 participants, 3.2%), and trial medication not interrupted due to AE according to the study protocol (36 participants, 3.1%). All other iPDs were reported in no more than 2% of participants overall.

The study enrolled 2 participants on background pirfenidone therapy (0.2%) even though nintedanib is the only treatment currently approved for PPF. These participants were categorised as having important protocol deviations but were included in the subgroup with background nintedanib therapy in the analyses as prespecified and continued during the trial.

Table 46: Number of patients with iPDs and iPD categories reported for at least 2 patients in any treatment group up to DBL1 – FAS (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
	N	%	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0	1176	100.0
Patients with at least one iPD	70	17.9	70	17.8	64	16.4	204	17.3
Eligibility criteria not met								
FEV1/FVC <0.7 at Visit 1	5	1.3	1	0.3	4	1.0	10	0.9
Active tuberculosis	5	1.3	3	0.8	2	0.5	10	0.9
Prednisone >15 mg/day or equivalent within 4 weeks of Visit 1; cyclophosphamide, tocilizumab, mycophenolate, pirfenidone within 8 weeks of Visit 1; rituximab within 6 months of Visit 1	2	0.5	2	0.5	2	0.5	6	0.5
Pirfenidone within 8 weeks before Visit 1[1]	1	0.3	0		1	0.3	2	0.2
Relevant chronic or acute infections including HIV and viral hepatitis	0		4	1.0	1	0.3	5	0.4
PDE4 and non–selective PDE inhibitors within 30 days before Visit 1	2	0.5	1	0.3	1	0.3	4	0.3
No diagnosis of PPF including not satisfying progressive at screening	2	0.5	1	0.3	0		3	0.3
Informed consent								
Informed consent given too late for screened or re-screened patients	0		2	0.5	0		2	0.2
Trial medication and randomisation								
Trial medication not interrupted due to AE according to protocol	16	4.1	11	2.8	9	2.3	36	3.1
Overall compliance between randomisation and Week 52 <80% (or non-compliance based on investigator assessment)	4	1.0	6	1.5	6	1.5	16	1.4
Concomitant medication								
Prednisone >15 mg/day or equivalent between randomisation and EOT	23	5.9	21	5.3	16	4.1	60	5.1
PDE4 and non-selective PDE inhibitors, or pirfenidone between randomisation and EOT	11	2.8	16	4.1	11	2.8	38	3.2
Potent CYP3A4 inhibitors between randomisation and EOT and with 18 mg trial drug treatment	0		0		9	2.3	9	0.8
Cyclophosphamide, tocilizumab, rituximab, mycophenolate between randomisation and EOT	1	0.3	2	0.5	1	0.3	4	0.3
Privacy/data protection								
Privacy and/or data protection violated	4	1.0	1	0.3	4	1.0	9	0.8
Safety procedures/SAE reporting								
Critical safety procedure not followed	0		3	0.8	0		3	0.3

Between DBL1 and DBL2, the proportions of patients with iPDs was 29.1% overall, with lower proportion in patients under 9 mg bid nerandomilast (26.7%) than under placebo (29.1%) or 18 mg bid nerandomilast (31.5%). Up to DBL2, the trends regarding iPDs were consistent with those described for DBL1. The most common iPD remained the use of prednisone >15 mg/day or equivalent between randomisation and EOT (14.9% of patients), followed by the use of PDE4 and non-selective PDE inhibitors between randomisation and EOT and trial medication not interrupted due to AE according to the study protocol (each 5.2%). All other iPDs were reported in no more than 2% of patients overall.

Baseline data

Demographics

Of the randomised and treated participants, more than half were male (male: 55.6%; female: 44.4%). Almost all participants were either White (58.2%) or Asian (39.1%, including Asian, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander), 16 participants were Black or African American (1.4%), and 15 participants were multiple race respondents (1.3%). The mean age was 66.4 years (standard deviation [SD] 10.0) and the median time since ILD diagnosis was 2.9 years (Q1 1.4, Q3 5.8) before the trial. Participants mean BMI was 26.6 (SD: 5.3). Participant demographics were evenly distributed amongst the treatment groups.

Table 47: Demographic data at baseline (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Number of patients (N %)	392	100.0	393	100.0	391	100.0	1176	100.0
Sex (N %)								
Male	231	58.9	203	51.7	220	56.3	654	55.6
Female	161	41.1	190	48.3	171	43.7	522	44.4
Race (subgroup) (N %)[1]								
White	226	57.7	224	57.0	235	60.1	685	58.2
Asian[2]	154	39.3	161	41.0	145	37.1	460	39.1
Black/African American	7	1.8	3	0.8	6	1.5	16	1.4
Ethnicity (N %)								
Not Hispanic/Latino	339	86.5	333	84.7	334	85.4	1006	85.5
Hispanic/Latino	53	13.5	60	15.3	57	14.6	170	14.5
Age [years] (mean, SD)	66.6	10.3	66.5	9.8	66.0	9.8	66.4	10.0
<65 (N %)	149	38.0	142	36.1	152	38.9	443	37.7
≥65 (N %)	243	62.0	251	63.9	239	61.1	733	62.3
≥65 to <75 (N %)	153	39.0	167	42.5	173	44.2	493	41.9
≥75 (N %)	90	23.0	84	21.4	66	16.9	240	20.4
Body weight [kg] (mean, SD)	73.4	17.9	72.1	17.5	73.2	17.1	72.9	17.5
Height [cm] (mean, SD)	165	10.2	164	10.4	166	10.1	165	10.2
BMI [kg/m^2] (mean, SD)	26.7	5.3	26.6	5.5	26.6	5.0	26.6	5.3
Smoking status (N %)								
Never	186	47.4	200	50.9	191	48.8	577	49.1
Former	200	51.0	186	47.3	189	48.3	575	48.9
Current	6	1.5	7	1.8	11	2.8	24	2.0

Stratification Demographics

Table 48: Trial indication and nintedanib therapy at baseline (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Number of patients (N %)	392	100.0	393	100.0	391	100.0	1176	100.0
Time since first ILD diagnosis [years]								
Mean, SD	3.93	3.63	4.10	4.32	4.59	4.84	4.21	4.30
Median (Q1, Q3)	2.7	1.5, 5.7	2.6	1.1, 5.8	3.2	1.5, 6.1	2.9	1.4, 5.8
≤1 (N %)	63	16.1	83	21.1	66	16.9	212	18.0
>1 to 3 (N %)	153	39.0	129	32.8	117	29.9	399	33.9
>3 to 5 (N %)	63	16.1	67	17.0	85	21.7	215	18.3
>5 (N %)	113	28.8	114	29.0	123	31.5	350	29.8
Baseline AF therapy (N %)	170	43.4	173	44.0	171	43.7	514	43.7
Nintedanib	169	43.1	173	44.0	170	43.5	512	43.5
Pirfenidone[1]	1	0.3	0		1	0.3	2	0.2
Duration on current AF treatment [months] (mean, SD)	15.7	12.6	17.1	14.3	21.9	23.9	18.2	17.8
No baseline AF therapy (N %)	222	56.6	220	56.0	220	56.3	662	56.3
Previous AF use	53	13.5	44	11.2	44	11.3	141	12.0
AF naïve	169	43.1	176	44.8	176	45.0	521	44.3
Baseline supplemental oxygen use (N %)	110	28.1	97	24.7	117	29.9	324	27.6
Baseline HRCT pattern (N %)								
UIP or UIP-like fibrotic pattern	275	70.2	290	73.8	275	70.3	840	71.4
Other fibrotic patterns	117	29.8	103	26.2	116	29.7	336	28.6

Underlying ILD

The most frequent underlying clinical ILD diagnosis category was autoimmune ILDs (325 participants, 27.6%), followed by hypersensitivity pneumonitis (233, 19.8%), unclassifiable idiopathic interstitial pneumonia (231, 19.6%), idiopathic nonspecific interstitial pneumonia (228, 19.4%), and other ILDs (159, 13.5%).

Table 49: Underlying ILD diagnosis at baseline (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Underlying clinical ILD diagnosis (subgroup) (N %)								
Idiopathic nonspecific interstitial pneumonia[2]	73	18.6	73	18.6	82	21.0	228	19.4
Unclassifiable idiopathic interstitial pneumonia[2]	82	20.9	76	19.3	73	18.7	231	19.6
Hypersensitivity pneumonitis[2]	77	19.6	83	21.1	73	18.7	233	19.8
Autoimmune ILDs	100	25.5	112	28.5	113	28.9	325	27.6
Rheumatoid arthritis associated ILDs[2]	32	8.2	45	11.5	41	10.5	118	10.0
Mixed connective tissue disease[2]	12	3.1	16	4.1	19	4.9	47	4.0
Systemic sclerosis associated ILDs[2]	23	5.9	25	6.4	27	6.9	75	6.4
Other autoimmune fibrosing	33	8.4	26	6.6	26	6.6	85	7.2

ILDs								
Other ILDs[3]	60	15.3	49	12.5	50	12.8	159	13.5
Exposure-related ILDs[2]	12	3.1	11	2.8	9	2.3	32	2.7
Sarcoidosis[2]	8	2.0	6	1.5	3	0.8	17	1.4
Other non-autoimmune fibrosing ILDs	40	10.2	32	8.1	38	9.7	110	9.4
Documented to also meet the criteria for PPF as proposed in the 2022 ATS/ERS/JRS/ALAT Guideline	344	87.8	341	86.8	340	87.0	1025	87.2

Baseline Lung Function

The mean baseline FVC % predicted was 70.1% (SD 15.8), mean DLCO % predicted 49.3% (SD 16.9) and mean L-PF total score 31.8 (SD: 17.9) with these parameters generally being balanced across the treatment groups.

Table 50: Baseline lung function and PRO variables (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Number of patients (N %)	392	100.0	393	100.0	391	100.0	1176	100.0
FVC [mL] (mean, SD)	2354	766	2326	768	2381	723	2353	752
FVC [% predicted] (mean, SD)	69.7	16.2	70.3	15.7	70.4	15.5	70.1	15.8
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	49.7	16.5	48.7	16.8	49.4	17.5	49.3	16.9
L-PF total score (mean, SD)	31.0	17.5	32.0	18.2	32.4	17.9	31.8	17.9
L-PF impact total score	35.1	20.0	36.2	20.9	36.6	21.0	36.0	20.6
L-PF symptoms total score	26.8	16.9	28.0	17.3	28.2	16.7	27.7	17.0
L-PF symptoms cough domain	30.0	23.7	31.8	26.3	33.4	26.3	31.7	25.5
L-PF symptoms dyspnea domain	18.0	17.1	18.1	17.1	16.8	15.2	17.7	16.5
L-PF symptoms fatigue domain	32.5	19.4	34.0	19.8	34.4	18.1	33.6	19.1

Stratification Lung Function

Table 51: Baseline lung function variables based on stratification (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Patients without background nintedanib therapy								
Number of patients (N %)	222	100.0	220	100.0	220	100.0	662	100.0
FVC [mL] (mean, SD)	2264	740	2244	759	2354	715	2287	738
FVC [% predicted] (mean, SD)	70.1	16.0	70.9	16.0	72.4	15.8	71.1	16.0
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	52.4	16.5	52.3	16.3	52.8	17.4	52.5	16.7
Patients with background nintedanib therapy[1]								
Number of patients (N %)	170	100.0	173	100.0	171	100.0	514	100.0
FVC [mL] (mean, SD)	2471	786	2430	769	2417	733	2439	762
FVC [% predicted] (mean, SD)	69.1	16.5	69.5	15.2	67.8	14.9	68.8	15.5
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	46.2	15.8	44.3	16.2	45.0	16.6	45.1	16.2

	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Patients with baseline UIP or UIP-like fibrotic pattern								
Number of patients (N %)	275	100.0	290	100.0	275	100.0	840	100.0
FVC [mL] (mean, SD)	2450	749	2365	752	2452	740	2421	747
FVC [% predicted] (mean, SD)	71.9	16.5	70.9	15.9	72.9	15.3	71.9	15.9
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	51.4	16.7	49.5	17.2	49.6	17.6	50.2	17.2
Patients with baseline other fibrotic pattern								
Number of patients (N %)	117	100.0	103	100.0	116	100.0	336	100.0
FVC [mL] (mean, SD)	2126	761	2216	804	2214	653	2184	739
FVC [% predicted] (mean, SD)	64.6	14.3	68.7	15.1	64.5	14.5	65.8	14.7
DL_{CO} [% predicted] (corrected for haemoglobin) (mean, SD)	45.7	15.2	46.5	15.2	48.8	17.2	47.0	16.0

Outcomes and estimation

Primary endpoint (absolute change from baseline in FVC [mL] at Week 52)

The adjusted mean change from baseline in FVC [mL] at Week 52 was -165.8 (95% CI -190.5, -141.0) in the placebo group, -84.6 (95% CI -109.6, -59.7) in the 9 mg bid nerandomilast group, and -98.6 (95% CI -123.7, -73.4) in the 18 mg bid nerandomilast group. The differences of nerandomilast 9 and 18 mg bid to placebo were both statistically significant. The adjusted mean difference in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 81.1 (95% CI 46.0, 116.3, p<0.0001) and between 18 mg bid nerandomilast and placebo groups was 67.2 (95% CI 31.9, 102.5, p = 0.0002).

The adjusted mean of absolute change from baseline in FVC in both nerandomilast dose groups started to separate from the placebo group early after randomisation at Week 2 and the separation was sustained up to Week 52. The curves were almost superimposable for both nerandomilast dose groups.

Table 52: Absolute change from baseline in FVC [mL] at Week 52 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in FAS, N	392		393		391	
Number of patients analysed, N[1]	391		390		390	
Baseline (mean, SD)	2353.6	766.2	2325.5	767.6	2381.4	722.8
Week 52 change from baseline						
Adjusted mean	-165.8		-84.6		-98.6	
95% CI	-190.5	-141.0	-109.6	-59.7	-123.7	-73.4
Comparison vs. placebo						
Adjusted mean	--		81.1		67.2	
95% CI	--		46.0	116.3	31.9	102.5
p-value[2]	--		<0.0001			0.0002

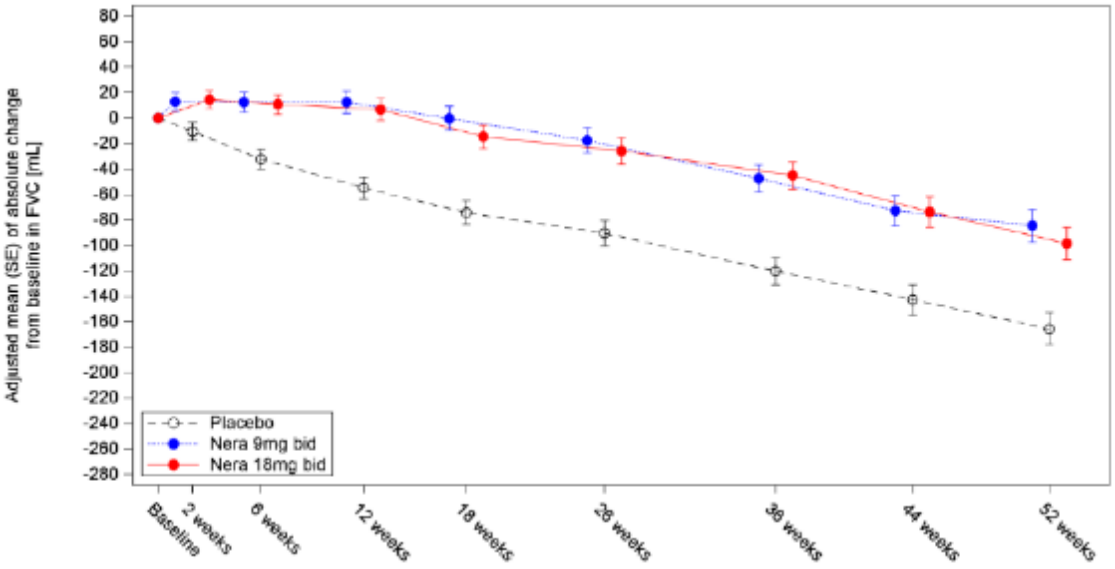


Figure 39: Adjusted mean (SE) of absolute change from baseline in FVC [mL] over 52 weeks (CSR 1305-0023)

Based on a graphical testing procedure that maintained an overall type I error rate of 5%, both nerandomilast doses were superior to placebo for the primary endpoint: p = 0.0002 for 18 mg bid dose was below the initially assigned alpha level of 0.04; p<0.0001 for 9 mg bid dose was below the updated alpha level of 0.03. As the primary endpoint was significant for both doses, a total alpha level of 0.05 was passed to test the key secondary endpoint for 18 mg bid nerandomilast vs. placebo

Secondary endpoint

Key secondary endpoint primary analysis

The confirmatory key secondary endpoint was the time to the first occurrence of any of the components of the composite endpoint: acute ILD exacerbation (either confirmed with CT data or suspected Sensitivity analysis of the secondary endpoint events without CT data), first hospitalisation for respiratory cause, or death over the duration of the trial. Acute ILD exacerbations and hospitalisations for respiratory cause were not independently adjudicated.

From DBL1

The hypothesis testing of the key secondary endpoint was based on data over the whole trial up to DBL1. Key secondary endpoint events occurred in numerically lower proportion of patients in both nerandomilast groups (9 mg bid: 110 patients, 28.0%; 18 mg bid: 95 patients, 24.3%) than placebo (122 patients, 31.1%), with the lowest proportion in the 18 mg bid treatment group. Hospitalisations for respiratory cause were the most common first events contributing to the key secondary endpoint (more than half of the first events.)

The risk of having a key secondary endpoint event was numerically lower in both nerandomilast dose groups than placebo, with the lowest risk in the 18 mg bid nerandomilast group, although no statistical significance in the treatment effect was shown according to the predefined graphical testing procedure (HR vs. placebo for 9 mg bid 0.88, 95% CI 0.68, 1.14, p = 0.3398; for 18 mg bid 0.77, 95% CI 0.59, 1.01, p = 0.0602).

At Week 52, the estimated percentage of patients with events was lower in the 18 mg bid nerandomilast group than placebo (-6.6%, 95% CI -12.5, -0.7). The estimated percentage difference vs. placebo was -3.7% (95% CI -9.7, 2.3) in the 9 mg bid nerandomilast group.

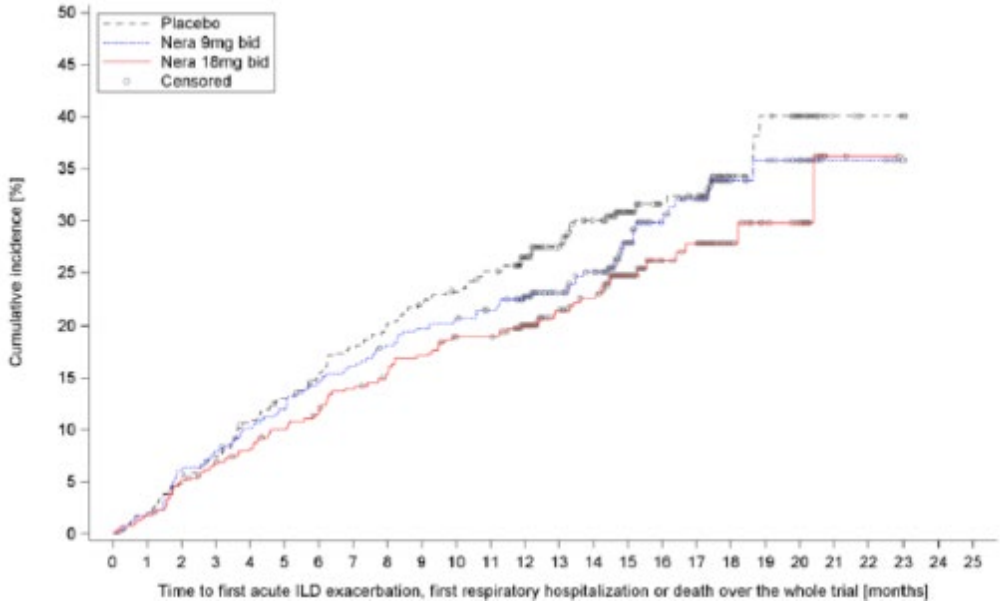


Figure 40: **Time to the first acute ILD exacerbation, first hospitalisation for respiratory cause, or death (whichever occurs first) over the duration of the trial up to DBL1, estimated cumulative incidence function (CSR 1305-0023)**

From DBL2

The confirmatory testing for the key secondary endpoint was performed at DBL1 and the p-values at DBL2 were not adjusted for multiple testing (i.e. nominal p-values). With additional treatment exposure (about 0.7 month) and observation time (about 1.6 months) at DBL2, the number of events for the key secondary endpoint increased across treatment groups.

Between DBL1 and DBL2, 45 additional events contributing to the key secondary endpoint occurred, representing an increase of approximately 14% of the 327 key secondary endpoint events that had occurred until DBL1. Most additional events after DBL1 were reported in the placebo group (+21 events), followed by the 18 mg bid nerandomilast group (+18 events), and the 9 mg bid nerandomilast group (+6 events).

Over the duration of the trial up to DBL2, key secondary endpoint events (372 events in total) occurred in 143 patients (36.5%) in the placebo group, 116 patients (29.5%) in the 9 mg bid nerandomilast group, and 113 patients (28.9%) in the 18 mg bid nerandomilast group. Compared with placebo, the HR (95% CI) was 0.78 (0.61, 1.00) for 9 mg bid nerandomilast (p = 0.0507) and 0.77 (0.60, 0.99) for 18 mg bid nerandomilast (p = 0.0395).

Other and further secondary endpoints

All analyses of other secondary and further endpoints are descriptive, and the p-values for treatment comparisons are nominal and not adjusted for multiple testing.

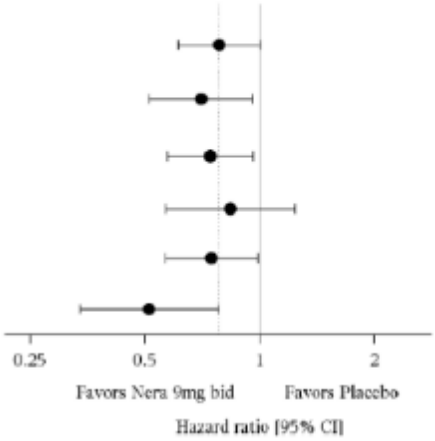
Table 53: Endpoints based on the time to the first clinical event over the duration of the trial up to DBL1 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in the FAS (N %)	392	100.0	393	100.0	391	100.0
Patients with acute ILD exacerbation or death (N %)	83	21.2	65	16.5	48	12.3
HR vs. placebo	--		0.78		0.59	
95% CI			0.56	1.08	0.41	0.84
p-value			0.1348		0.0036	
Acute ILD exacerbation (N %)	52	13.3	42	10.7	30	7.7
HR vs. placebo	--		0.85		0.60	
95% CI			0.57	1.29	0.38	0.94
p-value			0.4499		0.0274	
Patients with hospitalisation for respiratory cause or death (N %)	110	28.1	97	24.7	84	21.5
HR vs. placebo	--		0.83		0.75	
95% CI			0.63	1.10	0.56	1.00
p-value			0.1990		0.0499	
Hospitalisation for respiratory cause (N %)	95	24.2	86	21.9	79	20.2
HR vs. placebo	--		0.85		0.82	
95% CI			0.64	1.15	0.61	1.11
p-value			0.2930		0.1919	
Death (N %)	50	12.8	33	8.4	24	6.1
HR vs. placebo	--		0.60		0.48	
95% CI			0.38	0.95	0.30	0.79
p-value			0.0284		0.0036	
Patients with non-elective hospitalisation for any cause or death (N %)	138	35.2	122	31.0	131	33.5
HR vs. placebo	--		0.83		0.94	
95% CI			0.65	1.07	0.74	1.19
p-value			0.1461		0.6008	

At DBL2, the results of all sensitivity and supplementary analyses remained consistent with the primary analysis of the key secondary endpoint.

Nerandomilast 9 mg bid vs. placebo

	N with event / N analyzed		Hazard ratio	
	Placebo	Nera 9mg bid	[95% CI]	p-value *
Key secondary endpoint	143/392	116/393	0.78 [0.61, 1.00]	0.0507
Time to first acute ILD exacerbation or death	97/392	70/393	0.70 [0.51, 0.96]	0.0258
Time to first hospitalization for respiratory cause or death	131/392	103/393	0.74 [0.57, 0.96]	0.0237
Time to first acute ILD exacerbation	57/392	46/393	0.84 [0.57, 1.24]	0.3725
Time to first hospitalization for respiratory cause	113/392	90/393	0.75 [0.56, 0.99]	0.0393
Time to death	64/392	36/393	0.51 [0.34, 0.78]	0.0017



Nerandomilast 18 mg bid vs. placebo

	N with event / N analyzed		Hazard ratio	
	Placebo	Nera 18mg bid	[95% CI]	p-value *
Key secondary endpoint	143/392	113/391	0.77 [0.60, 0.99]	0.0395
Time to first acute ILD exacerbation or death	97/392	59/391	0.59 [0.43, 0.82]	0.0017
Time to first hospitalization for respiratory cause or death	131/392	103/391	0.76 [0.59, 0.99]	0.0427
Time to first acute ILD exacerbation	57/392	35/391	0.62 [0.41, 0.95]	0.0280
Time to first hospitalization for respiratory cause	113/392	94/391	0.81 [0.61, 1.06]	0.1299
Time to death	64/392	34/391	0.51 [0.34, 0.78]	0.0018

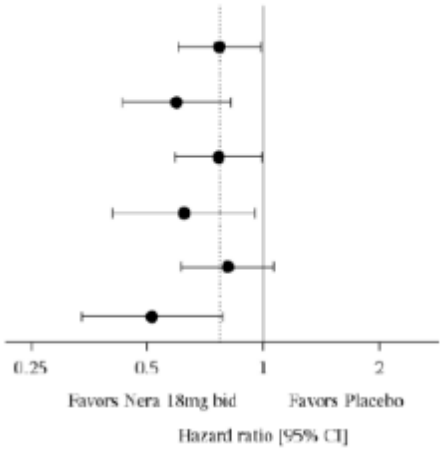


Figure 41: Endpoints based on the time to the first clinical event over the duration of the trial up to DBL2 – FAS (CSR 1305-0023)

Acute ILD exacerbation alone (further endpoint) or combined with death (secondary endpoint)

Up to DBL1, acute ILD exacerbations (confirmed or suspected) or deaths over the duration of the trial occurred in 21.2% of the patients in the placebo group, 16.5% in the 9 mg bid nerandomilast group, and 12.3% in the 18 mg bid nerandomilast group. The risk of acute ILD exacerbations or deaths was reduced by 41% for the 18 mg bid nerandomilast group vs. placebo (HR 0.59, 95% CI 0.41, 0.84, p = 0.0036). In the 9 mg bid nerandomilast group, a numerically lower risk was observed vs. placebo (HR 0.78, 95% CI 0.56, 1.08, p = 0.1348).

Additional information collected on specific ILD exacerbations eCRF pages.

The number (%) of patients with at least one acute ILD exacerbation reported on the AE page by the investigator was lowest in the 18 mg bid nerandomilast group (35 patients, 9.0%) and lower in the 9 mg bid nerandomilast group (52 patients, 13.2%) compared with the placebo group (60 patients, 15.3%).

Table 54: Summary of acute ILD exacerbations with additional information collection on eCRF over the whole trial up to DBL1 – FAS (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0
Patients with at least one ILD exacerbation adverse event	61		51		35	
Patients with additional information completed on specific ILD eCRF pages	60		52		35	
Patients with acute ILD exacerbations (confirmed or suspected)	52	13.3	42	10.7	30	7.7
Number of events						
Number of specific ILD exacerbation eCRF pages completed	90	100.0	74	100.0	55	100.0
Meets protocol definition of acute/suspected ILD exacerbation, based on site response on eCRF page						
Yes	79	87.8	60	81.1	50	90.9
No	11	12.2	14	18.9	5	9.1
Confirmed vs. suspected exacerbation, derived from the TSAP definition[1]						
Confirmed or suspected events	74	82.2	58	78.4	48	87.3
Confirmed events	50	55.6	46	62.2	34	61.8
Suspected events	24	26.7	12	16.2	14	25.5
Neither confirmed nor suspected events[2]	16	17.8	14	18.9	6	10.9
Derivation not feasible[3]	0		2	2.7	1	1.8

1 See Section 9.5.2.2.2 for the TSAP definition. Both confirmed (with CT data, per eCRF page) and suspected events (without CT data, per eCRF page) were considered for the endpoint evaluation. The definition is based on eCRF response on questions "acute respiratory deterioration within the last month (yes/no)", "extra-parenchymal cause identified (yes/no)", and "new, bilateral GGO/consolidation on chest CT (yes/no/chest CT not performed)" (Table 5.2.1: 1 in the TSAP [Appendix 16.1.9]).

2 The events were considered as neither confirmed nor suspected based on TSAP definition. These exacerbations were not included in the key secondary endpoint analysis.

3 The derivation from TSAP definition could not be performed due missing information on the eCRF page. These exacerbations were not included in the key secondary endpoint analysis.

Over the duration of the trial up to DBL2, acute ILD exacerbations or deaths occurred in 24.7% of the patients in the placebo group, 17.8% in the 9 mg bid nerandomilast group, and 15.1% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were 0.70 (0.51, 0.96) for 9 mg bid nerandomilast (p = 0.0258) and 0.59 (0.43, 0.82) for 18 mg bid nerandomilast (p = 0.0017). Over the duration of the trial up to DBL2, acute ILD exacerbations occurred in 14.5% of the patients in the placebo group, 11.7% in the 9 mg bid nerandomilast group, and 9.0% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were 0.84 (0.57, 1.24) for 9 mg bid nerandomilast (p = 0.3725) and 0.62 (0.41, 0.95) for 18 mg bid nerandomilast (p = 0.0280).

Hospitalisation for respiratory cause alone (further endpoint) or combined with death (secondary endpoint)

Up to DBL1, hospitalisations for respiratory cause or deaths over the duration of the trial occurred in 28.1% of the patients in the placebo group, 24.7% in the 9 mg bid nerandomilast group, and 21.5% in the 18 mg bid nerandomilast group. The risk of hospitalisations for respiratory cause or deaths was

reduced by 25% for the 18 mg bid nerandomilast group vs. placebo (HR 0.75, 95% CI 0.56, 1.00, p = 0.0499). In the 9 mg bid nerandomilast group, a numerically lower risk was observed vs. placebo (HR 0.83, 95% CI 0.63, 1.10, p = 0.1990).

Over the duration of the trial up to DBL2, hospitalisations for respiratory cause or deaths occurred in 33.4% of the patients in the placebo group, 26.2% in the 9 mg bid nerandomilast group, and 26.3% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were 0.74 (0.57, 0.96) for 9 mg bid nerandomilast (p = 0.0237), and 0.76 (0.59, 0.99) for 18 mg bid nerandomilast (p = 0.0427). Over the duration of the trial up to DBL2, hospitalisations for respiratory cause occurred in 28.8% of the patients in the placebo group, 22.9% in the 9 mg bid nerandomilast group, and 24.0% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were 0.75 (0.56, 0.99) for 9 mg bid nerandomilast (p = 0.0393) and 0.81 (0.61, 1.06) for 18 mg bid nerandomilast (p = 0.1299).

Death (secondary endpoint)

Up to DBL1, deaths over the duration of the trial occurred at a lower frequency in either nerandomilast dose than in placebo: in 50 patients (12.8%) in the placebo group, 33 patients (8.4%) in the 9 mg bid nerandomilast group, and 24 patients (6.1%) in the 18 mg bid nerandomilast group. The risk of death was reduced by 40% for the 9 mg bid nerandomilast group vs. placebo (HR 0.60, 95% CI 0.38, 0.95, p = 0.0284) and by 52% for the 18 mg bid nerandomilast group vs. placebo (HR 0.48, 95% CI 0.30, 0.79, p = 0.0036). The cumulative incidence rate of deaths in both nerandomilast groups was numerically lower than in the placebo group starting at 4 months and continued to diverge from placebo throughout the trial.

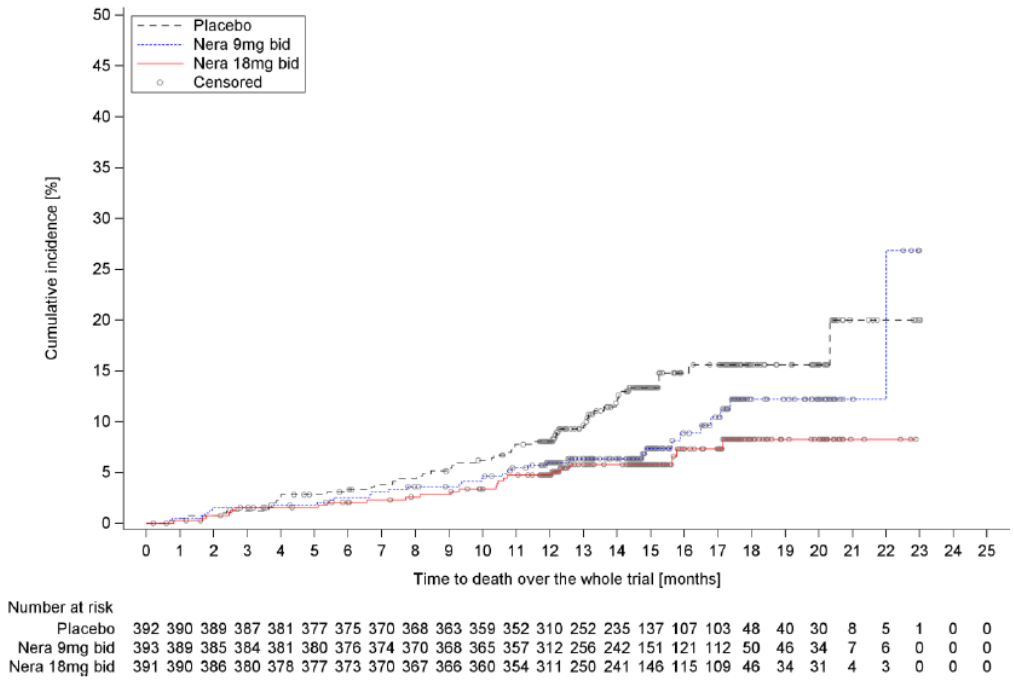


Figure 42: Cumulative incidence rate of deaths in both nerandomilast groups- FAS DBL1

An independent adjudication committee reviewed the fatal cases in a blinded manner to determine the primary cause of death. In all treatment groups, respiratory causes were the most frequent primary causes of death (66.0% of the 97 adjudicated deaths), and the main driver of the observed risk reduction

in deaths in the nerandomilast groups vs. placebo. Underlying interstitial lung disease was the most frequent adjudicated cause of death within respiratory causes.

Table 55: Adjudicated cause of death over the duration of the trial up to DBL1 – FAS (1305-023)

Adjudicated cause of death Specific cause of death	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in the FAS (N %)	392	100.0	393	100.0	391	100.0
All deaths (N %)	50	12.8	33	8.4	24	6.1
Adjudicated deaths (N %)	44	11.2	30	7.6	23	5.9
Respiratory cause	33	8.4	17	4.3	14	3.6
Underlying interstitial lung disease	22	5.6	9	2.3	7	1.8
Pneumonia	10	2.6	8	2.0	5	1.3
Other respiratory causes	1	0.3	0		2	0.5
Cardiovascular (CV) cause (fatal MACE)	2	0.5	5	1.3	3	0.8
Sudden cardiac death	2	0.5	3	0.8	2	0.5
Cardiovascular procedure	0		1	0.3	1	0.3
Other cardiovascular causes	0		1	0.3	0	
Non-CV, non-respiratory cause	2	0.5	5	1.3	1	0.3
Malignancy (new or worsening)	0		3	0.8	0	
Infection (including sepsis)	1	0.3	1	0.3	0	
Gastrointestinal causes	0		1	0.3	0	
Other non-CV, non-respiratory causes	1	0.3	0		0	
Trauma	0		0		1	0.3
Cause undetermined	7	1.8	3	0.8	5	1.3

Only the adverse events of death which were entered into CRF pages by sites before 11 Dec 2024 were adjudicated before DBL1 data snapshot. Therefore, 6 events in the placebo group (#[redacted], #[redacted], #[redacted], #[redacted], #[redacted], #[redacted]), 3 events in the 9 mg bid nerandomilast group (#[redacted], #[redacted], #[redacted]), and 1 event in the 18 mg bid nerandomilast group (#[redacted]) had not been adjudicated by DBL1 [Appendix 16.2.7, Listing 1.4].

Over the whole trial up to DBL2, deaths occurred in 64 patients in the placebo group (16. %), 36 patients in the 9 mg bid nerandomilast group (9.2%), and 34 patients in the 18 mg bid nerandomilast group (8.7%). The HRs (95% CI) vs. placebo were 0.51 (0.34, 0.78) for 9 mg bid nerandomilast (p = 0.0017) and 0.51 (0.34, 0.78) for 18 mg bid nerandomilast (p = 0.0018). All deaths reported over the duration of the trial could be adjudicated and respiratory causes were confirmed as the most frequent primary causes of death (accounting for 86 of the 134 adjudicated deaths, i.e. 64%). The risk of having an adjudicated respiratory-related death over the whole trial was lower with nerandomilast treatments vs. placebo (HRs [95% CI] vs. placebo were 0.38 [0.22, 0.65], p = 0.0005 for 9 mg bid nerandomilast and 0.43 [0.25, 0.72], p = 0.0015 for 18 mg bid nerandomilast).

Absolute change from baseline in FVC % predicted (secondary and further endpoints)

The adjusted mean (95% CI) change from baseline in FVC % predicted at Week 52 was -4.88 (-5.61, -4.15) in the placebo group, -2.69 (-3.43, -1.95) in the 9 mg bid nerandomilast group, and -2.94 (-3.68, -2.19) in the 18 mg bid nerandomilast group. The adjusted mean difference (95% CI) in FVC % predicted change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups (p<0.0001) was 2.19 (1.15, 3.23) and between 18 mg bid nerandomilast and placebo groups (p = 0.0003) was 1.94 (0.90, 2.98). The patterns were the same as for the primary endpoint based on FVC in mL.Absolute change from baseline in DLCO % predicted (corrected for haemoglobin) (secondary and further endpoints)

Table 56: Absolute change from baseline in DLCO % predicted (corrected for haemoglobin) at Week 26 and Week 52 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in FAS, N	392		393		391	
Number of patients analysed, N	381		377		371	
Baseline (mean, SD)	49.7	16.5	48.7	16.8	49.4	17.5
Week 26 change from baseline						
Adjusted mean	-1.16		-0.64		-0.49	
95% CI	-2.55	-0.23	-2.06	0.79	-1.90	-0.93
Comparison vs. placebo						
Adjusted mean	--		0.52		0.67	
95% CI	--		-1.47	2.51	-1.31	2.65
p-value			0.6065		0.5060	
Week 52 change from baseline						
Adjusted mean	-2.48		-3.38		-2.97	
95% CI	-3.89	-1.07	-4.80	-1.96	-4.40	-1.53
Comparison vs. placebo						
Adjusted mean	--		-0.90		-0.49	
95% CI	--		-2.90	1.11	-2.50	1.53
p-value			0.3793		0.6354	

Up to DBL2, the difference vs. placebo in FVC decline was sustained over time for both nerandomilast dose groups and continued to diverge from placebo beyond 52 weeks (with about 77% of treated patients with available assessment at Week 64 and 52% at Week 76. There was a sharp decline in the absolute change from baseline in FVC (mL) between Week 88 and Week 100 for 18mg nerandomilast, however participants went from 93 to 31 respectively. The point estimate remained above Placebo and the 9mg dose was elevated within the same period of time.

Time to absolute decline in DLCO % predicted of >15% from baseline or death over the duration of the trial (secondary endpoint)

Up to DBL1, an absolute decline in DLCO % predicted of >15% from baseline or death over the duration of the trial (at Weeks 12, 26, 52, and EOT) occurred in 18.6% of the patients in the placebo group, 17.3% in the 9 mg bid nerandomilast group, and 15.6% in the 18 mg bid nerandomilast group. Compared with placebo, the HR (95% CI) was 0.89 (0.64, 1.25) for 9 mg bid nerandomilast (p = 0.5123) and 1.03 (0.73, 1.45) for 18 mg bid nerandomilast (p = 0.8541).

As for DBL1, no relevant differences between treatment groups were observed at EOT at DBL2.

Absolute change from baseline in L-PF and time to deterioration (secondary and further endpoints)

For L-PF absolute change from baseline at Week 52, the following endpoints were defined:

- L-PF Symptoms Dyspnea domain score – secondary endpoint
- L-PF Symptoms Cough domain score – secondary endpoint
- L-PF Symptoms Fatigue domain score – secondary endpoint
- L-PF Symptoms total score – further endpoint
- L-PF Impact score – further endpoint
- L-PF Total score – further endpoint

Table 57: Absolute change from baseline in L-PF at Week 52 (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients in FAS, N	392		393		391	
L-PF Symptoms Dyspnea domain score, N analysed	381		377		376	
Baseline (mean, SD)	18.0	17.1	18.1	17.1	16.8	15.2
Week 52 change from baseline						
Adjusted mean	5.75		4.87		4.48	
95% CI	4.04	7.46	3.15	6.58	2.76	6.20
Comparison vs. placebo						
Adjusted mean	--		-0.88		-1.27	
95% CI	--		-3.30	1.54	-3.69	1.15
p-value			0.4748		0.3042	
L-PF Symptoms Cough domain score, N analysed	381		377		376	
Baseline (mean, SD)	30.0	23.7	31.8	26.3	33.4	26.3
Week 52 change from baseline						
Adjusted mean	3.05		1.17		3.19	
95% CI	0.79	5.31	-1.09	3.44	0.92	5.46
Comparison vs. placebo						
Adjusted mean	--		-1.88		0.14	
95% CI	--		-5.08	1.33	-3.07	3.35
p-value			0.2506		0.9311	
L-PF Symptoms Fatigue domain score, N analysed	381		377		376	
Baseline (mean, SD)	32.5	19.4	34.0	19.8	34.4	18.1
Week 52 change from baseline						
Adjusted mean	2.95		3.01		3.89	
95% CI	1.18	4.73	1.23	4.78	2.11	5.68
Comparison vs. placebo						
Adjusted mean	--		0.05		0.94	
95% CI	--		-2.46	2.57	-1.58	3.46
p-value			0.9668		0.4644	
L-PF Symptoms total score, N analysed	381		377		376	
Baseline (mean, SD)	26.8	16.9	28.0	17.3	28.2	16.7
Week 52 change from baseline						
Adjusted mean	4.06		3.01		3.77	
95% CI	2.48	5.65	1.41	4.60	2.17	5.37
Comparison vs. placebo						
Adjusted mean	--		-1.06		-0.29	
95% CI	--		-3.31	1.19	-2.55	1.96
p-value			0.3568		0.7982	

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
L-PF Impact total score, N analysed	377		374		373	
Baseline (mean, SD)	35.1	20.0	36.2	20.9	36.6	21.0
Week 52 change from baseline						
Adjusted mean	2.58		1.92		1.53	
95% CI	0.76	4.40	0.10	3.73	-0.30	3.36
Comparison vs. placebo						
Adjusted mean	--		-0.66		-1.05	
95% CI	--		-3.24	1.91	-3.63	1.53
p value			0.6128		0.4257	
L-PF Total score, N analysed	377		374		373	
Baseline (mean, SD)	31.0	17.5	32.0	18.2	32.4	17.9
Week 52 change from baseline						
Adjusted mean	3.44		2.42		2.58	
95% CI	1.83	5.06	0.81	4.04	0.95	4.20
Comparison vs. placebo						
Adjusted mean	--		-1.02		-0.87	
95% CI	--		-3.30	1.27	-3.16	1.43
p-value			0.3826		0.4583	

As for DBL2, no relevant differences between treatment groups were observed since DBL1.

Time to first use of nintedanib or immunosuppressive therapy as rescue therapy over the duration of the trial

Up to DBL1, the use of rescue therapy (nintedanib [in patients not using nintedanib at baseline] or immunosuppressives) occurred in 41 patients (11.1%) in the placebo group, 44 patients (12.3%) in the 9 mg bid nerandomilast group, and 41 patients (11.5%) in the 18 mg bid nerandomilast group (Table 11: 18). Compared with placebo, the HR (95% CI) was 1.06 (0.69, 1.63) for 9 mg bid nerandomilast (p = 0.7752) and 0.99 (0.64, 1.52) for 18 mg bid nerandomilast (p = 0.9519).

Table 58: Time to first use of nintedanib (non-nintedanib group) or immunosuppressive therapy over the whole trial up to DBL1 – FAS (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	369	100.0	359	100.0	358	100.0
Patients with event (N %)	41	11.1	44	12.3	41	11.5
Initiation of nintedanib as the 1st event (N %)	24	6.5	19	5.3	22	6.1
Initiation of immunosuppressives as the 1st event (N %)	17	4.6	25	7.0	19	5.3
HR vs. placebo[1]	--		1.06		0.99	
95% CI			0.69	1.63	0.64	1.52
p-value			0.7752		0.9519	

1 Based on Cox proportional hazards model including treatment, baseline nintedanib therapy, baseline HRCT pattern, age, baseline FVC % predicted, and baseline DL_{CO} % predicted (corrected for haemoglobin) as covariates. Eight patients were excluded from the analysis due to missing baseline DLCO % predicted.

p-values not adjusted for multiplicity

Between DBL1 and DBL2, 10 additional initiations of nintedanib or immunosuppressive therapy occurred (+3, +4, and +3 in the placebo, 9 mg bid nerandomilast, and 18 mg bid nerandomilast groups, respectively. Over the duration of the trial up to DBL2, cases for initiating nintedanib or immunosuppressive therapy occurred in 11.9% of the patients in the placebo group, 13.4% in the 9 mg bid nerandomilast group, and 12.3% in the 18 mg bid nerandomilast group. The HRs (95% CI) vs. placebo were 1.09 (0.73, 1.65) for 9 mg bid nerandomilast (p = 0.6696) and 0.98 (0.65, 1.49) for 18 mg bid nerandomilast (p = 0.9303).

Pre-defined and post-hoc subgroup analyses

Nintendanib background therapy

In the placebo group, patients on background nintedanib therapy had a numerically greater loss of FVC over 52 weeks (about -180 mL) than patients without background nintedanib therapy (about -150 mL).

The treatment effect of nerandomilast (9 and 18 mg bid) was observed across subgroups by background nintedanib therapy, with similar relative reduction (range 38% to 51% across doses and subgroups) in FVC decline over 52 weeks. Relative reductions in FVC decline vs. placebo (9 mg: [71.8 mL 95% CI (24.9,118.8)], 18 mg [58.9 mL 95% CI (12.1,105.8)] for patients not on background therapy; 9 mg: [93.1 mL 95% CI (39.9,146.3)], 18 mg [78mL 95% CI (24.2,131.8)] for patients on background therapy).

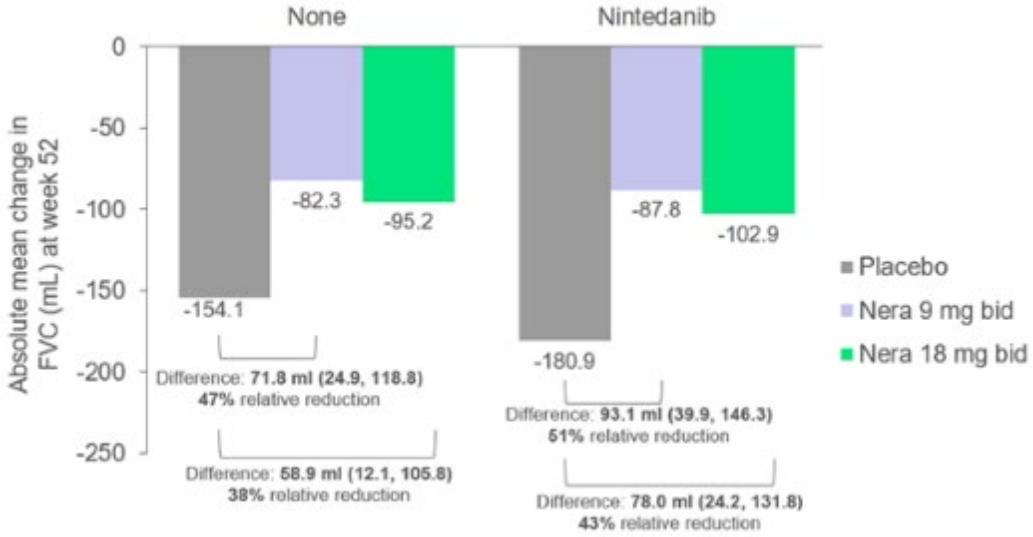


Figure 43: Absolute change from baseline in FVC (in mL) at Week 52 by background nintedanib therapy (CSR 1305-0023)

Table 59: Absolute change from baseline in FVC (in mL) at Week 52 by background nintedanib therapy (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients without background nintedanib therapy, N analysed[1]	222		217		220	
Baseline (mean, SD)	2264.1	739.8	2243.7	758.6	2354.0	715.0
Week 52 change from baseline						
Adjusted mean	-154.1		-82.3		-95.2	
95% CI	-187.1	-121.2	-115.9	-48.8	-128.6	-61.9
Comparison vs. placebo						
Adjusted mean	--		71.8		58.9	
95% CI	--		24.9	118.8	12.1	105.8
Patients with background nintedanib therapy, N analysed[1,2]	169		173		170	
Baseline (mean, SD)	2470.6	786.3	2429.6	768.7	2416.6	733.4
Week 52 change from baseline						
Adjusted mean	-180.9		-87.8		-102.9	
95% CI	-218.6	-143.2	-125.4	-50.2	-141.2	-64.5
Comparison vs. placebo						
Adjusted mean	--		93.1		78.0	
95% CI	--		39.9	146.3	24.2	131.8

Baseline HRCT pattern

Overall, a qualitatively consistent treatment effect of nerandomilast (9 and 18 mg bid) was observed in both subgroups by baseline HRCT pattern. For nerandomilast 9 mg bid, the treatment effect was similar in both subgroups vs. placebo. While a positive treatment effect was observed for both subgroups with 18 mg nerandomilast bid, the effect seemed to be numerically greater in the subgroup of patients with other fibrotic pattern (interaction p-value 0.0384). Relative reductions in FVC decline vs. placebo (9 mg: [83.9mL 95% CI (42.7,125.1)], 18mg [43mL 95% CI (1.1,85.0)] in the UIP or UIP-like fibrotic pattern; 9 mg: [69.02mL 95% CI (1.5,136.5)], 18mg [124.6mL 95% CI (59.9,189.3)] in the other fibrotic pattern).

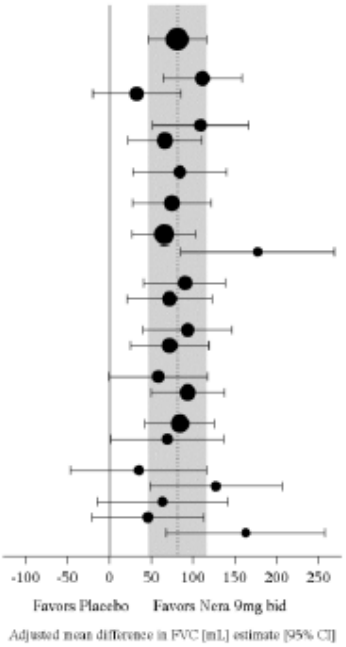
Table 60: Absolute change from baseline in FVC (in mL) at Week 52 by baseline HRCT pattern. (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients with UIP or UIP-like fibrotic pattern on baseline HRCT, N analysed[1]	274		288		274	
Baseline (mean, SD)	2450.4	748.9	2364.5	751.9	2451.9	740.2
Week 52 change from baseline						
Adjusted mean	-156.4		-72.4		-113.3	
95% CI	-185.9	-126.9	-101.2	-43.7	-143.3	-83.4
Comparison vs. placebo						
Adjusted mean	--		83.9		43.0	
95% CI	--		42.7	125.1	1.1	85.0
Patients with other fibrotic patterns on baseline HRCT, N analysed[1]	117		102		116	
Baseline (mean, SD)	2126.3	761.4	2215.9	804.1	2214.1	653.0
Week 52 change from baseline						
Adjusted mean	-188.7		-119.7		-64.1	
95% CI	-234.3	-143.1	-169.6	-69.7	-110.3	-18.0
Comparison vs. placebo						
Adjusted mean	--		69.02		124.6	
95% CI	--		1.5	136.5	59.9	189.3

Subgroups analysis

Nerandomilast 9 mg bid vs. placebo

	N	FVC decline [mL]	N	FVC decline [mL]	Adjusted Mean difference in FVC[mL] Estimate [95% CI]	Treatment-by-subgroup interaction p-value
		Placebo		Nera 9mg bid		
Overall	391	-165.77	390	-84.64	81.14 [45.95,116.32]	
Sex						0.0293
Male	231	-210.65	200	-99.57	111.08 [64.20,157.96]	
Female	160	-100.60	190	-67.88	32.72 [-19.93,85.36]	
Age group						0.2476
<65 years	149	-154.42	142	-45.58	108.84 [51.14,166.55]	
>=65 years	242	-172.72	248	-106.71	66.01 [21.82,110.19]	
Race						0.6652
Asian	153	-152.98	160	-68.83	84.15 [28.17,140.14]	
Black or African American [1]	7	-193.22	3	34.39	227.60 [-109.61,564.81]	
White	226	-172.28	222	-97.95	74.33 [27.59,121.07]	
Ethnicity						0.0282
Not Hispanic or Latino	338	-154.40	330	-89.17	65.23 [27.22,103.24]	
Hispanic or Latino	53	-237.07	60	-60.52	176.55 [84.68,268.41]	
Baseline FVC [%pred]						0.6070
<=70%	214	-176.70	201	-86.66	90.04 [41.32,138.76]	
>70%	177	-153.11	189	-81.55	71.55 [20.53,122.57]	
Baseline Antifibrotic						0.5555
AF	169	-180.88	173	-87.75	93.13 [39.93,146.33]	
non-AF	222	-154.14	217	-82.32	71.82 [24.89,118.75]	
Baseline Bodyweight						0.3495
<65 kg	130	-150.05	150	-91.80	58.26 [-1.07,117.58]	
>=65 kg	261	-173.54	240	-80.13	93.42 [49.63,137.20]	
Baseline HRCT pattern						0.7118
UIP or UIP-like fibrotic pattern	274	-156.35	288	-72.43	83.91 [42.73,125.09]	
Other fibrotic patterns	117	-188.68	102	-119.66	69.02 [1.52,136.51]	
Underlying clinical ILD diagnosis						0.1540
Idiopathic nonspecific interstitial pneumonia	73	-142.78	72	-107.84	34.94 [-46.40,116.27]	
Unclassifiable idiopathic interstitial pneumonia	82	-187.14	76	-60.24	126.90 [48.24,205.56]	
Hypersensitivity pneumonitis	77	-196.73	81	-133.33	63.40 [-14.89,141.70]	
Autoimmune ILD	99	-107.07	112	-61.20	45.86 [-20.84,112.57]	
Other ILD	60	-225.60	49	-63.00	162.60 [68.04,257.15]	



Nerandomilast 18 mg bid vs. placebo

	N	FVC decline [mL]	N	FVC decline [mL]	Adjusted Mean difference in FVC[mL] Estimate [95% CI]	Treatment-by-subgroup interaction p-value
		Placebo		Nera 18mg bid		
Overall	391	-165.77	390	-98.59	67.18 [31.91,102.46]	
Sex						0.2552
Male	231	-210.65	219	-129.87	80.78 [34.48,127.09]	
Female	160	-100.60	171	-60.97	39.62 [-14.03,93.28]	
Age group						0.6146
<65 years	149	-154.42	152	-75.93	78.49 [21.72,135.27]	
>=65 years	242	-172.72	238	-112.81	59.91 [15.06,104.76]	
Race						0.8224
Asian	153	-152.98	144	-98.17	54.81 [-2.88,112.50]	
Black or African American [1]	7	-193.22	6	-68.87	124.35 [-150.32,399.03]	
White	226	-172.28	235	-99.89	72.39 [26.15,118.63]	
Ethnicity						0.3171
Not Hispanic or Latino	338	-154.40	333	-94.05	60.35 [22.28,98.41]	
Hispanic or Latino	53	-237.07	57	-125.49	111.57 [18.71,204.44]	
Baseline FVC [%pred]						0.9591
<=70%	214	-176.70	194	-111.80	64.90 [15.72,114.08]	
>70%	177	-153.11	196	-86.35	66.75 [15.82,117.68]	
Baseline Antifibrotic						0.5997
AF	169	-180.88	170	-102.87	78.01 [24.23,131.79]	
non-AF	222	-154.14	220	-95.23	58.91 [12.06,105.76]	
Baseline Bodyweight						0.5321
<65 kg	130	-150.05	126	-99.04	51.02 [-10.81,112.84]	
>=65 kg	261	-173.54	264	-98.52	75.02 [32.01,118.03]	
Baseline HRCT pattern						0.0384
UIP or UIP-like fibrotic pattern	274	-156.35	274	-113.32	43.03 [1.05,85.00]	
Other fibrotic patterns	117	-188.68	116	-64.11	124.56 [59.85,189.27]	
Underlying clinical ILD diagnosis						0.9082
Idiopathic nonspecific interstitial pneumonia	73	-142.78	82	-89.30	53.48 [-25.89,132.85]	
Unclassifiable idiopathic interstitial pneumonia	82	-187.14	73	-114.34	72.81 [-6.60,152.21]	
Hypersensitivity pneumonitis	77	-196.73	72	-125.68	71.06 [-9.47,151.59]	
Autoimmune ILD	99	-107.07	113	-64.85	42.22 [-24.85,109.30]	
Other ILD	60	-225.60	50	-129.27	96.33 [2.65,190.00]	

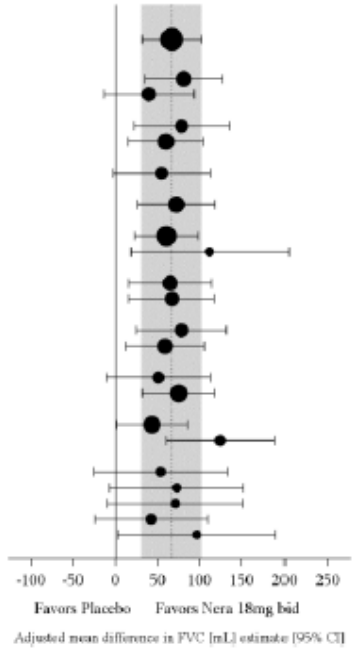


Figure 44: Subgroup analyses of the primary endpoint (CSR 1305-0023)

Secondary endpoints

Key secondary endpoint by baseline use of background nintedanib therapy

Table 61: The key secondary endpoint up to DBL1 by background nintedanib therapy (CSR 1305-0023*)*

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients without background nintedanib therapy (N %)	222	100.0	220	100.0	220	100.0
Patients with event (N %)	72	32.4	57	25.9	50	22.7
HR vs. placebo	--		0.78		0.70	
95% CI			0.55	1.11	0.49	1.01
Patients with background nintedanib therapy (N %)[1]	170	100.0	173	100.0	171	100.0
Patients with event (N %)	50	29.4	53	30.6	45	26.3
HR vs. placebo	--		1.02		0.87	
95% CI			0.69	1.50	0.58	1.30

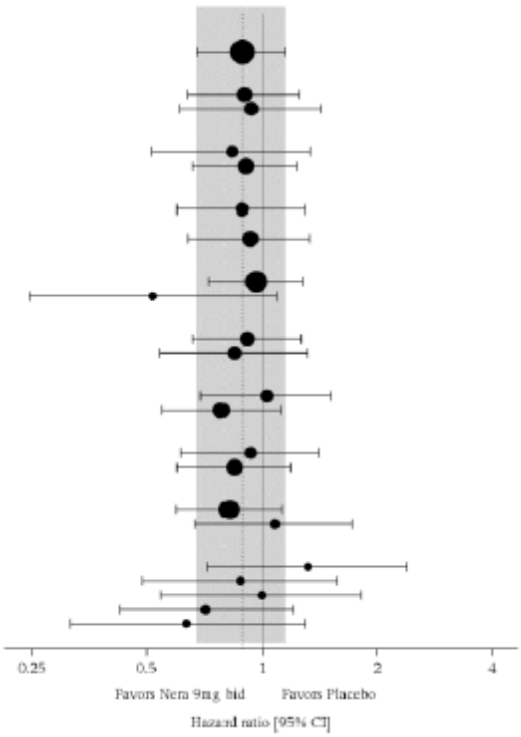
Key secondary endpoint by baseline HRCT pattern

Table 62: Absolute change from baseline in FVC (in mL) at Week 52 by baseline HRCT pattern (CSR 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Patients with UIP or UIP-like fibrotic pattern on baseline HRCT (N %)	275	100.0	290	100.0	275	100.0
Patients with event (N %)	82	29.8	77	26.6	71	25.8
HR vs. placebo	--		0.82		0.81	
95% CI			0.60	1.12	0.59	1.12
Patients with other fibrotic patterns on baseline HRCT (N %)	117	100.0	103	100.0	116	100.0
Patients with event (N %)	40	34.2	33	32.0	24	20.7
HR vs. placebo	--		1.07		0.68	
95% CI			0.67	1.71	0.41	1.12

Nerandomilast 9 mg bid vs. placebo

	N with event / N analyzed			
	Placebo	Nera 9mg bid	Hazard ratio [95% CI]	Interaction p-value
Overall	122/392	110/393	0.88 [0.68, 1.14]	
Sex				0.8818
Male	81/231	64/203	0.89 [0.64, 1.24]	
Female	41/161	46/190	0.93 [0.61, 1.42]	
Age group				0.7708
<65 years	38/149	31/142	0.83 [0.51, 1.33]	
>=65 years	84/243	79/251	0.90 [0.66, 1.23]	
Race				0.9828
Asian	55/154	51/161	0.88 [0.60, 1.29]	
Black or African American	2/7	0/3		
White	62/226	59/224	0.92 [0.64, 1.33]	
Ethnicity				0.1271
Not Hispanic or Latino	104/339	97/333	0.96 [0.73, 1.27]	
Hispanic or Latino	18/53	13/60	0.52 [0.25, 1.09]	
Baseline FVC [%predicted]				0.7784
<=70%	81/214	71/202	0.91 [0.66, 1.26]	
>70%	41/178	39/191	0.84 [0.54, 1.31]	
Baseline antifibrotic				0.3157
AF	50/170	53/173	1.02 [0.69, 1.50]	
non-AF	72/222	57/220	0.78 [0.55, 1.11]	
Baseline bodyweight				0.7209
<65 kg	43/131	48/150	0.93 [0.61, 1.40]	
>=65 kg	79/261	62/243	0.84 [0.60, 1.18]	
Baseline HRCT pattern				0.3480
UIP or UIP-like fibrotic pattern	82/275	77/290	0.82 [0.60, 1.12]	
Other fibrotic patterns	40/117	33/103	1.07 [0.67, 1.71]	
Underlying clinical ILD diagnosis				0.5101
Idiopathic nonspecific interstitial pneumonia	18/73	27/73	1.31 [0.72, 2.38]	
Unclassifiable idiopathic interstitial pneumonia	29/82	20/76	0.87 [0.49, 1.56]	
Hypersensitivity pneumonitis	21/77	24/83	0.99 [0.54, 1.81]	
Autoimmune ILD	31/100	27/112	0.71 [0.43, 1.20]	
Other ILD	23/60	12/49	0.64 [0.31, 1.29]	



Nerandomilast 18 mg bid vs. placebo

	N with event / N analyzed			
	Placebo	Nera 18mg bid	Hazard ratio [95% CI]	Interaction p-value
Overall	122/392	95/391	0.77 [0.59, 1.01]	
Sex				0.7140
Male	81/231	60/220	0.74 [0.53, 1.04]	
Female	41/161	35/171	0.83 [0.52, 1.30]	
Age group				0.8763
<65 years	38/149	28/152	0.74 [0.45, 1.21]	
>=65 years	84/243	67/239	0.78 [0.56, 1.07]	
Race				0.9128
Asian	55/154	40/145	0.74 [0.49, 1.12]	
Black or African American	2/7	1/6		
White	62/226	53/235	0.82 [0.57, 1.19]	
Ethnicity				0.4223
Not Hispanic or Latino	104/339	84/334	0.80 [0.60, 1.07]	
Hispanic or Latino	18/53	11/57	0.57 [0.26, 1.25]	
Baseline FVC [%predicted]				0.5577
<=70%	81/214	56/194	0.72 [0.51, 1.02]	
>70%	41/178	39/197	0.86 [0.55, 1.33]	
Baseline antifibrotic				0.4513
AF	50/170	45/171	0.87 [0.58, 1.30]	
non-AF	72/222	50/220	0.70 [0.49, 1.01]	
Baseline bodyweight				0.7117
<65 kg	43/131	34/127	0.83 [0.53, 1.30]	
>=65 kg	79/261	61/264	0.74 [0.53, 1.04]	
Baseline HRCT pattern				0.5533
UIP or UIP-like fibrotic pattern	82/275	71/275	0.81 [0.59, 1.12]	
Other fibrotic patterns	40/117	24/116	0.68 [0.41, 1.12]	
Underlying clinical ILD diagnosis				0.6208
Idiopathic nonspecific interstitial pneumonia	18/73	22/82	1.11 [0.59, 2.07]	
Unclassifiable idiopathic interstitial pneumonia	29/82	17/73	0.78 [0.43, 1.42]	
Hypersensitivity pneumonitis	21/77	16/73	0.82 [0.42, 1.58]	
Autoimmune ILD	31/100	26/113	0.56 [0.33, 0.96]	
Other ILD	23/60	14/50	0.77 [0.40, 1.51]	

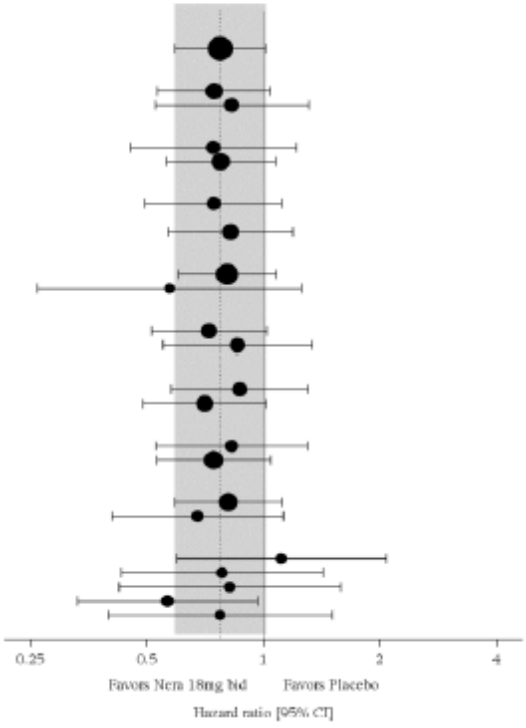


Figure 45: Subgroup analyses of the key secondary endpoint up to DBL1 (CSR 1305-0023)

Pre-defined and post-hoc sensitivity analyses

Sensitivity analysis of the primary endpoint

The results of all sensitivity and supplementary analyses, including all prespecified analyses and a *post hoc* analysis excluding the 2 patients with background pirfenidone therapy were consistent with the primary analysis of the primary endpoint. The sensitivity analyses for HRCT pattern mis-stratification and excluding outliers (patients with FVC increase or decrease from baseline at Week 52 of >1000 mL; also confirmed the primary analysis.

A tipping point analysis was carried out by using the Multiple Delta Adjustment method to assess how severe departures from the "missing at random (MAR)" assumption could be to reverse conclusions from the primary analysis. At Week 52, 32 patients (8.2%) in the placebo group, 45 patients (11.5%) in the 9 mg bid nerandomilast group, and 47 patients (12.0%) in the 18 mg bid nerandomilast group had missing FVC values not due to death.

A range of shifts from -20 to +10 mL/week was applied to the imputed FVC values for each treatment group. Departures from the MAR assumption for the missing FVC values not due to death would need to be extreme to reverse the conclusions from the primary analysis. Considering no shift in the placebo group (i.e. a shift of 0 mL/week), the shift with nerandomilast would have to be at least -19 mL/week for the 9 mg bid dose (equivalent to an annual FVC decline of 988 mL) and -12 mL/week for the 18 mg bid dose (equivalent to an annual FVC decline of 624 mL) to result in a p-value for the treatment difference above 0.05.

Up to DBL1, the results of all sensitivity and supplementary analyses, including all prespecified analyses and a *post hoc* analysis excluding the 2 patients with background pirfenidone therapy, were consistent with the primary analysis of the key secondary endpoint.

Ancillary analyses

Table 63: Pivotal study 1305-0023: Summary of the Key secondary outcome – time-to first clinical event (pulmonary exacerbation, hospitalization due to respiratory disease or death) – FAS and by stratified subgroups (background AF and HRCT pattern) - DBL1

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
FAS					
Key secondary endpoint	**122 (31.1)**	**110 (28.0)**	**95 (24.3)**	**0.88 (0.68, 1.14)**	**0.77 (0.59, 1.01)**
Pulmonary exacerbation[1]	83 (21.2)	65 (16.5)	48 (12.3)	0.78 (0.56, 1.08)	0.59 (0.41, 0.84)
Hosp. Resp. Cause[1]	110 (28.1)	97 (24.7)	84 (21.5)	0.83 (0.63, 1.10)	0.75 (0.56, 1.00)
Death	50 (12.8)	33 (8.4)	24 (6.1)	0.60 (0.38, 0.95)	0.48 (0.30, 0.79)
Stratification factor: AF therapy					
Without AF background (n= 662, 56%)					
Key secondary endpoint[2]	**72 (32.4)**	**57 (25.9)**	**50 (22.7)**	**0.78 (0.55, 1.11)**	**0.70 (0.49, 1.01)**
Pulmonary exacerbation[1, 3]	48 (21.6)	36 (16.4)	26 (11.8)	0.76 (0.49, 1.18)	0.59 (0.37, 0.96)
Hosp. Resp. Cause[1, 4]	65 (29.3)	51 (23.2)	43 (19.5)	0.75 (0.51, 1.08)	0.66 (0.45, 0.98)
Death[5]	30 (13.5)	21 (9.5)	11 (5.0)	0.64 (0.36, 1.14)	0.41 (0.21, 0.83)
With AF background (n=514, 44%)					
Key secondary endpoint[2]	**50 (29.4)**	**53 (30.6)**	**45 (26.3)**	**1.02 (0.69, 1.50)**	**0.87 (0.58, 1.30)**
Pulmonary exacerbation[1, 3]	35 (20.6)	29 (16.8)	22 (12.9)	0.80 (0.49, 1.31)	0.58 (0.34, 0.99)
Hosp. Resp. Cause[1, 4]	45 (26.5)	46 (26.6)	41 (24.0)	0.96 (0.64, 1.45)	0.87 (0.57, 1.34)
Death[5]	20 (11.8)	12 (6.9)	13 (7.6)	0.55 (0.27, 1.14)	0.57 (0.28, 1.15)
Stratification factor: HRCT UIP/UIP-like fibrotic pattern or other fibrotic pattern					
HRCT: UIP/UIP-like fibrotic pattern (n=840, 71.4%)					
Key secondary endpoint[6]	**82 (29.8)**	**77 (26.6)**	**71 (25.8)**	**0.82 (0.60, 1.12)**	**0.81 (0.59, 1.12)**
Pulmonary exacerbation[1, 7]	55 (20.0)	43 (14.8)	35 (12.7)	0.68 (0.45, 1.01)	0.61 (0.40, 0.93)
Hosp. Resp. Cause[1, 12]	74 (26.9)	70 (24.1)	66 (24.0)	0.81 (0.58, 1.12)	0.83 (0.60, 1.16)
Death[13]	36 (13.1)	24 (8.3)	19 (6.9)	0.56 (0.33, 0.95)	0.51 (0.29, 0.89)
HRCT: other fibrotic pattern (n=336, 28.6%)					
Key secondary endpoint[6]	**40 (34.2)**	**33 (32.0)**	**24 (20.7)**	**1.07 (0.67, 1.71)**	**0.68 (0.41, 1.12)**
Pulmonary exacerbation[1, 7]	28 (23.9)	22 (21.4)	13 (11.2)	1.07 (0.60, 1.89)	0.53 (0.27, 1.03)
Hosp. Resp. Cause[1, 8]	36 (30.8)	27 (26.2)	18 (15.5)	0.93 (0.56, 1.55)	0.56 (0.32, 0.99)
Death[9]	14 (12.0)	9 (8.7)	5 (4.3)	0.77 (0.32, 1.85)	0.41 (0.15, 1.14)

1 Death was considered as an event in a composite strategy
2 Treatment-by-subgroup interaction p = 0.3157 for 9 mg bid and 0.4513 for 18 mg bid vs. placebo
3 Treatment-by-subgroup interaction p = 0.8874 for 9 mg bid and 0.9546 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.3727 for 9 mg bid and 0.3510 for 18 mg bid vs. placebo
5 Treatment-by-subgroup interaction p = 0.7544 for 9 mg bid and 0.5217 for 18 mg bid vs. placebo
6 Treatment-by-subgroup interaction p = 0.3480 for 9 mg bid and 0.5533 for 18 mg bid vs. placebo
7 Treatment-by-subgroup interaction p = 0.2000 for 9 mg bid and 0.7360 for 18 mg bid vs. placebo
8 Treatment-by-subgroup interaction p = 0.6427 for 9 mg bid and 0.2389 for 18 mg bid vs. placebo
9 Treatment-by-subgroup interaction p = 0.5352 for 9 mg bid and 0.7233 for 18 mg bid vs. placebo

Table 64: Pivotal study 1305-0023: Secondary endpoint and components by underlying clinical ILD diagnosis – FAS, and ILD disease - DBL1

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
Key secondary endpoint[1]					
Idiopathic NSIP (n=228, 19.4%)	18 (24.7)	27 (37.0)	22 (26.8)	1.31 (0.72, 2.38)	1.11 (0.59, 2.07)
Unclassifiable idiopathic interstitial pneumonia (n=231, 19.6%)	29 (35.4)	20 (26.3)	17 (23.3)	0.87 (0.49, 1.56)	0.78 (0.43, 1.42)
Hypersensitivity ILD (n=233, 19.8%)	21 (27.3)	24 (28.9)	16 (21.9)	0.99 (0.54, 1.81)	0.82 (0.42, 1.58)
Auto-immune ILD (n=325, 27.6%)	31 (31.0)	27 (24.1)	26 (23.0)	0.71 (0.43, 1.20)	0.56 (0.33, 0.96)
Other ILD (n=159, 13.5%)	23 (38.3)	12 (24.5)	14 (28.0)	0.64 (0.31, 1.29)	0.77 (0.40, 1.51)
Pulmonary exacerbation[2, 3]					
Idiopathic NSIP	12 (16.4)	17 (23.3)	15 (18.3)	1.22 (0.58, 2.56)	1.16 (0.54, 2.48)
Unclassifiable idiopathic interstitial pneumonia	17 (20.7)	10 (13.2)	9 (12.3)	0.64 (0.28, 1.44)	0.64 (0.29, 1.45)
Hypersensitivity ILD	18 (23.4)	15 (18.1)	6 (8.2)	0.72 (0.35, 1.47)	0.34 (0.13, 0.86)
Auto-immune ILD	22 (22.0)	14 (12.5)	12 (10.6)	0.55 (0.28, 1.08)	0.41 (0.20, 0.84)
Other ILD	14 (23.3)	9 (18.4)	6 (12.0)	0.98 (0.42, 2.30)	0.61 (0.23, 1.60)
Hosp. Resp. Cause[2, 4]					
Idiopathic NSIP	14 (19.2)	23 (31.5)	18 (22.0)	1.44 (0.74, 2.80)	1.21 (0.60, 2.43)
Unclassifiable idiopathic interstitial pneumonia	28 (34.1)	19 (25.0)	17 (23.3)	0.86 (0.47, 1.56)	0.80 (0.44, 1.46)
Hypersensitivity ILD	18 (23.4)	21 (25.3)	15 (20.5)	0.92 (0.49, 1.74)	0.85 (0.43, 1.68)
Auto-immune ILD	28 (28.0)	24 (21.4)	21 (18.6)	0.69 (0.40, 1.19)	0.49 (0.27, 0.88)
Other ILD	22 (36.7)	10 (20.4)	13 (26.0)	0.51 (0.24, 1.09)	0.77 (0.38, 1.52)
Death[5]					
Idiopathic NSIP	6 (8.2)	8 (11.0)	9 (11.0)	1.07 (0.37, 3.10)	1.62 (0.58, 4.57)
Unclassifiable idiopathic interstitial pneumonia	11 (13.4)	6 (7.9)	4 (5.5)	0.61 (0.21, 1.75)	0.43 (0.14, 1.35)
Hypersensitivity ILD	10 (13.0)	6 (7.2)	4 (5.5)	0.39 (0.13, 1.15)	0.40 (0.12, 1.27)
Auto-immune ILD	14 (14.0)	8 (7.1)	6 (5.3)	0.49 (0.20, 1.16)	0.28 (0.11, 0.74)
Other ILD	9 (15.0)	5 (10.2)	1 (2.0)	0.78 (0.26, 2.35)	0.16 (0.02, 1.27)

1 Treatment-by-subgroup interaction p = 0.5101 for 9 mg bid and 0.6208 for 18 mg bid vs. placebo
2 Death was considered as an event in a composite strategy
3 Treatment-by-subgroup interaction p = 0.5614 for 9 mg bid and 0.2563 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.3145 for 9 mg bid and 0.4194 for 18 mg bid vs. placebo
5 Treatment-by-subgroup interaction p = 0.7017 for 9 mg bid and 0.1029 for 18 mg bid vs. placebo

Table *65*: Pivotal study 1305-0023: Summary of the key secondary endpoint and components – FAS, background AF en HRCT pattern-DBL2

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
FAS					
Key secondary endpoint	**143 (36.5)**	**116 (29.5)**	**113 (28.9)**	**0.78 (0.61, 1.00)**	**0.77 (0.60, 0.99)**
Pulmonary exacerbation[1]	97 (24.7)	70 (17.8)	59 (15.1)	0.70 (0.51, 0.96)	0.59 (0.43, 0.82)
Hosp. Resp. Cause[1]	131 (33.4)	103 (26.2)	103 (26.3)	0.74 (0.57, 0.96)	0 76 (0.59, 0.99)
Death	64 (16.3)	36 (9.2)	34 (8.7)	0.51 (0.34, 0.78)	0.51 (0.34. 0.78)
Stratification factor: AF therapy					
Without AF background (n= 662, 56%)					
Key secondary endpoint[2]	**83 (37.4)**	**60 (27.3)**	**55 (25.0)**	**0.69 (0.49, 0.97)**	**0.65 (0.46, 0.92)**
Pulmonary exacerbation[1, 3]	55 (24.8)	39 (17.7)	30 (13.6)	0.70 (0.46, 1.06)	0.57 (0.37, 0.90)
Hosp. Resp. Cause[1, 4]	76 (34.2)	54 (24.5)	49 (22.3)	0.66 (0.46, 0.94)	0.63 (0.44, 0.91)
Death[5]	36 (16.2)	22 (10.0)	15 (6.8)	0.55 (0.32, 0.95)	0.44 (0.24, 0.81)
With AF background (n=514, 44%)					
Key secondary endpoint[2]	**60 (35.3)**	**56 (32.4)**	**58 (33.9)**	**0.90 (0.63, 1.30)**	**0.93 (0.65, 1.34)**
Pulmonary exacerbation[1, 3]	42 (24.7)	31 (17.9)	29 (17.0)	0.71 (0.44, 1.13)	0.62 (0.38, 0.99)
Hosp. Resp. Cause[1, 4]	55 (32.4)	49 (28.3)	54 (31.6)	0.85 (0.58, 1.25)	0.95 (0.65, 1.38)
Death[5]	28 (16.5)	14 (8.1)	19 (11.1)	0.47 (0.25, 0.90)	0.59 (0.33, 1.06)
Stratification factor: HRCT UIP/UIP-like fibrotic pattern or other fibrotic pattern					
HRCT: UIP/UIP-like fibrotic pattern (n=840, 71.4%)					
Key secondary endpoint[6]	**96 (34.9)**	**83 (28.6)**	**85 (30.9)**	**0.75 (0.56, 1.01)**	**0.82 (0.61, 1.11)**
Pulmonary exacerbation[1, 7]	65 (23.6)	48 (16.6)	42 (15.3)	0.63 (0.43, 0.92)	0.60 (0.41, 0.89)
Hosp. Resp. Cause[1, 12]	87 (31.6)	75 (25.9)	80 (29.1)	0.74 (0.54, 1.01)	0.86 (0.63, 1.16)
Death[13]	45 (16.4)	26 (9.0)	26 (9.5)	0.48 (0.30, 0.79)	0.54 (0.33, 0.87)
HRCT: other fibrotic pattern (n=336, 28.6%)					
Key secondary endpoint[10]	**47 (40.2)**	**33 (32.0)**	**28 (24.1)**	**0.88 (0.56, 1.38)**	**0.65 (0.40, 1.03)**
Pulmonary exacerbation[1, 11]	32 (27.4)	22 (21.4)	17 (14.7)	0.90 (0.52, 1.57)	0.57 (0.32, 1.03)
Hosp. Resp. Cause[1, 8]	44 (37.6)	28 (27.2)	23 (19.8)	0.76 (0.47, 1.23)	0.57 (0.34, 0.94)
Death[9]	19 (16.2)	10 (9.7)	8 (6.9)	0.62 (0.28, 1.37)	0.45 (0.20, 1.04)

1 Death was considered as an event in a composite strategy
2 Treatment-by-subgroup interaction p = 0.2945 for 9 mg bid and 0.1660 for 18 mg bid vs. placebo
3 Treatment-by-subgroup interaction p = 0.9532 for 9 mg bid and 0.8260 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.3493 for 9 mg bid and 0.1314 for 18 mg bid vs. placebo
5 Treatment-by-subgroup interaction p = 0.7307 for 9 mg bid and 0.5101 for 18 mg bid vs. placebo
6 Treatment-by-subgroup interaction p = 0.5738 for 9 mg bid and 0.3859 for 18 mg bid vs. placebo
7 Treatment-by-subgroup interaction p = 0.3018 for 9 mg bid and 0.8852 for 18 mg bid vs. placebo
8 Treatment-by-subgroup interaction p = 0.9268 for 9 mg bid and 0.1707 for 18 mg bid vs. placebo
9 Treatment-by-subgroup interaction p = 0.6018 for 9 mg bid and 0.7360 for 18 mg bid vs. placebo

Table 66**: Pivotal study 1305-0023: Secondary endpoint and components by underlying clinical ILD diagnosis – FAS, and ILD disease 1305-0023 DBL2**

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
Key secondary endpoint[1]					
Idiopathic NSIP	23 (31.5)	28 (38.4)	27 (32.9)	1.12 (0.64, 1.95)	1.11 (0.63, 1.94)
Unclassifiable idiopathic interstitial pneumonia	33 (40.2)	21 (27.6)	19 (26.0)	0.78 (0.45, 1.36)	0.74 (0.42, 1.30)
Hypersensitivity ILD	25 (32.5)	27 (32.5)	23 (31.5)	0.91 (0.52, 1.59)	0.95 (0.54, 1.68)
Auto-immune ILD	33 (33.0)	27 (24.1)	28 (24.8)	0.66 (0.40, 1.10)	0.56 (0.33, 0.94)
Other ILD	29 (48.3)	13 (26.5)	16 (32.0)	0.51 (0.26, 0.99)	0.67 (0.36, 1.24)
Pulmonary exacerbation[2, 3]					
Idiopathic NSIP	16 (21.9)	19 (26.0)	18 (22.0)	1.05 (0.54, 2.05)	1.04 (0.53, 2.05)
Unclassifiable idiopathic interstitial pneumonia	21 (25.6)	11 (14.5)	12 (16.4)	0.56 (0.26, 1.18)	0.66 (0.33, 1.35)
Hypersensitivity ILD	20 (26.0)	17 (20.5)	9 (12.3)	0.71 (0.37, 1.39)	0.44 (0.20, 0.97)
Auto-immune ILD	23 (23.0)	14 (12.5)	13 (11.5)	0.51 (0.26, 0.99)	0.41 (0.21, 0.82)
Other ILD	17 (28.3)	9 (18.4)	7 (14.0)	0.79 (0.35, 1.79)	0.54 (0.22, 1.31)
Hosp. Resp. Cause[2, 4]					
Idiopathic NSIP	19 (26.0)	24 (32.9)	24 (29.3)	1.18 (0.65, 2.17)	1.22 (0.67, 2.24)
Unclassifiable idiopathic interstitial pneumonia	32 (39.0)	19 (25.0)	19 (26.0)	0 73 (0.41, 1.30)	0.75 (0.43, 1.33)
Hypersensitivity ILD	22 (28.6)	25 (30.1)	22 (30.1)	0.88 (0.49, 1.57)	0.99 (0.55, 1.80)
Auto-immune ILD	31 (31.0)	24 (21.4)	23 (20.4)	0.62 (0.36, 1.05)	0.48 (0.27, 0.84)
Other ILD	27 (45.0)	11 (22.4)	15 (30.0)	0.44 (0.22, 0.90)	0.70 (0.37, 1.32)
Death[5]					
Idiopathic NSIP	9 (12.3)	9 (12.3)	12 (14.6)	0.84 (0.33, 2.13)	1.34 (0.56, 3.18)
Unclassifiable idiopathic interstitial pneumonia	14 (17.1)	6 (7.9)	8 (11.0)	0.48 (0.17, 1.33)	0.65 (0.27, 1.56)
Hypersensitivity ILD	12 (15.6)	8 (9.6)	6 (8.2)	0.42 (0.16, 1.08)	0.47 (0.17, 1.25)
Auto-immune ILD	16 (16.0)	8 (7.1)	7 (6.2)	0.40 (0.17, 0.94)	0.28 (0.11, 0.69)
Other ILD	13 (21.7)	5 (10.2)	1 (2.0)	0.55 (0.20, 1.57)	0.11 (0.01, 0.81)

1 Treatment-by-subgroup interaction p = 0.4242 for 9 mg bid and 0.4323 for 18 mg bid vs. placebo
2 Death was considered as an event in a composite strategy
3 Treatment-by-subgroup interaction p = 0.5989 for 9 mg bid and 0.3528 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.2717 for 9 mg bid and 0.2076 for 18 mg bid vs. placebo
5 Treatment-by-subgroup interaction p = 0.8025 for 9 mg bid and 0.0617 for 18 mg bid vs. placebo

Table *67***: Pivotal study 1305-0023: The number of patients experiencing an absolute % deterioration in FVC > 10% from baseline up to week 52– FAS and by stratified subgroups and subgroups according to underlying disease– DBL1**

	Placebo (n, %)	9 mg bid (n, %)	18 mg bid (n, %)	HR (95% CI) 9 mg bid vs. placebo	HR (95% CI) 18 mg bid vs. placebo
FAS	**142 (36.2)**	**109 (27.7)**	**107 (27.4)**	**0.71 (0.55, 0.91)**	**0.74 (0.57, 0.95)**
Stratification factor: AF therapy[1]					
Without AF background	87 (39.2)	63 (28.6)	59 (26.8)	0.65 (0.46, 0.90)	0.66 (0.47, 0.92)
With AF background	55 (32.4)	46 (26.6)	48 (28.1)	0.80 (0.54, 1.19)	0.85 (0.58, 1.26)
Subgroup by baseline FVC % predicted[2]					
⩽70%	82 (38.3)	52 (25.7)	48 (24.7)	0.64 (0.45, 0.91)	0.61 (0.43, 0.88)
>70%	60 (33.7)	57 (29.8)	59 (29.9)	0.79 (0.55, 1.14)	0.88 (0.61, 1.27)
Stratification factor: HRCT UIP/UIP-like fibrotic pattern or other fibrotic pattern[3]					
HRCT: UIP/UIP-like fibrotic pattern	104 (37.8)	74 (25.5)	77 (28.0)	0.59 (0.43, 0.79)	0.69 (0.51, 0.92)
HRCT: other fibrotic pattern	38 (32.5)	35 (34.0)	30 (25.9)	1.13 (0.71, 1.81)	0.87 (0.54, 1.41)
Subgroup by underlying clinical ILD diagnosis[4]					
Idiopathic NSIP	28 (38.4)	24 (32.9)	27 (32.9)	0.77 (0.44, 1.32)	0.88 (0.52, 1.50)
Unclassifiable idiopathic interstitial pneumonia	34 (41.5)	20 (26.3)	22 (30.1)	0.62 (0.35, 1.09)	0.69 (0.40, 1.18)
Hypersensitivity ILD	27 (35.1)	19 (22.9)	21 (28.8)	0.59 (0.32, 1.08)	0.85 (0.48, 1.51)
Auto-immune ILD	29 (29.0)	31 (27.7)	23 (20.4)	0.89 (0.54, 1.48)	0.62 (0.36, 1.10)
Other ILD	24 (40.0)	15 (30.6)	14 (28.0)	0.67 (0.35, 1.29)	0.69 (0.36, 1.34)

Death was considered as an event in a composite strategy
1 Treatment-by-subgroup interaction p = 0.4030 for 9 mg bid and 0.3333 for 18 mg bid vs. placebo

2 Treatment-by-subgroup interaction p = 0.4060 for 9 mg bid and 0.1632 for 18 mg bid vs. placebo
3 Treatment-by-subgroup interaction p = 0.0203 for 9 mg bid and 0.4139 for 18 mg bid vs. placebo
4 Treatment-by-subgroup interaction p = 0.8295 for 9 mg bid and 0.8958 for 18 mg bid vs. placebo

5.3.3. Clinical studies in special populations

Table 68: Clinical studies in special populations

No overall differences in safety and efficacy were observed for patients aged below or above 65 years. To note, there was a limited number of elderly patients, but no dose adjustment is deemed to be necessary in this population.

No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment (eGFR ≥15 and <90 mL/min/1.73 m2, based on CKD-EPI formula). The pharmacokinetics, safety, and efficacy in patients with end stage renal disease (eGFR <15 mL/min/1.73 m2) have not been investigated. Treatment of patients with end stage renal disease (eGFR <15 mL/min/1.73 m2) with nerandomilast is not recommended.

No dose adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The pharmacokinetics, safety, and efficacy of nerandomilast in patients with severe (Child-Pugh class C) hepatic impairment have not been investigated. Treatment of patients with severe hepatic impairment with nerandomilast is not recommended.

The safety and efficacy in paediatric patients have not been established.

Fertility, pregnancy and lactation

There are no data from the use of nerandomilast in pregnant women. Based on findings in animal studies, nerandomilast may cause loss of pregnancy. In rats, embryo-foetal loss was observed at 5-times human exposure at the maximum recommended human dose (MRHD); this effect was not observed at approximately 3-times human exposure.

There are no data on the presence of nerandomilast in human milk or its effects on either the breast-fed child or on milk production. Studies in rats have shown excretion of nerandomilast in milk.

5.3.4. Supportive study

The applicant submitted a supportive Phase II trial 1305-0013. The objective of this was to investigate the efficacy of nerandomilast compared to placebo based on the change from baseline in FVC in patients with IPF and to investigate the safety and tolerability of nerandomilast in patients with IPF.

It was randomised, placebo-controlled, double-blind, parallel-group design over 12 weeks, including a screening period of up to 44 days, a 12-week treatment period, and a 1-week follow-up period in patients with IPF stratified by baseline antifibrotic treatment (non-AF stratum: patients not on background antifibrotic treatment at baseline; AF stratum: stable antifibrotic treatment with nintedanib or pirfenidone at baseline).

Patients aged ≥40 years could be included, with a diagnosis of IPF (based on the ATS/ERS/JRS/ALAT 2018 guideline) and with UIP or probable UIP HRCT pattern consistent with the clinical diagnosis of IPF. Patients had to have an FVC ≥45% and a DLCO ≥25% and <80%. Patients also had to have received either stable treatment with antifibrotic standard of care or no treatment with antifibrotic standard of care for at least 8 weeks prior to screening, mirroring the inclusion criteria of the 1305-0014 pivotal study.

Patients received 18mg Nerandomilast oral twice daily (36 mg daily) or matching placebo for a total of 12 weeks. A total of 147 patients were randomised and treated, 97 with nerandomilast and 50 with placebo.

The primary endpoint in this trial was the change from baseline in FVC at 12 weeks [mL]. Further efficacy endpoints included the changes from baseline in FVC [mL and % predicted], patient-reported outcome questionnaires (L-PF, LCQ, VAS severity, urge to cough and shortness of breath), and DLCO corrected for Hb [% predicted].

The mean age (SD) of the treated patients was 69.6 years (8.4), with a majority of male patients (76.9%). A total of 78.2% of the patients were White, while the remaining were Asian. Approximately half of the patients (48.3%) were overweight (BMI ≥25 and <30 kg/m²) and 21.1% were obese (≥30 kg/m²). The majority of patients were former smokers (63.9%).

Table 69: Adjusted change from baseline in FVC [mL] at 12 weeks (MMRM) - FAS (while on treatment) - non-AF stratum

Treatment	Baseline FVC[1]	Change from baseline in FVC to Week 12		Treatment difference (comparison vs. placebo)	
	Mean (SD)	Adjusted mean (SE)[2]	(95% CI)	Adjusted mean (SE)[2]	(95% CI)
Placebo (n=25)	2864.92 (1015.10)	-95.62 (30.75)	(-157.13, -34.10)		
BI 1015550 (n=47)	2766.51 (836.26)	6.10 (22.90)	(-39.67, 51.88)	101.72 (38.35)	(25.02, 178.41)

In the non-AF stratum, based on the MMRM analysis, the adjusted mean change from baseline in FVC at Week 12 was +6.10 mL (SE 22.90) in the nerandomilast group and -95.62 mL (SE 30.75) in the placebo group, with an estimated mean difference between groups of 101.72 mL (95% CI 25.02, 178.41; nominal p-value = 0.0102). In the primary analysis that uses the Bayesian borrowing approach and takes historical prior data into account, the median posterior difference was 88.4 mL (95% credible interval: 29.5, 154.2) in favour of the nerandomilast group, translating into a 99.8% probability that nerandomilast is superior to placebo.

Table 70: Adjusted change from baseline in FVC [mL] at 12 weeks (MMRM) - FAS (while on treatment) - AF stratum

Treatment	Baseline FVC[1]	Change from baseline in FVC to Week 12		Treatment difference (comparison vs. placebo)	
	Mean (SD)	Adjusted mean (SE)[2]	(95% CI)	Adjusted mean (SE)[2]	(95% CI)
Placebo (n=25)	2690.00 (889.99)	-77.70 (23.60)	(-124.87, -30.53)		
BI 1015550 (n=48)	2865.29 (757.31)	2.72 (18.13)	(-33.46, 38.89)	80.42 (29.82)	(20.85, 139.99)

In the AF stratum, based on the MMRM analysis, the adjusted mean change from baseline in FVC at Week 12 was +2.72 mL (SE 18.13) in the nerandomilast group and -77.70 mL (SE 23.60) in the placebo group, with an estimated mean difference between groups of 80.42 mL (95% CI 20.85, 139.99; nominal p-value = 0.0089). Using the Bayesian borrowing approach, the median posterior difference was 62.4 mL (95% credible interval 6.3, 125.5) in favour of the nerandomilast group, translating into a 98.6% probability that nerandomilast is superior to placebo.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant performed a comparison of the results between FIBRONEER-IPF and FIBRONEER-ILD and these two pivotal trials were pooled for a pre-defined efficacy analysis. All p-values are nominal and not controlled for multiplicity.

For EFF1c (non-pirfenidone population), the pooling without participants with pirfenidone background therapy (taking into account the identified drug-drug interaction resulting in reduced exposure to nerandomilast by 50%), the adjusted mean difference (95% CI, p-value) between 9 mg twice daily nerandomilast and placebo groups was 74.89 (46.73, 103.04, p<0.0001) and between 18 mg twice daily nerandomilast and placebo groups was 69.08 (40.72, 97.44, p<0.0001).

Table 71: Absolute change from baseline in FVC [mL] at Week 52 – FAS EFF1 and EFF1c (1305-0014 and 1305-0023 pooled)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
EFF1 (overall population), N	782		780		782	
Baseline (mean, SD)	2609.08	825.65	2581.03	815.30	2604.66	773.00
Week 52 change from baseline						
Adjusted mean	-174.74		-111.56		-106.66	
95% CI	-193.17	-156.31	-129.96	-93.15	-125.17	-88.14
Comparison vs. placebo						
Adjusted mean	--		63.18		68.08	
95% CI	--		37.13	89.23	41.96	94.20
p-value			<0.0001		<0.0001	
EFF1c (non-pirfenidone population), N	649		660		654	
Baseline (mean, SD)	2582.06	841.07	2552.73	828.33	2563.64	784.47
Week 52 change from baseline						
Adjusted mean	-170.39		-95.50		-101.31	
95% CI	-190.38	-150.40	-115.32	-75.69	-121.44	-81.19
Comparison vs. placebo						
Adjusted mean	--		74.89		69.08	
95% CI	--		46.73	103.04	40.72	97.44
p-value			<0.0001		<0.0001	

The adjusted mean of absolute change from baseline in FVC in the nerandomilast groups started to separate from the respective placebo group as early as Week 2 and continued to diverge up to Week 52.

EFF1c (non-pirfenidone population)

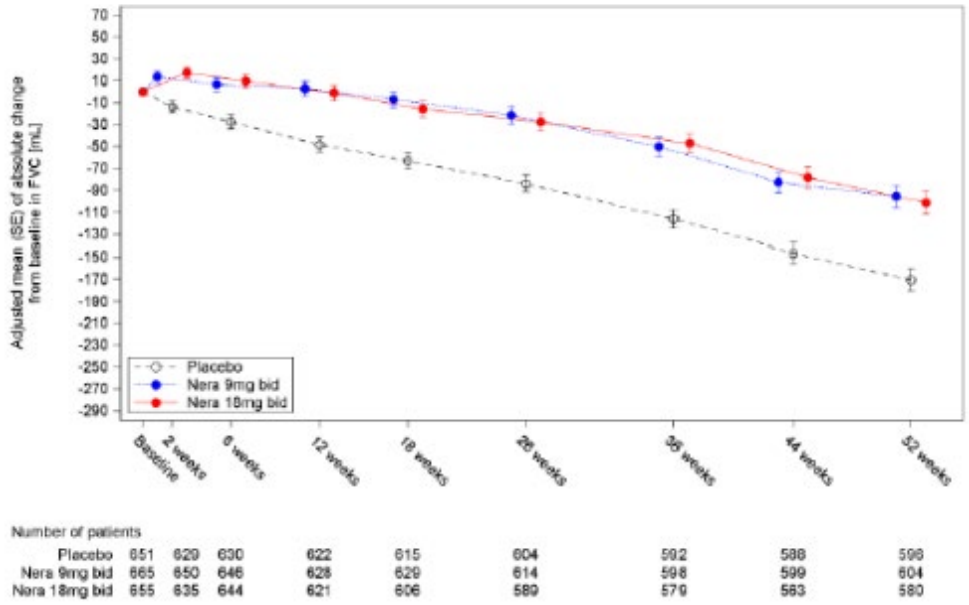


Figure 46: Absolute change from baseline in FVC [mL] at Week 52 – FAS EFF1 and EFF1c

A treatment effect in favour of both nerandomilast doses vs. placebo was observed in the subgroups, except for the subgroup with pirfenidone background treatment with 9 mg twice daily.In EFF1c, a key secondary composite endpoint event was observed in 195 participants (30.0%) in the placebo group, 164 participants (24.7%) in the 9 mg twice daily nerandomilast group, and 156 participants (23.8%) in the 18 mg twice daily nerandomilast group (HR vs. placebo for 9 mg twice daily 0.84, 95% CI 0.68, 1.03, p = 0.0955; for 18 mg twice daily 0.80, 95% CI 0.65, 0.99, p = 0.0447).

A breakdown of the remaining analysis can be seen below, showing similar effects to the two clinical trials and consistency across the subgroup analysis (bar participants on pirfenidone as a background therapeutic and, in the 9 mg twice daily dose, the subgroup with other fibrotic patterns on baseline HRCT):

Table 72: Time to the first clinical event (first event of acute IPF/ILD exacerbation, hospitalisation for respiratory cause, or death) over the duration of the trial up to 1305-0014 DBL2 and 1305-0023 DBL1 (pooled) – FAS EFF1c

EFF1c (non-pirfenidone population) (N %)	651	100.0	665	100.0	655	100.0
Key secondary composite endpoint (N %)	195	30.0	164	24.7	156	23.8
Acute IPF/ILD exacerbation as the 1st event	67	10.3	50	7.5	51	7.8
Hospitalisation for respiratory cause as the 1st event	102	15.7	96	14.4	94	14.4
Death as the 1st event	26	4.0	18	2.7	11	1.7
HR vs. placebo	--		0.84		0.80	
95% CI			0.68	1.03	0.65	0.99
p-value			0.0955		0.0447	
Acute IPF/ILD exacerbation or death (N %)	131	20.1	101	15.2	79	12.1
HR vs. placebo	--		0.78		0.62	
95% CI			0.60	1.02	0.47	0.82
p-value			0.0669		0.0008	
Hospitalisation for respiratory cause or death (N %)	175	26.9	145	21.8	140	21.4
HR vs. placebo	--		0.81		0.80	
95% CI			0.65	1.01	0.64	1.00
p-value			0.0640		0.0498	
Death (N %)	79	12.1	54	8.1	37	5.6
HR vs. placebo	--		0.67		0.48	
95% CI			0.47	0.95	0.32	0.71
p-value			0.0241		0.0002	

Of note, there is a consistent trend for a reduced risk of mortality across all the studies for both the 9 mg and 18 mg twice daily nerandomilast treatment groups with 18 mg being superior to the 9 mg counterpart (18 mg nerandomilast HR 0.56, 95% CI 0.40, 0.80, p = 0.0011) (9 mg nerandomilast HR 0.75, 95% CI 0.54, 1.02, p = 0.0696). A similar trend was also seen for acute IPF/ILD exacerbation or death (18 mg nerandomilast HR 0.62, 95% CI 0.47, 0.82, p = 0.0008) (9 mg nerandomilast HR 0.78, 95% CI 0.60, 1.02, p = 0.0669).

5.3.6. Patient experience data

CHMP received input from the European Pulmonary Fibrosis Federation (EU-PFF) relating to Nerandomilast for the treatment of adult patients with IPF and ILD-PPF on the 17th of July 2025. EU-PFF is a European Umbrella Organisation for member Patient Organisations focussed on IPF and PPF. EU-PFF acknowledge that there are currently limited options for patients in terms of treatment and those currently available have significant adverse effects. This leads to the need for complex and individually tailored clinical care decisions and interventions including dosage reduction, cessation, symptom mitigation & management, switching between the authorized treatments and ultimately transplant referral.

EU-PFF highlights that adverse effects are not consistent across the patient population whilst neither are the treatment benefits. However, due to the severe life-threatening nature of the diagnosis, adverse effects will be tolerated. A new medicine will provide an additional choice for those patients who cannot tolerate either current treatment and or gain none or reduced therapeutic benefit a possibility of improved survival and/or quality of life.

Between the significant adverse effects, tolerability, and varying efficacy of the current treatments, there is a need for new treatment options.

5.3.7. Healthcare professional engagement

CHMP received input from the healthcare professionals' organisation, European Respiratory Society (ERS) relating to Nerandomilast for the treatment of adult patients with IPF and ILD-PPF on the 24th of June 2025. The ERS agreed that there is a clear need for new treatments for IPF and PPF and this treatment should be initiated at diagnosis in patients with a high risk of progression rather than waiting for progression to occur.

- Pulmonary fibrosis still suffers from a lack of awareness regarding early diagnosis and given the complexity of pulmonary fibrosis, combination therapies are likely needed.
- Improved tolerance and fewer side effects are essential as drug tolerance is a significant issue as only approximately 50% of patients starting an antifibrotic medication tolerate the full dosage, about 30% require dose reduction, and the remaining patients either switch to the alternative antifibrotic drug or discontinue treatment mostly due to concerns about adverse events.

5.3.8. Overall discussion and conclusions on clinical efficacy

5.3.8.1. Discussion on Idiopathic pulmonary fibrosis indication

The claimed indication was agreed as : "Jascayd is indicated for the treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF)

The pivotal trial supporting this indication was the phase III 1305-0014 FIBRONEER trial. The main analysis was conducted after DBL1 (03 Sep 2024; data cut-off: 16 Aug 2024), once the last patient reached Week 52. Final database lock (DBL2) occurred on 03 Feb 2025 after all patients completed the trial. The phase II trial 1305-0013 was supportive.

Patients were randomised 1:1:1 to receive nerandomilast 9 mg bid 18 mg bid, or matching placebo twice daily. Randomisation was stratified by the presence or absence of antifibrotic (AF) treatment at baseline, allowing inclusion without altering ongoing standard of care.

The placebo-controlled design of the main clinical trials was considered acceptable for both target indications in previous obtained scientific advice (EMA/SA/0000078671) considering nerandomilast will be given on top of approved antifibrotic standard of care (i.e., patients on AF therapy) or as monotherapy in case the patients are not treated with anti-fibrotic treatment (non-AF patients) due to intolerance to such medicines or unavailability of nintedanib or pirfenidone.

The inclusion criteria for this study were similar to previous IPF trials (INPULSIS and INBUILD). As per eligibility criteria, patients were enrolled with a FVC ≥45% of predicted normal and DLCO ≥25% of predicted normal corrected for haemoglobin (Hb), which allowed for patients with mild to severe disease to be included in the study. The efficacy of nerandomilast in patients with more severe lung impairment was not directly studied. However, the applicant provided additional evidence showing that efficacy data from IPF and PPF can be extrapolated to this population and explained why a dedicated study was not necessary. Respective inclusion criteria related to FVC and DLCO at baseline have been introduced into section 5.1 of the SmPC.

The protocols of both trials did not stipulate a specific exclusion criterion related to the presence of pulmonary hypertension (PH). In the FIBRONEER-IPF trial, 37 patients (3.1%) had pulmonary hypertension at baseline, while in the FIBRONEER-ILD trial, 55 patients (4.7%) had this condition. In

both studies, treatment effects on the primary endpoint were consistent within this subgroup, supporting extrapolation of the pivotal trial results to patients with pulmonary hypertension.

The applicant has also proposed to describe the proportion of patients with pulmonary hypertension included in each trial in section 5.1 in the SmPC which has been agreed.

IPF Diagnosis

Patients were enrolled with an IPF diagnosis in line with ATS/ERS guidance. Patients could also be enrolled with an "IPF likely" diagnosis. The latter is not consistent with scientific advice received from the CHMP, which recommended the inclusion only of patients with a confirmed IPF diagnosis. It was argued however that this allowed for appropriate patient selection in alignment with international guidelines and expert consensus. In support of this, a sensitivity analysis performed for the primary endpoint, excluding patients that did not have a definite or probable UIP HRCT pattern, but were randomised with an IPF-likely diagnosis as per guideline based on additional available histology information from a lung biopsy, showed a consistent treatment effect compared with the overall population.

Use of standard of care treatment in the study

Patients were stratified according to background standard of care, AF therapy (nintedanib or pirfenidone or none). The non-AF group included patients who were treatment naïve and those who had previously discontinued AF therapies at least 8 weeks prior to study Visit 1, and who did not plan to start or re-start AF treatment. When queried, the applicant could not comment on potential reasons why patients were not receiving AF therapies at baseline in the study (e.g. newly diagnosed, contraindicated, access/reimbursement, intolerant or discontinuation, other reasons) as this data was not available. Similarly, no definition was provided to clarify how intolerance of approved treatments (nintedanib or pirfenidone) was defined.

In the FIBRONEER-IPF trial, a total of 262 (22.3%) patients had no AF therapy at baseline; the majority (172 patients, 14.6% of overall population) were naïve to AF therapy. No major differences in demographics according to background AF therapy were observed that would affect the assessment of the therapeutic effect. In IPF, improvements for the primary and key secondary endpoint were observed in all groups (previously AF treated and AF treatment-naïve patients on 9 mg or 18 mg nerandomilast). The treatment effect was numerically larger in previously AF treated patients compared to treatment-naïve patients, the relative reduction to placebo was comparable between the subgroups.

Patients with a pre-bronchodilator FEV1/FVC < 0.7 at Visit 1 were excluded, which is acceptable to avoid confounding by obstructive lung disease.

Dose de-escalation

The posology of nerandomilast states that the recommended dosage is 18 mg twice daily, and based on individual patient tolerability, the dosage may be reduced to 9 mg twice daily. The proposed posology differs from that studied in the clinical trial as dose de-escalation was not allowed in the study. As the proposed dose de-escalation strategy was not tested in this trial there is uncertainty as to how the treatment tolerance will improve with de-escalation and what criteria should be used to reduce the treatment. Further, it is not clear how frequently this dose de-escalation is likely to occur in clinical practice.

Rescue treatment

Patients not receiving antifibrotics at enrolment continued nerandomilast monotherapy, with antifibrotic therapy prohibited for the first 12 weeks and permitted thereafter as rescue treatment at the prescriber's discretion.

As only a small number of subjects started antifibrotics as rescue therapy (9 of 87 of patients (10.3%) in the placebo group, 3 of 88 of patients (3.4%) in the 9 mg bid nerandomilast group, and 6 of 87 of patients (6.9%) in the 18 mg bid nerandomilast group).The reasons for initiating anti-fibrotic rescue treatment were either "disease under study" or an "adverse event" associated with worsening of the disease under study.

Objectives and Outcomes/endpoints

The 1305-0014 trial had a single primary endpoint, one key secondary endpoint under type I error control and 10 other secondary endpoints not under type I error control.

The primary objective of the trial was to demonstrate superiority of nerandomilast to placebo in reducing lung function decline as measured by the change from baseline in FVC [mL] at Week 52 in patients with IPF. The main secondary objective was to demonstrate superiority of nerandomilast to placebo in reducing the risk of clinically meaningful events (acute IPF exacerbation, hospitalisation for respiratory cause, or death) over the duration of the trial.

The primary endpoint of the trial was the absolute change from baseline in FVC [mL] at Week 52. The 52-week duration is the minimum treatment duration recommended in guidance from the American and European Clinicians organizations on the investigation of treatment effects on Forced Vital Capacity (2015 ATS/ERS/JRS/ALAT Guideline. A correlation between treatment effects on FVC and on mortality in patients with IPF has been consistently demonstrated, resulting in FVC being adopted as an endpoint in registrational trials. Of note, change from baseline in FVC % predicted at week 52 was investigated as a secondary endpoint, but not multiplicity controlled.

It is important to highlight that the annual rate of decline in forced vital capacity (FVC) is only a surrogate endpoint and therefore it is considered that a positive trend in other endpoints investigating direct clinical effects is also necessary.

The key secondary endpoint in this trial was time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalisation for respiratory cause, or death (whichever occurred first) over the duration of the trial. At the time the CHMP scientific advice was issued, this endpoint was planned as a secondary endpoint and was later upgraded to the key secondary endpoint before trial start, replacing the L-PF dyspnoea and cough symptom scores at Week 52.

The applicant acknowledged that the 3 components of the key secondary endpoint are associated with varying levels of clinical significance, thus creating uncertainty and challenges in the interpretation of the results. Further, AEs and hospitalisations were not independently adjudicated, contrary to the scientific advice recommendation. Of note, the cause of death was adjudicated and attributed as respiratory, cardiovascular, non-CV, non-respiratory cause or cause undetermined.

Therefore, the applicant performed a post hoc win ratio analysis based on clinical importance, with the following hierarchy: death > acute exacerbation with hospitalisation > other respiratory hospitalisation > acute exacerbation without hospitalisation.

The treatment effect was more pronounced in the PPF study (1.33; 1.42 for nerandomilast 9 mg and 18g vs placebo respectively) when compared to the IPF study (1.10; 1.07 for nerandomilast 9 mg and 18g vs placebo respectively) at DBL2.

The patient reported outcome measures consisted of the Absolute change from baseline in L-PF Symptoms Dyspnoea domain score at Week 52, Absolute change from baseline in L-PF Symptoms Cough domain score at Week 52, Absolute change from baseline in L-PF Symptoms Fatigue domain score at Week 52. The validity of L-PF questionnaires was questioned at the time of CHMP scientific advice as the MCID had not been discussed. Overall, the results suggest that L-PF is not sensitive enough to compare symptom burden between treatment arms with the given study duration and size.

Statistical methods (both indications)

The definition of the analysis sets is considered acceptable. The full analysis set includes all randomised patients who received at least one dose of the study drug and is thus a modified ITT population, however, all randomised patients received at least one dose. Two database locks (DBL) were defined, DBL1 was used for the main analysis of the primary and secondary endpoints. DBL2 was after conclusion of the main analysis and was used for re-analysis of the time-to-event endpoints. As confirmatory testing was performed in the DBL1 and DBL2 was mainly used for a better estimation of time-to-event endpoints, this is agreed.

The primary endpoint change from baseline in FVC at Week 52 was analysed using a REML-based MMRM including baseline values and stratification factors. This is considered a suitable method to estimate the treatment effect. In this analysis, missing data will be considered to be random, which may not follow the treatment policy strategy defined in the estimand. However, sensitivity analyses were performed assuming missing not at random (retrieved drop-out, follow reference, tipping point), testing the influence of missing data handling, which, in hindsight, was small. Other sensitivity analyses investigated the influence of mis-stratification, covariates, outliers and poor case imputation after death. Together these analyses allow assessment of the robustness of the primary analysis.

Multiplicity for the primary and key secondary endpoint and the two dose arms was controlled. The hypothesis testing strategy controlled the overall type I error rate and is acceptable. In both trials, the focus of the hierarchical testing was on the primary endpoint and the key secondary endpoint. Therefore, all other endpoints were not type I protected and must be regarded as exploratory.

The applicant defined the intercurrent events, and almost all were used according to the treatment policy strategy, except for long transplantation and death. This approach is accepted, as the treatment policy approach aligns most with clinical practice. Lung transplantation was approached as a hypothetical strategy, which is justified as this event occurs randomly. Death was handled according to a composite strategy, implemented by a 'worst' case imputation using the 10th percentile of observed values, which is a reasonable approach.

Intercurrent events were generally balanced between treatment arms or, in case of disbalance, would likely favour the placebo arm and thus lead to a conservative estimate of the treatment effect. The key secondary endpoint, time to first acute exacerbation, hospitalisation for a respiratory cause, or death, was analysed using a Cox regression model.

<u>Efficacy data and additional analyses</u>

1177 patients were randomised in the trial and all received at least one dose of study treatment. The disposition of patients was mostly balanced across the treatment groups. Treatment was prematurely discontinued in 20.6% of patients in the placebo group, 21.2% of patients in the 9 mg bid nerandomilast group, and 21.7% of patients in the 18 mg bid nerandomilast group. In both non-AF and AF strata, the rate of treatment discontinuation (mainly due to AEs) was similar in the placebo group and 9 mg bid nerandomilast group (ranging from 19.3% to 21.8%). However, the 18 mg bid nerandomilast group showed differential trends between the strata: fewer discontinuations in

the non-AF stratum (11.5%) while more discontinuations in the AF stratum (24.6%) were observed.

More treatment discontinuations were observed on nerandomilast (25.0% for 9 mg bid and 29.8% for 18 mg bid) than placebo (19.7%) in patients with nintedanib background treatment, while fewer discontinuations were observed on nerandomilast (16.7% for 9 mg bid and 17.3% for 18 mg bid) than placebo (21.1%) in patients with pirfenidone background treatment. This may be partly explained by the reduced exposure to nerandomilast (~50%) observed in patients currently on pirfenidone treatment (please refer to safety section).

Baseline characteristics

Patients were recruited primarily from Europe (37.6%), Asia (30.4%) and the USA (16.7%). The vast majority of the population in the trial were white (67.7%), male (83%), over 65 (79%) currently taking antifibrotic medication (77.7%) which is reflective of the disease population in general. The average age in this trial was 70.2 years and the majority of the population (47.9%) was between ≥65 to <75 years old. Most participants in this trial were former smokers (68.8%) and 2.2% were current smokers, however 29% of the patients in this trial were never smokers. This is in line with the literature, where current and former smokers are consistently overrepresented in IPF.

Baseline disease characteristics

The mean FVC% predicted for patients in this trial was 78.2%, DLCO % predicted was 50.9%, and mean L-PF score was 25.24 which would indicate a mild-moderate level of disease severity.

915 patients (77.7%) were on background antifibrotics (AF) treatment at baseline. A total of 262 (22.3%) patients had no AF therapy at baseline; among these patients, the majority (172 patients, 14.6% of overall population) were naïve to AF therapy with the remainder (7.6%) having previous AF use but discontinued treatment.

The mean time since IPF diagnosis at baseline was 3.5 years. These data were generally balanced across the treatment groups, as were age, BMI and smoking status.

Patients on background AF therapy had lower FVC% predicted and DLCO% predicted values and more frequent oxygen use than those without, likely due to longer disease duration (~3.4 years with nintedanib, ~4.1 years with pirfenidone years vs. ~2.8 years in non-AF group). This suggests greater disease progression and symptom burden in patients on background AF therapy. This observation is further supported by the comparison of the placebo results between AF background patients (-191.6 mL nintedanib, -197.0 mL pirfenidone) and non-AF patients (-148.7 mL) for the rate of FVC decline from baseline over 52 weeks.

Primary endpoint results

Treatment with Nerandomilast 9 mg and 18 mg bid resulted in a statistically significant decrease in the rate of FVC decline compared to placebo. The adjusted mean (95% CI) change from baseline in FVC [mL] at Week 52 was -183.5 (-210.9, -156.1) in the placebo group, -138.6 (-165.6, -111.6) in the 9 mg bid nerandomilast group, and -114.7 (-141.8, -87.5) in the 18 mg bid nerandomilast group. The adjusted mean difference (95% CI, p-value) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 44.9 mL (6.4, 83.3, p = 0.0222) and between 18 mg bid nerandomilast and placebo groups was 68.8 mL (30.3, 107.4, p = 0.0005), therefore both nerandomilast doses were superior to placebo for the primary endpoint. The results of all sensitivity and supplementary analyses were consistent with and supported primary analysis of the primary endpoint.

The observed reductions in the rate of decline relative to placebo are considered statistically and clinically relevant.

Additionally, change from baseline in FVC % predicted at week 52 (preferred endpoint of CHMP), demonstrated similar efficacy as the primary endpoint. The adjusted mean difference (95% CI) in FVC % predicted change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 1.2 (0.1, 2.2,) and between 18 mg bid nerandomilast and placebo groups was 1.7 (0.7, 2.8)

A positive treatment effect was also seen for the absolute decline from baseline in FVC % predicted of >10% endpoint which at DBL2 for 18 mg dose reached statistical (nominal) significance. In IPF patients, a decline of more than 10% in Forced Vital Capacity (FVC) % predicted is considered a significant indicator of disease progression and is associated with a higher risk of mortality.

The Phase 2 study in IPF supports the positive outcomes with regard to lung function.

Exclusion of patients receiving background pirfenidone therapy led to increases in the magnitude of the treatment effect compared to placebo, from 44.9 mL to 66.4 mL in the 9 mg bid group and 68.8 mL to 71.6 mL in the 18 mg bid group.

Although nerandomilast showed a statistically significant reduction in FVC decline at Week 52 in FIBRONEER-IPF, this surrogate endpoint requires support from clinically meaningful outcomes (see below).

Early improvement in FVC

The adjusted mean of absolute change from baseline in FVC in both nerandomilast dose groups separated from the placebo group from Week 2 until Week 52. At the week 2 and week 6 timepoints, there was an increase in FVC from baseline in patients receiving nerandomilast treatment of 9mg and 18mg. Current information does not allow to explain the reason behind this increase in FVC, unlikely to be due to an antifibrotic effect seen so early after treatment initiation. This uncertainty is deemed acceptable.

Subgroup analyses for primary endpoint

Observed treatment effects were generally consistent across the subgroups investigated.

For 9 mg nerandomilast, the primary endpoint favoured placebo in patients <65 years but normalised after removal of an outlier. For the 18 mg dose in the Hispanic or Latino subgroup, the endpoint favours placebo with a wide confidence interval. These data do not indicate a negative treatment effect in Hispanic or Latino patients, as the observed trend was not consistent across endpoints, and no safety concerns were identified in this subgroup.

Key secondary endpoint

The key secondary endpoint :was not met. Key secondary endpoint events occurred in 80 patients (20.4%) in the placebo group, 79 patients (20.2%) in the 9 mg bid nerandomilast group, 85 patients (21.7%) in the 18 mg bid nerandomilast group. There was no statistically significant treatment difference to placebo for either nerandomilast dose (HR vs. placebo for 9 mg bid 1.03, 95% CI 0.75, 1.41, p = 0.8568; for 18 mg bid 1.17, 95% CI 0.86, 1.59, p = 0.3102).

Also up to DBL2, no difference in risk for the key secondary endpoint was observed between treatment groups; although hazard ratios for nerandomilast were numerically lower than placebo, these exploratory results were not multiplicity controlled.In a post hoc analysis excluding patients

with pirfenidone background treatment, the HRs (95% CI) vs. placebo were 0.77 (0.54, 1.09) for 9 mg bid and 0.88 (0.63, 1.24) for 18 mg bid nerandomilast.

Overall, results up to DBL2 appeared more favourable than at DBL1, and while an increase in events might be expected over longer follow-up or seasonal periods, the available data do not suggest this influenced the findings.

Components of the key secondary endpoint

At DBL1 no treatment difference compared to placebo for either nerandomilast dose was observed for any of the 3 components of the key secondary endpoint as stand-alone endpoints.

For most endpoints with the exception of mortality, there was no clear advantage of the 18 mg dose compared to the 9 mg bid dose.

There was no significant difference in occurrence of acute IPF exacerbations between the treatment groups. Up to DBL2 HRs (95% CI) vs. placebo were 0.97 (0.62, 1.51) for 9 mg bid nerandomilast and 1.05 (0.68, 1.62) for 18 mg bid nerandomilast.

There was no significant difference in occurrence of hospitalisation for respiratory cause between the treatment groups. Up to DBL2, compared with placebo, the HR (95% CI) was 0.91 (0.65, 1.26) for 9 mg bid nerandomilast and 1.07 (0.78, 1.47) for 18 mg bid nerandomilast. As indicated by the applicant, further analysis of hospitalisation events suggests that some hospitalisations were in fact not due to respiratory cause: the absence of an adjudication committee for this endpoint is therefore an important limitation of the study design.

Up to DBL1, the effect of nerandomilast on mortality over the duration of the trial was modest. Deaths occurred in 28 patients in the placebo group (7.1%), 26 patients in the 9 mg bid nerandomilast group (6.6%), and 21 patients in the 18 mg bid nerandomilast group (5.4%). However, over the whole trial up to DBL2, the effect of 18 mg nerandomilast on mortality is more apparent. Deaths occurred in 42 patients in the placebo group (10.7%), 36 patients in the 9 mg bid nerandomilast group (9.2%), and 26 patients in the 18 mg bid nerandomilast group (6.6%). The HR (95% CI) vs. placebo was 0.95 (0.61, 1.49) for 9 mg bid nerandomilast and 0.66 (0.41, 1.08) for 18 mg bid nerandomilast. All deaths, except one, reported over the duration of the trial could be adjudicated. The imbalance in deaths in favour of nerandomilast was seen for respiratory deaths which were the most common but an imbalance in favour of nerandomilast was also observed for cardiovascular and non-CV, non-respiratory deaths.

In a *post hoc* analysis excluding patients with pirfenidone background treatment, the HRs (95% CI) vs. placebo were 0.84 (0.48, 1.48) for 9 mg bid and 0.47 (0.25, 0.90) for 18 mg bid nerandomilast.

The observed effect on deaths in favour of nerandomilast is considered as important and relevant for this patient population, although considering that the study was not powered to assess this effect, chance cannot be fully excluded.

Conclusion on the key secondary endpoint results

Although the composite key secondary endpoint was not formally met in FIBRONEER-IPF, nerandomilast showed encouraging numerical trends, particularly for mortality, which became more favourable at the final analysis. Together with consistent benefits on FVC, these findings support a clinically meaningful treatment effect despite variability across individual components of the composite endpoint.

Subgroup analyses for secondary endpoint

At DBL2, the hazard ratios versus placebo in patients with baseline FVC ≤ 70% predicted were close to unity for 9 mg bid (HR 0.97) and slightly above unity for 18 mg bid (HR 1.21); however, considering the overall positive effects on FVC, these findings do not raise a concern for this subgroup.

Effect on DLCO

Further supporting evidence for efficacy of nerandomilast came from the DLCO related endpoints. The numerical reduction in DLCO % predicted decline from baseline that was observed in the nerandomilast groups compared with placebo at Week 52 was maintained at the end of the trial. The adjusted mean difference (95% CI) in DLCO % predicted (corrected for haemoglobin) change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 2.5 (0.8, 4.2) and between 18 mg bid nerandomilast and placebo groups was 1.7 (0.0, 3.4)

Effect on symptoms

Based on L-PF scores for symptoms of Dyspnoea, Cough, Fatigue, total score and impact score, there was no difference in symptoms or health related quality of life for patients treated with nerandomilast compared to placebo.

Nerandomilast as a Monotherapy (non-AF group)

In the subgroup of patients receiving nerandomilast as a monotherapy, treatment with nerandomilast 9 mg bid and 18 mg bid resulted in a decrease in the rate of FVC decline compared to placebo, although statistically significant (nominal) differences were not observed. The adjusted mean difference (95% CI) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 78.3 (-3.2, 159.8) and between 18 mg bid nerandomilast and placebo groups was 69.4 (-12.3, 151.2) corresponding to 53% and 47% relative reduction respectively. The HRs (95% CI) vs. placebo for time to death over the whole trial were 0.56 (0.21, 1.49) for 9 mg bid nerandomilast and 0.26 (0.07, 0.91) for 18 mg bid nerandomilast.

Monotherapy is intended for broad use irrespective of disease severity; although patients in the monotherapy group were generally less severe than those receiving background antifibrotic therapy, there is no evidence that IPF/PPF pathophysiology or treatment response differs by lung function impairment, and subgroup results in treatment-naïve patients were consistent with the overall population, supporting its use as monotherapy across IPF severity. The disease status of the non-AF group is described in the SmPC.

Nerandomilast in combination with nintedanib

The reduction in FVC decline in patients receiving background therapy with nintedanib was smaller compared to patients with no background therapy, however the nintedanib treated population was more severe in respect to lung function decline.

For the group of patients receiving nintedanib background therapy the adjusted mean difference (95% CI) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 60.9 mL (4.3, 117.5) and between 18 mg bid nerandomilast and placebo groups was 73.0 mL (15.3, 130.8) corresponding to 32% and 38% relative reduction respectively.

In relation to the key secondary endpoint in patients with nintedanib background treatment at DBL2 the frequency of events was similar across treatment groups, with HRs vs. placebo of 0.98 (0.63, 1.53) for 9 mg bid nerandomilast and 1.07 (0.70, 1.64) for 18 mg bid nerandomilast.

In relation to the effect on mortality, the Cox model for time to death over the whole trial showed no effect on mortality for the 9 mg bid nerandomilast group, whereas the hazard ratio (95% CI) for the 18 mg bid nerandomilast group was 0.64 (0.30, 1.37).

Of note, in patients with nintedanib background treatment more treatment discontinuations were observed on nerandomilast (26.6% for 9 mg bid and 32.0% for 18 mg bid) than placebo (24.9%)

Nerandomilast in combination with pirfenidone

As has been discussed already, combination use with pirfenidone led to a 55% decrease in nerandomilast plasma exposure in the 9 mg bid group and 48% plasma exposure in the 18 mg group, compared to patients not taking Pirfenidone. It needs to be highlighted that this assessment of reduced exposure was based on the population pk data from the clinical studies, and no formal drug-drug interaction study was performed, which is considered as a limitation (see PK section). As highlighted in the SmPC the use of 9 mg bid nerandomilast with pirfenidone is not recommended, which is supported.

With nerandomilast 18 mg bid plus pirfenidone, an initial numerical excess in mortality was observed at DBL1 compared with placebo (11 [8.7%] vs 7 [5.3%]), despite an improvement in FVC at Week 52 (difference vs placebo 63.4 mL; 95% CI −3.6, 130.4). By DBL2, this imbalance had resolved (pirfenidone 18 mg: 12 [9.4%] vs placebo: 13 [9.8%]; HR 1.12, 95% CI 0.51–2.47), indicating no sustained increase in mortality, with earlier differences likely driven by small event numbers.

Mortality is a key outcome, with the strongest effect observed in patients without background antifibrotic therapy; therefore, SmPC section 5.1 includes stratified results by background AF use and for the pirfenidone subgroup, covering primary, key secondary, and mortality outcomes.

Positioning of Nerandomilast in the Current Treatment Landscape

The study design allows conclusions of added benefit of nerandomilast to existing anti-fibrotic (AF) treatment. The applied indication includes treatment naïve patients: i.e. patients with available alternative treatment options and without intolerance issues to existing therapies. Since there are no established treatment guidelines for IPF/PPF, recommendations for preferred first-line antifibrotic therapy cannot be given. An active controlled trial comparing nerandomilast vs. nintedanib or pirfenidone (IPF), could better place nerandomilast in the current treatment landscape, and would better inform management of naïve patients.

Justification the dose selection

The recommended dose of nerandomilast 18 mg bid is mainly based on popPK modelling. The proposed reduced 9 mg bid dose is investigated only in the main Phase 3 trials.

The data from FIBRONEER-IPF has shown that both 9mg and 18mg nerandomilast treatment significantly improved the rate of FVC decline in IPF patients, not including those on background pirfenidone. This data was supported by sensitivity and supplemental analysis. However, while both doses significantly improved the rate of FVC decline, the higher dose is numerically superior to 9mg in relation to mortality and in other key secondary endpoints. Exploratory post-hoc analysis provided by the applicant demonstrated a reduced mortality risk as plasma exposure increased. All taken together this demonstrates better patient outcomes are observed at the 18mg dose compared to the 9mg dose. This is in addition to no additional serious safety concerns with the increased dose, therefore justifying use of the 18mg dose as the starting dose for the treatment as stated in the SmPC. The dosage dose may be reduced to 9 mg twice daily based on individual patient tolerability (see safety section).

5.3.8.2. Discussion on progressive pulmonary fibrosis indication

Unlike nintedanib, which was approved for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype in 2020, the proposed indication for nerandomilast "treatment of adult patients with Progressive Pulmonary Fibrosis (PPF)" does not reference ILD. The term "PPF" has been formally adopted by the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline in place of "progressive fibrosing ILD." Accordingly, the use of "Progressive Pulmonary Fibrosis (PPF)" in the claimed indication is considered appropriate. Of note, patients were recruited to the PPF pivotal study independently from the underlying cause of their ILDs and later classified into ILD subtypes.

Design and conduct of clinical studies

The FIBRONEER-ILD study (Study 1305-0023), pivotal study for this application, was a confirmatory, multicentre, multinational, prospective study, placebo-controlled, double-blind parallel trial design, randomised 1:1:1 ratio of 9 mg nerandomilast, 18 mg nerandomilast, or placebo matched control to be taken twice daily.

The study duration (part A) of 52 weeks and parallel design are overall acceptable and similar to that used for other products (nintedanib) approved for the same condition in line with the 2015 ATS/ERS/JRS/ALAT Guideline. Part B consisted of a variable treatment period to provide supportive long-term efficacy and safety data in PFF subjects. The data for the FIBRONEER-ILD trial was provided up until DBL1 (24 Jan 2025, with a data cut-off date of 11 Dec 2024). The main analysis of trial 1305-0023 had been performed after DBL1. Following trial completion and final DBL2, a final analysis was performed using all data available at the time of DBL2.

Dose reduction

The proposed posology recommends nerandomilast 18 mg twice daily, administered approximately 12 hours apart. Based on individual patient tolerability, the dosage may be reduced to 9 mg twice daily. In the pivotal study however two nerandomilast doses were investigated separately and dose reductions were not allowed.

Study Population

Inclusion criteria

- The FIBRONEER-ILD study enrolled adult participants (≥18 years of age) with a confirmed diagnosis of progressive fibrosing ILD (independent of the underlying diagnosis), as defined by presence of fibrotic lung disease on HRCT (>10% disease extent) and one of the following within the past 24 months: Clinically significant decline in FVC % predicted based on a relative decline of ≥10%
- Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with worsening of respiratory symptoms
- Marginal decline in FVC % predicted based on a relative decline of ≥5-<10% combined with increasing extent of fibrotic changes on chest imaging
- Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging.

The applicant used inclusion criteria similar to those of the INBUILD clinical trial (supporting the PPF indication for nintedanib) and slightly different than the 2022 ATS/ERS/JRS/ALAT guideline but can be

accepted. Retrospective analysis performed by the applicant showed that 87.2% of the randomised population met the ATS/ERS/JRS/ALAT 2022 criteria.

Exclusion criteria

Exclusion criteria were broadly similar between the FIBRONEER-ILD and INBUILD trials. Patients with relevant airways obstruction with prebronchodilator FEV1/FVC <0.7 at Visit 1 were excluded from the study as FVC measurements for these patients could be confounded.

There is no evidence that fibrotic remodelling would differ depending on degree of concomitant COPD/emphysema. In post-hoc subgroup analyses by presence of emphysema (Y/N) and by FEV1/FVC ratio, no relevant heterogeneity in the treatment effect of nerandomilast was observed.

Severity of disease

The 2022 ATS/ERS/JRS/ALAT guideline defines severe lung derangement as FVC <50% and DLCO <35% predicted. FIBRONEER-ILD included patients with normal to severely reduced lung function (DLCO ≥25%, FVC ≥45%), in line with other trials such as INBUILD. Although nerandomilast was not investigated in a dedicated study of patients with very severe lung impairment, subgroup analyses by baseline FVC and DLCO showed consistent efficacy across levels of lung function, supporting extrapolation beyond the studied population. Baseline inclusion criteria are described in SmPC section 5.1

The applicant also has presented the efficacy data in patients with pulmonary hypertension which showed consistent results with overall population.

Background therapy

Patients were enrolled in the study without background therapy or with background therapy with nintedanib. Patients that were not treated with nintedanib can be divided into 3 subgroups: naïve, discontinued because intolerant to nintedanib, discontinued but tolerant to nintedanib. As expected, in both the IPF and PPF study, patients naïve to approved treatments had on average shorter time since diagnosis, less frequent supplemental oxygen and higher FVC- and DLCO % predicted. It is acknowledged that there is still substantial overlap in degree of functional impairment with the non-AF background group and with the patient population treated with AF at baseline.

Stratification

In the study there were two stratification factors:

- Stable antifibrotic medication stratification was intended to correspond to the current treatment/prescription practices across the participating countries (30% vs. 70% for antifibrotic and non-antifibrotic medication respectively).
- HCRT pattern stratified participants into "Usual interstitial pneumonia (UIP)/UIP-like fibrotic pattern" or "Other fibrotic patterns". HRCT pattern stratification parameters were the same for the INBUILD study assessing nintedanib.

Concomitant and rescue medication

Immunomodulatory treatment as rescue therapy

Initiation or modification of immunomodulatory therapies (e.g., cyclophosphamide, tocilizumab, mycophenolate, rituximab, and high-dose steroids) was restricted during the first 6 months of blinded treatment, in line with CHMP scientific advice recommending stability of immunosuppressive medication during this period. Adjustments to prednisone doses up to 15 mg/day were permitted. After

6 months, treatment changes were allowed as medically indicated. Prednisone >15 mg/day was permitted during suspected acute ILD exacerbations.

The number of patients who started immunomodulatory rescue therapy was low: immunomodulatory rescue therapy was used in 17 (4.6%) in the placebo group, 25 (7%) in the 9 mg bid nerandomilast group, and 18 (5.3%) of patients in the 18 mg bid nerandomilast group.

In trial FIBRONEER-ILD, 62 patients (5.3%) used restricted immunomodulatory treatment or prednisone >15 mg/d on-treatment up to DBL1. When immunosuppressive medications were also taken into account, 108 patients (9.2%) used these medications (36 patients 9.2% in the placebo group; 41 patients 10.4% in the nerandomilast 9 mg bid group; 31 patients, 7.9% in the nerandomilast 18 mg bid group). Supplementary analyses using a hypothetical approach were carried out as requested and the results were consistent with the main analyses of the primary endpoint and the key secondary endpoint. Several of the more frequently used immunosuppressive medications in PPF (cyclosporine, tocilizumab mycophenolate mofetil or mycophenolate sodium, rituximab, or oral glucocorticoids (at a dose of more than 15 mg per day) were not permitted in trial 1305-0023.

Nintedanib as rescue therapy

Patients in the non-AF group were permitted to take nintedanib after 12-weeks as rescue medication in case of disease worsening. Of note, nintedanib recuse therapy was used in 24 (6.5%) in the placebo group, 19 (5.3%) in the 9 mg bid nerandomilast group, and 22 (6.1 %) of patients in the 18 mg bid nerandomilast group. To address the potential impact of rescue therapy on efficacy results, the applicant assigned a treatment policy approach for the primary analysis and performed supplementary analyses using a hypothetical approach that excluded values after initiation of nintedanib therapy and using a composite approach that assigned a poor value after initiation of nintedanib therapy for the non-AF group.

Objectives and Outcomes/endpoints

Study 1305-0023 was a superiority trial with a primary endpoint and one key composite secondary endpoint under type I error control. The primary endpoint investigated absolute change from baseline in FVC [mL]. This endpoint is considered acceptable; however, the annual rate of decline in forced vital capacity (FVC) is only a surrogate endpoint and therefore a positive trend in other endpoints investigating direct clinical effects needs to be shown. In line with CHMP scientific advice, the percent predicted FVC was added as a secondary endpoint.

In addition, time to progression (defined as a ≥10% absolute decline in FVC % predicted) or death over 52 weeks and proportion of patients with a relative decline from baseline in FVC % predicted of >10% at Week 52 were investigated as secondary endpoints.

The key composite secondary endpoint in this trial was time to the first occurrence of any of the components of the composite endpoint: time to first acute ILD exacerbation, first hospitalisation for respiratory cause, or death (whichever occurred first). This decision to use the composite key secondary endpoints was questioned since AEs and hospitalisations were not independently adjudicated, despite centralised adjudication being recommended by scientific advice. There was also no hierarchical structure to this composite endpoint, with all events being treated as equal. Of note, an independent adjudication committee performed central, blinded adjudication of all fatal cases, major adverse cardiac events (MACEs), and vasculitis events.

For acute PPF exacerbation both confirmed and suspected acute PPF exacerbation cases were considered for the endpoint evaluation.

Other secondary endpoints

In the study there were a number of time to first clinical event composite endpoints combining mortality with another outcome measure. The time to first acute ILD exacerbation or death as markers of disease progression were considered acceptable by scientific advice. The only PRO included in this trial was L-PF.

Efficacy data and additional analyses

1178 participants were enrolled to the FIBRONEER-ILD study. 393, 392 and 392 patients were randomised and received either placebo, nerandomilast 9 mg or nerandomilast 18 mg, respectively.

Treatment was prematurely discontinued in 111 (28.3%) of patients in the placebo group, 91 (23.2%) of patients in the 9 mg bid nerandomilast group, and 107 (27.4%) of patients in the 18 mg bid nerandomilast group.

Differential discontinuation rates across treatment arms were observed in patients with and without background nintedanib therapy. In patients without background nintedanib therapy, the rate of treatment discontinuation was higher with placebo compared with the nerandomilast groups (33.8%, vs. 28.2% with 9 mg bid and 25.9% with 18 mg bid), whereas in patients with background nintedanib therapy, the discontinuation rate was higher with 18 mg bid nerandomilast (36.3%) compared with 9 mg bid nerandomilast (27.7%) or placebo (27.1%). The main reason for discontinuation was an adverse event.

Baseline characteristics

The mean age of enrolled patients was 66.4 years. The arms were generally balanced for gender. Most of the participants were White (58.2%) or Asian (39.1%,). Mean BMI was 26.6 kg/m^2 and both weight and BMI in were very similar between treatment groups.

ILD diagnosis

The median time since ILD diagnosis was 2.9 years (Q1 1.4, Q3 5.8) before the trial enrolment. In the overall FIBRONEER-ILD study population, the most frequent underlying clinical ILD diagnosis category was autoimmune ILDs (27.6%), hypersensitivity pneumonitis (19.8%), unclassifiable idiopathic interstitial pneumonia (19.6%), idiopathic nonspecific interstitial pneumonia (19.4%), and other ILDs (13.5%) which included exposure-related ILDs (2.7%) and sarcoidosis (1.4%)

In comparison, in the INBUILD trial, pivotal for the nintedanib PF-ILD indication, about one quarter of patients had underlying ILD diagnoses of hypersensitivity pneumonitis (26%) or autoimmune ILDs (25%). Nearly one fifth of patients had idiopathic non-specific interstitial pneumonia (19%) or unclassifiable idiopathic interstitial pneumonia (17.25%). The remaining patients (12%) had other ILDs.

According to literature, absolute decline in FVC in patients with PPF differs depending on the ILD type, e.g. autoimmune diseases have a smaller FVC decline compared to patients with hypersensitivity pneumonitis or idiopathic interstitial pneumonia (Oldham et al. 2022). Differing risks of mortality have also been observed among patients with PPF and different ILD diagnoses (Nasser et al. 2021,2022).

There was a significant percentage of participants included in the study with idiopathic interstitial pneumonias and idiopathic nonspecific interstitial pneumonia. While the applicant cannot exclude with absolute certainty that no patient with undiagnosed IPF was included in the FIBRONEER-ILD trial, additional sensitivity analyses investigating the potential impact of patients that are most difficult to differentiate from IPF confirm the robustness and conclusions of the primary analysis.

HCRT pattern distribution

A total of 840 patients (71.4%) presented with an "UIP or UIP-like fibrotic pattern" on baseline HRCT and 336 patients (28.6%) presented with "other fibrotic patterns". There is some evidence that lung function decline may be more rapid in patients with PPF who have a UIP or UIP-like fibrotic pattern on HRCT and these patients have a higher risk of progression of their ILD (Bown et al. 2022; Nasser et al. 2021; Oldham et al. 2022).

In the FIBRONEER-ILD study patients presenting with UIP or UIP-like fibrotic pattern seem to be less severe as higher FVC % predicted was observed at baseline and they used supplemental oxygen less frequently than in patients presenting with another fibrotic pattern. This contrasts with evidence reported in the literature.

Background therapy with nintedanib

A total of 514 patients (43.7%) had been on background therapy with nintedanib at baseline. The remaining patients 662 (56.3%) were not receiving AF background therapy. 44.3% were naïve to these treatments.

Patients receiving background nintedanib were twice as likely to use supplemental oxygen at baseline, suggesting greater disease severity. This was supported by a larger FVC decline in placebo patients on anti-fibrotic therapy (-180.9 ml) compared with those without such therapy (-154.1 ml).

Concomitant therapy

A total of 283 patients (24.1%) used at least 1 immunosuppressive medication of interest at baseline. Up to DBL1, on-treatment restricted medications were used with similar frequency by patients across the treatment groups (8.2%, 8.4%, and 8.2% in the placebo, 9 mg bid nerandomilast, and 18 mg bid nerandomilast groups, respectively).

Primary endpoint results

The primary endpoint was the absolute change from baseline in FVC [mL] at Week 52. Both nerandomilast doses of 9 and 18 mg bid showed statistically significant reductions in FVC [mL] decline compared to placebo for the primary endpoint**.** The difference to placebo in the adjusted mean (95% CI, p-value) change from baseline at Week 52 in FVC [mL] was 81.1 (46.0, 116.3, $p<0.0001$) in the nerandomilast 9 mg bid group and 67.2 (31.9, 102.5, $p = 0.0002$) in the nerandomilast 18 mg bid group.

The results of all sensitivity and supplementary analyses were consistent with and supported the primary analysis of the primary endpoint.

An increase in participant FVC values between baseline and 2/6-weeks after treatment initiation in the nerandomilast's groups was observed similarly to the IPF study. As discussed earlier for the IPF indication the underlying mechanism contributing to this increase in FVC shortly after treatment initiation is unclear and unlikely to involve an anti-fibrotic effect due to the short timeline.

Key secondary endpoints

The key composite secondary endpoint was the time to the first occurrence of any of the following components over the whole duration of the trial up to DBL1: acute ILD exacerbation, first hospitalisation for respiratory cause, or death. Only the key secondary endpoint was adjusted for multiplicity. The confirmatory testing for the key secondary endpoint was performed at DBL1 and the p-values at DBL2 were not adjusted for multiple testing (i.e. nominal p-values). For other secondary

and further endpoints, analyses were descriptive, and the p-values for treatment comparisons were nominal and not adjusted for multiple testing.

The key secondary endpoint for both doses was not statistically significant. Nevertheless, there was a trend in improvements for the components of the key secondary endpoint. These events occurred in a slightly lower proportion of patients in both nerandomilast groups (9 mg bid: 110 patients, 28.0%; 18 mg bid: 95 patients, 24.3%) than placebo (122 patients, 31.1%), with the lowest proportion in the 18 mg bid treatment group. The risk of having a key secondary endpoint event was slightly lower in both nerandomilast dose groups than placebo, although no statistically significant treatment effect was shown (HR vs. placebo for 9 mg bid 0.88, 95% CI 0.68, 1.14; for 18 mg bid 0.77, 95% CI 0.59, 1.01). At Week 52, the estimated percentage of patients with events was lower in the 18 mg bid nerandomilast group than placebo (-6.6%, 95% CI -12.5, -0.7). The estimated percentage difference vs. placebo was -3.7% (95% CI -9.7, 2.3) in the 9 mg bid nerandomilast group. The results of all sensitivity and supplementary analyses were consistent for the key secondary endpoint.

With additional treatment duration and observation time between DBL1 and DBL2, the number of events for the key secondary endpoint (+14% compared with DBL1) and its components increased across all treatment groups. The treatment differences to placebo for the key secondary endpoint appeared to be similar for both doses of nerandomilast at DBL2 (9 mg bid: HR 0.78, 95% CI 0.61, 1.00; 18 mg bid: HR 0.77, 95% CI 0.60, 0.99).

Other secondary endpoints

Although not under multiplicity control, nerandomilast treatment, especially 18mg dose was able to reduce the risk of the following outcomes: acute ILD exacerbations or death, hospitalisation for respiratory causes or death, and death alone. The risk of acute ILD exacerbations or death was reduced by 41% for the 18 mg bid nerandomilast group vs. placebo (HR 0.59, 95% CI 0.41, 0.84). A positive treatment effect was also seen for acute ILD exacerbations when death was handled via a hypothetical strategy and patients were censored at the time of death. Of note, one third of the events contributing to this endpoint were suspected (i.e. not confirmed) events, which diminishes validity of this result.

There was no significant difference between the treatment groups for time to the first hospitalisation for respiratory cause. The risk of hospitalisation for respiratory cause or death was reduced by 25% for the 18 mg bid nerandomilast group vs. placebo (HR 0.75, 95% CI 0.56, 1.00). The risk of death due to any cause was reduced by 40% for the 9 mg bid nerandomilast group vs. placebo (HR 0.60, 95% CI 0.38, 0.95) and by 52% for the 18 mg bid nerandomilast group vs. placebo (HR 0.48, 95% CI 0.30, 0.79). However, it is again noted that this endpoint was not under type I error control and hence results cannot be considered as confirmatory.

The observed effect on all-cause mortality in favour of nerandomilast is considered as important and relevant for this patient population. The risk of death was reduced by 49% in both nerandomilast dose groups vs. placebo (HR 0.51, 95% CI 0.34, 0.78 for 9 mg bid nerandomilast and HR 0.51, 95% CI 0.34, 0.78 for 18 mg bid nerandomilast; mainly driven by respiratory causes as adjudicated). In addition, reduced risks were observed for "acute ILD exacerbation or death" and "hospitalisation for respiratory cause or death". The trends for other efficacy endpoints were similar between DBL1 and DBL2.

L-PF scores increased from baseline to Week 52 in all treatment groups, indicating a worsening in disease symptoms which is in line with the progressive nature of PPF.

Subgroup analysis

The results in subgroups were in general consistent with those reported for the overall study population.

Subgroup analysis by fibrotic pattern

The results in subgroups by fibrotic pattern were in general similar with those reported for the overall population. However, the treatment effect was slightly stronger for the other fibrotic pattern specially for the 18 mg dose (treatment by subgroup interaction p-value: 0.0384).

Subgroup analysis by underlying ILD diagnosis

The results in subgroups by underlying ILD diagnosis were in general similar with those reported for the overall population, although some small differences were noted.

Nerandomilast was slightly less effective in treating Idiopathic nonspecific interstitial pneumonia and autoimmune ILD (Adjusted Mean Difference in FVC: 34.94 mL and 45.86 mL for 9 mg twice daily and 53.48 mL and 42.22 mL for 18 mg twice daily for Idiopathic nonspecific interstitial pneumonia and autoimmune ILD) compared to the remaining underlying ILDs.

The only subgroup by underlying baseline ILD disease that did not show an improvement in the key secondary endpoint, including mortality, was the iNSIP subgroup. However, the numbers are low and should be interpreted with caution. Outcomes for this subgroup are presented in SmPC section 5.1.

Justification of the dose selection

In the FIBRONEER-ILD study, the 9 mg twice-daily dose showed a numerically greater effect on absolute FVC decline over 52 weeks compared with the 18 mg twice-daily dose (adjusted mean difference vs placebo: 81.14 mL and 67.18 mL, respectively).

However, the 18 mg twice-daily dose demonstrated a numerically greater benefit for clinically relevant outcomes, including mortality. The relative risk of death was reduced by 40% with 9 mg twice daily and by 52% with 18 mg twice daily versus placebo, noting that these analyses were not controlled for multiplicity.

Considering the totality of efficacy data, the 18 mg twice-daily dose is considered acceptable. Dose reduction to 9 mg twice daily may be considered based on individual tolerability, in line with the SmPC section 4.2.

Use of nerandomilast as monotherapy

The treatment effect of nerandomilast monotherapy (9 and 18 mg bid) when compared to placebo showed a reduction of 71.8 mL and 58.9 mL respectively, which is lower than seen in patients receiving nerandomilast as add-on therapy to nintedanib.

For the key secondary endpoint, as for the overall population, no statistically significant difference was shown although the effects appeared to be numerically larger in patients without background nintedanib therapy than in those with background nintedanib therapy.

Regarding death, the treatment effect of nerandomilast monotherapy (9 and 18 mg bid) when compared to placebo showed a difference of hazard ratio 0.64 and 0.41, respectively.

Nerandomilast monotherapy is intended for use across the PPF population irrespective of disease severity. Although patients receiving monotherapy were generally less severe than those receiving background antifibrotic therapy, there is no evidence to suggest that PPF pathophysiology or treatment response differs according to the degree of lung function impairment. Efficacy outcomes in treatment-naïve patients were consistent with those observed in the overall population, supporting the

use of nerandomilast as monotherapy across PPF disease severity. The disease characteristics of patients not receiving antifibrotic therapy are described in the SmPC section 5.1.

Nerandomilast as add-on therapy to nintedanib

The treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed a reduction of 93.1 mL and 78 mL respectively. Of note, in the placebo treatment group, patients on background nintedanib therapy had a worse absolute mean change in FVC at week 52 when compared to placebo patients not taking anti-fibrotic treatment.

Although nerandomilast efficacy on the key secondary endpoint (patients with events %) appeared to be numerically larger in patients without background nintedanib therapy than in those with background nintedanib therapy (especially for 9mg dose), there is no evidence of differential effects between the subgroups for either dose vs. placebo.

In relation to time to first acute ILD exacerbation or death, the treatment effect of nerandomilast (9 and 18 mg bid) as add-on therapy compared to placebo showed hazard ratios of 0.80 and 0.58, respectively. For the estimated cumulative incidence rates of first hospitalization for respiratory cause or death at week 52, nerandomilast (9 and 18 mg bid) compared to placebo showed differences of 2.66 and 0.41 respectively. Regarding death, the treatment effect of nerandomilast (9 and 18 mg bid) as add-on therapy compared to placebo showed hazard ratios of 0.55 and 0.57, respectively.

In conclusion, treatment with nerandomilast as add-on therapy to nintedanib is considered as justified. However, as suggested by the high discontinuation rate (22.5% for 9 mg dose and 33% for 18 mg dose) some patients may be unable to tolerate this combined treatment.

In contrast to the IPF population, the stratified subgroup according to background AF therapy showed generally comparable outcomes compared with the general population. However, for consistency with the IPF study, the results of the stratified subgroups (background AF therapy, HRCT UIP-UIP) have also been included in SmPC section 5.1.

In addition, the subgroup with iNSIP showed similarities with the IPF pirfenidone-nerandomilast 18 mg group, i.e. no improvement in the number of mortality events, although an improvement was observed for the primary efficacy variable (FVC). Like the pirfenidone subgroup in IPF, no clear rationale could be found while the number of events were limited.

5.3.8.3. Conclusions on the clinical efficacy

Idiopathic Pulmonary Fibrosis (IPF) indication

Treatment with nerandomilast 9 mg and 18 mg bid resulted in a statistically significant decrease in the rate of FVC decline compared to placebo. The observed reductions in the rate of decline relative to placebo could be both statistically and clinically significant.

At the primary analysis (DB1), a numerical reduction in mortality was observed with nerandomilast 18 mg twice daily versus placebo; however, no numerical improvement was observed for acute IPF exacerbations or respiratory-related hospitalisations, and no numerical benefit was seen with the 9 mg twice-daily dose across any component.

In contrast, at the final analysis (DBL2), numerical improvements were observed for both nerandomilast doses compared with placebo across the composite components, indicating a more consistent treatment effect at later follow-up. At DBL2, the differential trends between the two strata with or without background IPF treatment observed at DBL1 were still observed, although to a lesser extent and the HRs at DBL2 were generally lower than at DBL1. Although the outcomes for

pulmonary exacerbations and hospitalisations due to respiratory causes were inconsistent, the overall evidence, driven primarily by the FVC and mortality data, and the absence of major additional safety concerns, supports acceptance of the nerandomilast monotherapy indication and its use in combination with nintedanib or pirfenidone (for pirfenidone 18 mg only).

Progressive Pulmonary Fibrosis indication

Treatment with Nerandomilast 9 mg and 18 mg bid resulted in a statistically significant decrease in the rate of FVC decline compared to placebo. The observed reductions in the rate of decline relative to placebo could be considered as not only statistically significant but also clinically relevant. While the observed reduced decline in FVC was not supported with statistically significant differences in (key) secondary outcomes for PPF patients either, a consistent numerical improvement in mortality was observed in favour of nerandomilast across dosing groups and subgroups by background nintedanib treatment.

5.4. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety data is derived from two Phase 3 pivotal studies (1305-0014 and 1305-0023), an ongoing Phase 3 open-label extension study (1305-0031), one Phase 2 study (1305-0013), and one Phase 1c study (1305-0012). Safety data in patients with IPF and PPF are presented separately, as well as pooled.

IPF: Overall, 1177 IPF patients were treated in a Phase 3 study (1305-0014), of whom 393 received placebo, 392 received nerandomilast 9 mg bid, and 392 received nerandomilast 18 mg bid. Additionally, 147 IPF patients were treated in the Phase 2 study (1305-0013), of whom 50 received placebo and 97 received nerandomilast 18 mg bid.

PPF: A total of 1176 PPF patients were treated in a Phase 3 study (1305-0023), of whom 392 received placebo, 393 received nerandomilast 9 mg bid, and 391 received nerandomilast 18 mg bid.

Safety data up to DBL1 (Week 52; main analysis) and DBL2 (final analysis) is available for both studies 1305-0014 and 1305-0023. Pooled safety analyses are summarised based on whole trial data of both pivotal studies up to DBL2.

Pooled safety analysis methods

In addition to the safety analyses in the individual clinical trials, the data of both IPF and PPF pivotal clinical trials were pooled to have a larger sample size for the evaluation of events, especially infrequent events. Safety analyses were conducted on pooled trial data as follows:

Table *73*: Groupings of trials for clinical

Grouping	Trials	Description
SAF1	1305-0014, 1305-0023	Randomised, placebo-controlled, double-blind, long-term (≥52 weeks) pivotal trials in patients with IPF or PPF
SAF1c	1305-0014, 1305-0023	Randomised, placebo-controlled, double-blind, long-term (≥52 weeks) pivotal trials in patients with IPF or PPF – excluding patients with pirfenidone background treatment
SAF2	1305-0012, 1305-0013, 1305-0014[1], 1305-0023[1]	All randomised, placebo-controlled, double-blind trials in patients with IPF or PPF
SAF2-IPF	1305-0012, 1305-0013, 1305-0014[1]	Randomised, placebo-controlled, double-blind trials in patients with IPF
SAF3	All completed trials[2]	All trials with a DBL (or data snapshot) before or at project cut-off date for the evaluation of exposure and potential DILI
SAF3-CT	All controlled trials[3]	All controlled trials with a DBL before or at project cut-off date for the evaluation of exposure and potential DILI

1 For SAF2 and SAF2-IPF, the 9 mg nerandomilast bid treatment group of trials 1305-0014 and 1305-0023 is not included in the pooling (as this dose was not investigated in trials 1305-0012 and 1305-0013).

2 All trials in Table 1: 1; for trial 1305-0031, a data snapshot (but no DBL) had occurred before the project cut-off date

3 Including trials 1305-0001, 1305-0002, 1305-0011, 1305-0012, 1305-0013, 1305-0014, 1305-0017, 1306-0033, 1305-0034, and 1306-0038

After observing that nerandomilast plasma trough exposure in patients with pirfenidone background therapy was decreased by approximately 50% based on the DBL1 results of trial 1305-0014, an additional safety grouping (SAF1b) was defined in the ISS/SCS statistical analysis plan (SAP), pooling all patients from the 2 pivotal trials to match the exposure of 9 mg bid nerandomilast (i.e. 9 mg bid nerandomilast for patients with nintedanib or no background IPF treatment and 18 mg bid nerandomilast for patients with pirfenidone background treatment).

To support the recommended dosage for patients with IPF and PPF based on all data from trials 1305-0014 (DBL2; final analysis) and 1305-0023 (DBL1, main analysis); it was decided to replace SAF1b with a new safety grouping SAF1c (specified outside of the ISS/SCS SAP as CSAP analysis), which pools all patients from the 2 pivotal trials by randomised treatment excluding patients on background pirfenidone treatment at baseline. The pooling SAF1b was not carried out as it does not represent the recommended dosage.

Safety analyses

All safety analyses were exploratory, and the analysis methods at trial level and at pooled level were consistent. The types of safety analyses carried out for the pivotal trials and for the safety groupings are summarised in the Table below.

Table *74*: Safety analyses conducted at pivotal trial level and at pooled level (safety groupings)

Type of analysis	Trials 1305-0014/ 1305-0023[1]	SAF1[1]	SAF1c	SAF2 SAF2-IPF	SAF3/ SAF3-CT
Patient disposition and exposure	Yes	Yes	Yes	Yes	Limited[3]
Subgroups[2]	Yes	Yes	n.a	n.a	n.a.
Demographic and baseline data	Yes	Yes	Yes	Yes	n.a.
Subgroups[2]	Yes	Yes	n.a	n.a	n.a.
Treatment exposure	Yes	Yes	Yes	Yes	Yes
Subgroups[2]	Yes	Yes	n.a	n.a	n.a.
AEs (standard AE analyses and special safety topics)	Yes	Yes	Yes	Yes	Limited[3]
Subgroups[2]	Yes	Yes	n.a	n.a	n.a.
Safety laboratory parameters	Yes	Yes	n.a.	n.a.	Limited[3]
Vital signs and other safety observations	Yes	Yes	n.a.	n.a.	n.a.

n.a.: not analysed

1 Analyses over the whole trial and up to Week 52

2 Please refer to the Summary of Clinical Efficacy (SCE) for a description of subgroups

3 Limited to exposure, liver-related AEs, and hepatic enzyme/bilirubin values

Five AEs of special interest (AESIs) were predefined and specific analyses were performed for a number of other safety topics of interest (see Section 6.4.4 AESIs).

5.4.2. Patient exposure

Analyses including 1305-0014 DBL2 and 1305-0023 DBL1 data

1872 patients received nerandomilast in controlled trials (SAF3-CT), either as a single dose (0.02 mg to 48 mg) or twice daily with doses up to 18 mg. The total number of treated subjects in SAF3 included 276 patients on placebo and 285 patients on 9 mg bid nerandomilast in trial 1305-0014 who rolled over to 18 mg bid nerandomilast in trial 1305-0031. Among the 2738 patients in SAF3 that were treated for varying durations, the total exposure was 2148.3 patient-years. The total exposure of the 1872 patients included in SAF-CT across all doses was 1930.3 patient-years.

As of Jun 2025, the main analysis of trial 1305-0014 (in patients with IPF; DBL1: 03 Sep 2024) and the final analysis of trial 1305-0014 (DBL2: 03 Feb 2025) have been completed and the results of both DBLs are summarised in this overview. In addition, the main analysis of trial 1305-0023 (in patients with PPF, DBL1: 24 Jan 2025) has also been completed and the results of DLB1 are summarised in this section of the overview.

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 data

In addition, the final analysis of trial 1305-0023 (DBL2: 28 Apr 2025) have also been completed and the results of both DBLs for both trials are summarised in this section of the overview.

An overview of patients included in each of the safety groupings is provided in **Table** 75. SAF3 included 926 placebo-treated participants and 3,226 participants treated with nerandomilast, pooled from trials with database lock or data snapshots available at the project cut-off (02 May 2025).

Table *75*: Overview of groupings of trials up to trial 1305-0023 DBL2 and trial 1305-0014 DBL2

Grouping/ Trial or Grouping	Treated subjects Placebo	Treated subjects Nerandomilast
SAF1 total	785	1568
1305-0014	393	784
1305-0023	392	784
SAF1c total	651	1320
1305-0014	260	537
1305-0023	391	783
SAF2 total[1]	840	890
SAF2-IPF total[1]	448	499
1305-0012	5	10
1305-0013	50	97
1305-0014	393	392
1305-0023	392	391
SAF3 total[2]	926	3226
SAF3-CT total[3]	926	1872

1 For SAF2 and SAF2-IPF, the 9 mg nerandomilast bid treatment group of trials 1305-0014 and 1305-0023 is not included in the pooling (as this dose was not investigated in trials 1305-0012 and 1305-0013).

2 All nerandomilast clinical trials with a DBL or data snapshot before or on the project data cut-off date were pooled into SAF3 (see Table 1: 1 and Table 1: 2).

3 All controlled nerandomilast clinical trials with a DBL before or on the project data cut-off date were pooled into SAF3-CT (see Table 1: 1 and Table 1: 2).

Table *76*: Overview of clinical trials comprising patients with IPF, PPF, and healthy subjects exposed to nerandomilast

Study No.(s)	Healthy subjects or diagnosis	Patients N	Duration	Trial description	Doses studied	Trial status/ Data cutoff
1305-0001	Healthy male subjects	70	Single dose	**Phase 1**: Randomised, single-blind, placebo-controlled trial	Placebo; nerandomilast (n=54): 0.02, 0.06, 0.2, 0.6, 2, 4, 8, 16 and 24 mg single dose	Completed
1305-0002	Healthy male subjects	24	14 days	**Phase 1**: Randomised, double-blind, placebo-controlled trial	Placebo; nerandomilast (n=18): 1 mg and 6 mg bid	Completed
1305-0011	Healthy male subjects	42	Single dose (SRD part) and 14 days (MRD part)	**Phase 1**: Randomised, single-blind (SRD part) and double-blind (MRD part), placebo-controlled trial	Placebo; nerandomilast (n=28): 36 mg and 48 mg single dose (SRD part), and 6 mg and 12 mg bid (MRD part)	Completed
1305-0015	Healthy male subjects	16	Single dose	**Phase 1**: Non-randomised, fixed-sequence, open label trial	Nerandomilast: 6 mg single dose	Completed
1305-0016	Healthy male subjects	6	Single dose	**Phase 1**: Non-randomised, open-label, uncontrolled trial	Nerandomilast: 18 mg single dose	Completed
1305-0017	Healthy male Japanese subjects	16	Single dose	**Phase 1**: Randomised, double-blind, placebo-controlled trial (within each dose group)	Placebo; nerandomilast (n=12): 12 mg and 24 mg single dose	Completed
1305-0020	Healthy male subjects	12	Single dose	**Phase 1**: Randomised, open-label, 2-way cross-over trial	Nerandomilast: 24 mg single dose	Completed
1305-0024	Healthy male or female Chinese subjects	24	Single dose	**Phase 1**: Non-randomised, open-label, uncontrolled trial	Nerandomilast: 9 mg and 18 mg single dose	Completed

1305-0025	Healthy male and female subjects with or without renal impairment	26 (10 with no renal impairment)	Single dose	**Phase 1**: Non-randomised, open-label, individual-matched trial	Nerandomilast: 18 mg single dose	Completed
1305-0026	Healthy male and female subjects	46	Single dose	**Phase 1**: Randomised, double-blind, placebo-controlled, 5-way cross-over trial	Nerandomilast: 30 mg and 48 mg single dose	Completed
1305-0027	Healthy male and female subjects with or without hepatic impairment	28 (12 with no hepatic impairment)	Single dose	**Phase 1**: Non-randomised, open-label, individual-matched trial	Nerandomilast: 18 mg single dose	Completed
1305-0028	Healthy male and female subjects	24	Single dose	**Phase 1**: Randomised, open-label, 3-way cross-over trial	Nerandomilast: 18 mg single dose	Completed
1305-0029	TBD	15	TBD	**TBD**	TBD	TBD
1305-0030	Healthy male subjects	8	Single dose	**Phase 1**: Fixed-sequence, open label trial	Nerandomilast: 18 mg single dose	Completed
1305-0033	Healthy male subjects	15	14 days	**Phase 1**: Fixed-sequence, open label trial	Nerandomilast: 18 mg bid for 13 days and qd on the last day	Completed
1305-0034	Healthy male subjects	14	10 days	**Phase 1**: Fixed-sequence, open label trial	Nerandomilast: 18 mg bid	Completed
1305-0037	Healthy male and female subjects	64	Single dose	**Phase 1**: Randomised, open-label, 2-way cross-over trial	Nerandomilast: 18 mg single dose (formulation C2)	Completed
1305-0038	Healthy male Japanese subjects	12	Single dose	**Phase 1**: Non-randomised, open-label, uncontrolled trial	Nerandomilast: 9 mg and 18 mg single dose	Completed
1305-0039	Healthy male and female subjects	18	Single dose	**Phase 1**: Randomised, open-label, 2-way cross-over trial	Nerandomilast: 18 mg single dose (formulation C2)	Completed
1305-0051	Healthy male and female subjects	64	Single dose	**Phase 1**: Randomised, open-label, 2-way cross-over trial	Nerandomilast: 9 mg single dose (formulation C2)	Completed
Total healthy male and female subjects:		**542**			**Total healthy male and female subjects receiving nerandomilast: 502**	
1305-0012	IPF	15	Up to 12 weeks	**Phase 1**: Randomised, double-blind, placebo-controlled trial	Placebo; nerandomilast (n=10): 18 mg bid	Completed
1305-0013	IPF	147	12 weeks	**Phase 2**: Randomised, double-blind, placebo-controlled trial	Placebo; nerandomilast (n=97): 18 mg bid	Completed
1305-0014	IPF	1177	At least 52 weeks	**Phase 3**: Randomised, double-blind, placebo-controlled trial	Placebo; nerandomilast (n=784): 9 mg and 18 mg bid	Completed
1305-0031	IPF	843	Up to 7 months	**Phase 3:** OLE trial rolled over from trial 1305-0014	Nerandomilast: 18 mg bid	Ongoing
Total subjects with IPF:		**2182 (1339 excluding rollover)**			**Total subjects with IPF receiving nerandomilast: 1734 (1167 excluding duplicate subjects who rolled-over from a nerandomilast treatment group in 1305-0014 to the OLE)**	

1305-0023	PPF	1176	At least 52 weeks	**Phase 3**: Randomised, double-blind, placebo-controlled trial	Placebo; nerandomilast (n=784): 9mg and 18 mg bid	DBL1 (main analysis) Completed
1305-0031	PPF	792	Up to 7 months	**Phase 3:** OLE trial rolled over from trial 1305-0023	Nerandomilast: 18 mg bid	Ongoing
Total subjects with PPF:		**1176**			**Total subjects with PPF receiving nerandomilast: 784**	

Table *77*: Patient exposure (cut off)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range		Patients with long term** safety data
			9 mg bid	18 mg bid	
1305-0012 (placebo-controlled; up to 12 weeks)	15	10	0	10	0
1305-0013 (placebo-controlled; 12 weeks)	147	97	0	97	0
1305-0014 (placebo-controlled; at least 52 weeks)	1177	784	392	392	634
1305-0023 (placebo-controlled; at least 52 weeks)	1178	784	393	391	625
1305-0031 (OLE up to 7 months)***	1635	1635	1635		No data available

* Received at least 1 dose of active treatment
** refers to 12 months continuous exposure data, or intermittent exposure.
*** Patients in 1305-0031 rolled over from the parent trials 1305-0014 and 1305-0023. Therefore, patients on nerandomilast in the parent trials (563 patients in 1305-0014 and 534 patients in 1305-0023) continued to be exposed to nerandomilast in this trial. Patients on placebo in the parent trials (280 patients in 1305-0014 and 258 patients in 1305-0023) were newly exposed to nerandomilast in 1305-0031.

Disposition and overall exposure

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data (SAF1/SAF1c)

Approximately 80% of patients were exposed to study medication for at least 52 weeks (12 months) across all treatment groups. Mean exposure to trial medication was and 15 months (SD: 5 months) for all treatment groups, with more than 70% of patients treated for at least 15 months. Mean observation time was about 17 months (SD: approximately 4 months) for all treatment groups. Disposition and exposure of SAF1c were generally similar to those described for SAF1.

Table *78*: Exposure to study medication over the whole trial – TS–SAF1

	Placebo		Nera 9mg bid		Nera 18mg bid		Nera total	
Number of patients (N, %)	785	100.0	785	100.0	783	100.0	1568	100.0
Duration of exposure [months]								
N	785		785		783		1568	
Mean	15.01		15.04		14.80		14.92	
SD	5.27		5.38		5.59		5.49	
Min	0.0		0.1		0.1		0.1	
Q1	14.5		14.7		14.7		14.7	
Median	16.5		16.5		16.5		16.5	
Q3	17.9		17.9		17.9		17.9	
Max	26.2		25.0		25.4		25.4	
Duration of exposure in categories (N, %)								
>=0 months (1 day)	785	100.0	785	100.0	783	100.0	1568	100.0
>=3 months (91 days)	742	94.5	731	93.1	721	92.1	1452	92.6
>=6 months (182 days)	707	90.1	700	89.2	687	87.7	1387	88.5
>=12 months (365 days)	630	80.3	636	81.0	623	79.6	1259	80.3
>=15 months (456 days)	552	70.3	567	72.2	552	70.5	1119	71.4
>=18 months (546 days)	200	25.5	204	26.0	202	25.8	406	25.9
Duration of exposure [years]								
Sum (Patient-years) [1]	983.96		985.91		967.52		1953.43	

[1] The sum of duration of exposure [patient-years] is defined as the sum of duration of exposure of all patients [days]/365.25.
Containing data from trials: 1305-0014 and 1305-0023

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Disposition

For the pooled set SAF1, 1904 patients (80.9%) completed planned treatment up to Week 52 and 2147 patients (91.2%) completed planned observation for the primary endpoint assessment. A total of 1715 patients (72.9%) completed the planned treatment period over the whole trial and 638 (27.1%) discontinued trial medication. The most common reason for premature discontinuation of study medication was an AE (13.3%), followed by withdrawal by patient (6.8%) and "other" (6.5%). A total of 1976 patients (83.6%) completed the planned observation over the whole trial, 45 (1.9%) had lung transplant, and 238 (10.1%) died.

Table *79*: Disposition of patients by treatment – Entered Set – SAF1

	Placebo		Nera 9mg bid		Nera 18mg bid		Total	
	N	%	N	%	N	%	N	%
Entered							3500	
Not randomised							1145	
Randomised	786		785		784		2355	
Not treated	1		0		1		2	
Treated	785	100.0	785	100.0	783	100.0	2353	100.0
Completed planned 52 weeks treatment period [1]	637	81.1	640	81.5	627	80.1	1904	80.9
Prematurely discontinued from trial medication before Week 52	148	18.9	145	18.5	156	19.9	449	19.1
Study terminated by sponsor	0	0.0	0	0.0	0	0.0	0	0.0
Site terminated by sponsor	0	0.0	0	0.0	0	0.0	0	0.0
Lack of efficacy	1	0.1	0	0.0	0	0.0	1	0.0
Adverse event	77	9.8	78	9.9	87	11.1	242	10.3
Protocol deviation	1	0.1	0	0.0	1	0.1	2	0.1
Withdrawal by subject [4]	37	4.7	40	5.1	39	5.0	116	4.9
Lost to follow-up	1	0.1	0	0.0	1	0.1	2	0.1
Other	31	3.9	27	3.4	28	3.6	86	3.7
Completed planned treatment period over the whole trial [2]	563	71.7	581	74.0	571	72.9	1715	72.9
Prematurely discontinued from trial medication over the whole trial	222	28.3	204	26.0	212	27.1	638	27.1
Study terminated by sponsor	0	0.0	0	0.0	0	0.0	0	0.0
Site terminated by sponsor	0	0.0	0	0.0	0	0.0	0	0.0
Lack of efficacy	3	0.4	1	0.1	1	0.1	5	0.2
Adverse event	101	12.9	101	12.9	112	14.3	314	13.3
Protocol deviation	1	0.1	1	0.1	1	0.1	3	0.1
Withdrawal by subject[4]	53	6.8	52	6.6	54	6.9	159	6.8
Lost to follow-up	1	0.1	1	0.1	1	0.1	3	0.1
Other	63	8.0	48	6.1	43	5.5	154	6.5

	Placebo		Nera 9mg bid		Nera 18mg bid		Total	
	N	%	N	%	N	%	N	%
Completed planned 52 weeks observation or lung transplant or death [3]	720	91.7	716	91.2	711	90.8	2147	91.2
Completed planned 52 weeks observation [5]	651	82.9	664	84.6	666	85.1	1981	84.2
Lung transplant	12	1.5	7	0.9	12	1.5	31	1.3
Death	61	7.8	49	6.2	36	4.6	146	6.2
Not completed planned observation up to week 52 [3]	65	8.3	69	8.8	72	9.2	206	8.8
Completed planned observation over the whole trial or lung transplant or death	759	96.7	749	95.4	742	94.8	2250	95.6
Completed planned observation over the whole trial	634	80.8	667	85.0	666	85.1	1967	83.6
Lung transplant	19	2.4	10	1.3	16	2.0	45	1.9
Death	106	13.5	72	9.2	60	7.7	238	10.1
Not completed planned observation over the whole trial	26	3.3	36	4.6	41	5.2	103	4.4
Lost to follow-up	4	0.5	7	0.9	5	0.6	16	0.7
Withdrawal by subject	6	0.8	11	1.4	18	2.3	35	1.5
Other	9	1.1	11	1.4	11	1.4	31	1.3
Unknown [6]	7	0.9	7	0.9	7	0.9	21	0.9
Rolled over to study 1305-0031	543	69.2	558	71.1	546	69.7	1647	70.0

[1] Trial medication taken in or after planned time window for Week 52 visit (on or after Day 358)
[2] Based on End of Treatment CRF page
[3] Planned 52 weeks observation period is considered as having been completed if FVC assessment available at Week 52 visit (between Day 338 and Day 393 inclusive) or lung transplant or death occurred before Day 393
[4] 'Withdrawal by Subject' here means withdrawal of treatment by Subject
[5] Includes 6 patients who had Week 52 FVC measurement before lung transplant and 5 patients who had Week 52 FVC measurement before death
[6] Last contact date when patients known to be alive (as defined in TSAP chapter 5) is before Feb.6, 2025 (1305-0023) and Sep.26, 2024 (1305-0014), though answered 'Yes' to the question,'Did the subject complete the planned observation period?' on EOS page but with no data source supportive of this completion of observation.
Patients are displayed based on randomized treatment assignment
Containing data from trials: 1305-0014 and 1305-0023

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Table *80*: Summary of treatment interruptions and premature treatment discontinuations – Treated Set−SAF1

	Placebo		Nera 9mg bid		Nera 18mg bid		Nera Total	
Number of patients (N, %)	785	100.0	785	100.0	783	100.0	1568	100.0
Number of patients with at least one interruption (N, %)	172	21.9	199	25.4	214	27.3	413	26.3
Number of interruptions per patient in categories (N, %)								
0	613	78.1	586	74.6	569	72.7	1155	73.7
1	131	16.7	142	18.1	158	20.2	300	19.1
2	30	3.8	40	5.1	35	4.5	75	4.8
>2	11	1.4	17	2.2	21	2.7	38	2.4
Total number of interruptions	226		282		315		597	
Duration of interruptions (days)								
N	172		199		214		413	
Mean	32.03		37.42		27.25		32.15	
SD	49.44		66.11		46.65		57.02	
Min	1.0		1.0		1.0		1.0	
Q1	6.0		7.0		6.0		7.0	
Median	13.0		15.0		12.0		13.0	
Q3	35.0		40.0		30.0		34.0	
Max	278.0		523.0		370.0		523.0	
Reasons for interruption [1] (N, %)								
Related AE [2]	101	44.7	108	38.3	118	37.5	226	37.9
Unrelated AE [2]	46	20.4	62	22.0	61	19.4	123	20.6
Other	47	20.8	49	17.4	59	18.7	108	18.1
Number of patients with premature treatment discontinuation (N, %)	222	28.3	204	26.0	212	27.1	416	26.5
Time to premature treatment discontinuation (days)								
N	222		204		212		416	
Mean	257.38		238.05		222.59		230.18	
SD	156.19		161.31		156.96		159.10	
Min	1.0		4.0		4.0		4.0	
Q1	121.0		81.5		79.0		79.5	
Median	246.5		233.0		208.5		220.0	
Q3	386.0		373.0		364.0		367.0	
Max	621.0		592.0		612.0		612.0	

[1] A patient may have more than one reason of interruption. Percentage is based on the total number of interruptions.
[2] Based on the information for the field of 'Realtionship to Study Treatment' on AE CRF page.
Containing data from trials: 1305-0014 and 1305-0023

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Patient baseline characteristics

For the pooled set SAF1, the majority of patients were male (69.3%; female: 30.7%). Almost all patients were either White (63.0%) or Asian (34.6%) and twenty-two patients were Black or African American (0.9%). Hispanic or Latino ethnicity was reported by 11.2% of the patients. Most patients were elderly (mean age 68.3 years, SD 9.1, range: 26 to 90 years).

A total of 60.7% of the patients had been on background treatment with nintedanib (44.5%) or pirfenidone (16.2%) at baseline with a mean treatment duration of 25.6 months. Of the patients on nintedanib, 68.3% were taking 300 mg daily dose (or higher) when entering the trial. A total of 39.3% patients had neither nintedanib nor pirfenidone at baseline; among these patients, the majority of patients (75.0%) were naïve to nintedanib and pirfenidone.

The mean time since IPF/ILD diagnosis was 3.9 years (SD 3.6) before the trial, and about half of the patients (48.8%) had been diagnosed for more than 3 years.

The mean (SD) baseline FVC was 2598 (805) mL and 74.2 (17.1) % of predicted normal. The mean DLCO was 50.0 (16.6) % of predicted. These characteristics were balanced between the treatment groups. Demographics and baseline lung function of SAF1c were similar to those of SAF1.

Of the randomised and treated patients in the pivotal 1305-0014 (IPF) study, the majority of were male (83.0%) in accordance with gender differences seen in IPF population. Almost all patients were either White (67.7%) or Asian (31.6%). Six patients were Black or African American (0.5%) and two patients were of multiple race (0.2%). Most of the trial population were elderly (mean age 70.2 years, SD 7.7) which is consistent with IPF pathogenesis. A total of 915 patients (78%) were on background treatment with approved AFs at baseline.

Almost all patients (98.9%) had at least one concomitant diagnosis at baseline, with the three most frequent being hypertension (46.5%), gastro-oesophageal reflux disease (31.7%), and diarrhoea (19.5%) at PT level. The frequency of diarrhoea as a baseline condition was higher in patients receiving nintedanib (37.9%), than in patients receiving pirfenidone (6.3%) or no background AF therapy (1.1%). A total of 396 patients (33.6%) were receiving immunosuppressive medication at baseline. These patients were balanced across the treatment groups.

Of the randomised and treated patients in the pivotal 1305-0023 (PPF) study, more than half were male (55.6%). There was a slightly higher percentage of men in the placebo arm (58.9%) compared to the nerandomilast treatment groups (54.0%). Almost all patients were either White (58.2%) or Asian (39.1%). Sixteen patients were Black or African American (1.4%) and fifteen patients were of multiple race (1.3%). Most of the trial population were elderly (mean age 66.4 years, SD 10.0) which is consistent with the pathogenesis of PPF. A total of 514 patients (43.7%) were on background treatment with AFs at baseline, of which 512 (43.5%) were on background nintedanib therapy.

Almost all patients (98.0%) had at least one concomitant diagnosis at baseline, with the three most frequent being hypertension (42.1%), gastro-oesophageal reflux disease (28.1%), and hyperlipidaemia (14.9%) at PT level. The frequency of diarrhoea as a baseline condition was higher in patients receiving background nintedanib therapy (27.4%) than in patients with no background nintedanib therapy (2.3%) and the frequency of rheumatoid arthritis was lower in patients receiving background nintedanib therapy (7.4%) than in patients with no background nintedanib therapy (14.4%). A total of 283 patients (24.1%) used at least one immunosuppressive medication of interest at baseline. These patients were balanced across the treatment groups.

Table *81*: Baseline immunosuppressant use by CDG (frequency >1% in any treatment group) – FAS

CDG	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Preferred name	N	%	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0	1176	100.0
Patients with at least 1 baseline immunosuppressive medication of interest[1]	97	24.7	97	24.7	89	22.8	283	24.1
Azathioprine	32	8.2	35	8.9	19	4.9	86	7.3
Methotrexate	14	3.6	14	3.6	25	6.4	53	4.5
Hydroxychloroquine sulfate	20	5.1	13	3.3	10	2.6	43	3.7
Hydroxychloroquine	8	2.0	14	3.6	11	2.8	33	2.8
Tacrolimus	10	2.6	10	2.5	8	2.0	28	2.4
Ciclosporin	7	1.8	10	2.5	4	1.0	21	1.8
Leflunomide	7	1.8	6	1.5	8	2.0	21	1.8
Abatacept	1	0.3	4	1.0	7	1.8	12	1.0
Colchicine	4	1.0	2	0.5	0		6	0.5
Methotrexate sodium	1	0.3	1	0.3	4	1.0	6	0.5

1 Two patients with background pirfenidone therapy at baseline were categorised into the subgroup of patients with background nintedanib therapy in all subgroup analyses.

A total of ninety-seven patients (8.2%) were put on at least 1 immunosuppressive medication of interest during the on-treatment period up to DBL1. The use of immunosuppressants was lower in the 18 mg bid nerandomilast group (5.6%, vs. 9.2% in the placebo group and 9.9% in the 9 mg bid nerandomilast group). The three most frequent immunosuppressive medications were mycophenolate mofetil (1.6%), azathioprine (1.1%), and tacrolimus (1.0%) at preferred name level.

Table *82*: On-treatment immunosuppressant use by CDG (frequency >1% in any treatment group) – FAS

CDG	Placebo		Nera 9 mg bid		Nera 18 mg bid		Total	
Preferred name	N	%	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0	1176	100.0
Patients with at least 1 on-treatment immunosuppressive medication of interest[1]	36	9.2	39	9.9	22	5.6	97	8.2
Mycophenolate mofetil	8	2.0	8	2.0	3	0.8	19	1.6
Azathioprine	7	1.8	3	0.8	3	0.8	13	1.1
Tacrolimus	5	1.3	5	1.3	2	0.5	12	1.0
Methotrexate	4	1.0	3	0.8	2	0.5	9	0.8
Ciclosporin	2	0.5	4	1.0	2	0.5	8	0.7
Hydroxychloroquine sulfate	2	0.5	4	1.0	2	0.5	8	0.7

1 Includes 6 patients (0.5% overall) who used pirfenidone while on-treatment.

In relation to the OLE study trial 1305-0031, 1635 patients have been treated with 18 mg nerandomilast for a duration of up to about 7 months (based on database snapshot on 02 May 2025). Of these, forty-four patients reduced dose from 18 mg bid to 9 mg bid of nerandomilast during the trial due to a protocol amendment but are displayed in the 18 mg bid treatment group (corresponding to their assigned dose at baseline) for all related data presented in this document. All of these patients were rolled over from trials 1305-0014 and 1305-0023.

5.4.3. Adverse events

Overall summary of adverse events-Trials 1305-0014 and 1305-0023 pooled (SAF1/SAF1c)

Table *83*: Overall summary of adverse events – TS (SAF1/SAF1c)

	Overall population[1]						Non-pirfenidone population[2]					
	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
Category of AE	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Patients with any AE	761	96.9	746	95.3	747	95.4	631	96.9	632	95.0	623	95.1
Severe AEs[3]	295	37.6	278	35.4	278	35.5	248	38.1	231	34.7	238	36.3
Investigator-defined drug-related AEs	283	36.1	337	42.9	390	49.8	233	35.8	295	44.4	350	53.4
AELDs	100	12.7	100	12.7	111	14.2	84	12.9	90	13.5	97	14.8
AEs leading to temporary treatment interruption	140	17.8	159	20.3	169	21.6	115	17.7	139	20.9	151	23.1
Serious AEs	351	44.7	306	39.0	317	40.5	285	43.8	260	39.1	264	40.3
Resulted in death	64	8.2	40	5.1	23	2.9	54	8.3	33	5.0	19	2.9
Life threatening	34	4.3	41	5.2	36	4.6	32	4.9	34	5.1	30	4.6
Disability or permanent damage	2	0.3	3	0.4	5	0.6	2	0.3	3	0.5	2	0.3
Required or prolonged hospitalisation	261	33.3	227	28.9	257	32.8	217	33.3	193	29.0	218	33.3
Other medically important serious events	155	19.8	124	15.8	126	16.1	124	19.1	104	15.6	100	15.3

AELDs: adverse events leading to permanent treatment discontinuation

1 Data from all patients by randomised treatment

2 Data from patients not taking pirfenidone as background therapy by randomised treatment

3 CTCAE grade >2

Table *84*: Patients with AEs (frequency >5% in any treatment group in the overall population at the PT level) – TS (SAF1/SAF1c)

SOC / PT	Overall population[1]						Non-pirfenidone population[2]					
	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Patients with any AE	761	96.9	746	95.3	747	95.4	631	96.9	632	95.0	623	95.1
Infections and infestations	530	67.5	506	64.5	512	65.4	443	68.1	425	63.9	419	64.0
COVID-19	119	15.2	118	15.0	108	13.8	97	14.9	91	13.7	86	13.1
Upper respiratory tract infection	110	14.0	93	11.9	109	13.9	90	13.8	78	11.7	94	14.4
Nasopharyngitis	99	12.6	97	12.4	94	12.0	83	12.8	84	12.6	79	12.1
Pneumonia	73	9.3	76	9.7	82	10.5	59	9.1	64	9.6	67	10.2
Bronchitis	71	9.0	65	8.3	62	7.9	54	8.3	52	7.8	49	7.5
Respiratory tract infection	32	4.1	46	5.9	53	6.8	25	3.8	39	5.9	43	6.6
Urinary tract infection	46	5.9	38	4.8	35	4.5	42	6.5	34	5.1	30	4.6
Influenza	44	5.6	30	3.8	44	5.6	40	6.1	27	4.1	39	6.0
Gastrointestinal disorders	348	44.3	406	51.7	440	56.2	300	46.1	362	54.4	378	57.7
Diarrhoea	174	22.2	254	32.4	311	39.7	163	25.0	236	35.5	280	42.8
Nausea	56	7.1	71	9.0	81	10.3	46	7.1	61	9.2	69	10.5
Vomiting	45	5.7	42	5.4	49	6.3	41	6.3	39	5.9	47	7.2
Respiratory, thoracic, and mediastinal disorders	343	43.7	321	40.9	301	38.4	283	43.5	254	38.2	245	37.4
Cough	135	17.2	127	16.2	133	17.0	100	15.4	99	14.9	102	15.6
Dyspnoea	106	13.5	94	12.0	83	10.6	85	13.1	74	11.1	66	10.1
General disorders and administration site conditions	271	34.5	244	31.1	248	31.7	231	35.5	203	30.5	204	31.2
Condition aggravated	123	15.7	93	11.9	88	11.2	107	16.4	77	11.6	71	10.8
Fatigue	49	6.2	57	7.3	53	6.8	39	6.0	44	6.6	42	6.4
Musculoskeletal and connective tissue disorders	189	24.1	198	25.2	202	25.8	158	24.3	170	25.6	162	24.7
Arthralgia	45	5.7	53	6.8	47	6.0	39	6.0	47	7.1	40	6.1
Back pain	28	3.6	41	5.2	54	6.9	23	3.5	34	5.1	43	6.6
Investigations	172	21.9	203	25.9	208	26.6	145	22.3	167	25.1	185	28.2
Weight decreased	70	8.9	81	10.3	104	13.3	62	9.5	66	9.9	94	14.4
Psychiatric disorders	163	20.8	160	20.4	168	21.5	129	19.8	138	20.8	143	21.8
Depression	86	11.0	77	9.8	80	10.2	66	10.1	66	9.9	66	10.1
Anxiety	74	9.4	73	9.3	78	10.0	59	9.1	64	9.6	64	9.8
Nervous system disorders	150	19.1	156	19.9	168	21.5	120	18.4	132	19.9	136	20.8
Headache	51	6.5	43	5.5	60	7.7	43	6.6	36	5.4	47	7.2
Dizziness	35	4.5	44	5.6	36	4.6	30	4.6	35	5.3	32	4.9
Metabolism and nutrition disorders	137	17.5	139	17.7	130	16.6	106	16.3	120	18.1	104	15.9
Decreased appetite	59	7.5	65	8.3	76	9.7	41	6.3	52	7.8	58	8.9

1 Data from all patients by randomised treatment
2 Data from patients not taking pirfenidone as background therapy by randomised treatment

Adverse events by intensity

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

For pooled trials 1305-0014 and 1305-0023, similar trends for severe AEs were observed as described for trials 1305-0014 and 1305-0023.

Adverse events assessed as drug-related by the investigator

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

For pooled trials 1305-0014 and 1305-0023, similar trends for investigator-defined drug-related AEs were observed as described for trials 1305-0014 and 1305-0023.

Table *85*: Overall summary of AEs over the whole trial up to DBL2-TS (trial 1305-0014)

	Placebo			Nerandomilast 9 mg bid			Nerandomilast 18 mg bid		
	N	**%**	**Rate/100PY**	**N**	**%**	**Rate/100PY**	**N**	**%**	**Rate/100PY**
Patients	393	100		392	100		392	100	
Patients with any AE	386	98.2	389.9	371	94.6	373.2	379	96.7	475.9
Severe AEs	135	34.4	31.9	132	33.7	30.7	126	32.1	31.4
Investigator-defined drug-related AEs	150	38.2	42.9	179	45.7	58.6	208	53.1	75.2
AEs leading to permanent discontinuation	51	13.0	10.6	53	13.5	10.9	63	16.1	13.2
AEs leading to temporary treatment interruption	68	17.3	15.5	83	21.2	19.5	88	22.5	21.1
Serious AEs	167	42.5	41.3	149	38.0	35.9	149	38.0	38.1
Resulted in death	26	6.6	5.4	21	5.4	4.3	11	2.8	2.3
Life-threatening	13	3.3	2.7	19	4.9	3.9	17	4.3	3.6
Disability or permanent damage	0	0	0	1	0.3	0.2	4	1.0	0.8
Requiring or Prolonged hospitalisation	117	29.8	27.6	104	26.5	23.9	113	28.8	27.2
Congenital anomaly or birth defect	0	0	0	0	0	0	0	0	0
Other medically important serious events	80	20.4	17.5	65	16.6	14.2	67	17.1	15.1

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 patient-years (PY).

Most frequently reported AEs (IPF)

Table *86*: Patients with AEs (frequency >5% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0014)

System organ class	Placebo			Nerandomilast 9 mg bid			Nerandomilast 18 mg bid		
Preferred term	N	%	Rate/100PY	N	%	Rate/100PY	N	%	Rate/100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with any AE	386	98.2	389.9	371	94.6	373.2	379	96.7	475.9
Infections and infestations	254	64.6	90.3	254	64.8	89.4	250	63.8	90.9
COVID-19	57	14.5	12.8	73	18.6	16.8	57	14.5	13.2
Upper respiratory tract infection	44	11.2	9.7	46	11.7	10.1	56	14.3	12.8
Nasopharyngitis	50	12.7	11.2	44	11.2	9.8	45	11.5	10.0
Bronchitis	39	9.9	8.5	31	7.9	6.6	35	8.9	7.7
Pneumonia	32	8.1	6.8	33	8.4	7.0	31	7.9	6.7
Respiratory tract infection	13	3.3	2.7	15	3.8	3.1	24	6.1	5.2
Urinary tract infection	20	5.1	4.2	12	3.1	2.5	13	3.3	2.8
Gastrointestinal disorders	164	41.7	49.2	209	53.3	73.6	231	58.9	90.2
Diarrhoea	72	18.3	17.3	126	32.1	34.7	166	42.4	52.7
Nausea	28	7.1	6.1	36	9.2	7.9	34	8.7	7.4
Vomiting	19	4.8	4.1	20	5.1	4.2	22	5.6	4.8
Constipation	20	5.1	4.2	7	1.8	1.4	13	3.3	2.7
Respiratory, thoracic, and mediastinal disorders	179	45.6	49.8	172	43.9	47.7	148	37.8	42.1
Cough	74	18.8	17.5	72	18.4	16.8	68	17.4	16.2
Dyspnoea	63	16.0	14.1	51	13.0	11.2	42	10.7	9.4
General disorders and administration site conditions	119	30.3	28.8	110	28.1	27.6	122	31.1	30.9
Condition aggravated	52	13.2	11.2	39	10.0	8.3	45	11.5	9.9
Fatigue	23	5.9	4.9	32	8.2	7.0	30	7.7	6.6
Investigations	82	20.9	19.3	102	26.0	24.4	99	25.3	24.8
Weight decreased	38	9.7	8.3	43	11.0	9.3	48	12.2	10.8
Musculoskeletal and connective tissue disorders	87	22.1	21.0	94	24.0	22.9	98	25.0	24.4
Back pain	16	4.1	3.4	24	6.1	5.1	28	7.1	6.1
Arthralgia	25	6.4	5.4	23	5.9	4.9	15	3.8	3.2
Nervous system disorders	85	21.6	20.5	82	20.9	19.5	83	21.2	20.1
Headache	23	5.9	4.9	25	6.4	5.4	28	7.1	6.2
Dizziness	22	5.6	4.7	27	6.9	5.8	19	4.9	4.1
Psychiatric disorders	75	19.1	17.1	69	17.6	15.6	77	19.6	18.1
Depression	36	9.2	7.8	36	9.2	7.7	36	9.2	7.9
Anxiety	32	8.1	6.9	31	7.9	6.6	33	8.4	7.2
Metabolism and nutrition disorders	66	16.8	14.9	69	17.6	15.6	64	16.3	14.8
Decreased appetite	27	6.9	5.8	38	9.7	8.2	40	10.2	8.9

PY: patient-years. Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

AEs by intensity (IPF)

Table *87*: Patients with severe AEs (CTCAE grade of at least 3, frequency ≥1% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0014)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with at least 1 severe AE	135	34.4	31.9	132	33.7	3.7	126	32.1	31.4
Infections and infestations	42	10.7	9.0	37	9.4	7.8	34	8.7	7.4
Pneumonia	19	4.8	4.0	14	3.6	2.9	14	3.3	2.8
COVID19	3	0.8	0.6	6	1.5	1.2	2	0.5	0.4
Pneumonia bacterial	2	0.5	0.4	6	1.5	1.2	1	0.3	0.2
Influenza	4	1.0	0.8	2	0.5	0.4	1	0.3	0.2
Respiratory, thoracic and mediastinal disorders	43	10.9	9.1	35	8.9	7.3	26	6.6	5.5
Dyspnoea	11	2.8	2.3	10	2.6	2.1	6	1.5	1.3
Idiopathic pulmonary fibrosis	6	1.5	1.2	10	2.6	2.1	5	1.3	1.0
Pulmonary embolism	6	1.5	1.2	3	0.8	0.6	4	1.0	0.8
Pulmonary hypertension	5	1.3	1.0	2	0.5	0.4	5	1.3	1.0
Acute respiratory failure	2	0.5	0.4	4	1.0	0.8	3	0.8	0.6
Pneumothorax	1	0.3	0.2	2	0.5	0.4	5	1.3	1.0
Respiratory failure	4	1.0	0.8	3	0.8	0.6	1	0.3	0.2
General disorders and administration site conditions	39	9.9	8.2	30	7.7	6.3	33	8.4	7.1
Condition aggravated	31	7.9	6.5	25	6.4	5.2	28	7.1	6.0
Gastrointestinal disorders	9	2.3	1.9	19	4.9	4.0	22	5.6	4.7
Diarrhoea	2	0.5	0.4	5[1]	1.3	1.0	10[2]	2.6	2.1

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

1 Since DBL1, 1 occurrence of diarrhoea, which had been considered severe and serious at DBL1, was reclassified by the investigator post-DBL1 to mild and non-serious AE

2 Since DBL1, the number of reported severe AEs of diarrhoea decreased; 1 occurrence of diarrhoea, which was considered severe (CTCAE 3) at DBL1, was reclassified (CTCAE 1) by the investigator post-DBL1.

AEs assessed as drug-related by the investigator (IPF)

Table *88*: Patients with drug-related AEs as assessed by the investigators (frequency ⩾1% in any treatment group at the PT level) over the whole trial up to DBL1 – TS (trial 1305-0014)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with at least 1 drug-related AE	142	36.1	44.6	181	46.2	66.0	199	50.8	78.1
Gastrointestinal disorders	70	17.8	18.9	129	32.9	40.9	156	39.8	53.8
Diarrhoea	39	9.9	9.8	88	22.5	24.6	134	34.2	43.2
Nausea	18	4.6	4.3	22	5.6	5.2	19	4.9	4.5
Vomiting	7	1.8	1.6	10	2.6	2.3	10	2.6	2.3
Flatulence	8	2.0	1.9	8	2.0	1.9	7	1.8	1.6
Frequent bowel movements	3	0.8	0.7	7	1.8	1.6	9	2.3	2.1
Abdominal pain	6	1.5	1.4	6	1.3	1.2	7	1.8	1.6
Abdominal discomfort	3	0.8	0.7	5	1.0	0.9	4	1.0	0.9
Abdominal pain upper	0	0	0	7	1.8	1.6	3	0.8	0.7
Dyspepsia	1	0.3	0.2	5	1.3	1.2	3	0.8	0.7
Gastroesophageal reflux disease	3	0.8	0.7	5	1.3	0.9	0	0	0
Investigations	28	7.1	6.7	32	8.2	1.6	41	10.5	10.3
Weight decreased	16	4.1	2.8	18	4.6	1.2	25	6.4	6.1
Lipase increased	1	0.3	0.2	4	1.0	1.2	3	0.8	0.7
Amylase increased	0	0	0	4	1.0	7.7	3	0.8	0.7
Aspartate aminotransferase increased	1	0.3	0.2	1	0.3	4.2	5	1.3	1.2
Metabolism and nutrition disorders	11	2.8	2.6	25	6.4	0.9	21	5.4	5.0
Decreased appetite	10	2.5	2.3	22	5.6	0.9	19	4.9	4.5
General disorders and administration site conditions	16	4.1	3.8	20	5.1	0.2	15	3.8	3.5
Fatigue	9	2.3	2.1	13	3.3	5.9	7	1.8	1.6
Asthenia	0	0	0	5	1.3	5.2	6	1.5	1.4
Nervous system disorders	12	3.1	2.8	19	4.9	4.8	18	4.6	4.3
Headache	7	1.8	1.6	12	3.1	3.0	9	2.3	2.1
Dizziness	5	1.3	1.2	3	0.8	1.2	5	1.3	1.2
Psychiatric disorders	13	3.3	3.0	17	4.3	4.5	17	4.3	4.0
Anxiety	6	1.5	1.4	5	1.3	2.8	6	1.5	1.4
Depression	6	1.5	1.4	6	1.5	0.7	4	1.0	0.9
Skin and subcutaneous tissue disorders	13	3.3	3.0	14	3.6	4.0	13	3.3	3.1
Rash	3	0.8	0.7	4	1.0	1.2	1	0.3	0.2
Respiratory, thoracic and mediastinal disorders	11	2.8	2.6	13	3.3	1.4	11	2.8	2.6
Cough	4	1.0	0.9	5	1.3	3.3	7	1.8	1.6
Dyspnoea	5	1.3	1.2	1	0.3	0.9	2	0.5	0.5
Musculoskeletal and connective tissue disorders	6	1.5	1.4	6	1.5	1.4	7	1.8	1.6
Myalgia	4	1.0	0.9	2	0.5	0.5	0	0	0
Pain in extremity	0	0	0	0	0	0	4	1.0	0.9

Trends in investigator-defined drug-related AEs up to DBL2 were similar to those seen up to DBL1

AEs in patients with background AF therapy (IPF)

Table *89*: Overall summary of AEs over the whole trial up to DBL2 by background AF therapy TS (trial 1305-0014)

	Placebo			Nerandomilast 9 mg bid			Nerandomilast 18 mg bid		
	N	%	Rate/100PY	N	%	Rate/100PY	N	%	Rate/100PY
Without background AF therapy	87	100.0		88	100.0		87	100.0	
Patients with any AE	87	100.0	349.3	79	89.8	292.9	81	93.1	331.3
Severe AEs	35	40.2	37.1	27	30.7	27.8	20	23.0	20.3
Investigator-defined drug-related AEs	26	29.9	31.2	29	33.0	36.8	41	47.1	61.2
AELDs	11	12.6	10.4	9	10.2	8.4	8	9.2	7.1
AEs leading to treatment interruption	19	21.8	19.9	12	13.6	11.8	15	17.2	14.7
Serious AEs	41	47.1	45.3	31	35.2	32.5	28	32.2	29.6
Resulted in death	8	9.2	7.5	3	3.4	2.8	2	2.3	1.8
With nintedanib background therapy	173	100.0		184	100.0		178	100.0	
Patients with any AE	170	98.2	428.9	178	96.7	474.2	175	98.3	728.1
Severe AEs	53	30.6	28.0	58	31.5	29.3	67	37.6	42.2
Investigator-defined drug-related AEs	75	43.4	53.3	108	58.7	95.7	127	71.4	153.4
AELDs	24	13.9	11.2	34	18.5	15.4	41	23.0	20.8
AEs leading to treatment interruption	24	13.9	12.2	51	27.7	28.2	55	30.9	33.8
Serious AEs	61	35.3	32.6	72	39.1	38.7	69	38.8	42.9
Resulted in death	8	4.6	3.7	11	6.0	4.9	5	2.8	2.5
With pirfenidone background therapy	133	100.0		120	100.0		127	100.0	
Patients with any AE	129	97.0	374.4	114	95.0	326.7	123	96.9	394.8
Severe AEs	47	35.3	33.8	47	39.2	34.8	39	30.7	27.0
Investigator-defined drug-related AEs	49	36.8	39.0	42	35.0	37.0	40	31.5	31.6
AELDs	16	12.0	9.8	10	8.3	6.4	14	11.0	8.4
AEs leading to treatment interruption	25	18.8	17.0	20	16.7	14.0	18	14.2	11.8
Serious AEs	65	48.9	51.2	46	38.3	34.4	52	40.9	38.4
Resulted in death	10	7.5	6.1	7	5.8	4.5	4	3.2	2.4

AELDs: AEs leading to treatment discontinuation, PY: patient-years, Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

PPF pivotal trial 1305-0023 (DBL2)

Table *90*: Overall summary of AEs over the whole trial up to DBL2 – TS (trial 1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with any AE	375	95.7	359.6	375	95.4	389.7	368	94.1	454.2
Severe AEs (CTCAE grade >2)	160	40.8	37.6	146	37.2	34.9	152	38.9	37.5
Investigator-defined drug-related AEs	133	33.9	35.8	158	40.2	47.9	182	46.6	59.6
AEs leading to permanent treatment discontinuation	49	12.5	9.9	47	12.0	9.4	48	12.3	9.9
AEs leading to temporary treatment interruption	72	18.4	16.0	76	19.3	17.1	81	20.7	19.0
Serious AEs	184	46.9	45.9	157	40.0	38.4	168	43.0	43.0
Resulted in death	38	9.7	7.6	19	4.8	3.8	12	3.1	2.5
Life threatening	21	5.4	4.2	22	5.6	4.5	19	4.9	3.9
Disability or permanent damage	2	0.5	0.4	2	0.5	0.4	1	0.3	0.2
Required or prolonged hospitalisation	144	36.7	33.8	123	31.3	28.7	144	36.8	35.0
Congenital anomaly or birth defect	0	0	0	0	0	0	0	0	0
Other medically important serious events	75	19.1	16.2	59	15.0	12.6	59	15.1	13.0

PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Most frequently reported AEs (PPF)

Table *91*: Patients with AEs (frequency >5% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0023)

SOC		Placebo			Nera 9 mg bid			Nera 18 mg bid	
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with any AE	375	95.7	359.6	375	95.4	389.7	368	94.1	454.2
Infections and infestations	276	70.4	110.8	252	64.1	94.1	262	67.0	104.3
Upper respiratory tract infection	66	16.8	14.9	47	12.0	10.3	53	13.6	12.0
COVID-19	62	15.8	13.9	45	11.5	9.8	51	13.0	11.3
Nasopharyngitis	49	12.5	10.6	53	13.5	11.7	49	12.5	10.9
Pneumonia	41	10.5	8.6	43	10.9	9.1	51	13.0	11.2
Bronchitis	32	8.2	6.7	34	8.7	7.2	27	6.9	5.8
Respiratory tract infection	19	4.9	3.9	31	7.9	6.5	29	7.4	6.2
Urinary tract infection	26	6.6	5.5	26	6.6	5.4	22	5.6	4.6
Influenza	28	7.1	5.8	19	4.8	3.9	26	6.7	5.5
Gastrointestinal disorders	184	46.9	57.6	197	50.1	66.9	209	53.5	77.3
Diarrhoea	102	26.0	25.3	128	32.6	34.3	145	37.1	43.2
Nausea	28	7.1	5.9	35	8.9	7.4	47	12.0	10.4
Vomiting	26	6.6	5.5	22	5.6	4.6	27	6.9	5.8
Gastrooesophageal reflux disease	16	4.1	3.3	20	5.1	4.1	12	3.1	2.5
Respiratory, thoracic, and mediastinal disorders	164	41.8	43.5	149	37.9	39.0	153	39.1	42.2
Cough	61	15.6	13.6	55	14.0	12.1	65	16.6	15.2
Dyspnoea	43	11.0	9.1	43	10.9	9.2	41	10.5	8.9
General disorders and administration site conditions	152	38.8	39.7	134	34.1	32.5	126	32.2	32.2
Condition aggravated	71	18.1	15.3	54	13.7	11.4	43	11.0	9.2
Fatigue	26	6.6	5.4	25	6.4	5.2	23	5.9	4.9
Pyrexia	24	6.1	5.0	13	3.3	2.6	16	4.1	3.4
Musculoskeletal and connective tissue disorders	102	26.0	24.6	104	26.5	24.9	104	26.6	25.9
Arthralgia	20	5.1	4.1	30	7.6	6.3	32	8.2	6.8
Back pain	12	3.1	2.4	17	4.3	3.5	26	6.7	5.6
Investigations	90	23.0	20.6	101	25.7	23.8	109	27.9	27.0
Weight decreased	32	8.2	6.7	38	9.7	8.0	56	14.3	12.4
Psychiatric disorders	88	22.5	20.3	91	23.2	21.4	91	23.3	21.5
Depression	50	12.8	10.8	41	10.4	8.8	44	11.3	9.6
Anxiety	42	10.7	8.9	42	10.7	9.0	45	11.5	9.9
Nervous system disorders	65	16.6	14.5	74	18.8	17.1	85	21.7	20.3
Headache	28	7.1	5.9	18	4.6	3.7	32	8.2	6.9
Metabolism and nutrition disorders	71	18.1	15.9	70	17.8	15.6	66	16.9	14.9
Decreased appetite	32	8.2	6.7	27	6.9	5.6	36	9.2	7.8
Vascular disorders	31	7.9	6.6	34	8.7	7.1	35	9.0	7.5
Hypertension	14	3.6	2.9	16	4.1	3.3	20	5.1	4.2

PY: patient years, Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Adverse events by intensity (PPF)

Table *92*: Patients with severe AEs (CTCAE grade of at least 3, frequency ≥1% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0023)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 severe AE	160	40.8	37.6	146	37.2	34.9	152	38.9	37.5
Infections and infestations	59	15.1	12.5	50	12.7	10.5	56	14.3	12.1
Pneumonia	27	6.9	5.5	26	6.6	5.3	29	7.4	6.1
COVID-19	7	1.8	1.4	6	1.5	1.2	2	0.5	0.4
Influenza	3	0.8	0.6	2	0.5	0.4	7	1.8	1.4
Pneumonia bacterial	4	1.0	0.8	4	1.0	0.8	3	0.8	0.6
Bronchitis	2	0.5	0.4	4	1.0	0.8	1	0.3	0.2
General disorders and administration site conditions	56	14.3	11.6	39	9.9	8.0	29	7.4	6.1
Condition aggravated	49	12.5	10.1	34	8.7	6.9	25	6.4	5.2
Disease progression	4	1.0	0.8	0	0	0	2	0.5	0.4
Respiratory, thoracic and mediastinal disorders	42	10.7	8.6	32	8.1	6.6	28	7.2	5.8
Respiratory failure	7	1.8	1.4	5	1.3	1.0	7	1.8	1.4
Dyspnoea	10	2.6	2.0	5	1.3	1.0	3	0.8	0.6
Interstitial lung disease	9	2.3	1.8	4	1.0	0.8	4	1.0	0.8
Pneumothorax	5	1.3	1.0	4	1.0	0.8	3	0.8	0.6
Pulmonary hypertension	3	0.8	0.6	1	0.3	0.2	5	1.3	1.0
Cardiac disorders	13	3.3	2.6	17	4.3	3.4	23	5.9	4.8
Atrial fibrillation	1	0.3	0.2	3	0.8	0.6	5	1.3	1.0
Coronary artery disease	2	0.5	0.4	4	1.0	0.8	1	0.3	0.2
Cardiac failure	2	0.5	0.4	0	0	0	4	1.0	0.8
Gastrointestinal disorders	8	2.0	1.6	17	4.3	3.5	12	3.1	2.5
Diarrhoea	2	0.5	0.4	5	1.3	1.0	2[1]	0.5	0.4
Nervous system disorders	8	2.0	1.6	10	2.5	2.0	14	3.6	2.9
Syncope	0	0	0	2	0.5	0.4	4	1.0	0.8
Psychiatric disorders	6	1.5	1.2	7	1.8	1.4	6	1.5	1.2
Depression	4	1.0	0.8	3	0.8	0.6	3	0.8	0.6
Vascular disorders	3	0.8	0.6	6	1.5	1.2	7	1.8	1.4
Hypertension	2	0.5	0.4	2	0.5	0.4	6	1.5	1.2

PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

1 Since DBL1, the number of reported severe AEs of diarrhoea decreased; 1 occurrence of diarrhoea, which was considered severe (CTCAE 3) at DBL1, was reclassified (CTCAE 2) by the investigator post-DBL1.

Adverse events assessed as drug-related by the investigator (PPF)

Table *93*: Patients with drug-related AEs as assessed by the investigators (frequency ⩾1% in any treatment group at the PT level) whole trial up to DBL2 – TS (trial 1305-0023)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 drug-related AE	133	33.9	35.8	158	40.2	47.9	182	46.6	59.6
Gastrointestinal disorders	76	19.4	17.9	113	28.8	30.3	130	33.3	36.7
Diarrhoea	53	13.5	11.8	86	21.9	21.1	106	27.1	28.1
Nausea	12	3.1	2.5	18	4.6	3.7	26	6.7	5.6
Vomiting	6	1.5	1.2	13	3.3	2.7	15	3.8	3.1
Frequent bowel movements	5	1.3	1.0	8	2.0	1.6	9	2.3	1.9
Abdominal pain	4	1.0	0.8	5	1.3	1.0	7	1.8	1.4
Flatulence	3	0.8	0.6	5	1.3	1.0	7	1.8	1.5
Dyspepsia	2	0.5	0.4	5	1.3	1.0	5	1.3	1.0
Abdominal distension	4	1.0	0.8	5	1.3	1.0	2	0.5	0.4
Abdominal pain upper	4	1.0	0.8	4	1.0	0.8	2	0.5	0.4
Gastrooesophageal reflux disease	2	0.5	0.4	5	1.3	1.0	3	0.8	0.6
Investigations	21	5.4	4.4	23	5.9	4.8	32	8.2	6.9
Weight decreased	8	2.0	1.6	11	2.8	2.2	20	5.1	4.2
Aspartate aminotransferase increased	4	1.0	0.8	2	0.5	0.4	0	0	0
Blood creatine phosphokinase increased	4	1.0	0.8	0	0	0	0	0	0
General disorders and administration site conditions	18	4.6	3.7	17	4.3	3.5	28	7.2	6.0
Fatigue	7	1.8	1.4	8	2.0	1.6	10	2.6	2.1
Condition aggravated	6	1.5	1.2	2	0.5	0.4	3	0.8	0.6
Asthenia	1	0.3	0.2	2	0.5	0.4	4	1.0	0.8
Psychiatric disorders	16	4.1	3.3	21	5.3	4.3	20	5.1	4.2
Depression	6	1.5	1.2	10	2.5	2.0	13	3.3	2.7
Anxiety	5	1.3	1.0	6	1.5	1.2	9	2.3	1.9
Insomnia	1	0.3	0.2	4	1.0	0.8	2	0.5	0.4
Metabolism and nutrition disorders	18	4.6	3.7	15	3.8	3.1	19	4.9	4.0
Decreased appetite	16	4.1	3.3	15	3.8	3.1	16	4.1	3.4
Nervous system disorders	11	2.8	2.2	16	4.1	3.3	19	4.9	4.0
Headache	4	1.0	0.8	8	2.0	1.6	8	2.1	1.7
Dizziness	3	0.8	0.6	2	0.5	0.4	4	1.0	0.8
Infections and infestations	17	4.3	3.5	10	2.5	2.0	18	4.6	3.8
Upper respiratory tract infection	5	1.3	1.0	2	0.5	0.4	3	0.8	0.6
Herpes zoster	1	0.3	0.2	0	0	0	4	1.0	0.8
Respiratory, thoracic and mediastinal disorders	19	4.9	3.9	11	2.8	2.2	13	3.3	2.7
Cough	6	1.5	1.2	7	1.8	1.4	4	1.0	0.8
Dyspnoea	6	1.5	1.2	2	0.5	0.4	5	1.3	1.0
Skin and subcutaneous tissue disorders	12	3.1	2.5	10	2.5	2.0	8	2.1	1.7
Rash	4	1.0	0.8	2	0.5	0.4	2	0.5	0.4

PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

AEs in patients with background AF therapy (PPF)

Table *94*: Overall summary of AEs over the whole trial up to DBL1 by background AF therapy TS (trial 1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Without background nintedanib therapy	222	100.0		220	100.0		220	100.0	
Any AE	207	93.2	310.5	206	93.6	333.4	203	92.3	387.9
Severe AEs (CTCAE grade >2)	85	38.3	38.2	78	35.5	34.0	68	30.9	29.3
Investigator-defined drug-related AEs	63	28.4	30.5	72	32.7	36.7	90	40.9	49.6
AELDs	28	12.6	10.6	22	10.0	8.2	21	9.6	7.9
AEs leading to treatment interruption	33	14.9	13.7	37	16.8	15.1	34	15.5	14.0
SAEs	98	44.1	46.5	85	38.6	37.6	80	36.4	35.5
Resulted in death	16	7.2	6.0	14	6.4	5.2	5	2.3	1.9
With nintedanib background therapy	170	100.0		173	100.0		171	100.0	
Any AE	162	95.3	424.3	163	94.2	476.7	161	94.2	567.6
Severe AEs (CTCAE grade >2)	61	35.9	33.0	61	35.3	35.7	77	45.0	51.3
Investigator-defined drug-related AEs	65	38.2	44.5	85	49.1	71.8	88	51.5	81.4
AELDs	18	10.6	8.7	17	9.8	8.3	23	13.5	12.0
AEs leading to treatment interruption	34	20.0	18.2	41	23.7	23.3	45	26.3	27.6
SAEs	70	41.2	40.1	65	37.6	38.9	74	43.3	49.4
Resulted in death	13	7.7	6.2	4	2.3	1.9	3	1.8	1.6

AELDs: AEs leading to treatment discontinuation, PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by background nintedanib therapy was generally consistent with trends exhibited in the entire trial population and also with trends reported by background nintedanib subgroup at DBL1.

5.4.3.1. Adverse drug reactions

Overview of screening algorithm to identify potential ADRs

Safety data of double-blind placebo-controlled trials in IPF and PPF patients were analysed systematically for imbalances between nerandomilast and placebo treatment groups with a focus on the pivotal trials. A screening algorithm with numerical thresholds was applied to each PT using the following numerical criteria:

- If the AE frequency in the nerandomilast group was ≥5% and the relative risk (risk ratio) versus the placebo group was ≥2-fold, the event was suggestive of a potential side effect (Criterion 1)
- If the AE frequency in the nerandomilast group was ≥2% and <5% and the relative risk (risk ratio) versus the placebo group was ≥2-fold (Criterion 2) OR
  if the AE frequency in the nerandomilast group was ≥5% and the relative risk (risk ratio) versus the placebo group was >1-fold and <2-fold (Criterion 3),
  other supportive data supporting a causal association were needed to suggest a side effect.

PTs identified by this screening algorithm for the 9 mg and 18 mg bid nerandomilast groups in trials 1305-0014 (up to DBL2) and trial 1305-0023 (up to DBL2) are shown in the table below.

Table *95*: Preferred terms identified by the screening algorithm for potential ADRs in the overall pooled population (SAF1, i.e. all data from trial 1305-0014 up to DBL2 and trial 1305-0023 up to DBL2) –

	Criterion met in overall pooled population (SAF1) for 9 mg and/or 18 mg bid nerandomilast	
Preferred term	52 weeks	Whole trial
Diarrhoea	Criterion 3[1]	Criterion 3[1]
Nausea	Criterion 3	Criterion 3[1]
Vomiting	Criterion 3	Criterion 3
Fatigue	Criterion 3	Criterion 3
Decreased appetite	Criterion 3	Criterion 3
Weight decreased	Criterion 3[1]	Criterion 3[1]
Headache	Criterion 3	Criterion 3
Dizziness	Criterion 3	Criterion 3
Nasopharyngitis	Criterion 3	-
Influenza	-	Criterion 3
Pneumonia	Criterion 3	Criterion 3
Respiratory tract infection	Criterion 3[1]	Criterion 3[1]
Anxiety	Criterion 3	Criterion 3
Arthralgia	Criterion 3	Criterion 3
Back pain	Criterion 1[1]	Criterion 3[1]
Frequent bowel movements	Criterion 2[1]	-
Arthritis	-	Criterion 2[1]
Atrial fibrillation	-	Criterion 2[1]
Epistaxis	-	Criterion 2[1]
Contusion	-	Criterion 2

1 Risk ratio is considered statistically significant (95% CIs not spanning 1). Based on the methods described in the Summary of Clinical Safety, 'diarrhoea', 'weight decreased', 'decreased appetite', 'nausea', and 'back pain' are proposed as ADRs for nerandomilast in the treatment of patients with IPF and PPF.

IPF trial 1305-0014, PPF trial 1305-0023, and Pooled Data

Based on the methods described above, 'diarrhoea', 'weight decreased', 'decreased appetite,' 'nausea' and 'back pain' are proposed as ADRs for nerandomilast in the treatment of patients with IPF and PPF. Data are displayed for the overall population as well as the non-pirfenidone population where applicable. This also covers the recommended dosage (18 mg bid nerandomilast for all patients as well as a reduced dose of 9 mg bid nerandomilast [for patients not taking pirfenidone as background therapy] to manage tolerability in individual patients).

Both for IPF and PPF patients as well as for the pooled patient population, frequencies of diarrhoea and weight decrease increased more from placebo to 18 mg bid nerandomilast than to 9 mg bid. For both ADRs, the relative risk (risk ratio) versus placebo in the pooled overall population over 52 weeks was higher for the 18 mg bid nerandomilast group (diarrhoea: 1.89, weight decrease: 1.55) than for 9 mg versus placebo (diarrhoea: 1.46, weight decrease: 1.13). A comparable trend for the risk ratios of 18 mg versus placebo (diarrhoea: 1.81, weight decrease: 1.58) and 9 mg versus placebo (diarrhoea: 1.42, weight decrease: 1.03) was observed for the pooled non-pirfenidone population. For all ADRs, incidences of serious events or events leading to treatment discontinuation were low across all treatment groups both in PPF and IPF patients.

Table** 96**: Frequencies of proposed ADRs over 52 weeks in trial 1305-0014 (IPF only) – TS

	Overall population[1]						Non-pirfenidone population[2]					
	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
Preferred term	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	393	100.0	392	100.0	392	100.0	260	100.0	272	100.0	265	100.0
Diarrhoea	63	16.0	122	31.1	162	41.3	53	20.4	106	39.0	133	50.2
Nausea	27	6.9	37	9.4	30	7.7	17	6.5	27	9.9	21	7.9
Decreased appetite	19	4.8	32	8.2	36	9.2	7	2.7	22	8.1	20	7.6
Weight decreased	30	7.6	35	8.9	40	10.2	24	9.2	25	9.2	34	12.8
Back pain	13	3.3	19	4.9	22	5.6	9	3.5	15	5.5	14	5.3

1 Data from all patients by randomised treatment
2 Data from patients with no IPF or on nintedanib background treatment by randomised treatment

Table *97*: Frequencies of proposed ADRs over 52 weeks in trial 1305-0023 (PPF only)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Preferred term	N	%	N	%	N	%
Number of patients	392	100.0	393	100.0	391	100.0
Diarrhoea	97	24.7	116	29.5	143	36.6
Nausea	26	6.6	30	7.6	40	10.2
Decreased appetite	28	7.1	25	6.4	32	8.2
Weight decreased	23	5.9	27	6.9	42	10.7
Back pain	10	2.6	14	3.6	23	5.9

Table *98*: Frequencies of proposed ADRs over 52 weeks in trials 1305-0014 and 1305-0023 (IPF and PPF) –

	Overall population[1]						Non-pirfenidone population[2]					
	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
Preferred term	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	655	100.0	655	100.0
Diarrhoea	162	20.6	237	30.2	306	39.1	152	23.4	221	33.2	277	42.3
Nausea	53	6.8	66	8.4	70	8.9	43	6.6	56	8.4	61	9.3
Decreased appetite	49	6.2	57	7.3	68	8.7	35	5.4	47	7.1	52	7.9
Weight decreased	55	7.0	62	7.9	85	10.9	49	7.5	52	7.8	78	11.9
Back pain	22	2.8	34	4.3	46	5.9	19	2.9	29	4.4	37	5.7

1 Data from all patients by randomised treatment
2 Data from patients with no IPF or on nintedanib background treatment by randomised treatment

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

5.4.4.1. ***AESIs and AEs in Safety Topics***

Five AEs of special interest (AESIs) were predefined within a number of safety topics and in both pivotal studies in IPF and PPF patients, protocol-specified AESIs were:

- Potential severe DILI, defined by an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN, or ALT and/or AST elevations ≥10-fold ULN
- Vasculitis, defined as any event term included in the MedDRA SMQ Vasculitis (broad)
- Severe infections (CTCAE >2), serious, opportunistic, or mycobacterium tuberculosis infections
- New onset of severe depression, defined as HADS sub score >14
- New onset of severe anxiety, defined as HADS sub score >14

Other safety topics potentially related to the mode of action of nerandomilast or important potential or identified risks of other PDE4 inhibitors include cardiovascular events (MACE, tachyarrhythmia, QT prolongation), psychiatric events (suicidal ideation and behaviour, depression, nervousness/anxiety, insomnia), weight decrease, gastrointestinal symptoms (diarrhoea, nausea, vomiting, abdominal pain), vasculitis, severe/serious/opportunistic infections, potential DILI, and malignancies.

Table *99*: TSAP-defined analyses of special safety topics

Safety topic	Analysis based on actively collected data	Analysis of reported AEs in a safety topic based on predefined MedDRA searches
Vasculitis	AESI: SMQ vasculitis (broad); information from pre-defined work-up; adjudication	SMQ vasculitis (narrow)
Suicidal ideation and behaviour	C-SSRS questionnaire in eCRF	SMQ suicide/self-injury (narrow)
Depression	AESI: Severe depression (new onset of HADS depression subscore >14); HADS questionnaire (depression subscore)	Sub-SMQ depression (excluding suicide and self-injury) (narrow)
Nervousness and anxiety	AESI: Severe anxiety (HADS anxiety subscore >14); HADS questionnaire (anxiety subscore)	HLGT anxiety disorders and symptoms
Insomnia	--	HLT disturbances in initiating and maintaining sleep
Weight decrease	Weight on eCRF	BIcMQ weight loss (narrow)
Gastrointestinal symptoms	--	All below
Diarrhoea	Additional data on eCRF	PT diarrhoea
Nausea	--	PT nausea
Vomiting	--	PT vomiting
Abdominal pain	--	HLT gastrointestinal and abdominal pains (excluding oral and throat)
Malignancies	--	Sub-SMQ malignant tumours (narrow)
Severe, serious, and opportunistic infections including *M. tuberculosis* infection	AESI: CTCAE >2, serious, opportunistic, or *M. tuberculosis* infections; Tuberculosis testing	SOC infections and infestations AND serious OR CTCAE >2 SMQ opportunistic infections (narrow)
MACE	Adjudication	BIcMQ 3-point MACE (narrow)
Tachyarrhythmia	--	SMQ tachyarrhythmias (including supraventricular and ventricular tachyarrhythmias) (narrow)
QT prolongation	--	SMQ torsade de pointes/QT prolongation (narrow)
Foetal loss	Regular pregnancy testing and DEDP reporting of pregnancy	SMQ termination of pregnancy and risk of abortion (narrow)
Potential DILI	AESI: potential severe DILI based on changes in hepatic lab parameters (ALT and/or AST elevation ≥10x ULN **or** ALT and/or AST elevation ≥3-fold ULN combined with total bilirubin elevation ≥2x ULN in the same blood sample or in samples drawn within 30 days of each other); hepatic enzyme evaluation	Sub-SMQ Cholestasis and jaundice of hepatic origin (narrow) Sub-SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow) Sub-SMQ Liver related investigations, signs, and symptoms (narrow) Sub-SMQ Hepatitis, non-infectious (narrow)

Table 100**: Patients reported with AEs in special safety topics and AESIs – TS (SAF1/SAF1c)**

	Overall population[2]						Non-pirfenidone population[3]					
Safety topic/ PT or HLT	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Vasculitis (SMQ narrow)	4	0.5	7	0.9	6	0.8	3	0.5	7	1.1	3	0.5
AESI 'vasculitis' (SMQ broad)	6	0.8	7	0.9	6	0.8	4	0.6	7	1.1	3	0.5
Confirmed as vasculitis by adjudication[4]	2	0.3	3	0.4	5	0.6	2	0.3	3	0.5	2	0.3
Suicidal ideation and behaviour (SMQ narrow)	4	0.5	5	0.6	6	0.8	2	0.3	5	0.8	6	0.9
Depression (sub-SMQ narrow)	97	12.4	92	11.7	97	12.4	75	11.5	77	11.6	83	12.7
AESI 'new onset of severe depression'	11	1.4	12	1.5	10	1.3	8	1.2	12	1.8	10	1.5
Nervousness and anxiety (HLGT)	82	10.5	77	9.8	84	10.7	66	10.1	67	10.1	70	10.7
AESI 'new onset of severe anxiety'	9	1.2	9	1.2	8	1.0	8	1.2	9	1.4	7	1.1
Insomnia (HLT)	30	3.8	31	4.0	25	3.2	24	3.7	27	4.1	21	3.2
Weight decrease (BIcMQ narrow)	70	8.9	82	10.5	106	13.5	62	9.5	66	9.9	96	14.7
Gastrointestinal symptoms (MedDRA query)	239	30.5	315	40.1	366	46.7	219	33.6	286	43.0	321	49.0
Diarrhoea (PT)	174	22.2	254	32.4	311	39.7	163	25.0	236	35.5	280	42.8
Nausea (PT)	56	7.1	71	9.0	81	10.3	46	7.1	61	9.2	69	10.5
Vomiting (PT)	45	5.7	42	5.4	49	6.3	41	6.3	39	5.9	47	7.2
Abdominal pain (HLT)	42	5.4	48	6.1	52	6.6	40	6.1	43	6.5	46	7.0
Malignancies (sub-SMQ narrow)	36	4.6	31	4.0	29	3.7	27	4.2	30	4.5	23	3.5
Severe, serious, and opportunistic infections incl. *M. tuberculosis* infections (SOC, SMQ narrow)	117	14.9	103	13.1	110	14.1	99	15.2	90	13.5	95	14.5
AESI 'severe, serious, opportunistic, or *M. tuberculosis* infections'	100	12.7	92	11.7	104	13.3	83	12.8	79	11.9	90	13.7
MACE (BIcMQ narrow)	16	2.0	20	2.6	15	1.9	12	1.8	15	2.3	15	2.3
Confirmed as MACE by adjudication[4]	18	2.3	18	2.3	16	2.0	15	2.3	13	2.0	16	2.4
Tachyarrhythmia (SMQ narrow)	22	2.8	28	3.6	37	4.7	19	2.9	23	3.5	33	5.0
QT prolongation (SMQ narrow)	2	0.3	3	0.4	3	0.4	1	0.2	3	0.5	3	0.5
Potential DILI (sub-SMQs narrow)	52	6.6	49	6.2	40	5.1	48	7.4	43	6.5	36	5.5
AESI 'potential severe DILI'	6	0.8	2	0.3	7	0.9	6	0.9	2	0.3	6	0.9

BIcMQ: Boehringer Ingelheim customised MedDRA query; HLGT: High Level Group Term; HLT: High Level Term; n.a.: not analysed, SMQ: standardised MedDRA query

2 Data from all patients by randomised treatment

3 Data from patients not taking pirfenidone as background therapy by randomised treatment

4 All AEs categorised as vasculitis (vasculitis broad SMQ) and as MACE were referred for adjudication.

5.4.4.1.1. **Vasculitis**

Pooled data: Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 data (AEs 'vasculitis')

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, 17 patients overall reported AEs in the vasculitis safety topic. This comprised 4 (0.5%) patients in the placebo group, 7 (0.9%) patients in the 9 mg bid nerandomilast group, and 6 (0.8%) patients in the 18 mg bid nerandomilast group. A total of 6 AE leading to discontinuation (AELDs) were reported in the vasculitis safety topic. This

comprised 1 (0.1%) patient each in the placebo group and the 9 mg bid nerandomilast group, and 4 (0.5%) patients in the 18 mg bid nerandomilast group. A total of 11 SAEs in the vasculitis safety topic were reported. This comprised 2 (0.3%) patients in the placebo group, 5 (0.6%) patients in the 9 mg bid nerandomilast group, and 4 (0.5%) patients in the 18 mg bid nerandomilast group. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

The frequency of AEs that were adjudicated as vasculitis was low, with 2 (0.3%) events in the placebo group, 3 (0.4%) events in the 9 mg bid nerandomilast group, and 5 (0.6%) events in the 18 mg bid nerandomilast group in trials 1305-0014 and 1305-0023 pooled. Suggested diagnoses by the adjudicators included overall 6 events of microscopic polyangiitis (2 events in the placebo group, 1 event in the 9 mg bid nerandomilast group, and 3 events in the 18 mg bid nerandomilast group), 2 events of cutaneous vasculitis (1 event each in the 9 mg and 18 mg bid nerandomilast groups), and 2 events of giant cell arteritis (1 event each in the 9 mg and 18 mg bid nerandomilast groups).

IPF: The number of vasculitis events was low with 12 patients overall reported with AEs in the vasculitis safety topic (SMQ narrow). This comprised 3 (0.8%) patients in the placebo group, 4 (1.0%) patients in the 9 mg bid nerandomilast group, and 5 (1.3%) patients in the 18 mg bid nerandomilast group. Most AEs in the vasculitis safety topic were considered serious by the investigator. Four (1.0%) patients in the 18 mg bid nerandomilast group, none in the 9 mg bid nerandomilast group, and 1 (0.3%) patient in the placebo group were reported with AEs in the vasculitis safety topic that led to treatment discontinuation. Up to DBL2, the results of adjudication were available for 13 patients who were reported with an AE that was categorised as vasculitis (SMQ broad). The events were adjudicated as vasculitis for 1 (0.3%) patient in the placebo group, 1 (0.3%) patient in the 9 mg bid nerandomilast group, and 4 (1.0%) patients in the 18 mg bid nerandomilast group up to DBL2.

PPF: 2 (0.5%) patients in the placebo group, 3 (0.8%) patients in the 9 mg bid nerandomilast group, and 1 (0.3%) patient in the 18 mg bid nerandomilast group were reported with vasculitis AEs that were assessed as AESIs by the investigator. This comprised five patients with AEs in the 'vasculitis' safety topic and one patient in the placebo group reported with a non-serious and not drug-related AE of increased antineutrophil cytoplasmic antibody. Up to DBL2, the results of adjudication were available for 6 patients who were reported with an AE that was categorised as vasculitis (SMQ broad). The events were adjudicated as vasculitis for 1 (0.3%) patient in the placebo group, 2 (0.5%) patients in the 9 mg bid nerandomilast group, and 1 (0.3%) patient in the 18 mg bid nerandomilast group.

5.4.4.1.2. **Psychiatric events**

Pooled data: Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 data

A total of 15 AEs were reported in the suicidal ideation and behaviour (SMQ narrow) safety topic. This comprised 4 (0.5%) patients each in the placebo group, 5 (0.6%) in the 9 mg bid nerandomilast group, and 6 (0.8%) patients in the 18 mg bid nerandomilast group. All these patients were reported with an SAE of suicidal ideation (as required per CTP; see 'AEs considered "Always serious"'). The AEs were assessed as drug-related by the investigator in 2 (0.3%) patients in the placebo group, 4 (0.5%) patients in the 9 mg bid nerandomilast group, and 3 (0.4%) patients in the 18 mg bid nerandomilast group. Overall, 10 out of 15 patients with on-treatment suicidal ideation AEs had baseline psychiatric disorders (such as insomnia, anxiety, depression), 7 patients had a medical history of suicidal ideation or behaviour (type 1 to 9; based on C-SSRS results collected at baseline), and 8 patients received relevant therapy with psychiatric side effects at the time of the onset of the suicidal ideation AE. Among patients with suicidal ideation and behaviour AEs while on nerandomilast, all but 1 patient had identified triggers confounding suicidal ideation.

No meaningful differences across treatment groups were observed in insomnia, nervousness and anxiety, and depression. A total of 13/15 SAEs in the Suicidal ideation and behaviour (SMQ narrow) safety topic were reported in this group. This comprised 4 (0.5%) patient each in the placebo group, 5 (0.6%) in the 9 mg bid nerandomilast group, and 6 (0.8%) patients in the 18 mg bid nerandomilast group.

C-SSRS and HADS questionnaires

More than 95% of patients in all treatment groups did not show suicidal ideation. In general, no clinically meaningful changes and meaningful differences between treatment groups in the C-SSRS were observed. 1 patient in trial 1305-0023 receiving 9 mg bid nerandomilast had an SAE of suicide attempt, which was not reflected in the C-SSRS results. One patient treated in trial 1305-0014 died by an SAE of physician-assisted suicide 82 days (75 days beyond the REP of nerandomilast) after discontinuation of trial medication.

No relevant mean changes from baseline in HADS depression and anxiety scores and no relevant differences between treatment groups were observed for both depression and anxiety total scores.

AESIs with new onset of severe depression (HADS >14) or severe anxiety (HADS >14)

The frequency of AESIs of new onset of severe depression and AESIs of new onset of severe anxiety, both defined as HADS subscore >14, was low and balanced across treatment groups. At the PT level, depression and anxiety AESIs were reported most frequently. Similar trends were observed for the population of patients not taking pirfenidone as background.

IPF: In the pivotal IPF clinical trial, no relevant imbalances across treatment groups were observed in the frequencies of AEs in the insomnia, nervousness and anxiety, depression, and suicidal ideation and behaviour safety topics. All patients with on-treatment AEs up to DBL2 in the suicidal ideation and behaviour safety topic were reported with an SAE of suicidal ideation (placebo: 0.5%; 9 mg bid nerandomilast: 0.8%; 18 mg bid nerandomilast: 0.8%). The AEs were assessed as drug-related by the investigator in 3 (0.8%) patients in the 9 mg bid nerandomilast group and in 2 (0.5%) patients in the 18 mg bid nerandomilast group, and in no patients receiving placebo. Overall, 6 out of 8 patients with on-treatment suicidal ideation AEs had baseline psychiatric disorders (such as insomnia, anxiety, depression), five patients received relevant therapy with psychiatric side effects at the time of the onset of the suicidal ideation AE, and three patients had been reported with suicidal ideation (type 1 or 2) before first trial drug administration.

PPF: In the pivotal PPF study, no relevant imbalances across treatment groups were observed in the frequencies of AEs in the insomnia, nervousness and anxiety, depression, and suicidal ideation and behaviour safety topics.

One patient (0.3%) in the 9 mg bid nerandomilast group had an SAE of suicide attempt, the other patients with an SAE in this safety topic were reported with suicidal ideation.

The AEs were assessed as drug-related by the investigator in 2 (0.5%) patients in the placebo group for suicidal ideation, 1 (0.3%) patient in the 9 mg bid nerandomilast group for suicide attempt, and in 1 (0.3%) patient in the 18 mg bid nerandomilast group for suicidal ideation.

Overall, 5 out of 7 patients with on-treatment suicidal ideation and behaviour AEs had baseline psychiatric disorders (such as insomnia, anxiety, depression) or suicidal ideation prior to first trial drug administration, 3 patients received relevant therapy with psychiatric side effects at the time of the onset of the suicidal ideation AE. In all but 2 patient triggers confounding suicidal ideation were identified.

Up to DBL2, all trends in psychiatric-related safety topics were generally similar to those reported at DBL1. No new cases of on-treatment AEs in the 'suicidal ideation and behaviour' safety topic were

reported between DBL1 and DBL2. The results of C-SSRS and HADS questionnaires followed the trends as described for DBL1. No new clinically relevant findings were reported up to DBL2.

5.4.4.1.3. **Severe, serious, or opportunistic M. tuberculosis infections**

Severe, serious, and opportunistic infections: Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

In the overall patient population, at the PT level, most commonly reported AEs (i.e. reported in >5 patients in any treatment group) in the safety topic 'severe (CTCAE >2), serious, and opportunistic infections including *Mycobacterium tuberculosis* infection' were pneumonia (placebo: 6.8%; 9 mg bid nerandomilast: 6.0%; 18 mg bid nerandomilast: 6.3%), COVID-19 (1.5%; 1.5%; 0.9%), influenza (0.9%; 0.5%; 1.2%), bacterial pneumonia (0.8%; 1.3%; 0.5%), and respiratory tract infection (0.4%; 0.8%; 0.8%).

Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

AESIs with respect to severe (CTCAE >2), serious, opportunistic, or *Mycobacterium tuberculosis* infections

Table *101*: Patients with respiratory tract infection AEs in trials 1305-0014 (up to DBL2) and 1305-0023 (up to DBL2)

	Trial 1305-0014						Trial 1305-0023					
HLGT HLT	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	393	100.0	392	100.0	392	100.0	392	100.0	393	100.0	391	100.0
Respiratory tract infections	216	55.0	227	57.9	224	57.1	241	61.5	218	55.5	239	61.1
Lower respiratory tract infections	130	33.1	132	33.7	125	31.9	135	34.4	119	30.3	134	34.3
Upper respiratory tract infections	127	32.3	125	31.9	131	33.4	154	39.3	132	33.6	134	34.3

HLGT: high level group term, HLT: high level term. For respiratory tract infections (RTIs), all terms belonging to the HLGT RTIs were considered. The HLTs bacterial, fungal, parasitic, viral, and lower not elsewhere classified RTIs were used to analyse lower RTIs; the HLTs bacterial, fungal, viral, and upper not elsewhere classified RTIs were used to analyse upper RTIs.

5.4.4.1.4. **Potential severe DILI**

Pooled data: Analyses including 1305-0014 DBL2 and 1305-0023 DBL1 data

Table *102*: Overall summary of adverse events by safety topic and treatment

Safety topic	Placebo N	Placebo %	Placebo Time at risk [pt-yrs]	Placebo Rate/100 pt-yrs	Nera 9mg bid N	Nera 9mg bid %	Nera 9mg bid Time at risk [pt-yrs]	Nera 9mg bid Rate/100 pt-yrs	Nera 18mg bid N	Nera 18mg bid %	Nera 18mg bid Time at risk [pt-yrs]	Nera 18mg bid Rate/100 pt-yrs
Number of patients	785	100.00			785	100.00			783	100.00		
Vasculitis												
Patients with any AE	4	0.51	987.41	0.41	7	0.89	985.50	0.71	6	0.77	971.74	0.62
Patients with severe AEs (CTCAE grade of at least 3)	2	0.25	988.06	0.20	0	0.00	990.52	0.00	2	0.26	971.83	0.21
Patients with investigator defined drug-related AEs	0	0.00	988.67	0.00	0	0.00	990.52	0.00	4	0.51	972.48	0.41
Patients with AEs leading to permanent discontinuation of trial medication	1	0.13	988.65	0.10	1	0.13	990.45	0.10	4	0.51	972.46	0.41
Patients with AEs leading to temporary interruption of trial medication	2	0.25	987.89	0.20	3	0.38	987.35	0.30	0	0.00	972.56	0.00
Patients with AEs of special interest	4	0.51	987.41	0.41	7	0.89	985.50	0.71	6	0.77	971.74	0.62
Patients with serious AEs	2	0.25	988.20	0.20	5	0.64	986.24	0.51	4	0.51	971.78	0.41
Results in death	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Is life threatening	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Disability or permanent damage	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Requires or prolongs hospitalization	0	0.00	988.67	0.00	0	0.00	990.52	0.00	3	0.38	971.81	0.31
Congenital anomaly or birth defect	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Other medically Important serious event	2	0.25	988.20	0.20	5	0.64	986.24	0.51	1	0.13	972.53	0.10

Percentages are calculated using total number of patients per treatment as the denominator.
A patient may have serious AE(s) with multiple seriousness criteria.
MedDRA version used for reporting: 27.1
Containing data from trials: 1305-0014 and 1305-0023

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Safety topic	Placebo N	Placebo %	Placebo Time at risk [pt-yrs]	Placebo Rate/100 pt-yrs	Nera 9mg bid N	Nera 9mg bid %	Nera 9mg bid Time at risk [pt-yrs]	Nera 9mg bid Rate/100 pt-yrs	Nera 18mg bid N	Nera 18mg bid %	Nera 18mg bid Time at risk [pt-yrs]	Nera 18mg bid Rate/100 pt-yrs
Potential DILI												
Patients with any AE	52	6.62	953.03	5.46	49	6.24	956.04	5.13	40	5.11	946.06	4.23
Patients with severe AEs (CTCAE grade of at least 3)	11	1.40	984.79	1.12	11	1.40	985.51	1.12	7	0.89	969.31	0.72
Patients with investigator defined drug-related AEs	22	2.80	972.02	2.26	12	1.53	981.01	1.22	14	1.79	960.93	1.46
Patients with AEs leading to permanent discontinuation of trial medication	4	0.51	988.55	0.40	1	0.13	990.50	0.10	0	0.00	972.56	0.00
Patients with AEs leading to temporary interruption of trial medication	9	1.15	981.58	0.92	5	0.64	986.43	0.51	6	0.77	968.74	0.62
Patients with AEs of special interest	6	0.76	986.80	0.61	2	0.25	990.49	0.20	7	0.89	970.24	0.72
Patients with serious AEs	9	1.15	985.95	0.91	8	1.02	988.98	0.81	5	0.64	969.68	0.52
Results in death	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Is life threatening	0	0.00	988.67	0.00	1	0.13	990.50	0.10	1	0.13	972.26	0.10
Disability or permanent damage	0	0.00	988.67	0.00	1	0.13	990.50	0.10	0	0.00	972.56	0.00
Requires or prolongs hospitalization	5	0.64	988.22	0.51	4	0.51	990.06	0.40	2	0.26	971.91	0.21
Congenital anomaly or birth defect	0	0.00	988.67	0.00	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Other medically Important serious event	5	0.64	986.38	0.51	4	0.51	989.44	0.40	3	0.38	970.34	0.31

Percentages are calculated using total number of patients per treatment as the denominator.
A patient may have serious AE(s) with multiple seriousness criteria.
MedDRA version used for reporting: 27.1
Containing data from trials: 1305-0014 and 1305-0023

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<u>AEs in the safety topic 'potential DILI'</u>

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of AEs in the safety topic 'potential DILI' is presented across treatment groups in the above table. At the PT level, most frequently reported AEs (i.e. reported in >5 patients in any treatment group) were increased AST

(placebo: 1.4%; 9 mg bid nerandomilast: 1.8%; 18 mg bid nerandomilast: 1.4%), increased ALT (0.8%; 1.8%; 1.3%), increased GGT (1.2%; 1.7%; 0.8%), abnormal hepatic function (1.7%; 0.1%; 0.6%), and increased hepatic enzyme (0.8%; 0.9%; 0.6%).

Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

AESIs with respect to potential severe DILI

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of AESIs of potential severe DILI was balanced across treatment groups (placebo: 0.8%; 9 mg bid nerandomilast: 0.3%; 18 mg bid nerandomilast: 0.9%). Of 15 patients reported with AESIs of potential severe DILI, 12 received nintedanib or pirfenidone background therapy at onset of the AE. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Liver enzymes and bilirubin elevations

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, no clinically meaningful changes over time and no clinically meaningful differences between treatment groups were observed in liver enzymes and bilirubin parameters. PCSAs in patients with normal values at baseline were rare and generally balanced between treatment groups. The majority of patients in all treatment groups were within the normal ranges at baseline and mainly remained within these ranges during treatment, with minimal shifts that were considered not relevant.

The frequency of patients with elevated liver enzyme values over the whole trial in both trials 1305-0014 and 1305-0023 was low and balanced between treatment groups. Potential severe DILI cases (as per the CTP definition) were identified in 2 patients in trial 1305-0014 (1 patient each in the placebo group and the 9 mg bid nerandomilast group) and 5 patients in trial 1305-0023 [2 patients in the placebo group (1 on nintedanib treatment; the other without nintedanib background), 1 patient in the 9 mg bid nerandomilast group (without nintedanib treatmemt), and 2 patients in the 18 mg bid nerandomilast group (on nintedanib treatment)].

Table *103*: Patients with elevated liver enzyme values over the whole trial – TS (SAF1)

Elevated liver enzymes criteria	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0
ALT and/or AST						
≥3x ULN	19	2.4	7	0.9	6	0.8
≥5x ULN	10	1.3	2	0.3	4	0.5
≥10x ULN	5	0.6	0	0	2	0.3
≥20x ULN	1	0.1	0	0	0	0
ALT and/or AST ≥3x ULN, combined with[1]						
Total bilirubin ≥2x ULN	2	0.3	2	0.3	0	0
Total bilirubin ≥2x ULN and ALKP <2x ULN	1	0.1	0	0	0	0

1 Within 30 days after ALT and/or AST elevation.

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 data (SAF3/SAF3-CT)

Table *104*: Overall summary of liver-related adverse events by treatment – TS (SAF3)

Category of AEs	Placebo	Nerandomilast				
		Single dose total	Multiple dose			
			<9 mg bid	9 mg bid	>9 mg and <18 mg bid	18 mg bid
Number of patients (N, %)	926 (100.0)	440 (100.0)	26 (100.0)	785 (100.0)	8 (100.0)	2012 (100.0)
Patients with any liver-related AE (N, %)	54 (5.8)	3 (0.7)	0	49 (6.2)	0	65 (3.2)
AEs leading to permanent treatment discontinuation	4 (0.4)	0	0	1 (0.1)	0	0
DILI (PT)	0	0	0	1 (0.3)	0	0
Hepatic function abnormal	1 (0.1)	0	0	0	0	0
Suspected DILI (PT)	1 (0.1)	0	0	0	0	0
Alanine aminotransferase increased	1 (0.1)	0	0	0	0	0
Aspartate aminotransferase increased	1 (0.1)	0	0	0	0	0
Hepatopulmonary syndrome	1 (0.1)	0	0	0	0	0
Serious AEs	9 (1.0)	0	0	8 (1.0)	0	7 (0.4)
Resulted in death	0	0	0	0	0	0
Required or prolonged hospitalisation	5 (0.5)	0	0	4 (0.5)	0	2 (0.1)

Table *105*: Summary of liver enzyme and bilirubin elevations by treatment – TS (SAF3)

Elevated liver enzymes criteria	Placebo	Nerandomilast				
		Single dose total[3]	Multiple dose[3]			
			<9 mg bid	9 mg bid	>9 mg and <18 mg bid	18 mg bid
Number of patients (N, %)	926 (100.0)	440 (100.0)	26 (100.0)	785 (100.0)	8 (100.0)	1479 (100.0)
ALT and/or AST (N, %)						
≥3x ULN	19 (2.1)	2 (0.5)	0	7 (0.9)	0	9 (0.4)
≥5x ULN	10 (1.1)	1 (0.2)	0	2 (0.3)	0	5 (0.2)
≥10x ULN	5 (0.5)	0	0	0	0	2 (0.1)
≥20x ULN	1 (0.1)	0	0	0	0	0
ALT and/or AST ≥3x ULN, combined with[1]						
Total bilirubin ≥2x ULN	2 (0.2)	0	0	2 (0.3)	0	0
ALKP ≥2x ULN	1 (0.1)[2]	0	0	2 (0.3)[2]	0	0
ALKP <2x ULN	1 (0.1)	0	0	0	0	0

1 Within 30 days after ALT and/or AST elevation.

2 As ALT and/or AST ≥3x occurred in combination with total bilirubin ≥2x ULN and ALKP ≥2x ULN, Hy's law was not fulfilled for these cases.

3 A total of 276 patients who received placebo and 285 patients on 9 mg bid nerandomilast in trial 1305-0014, and 258 patients who received placebo and 271 patients on 9 mg bid nerandomilast in trial 1305-0023, rolled over to 18 mg bid nerandomilast in trial 13050031. As these patients belong to 2 dose categories, they were counted twice into SAF3.

*5.4.4.2. **Other safety topics***

5.4.4.2.1. **Gastrointestinal events**

Analyses including pivotal trial 1305-0014 DBL2 and 1305-0023 DBL2 pooled data:

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of AEs in the safety topic 'gastrointestinal symptoms' was higher under nerandomilast treatment than in the placebo group. This was mostly driven by the AEs in PT 'diarrhoea' which were observed more frequently in the nerandomilast treatment groups than in the placebo group. A numerical increase was also observed in the frequency of nausea under nerandomilast treatment compared with placebo. The frequencies of PT vomiting and HLT abdominal pain were generally balanced across the three treatment groups.

The percentage of patients reported with diarrhoea of severe intensity was generally low and higher in the nerandomilast groups (9 mg bid nerandomilast: n = 10 [1.3%]; 18 mg bid nerandomilast: n = 12 [1.5%]) than in the placebo group (n = 4 [0.5%]). The percentage of patients who permanently discontinued trial drug due to diarrhoea AE was the highest in the 18 mg bid nerandomilast group. Only five patients had diarrhoea events that were considered serious. This comprised 2 (0.3%) patients in the placebo group, 2 (0.3%) patients in the 9 mg bid nerandomilast group, and 1 (0.1%) patient in the 18 mg bid nerandomilast group. Most patients had first onset of diarrhoea AEs within the first 3 months of the trials. HRs (95% CIs) indicating increased risk of diarrhoea AEs versus placebo for pooled trials 1305-0014 and 1305-0023 were 1.61 (1.33, 1.96) for 9 mg bid nerandomilast and 2.11 (1.76, 2.55) for 18 mg bid nerandomilast.

In trials 1305-0014 and 1305-0023 pooled, the frequencies of nausea AELDs were low and the highest in the 18 mg bid nerandomilast group (placebo: 0.3%, 9 mg bid nerandomilast: 0.3%, 18 mg bid nerandomilast: 0.8%). There was one SAE of nausea (in trial 1305-0014) and 1 severe AE of nausea (in trial 1305-0023), both reported in the 18 mg bid nerandomilast group. The first onset of nausea AEs was mostly observed in the first 3 months of trial treatment. HRs (95% CIs) indicating increased risk of nausea AEs versus placebo were 1.28 (0.90, 1.82) for 9 mg bid nerandomilast and 1.49 (1.06, 2.10) for 18 mg bid nerandomilast.

Similar trends for the AEs in the 'gastrointestinal symptoms' safety topic (also at the PT/HLT level) were observed for the population of patients not taking pirfenidone as background therapy.

AEs in the 'gastrointestinal symptoms' safety topic in subgroups

In pooled trials 1305-0014 and 1305-0023, an increase in the frequency of AEs in the 'gastrointestinal symptoms' safety topic and diarrhoea AEs with increasing dose of nerandomilast was observed consistently in all analysed subgroups, except for those with low number of patients for which comparisons could not be done. With respect to nausea frequencies in the three treatment groups, there were no relevant differences with a clinically meaningful pattern for any of the pre-specified subgroups.

In both trials 1305-0014 and 1305-0023, diarrhoea and nausea AEs were observed more frequently in patients with background nintedanib or pirfenidone therapy than in patients without background therapy, independent of the trial treatment. In all background therapy subgroups, consistent increases in the frequency of diarrhoea AEs were observed under nerandomilast treatment compared with placebo. Most diarrhoea AELDs were reported in patients with background nintedanib therapy.

Table *106*: Hazard ratios of diarrhoea AEs overall and by background therapy type in trials 1305-0014 (up to DBL2) and 1305-0023 (up to DBL2)

	Trial 1305-0014				Trial 1305-0023			
	Nera 9 mg bid		Nera 18 mg bid		Nera 9 mg bid		Nera 18 mg bid	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall population	1.95	1.46, 2.61	2.76	2.09, 3.64	1.37	1.06, 1.78	1.66	1.29, 2.15
No background therapy	2.27	0.93, 5.57	3.89	1.67, 9.02	1.06	0.68, 1.65	1.78	1.19, 2.67
Nintedanib therapy	1.95	1.40, 2.73	2.72	1.96, 3.77	1.58	1.14, 2.17	1.59	1.15, 2.20
Pirfenidone therapy[1]	1.83	0.86, 3.87	3.12	1.57, 6.20	n.a		n.a	

CI: confidence interval, HR: hazard ratio, n.a.: not analysed

IPF pivotal trial 1305-0014:

Table *107*: Patients with diarrhoea AEs in subgroups over the whole trial up to DBL1 – TS (trial 1305-0014)

Subgroup	Placebo				Nera 9 mg bid				Nera 18 mg bid			
	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY
All patients	393	66	16.8	17.5	392	123	31.4	37.6	392	163	41.6	56.8
Sex												
Male	337	59	17.5	18.7	317	93	29.3	34.3	323	132	40.9	55.1
Female	56	7	12.5	11.6	75	30	40.0	53.5	69	31	44.9	64.9
Age												
<65 years	86	13	15.1	15.5	78	21	26.9	28.5	83	29	34.9	41.1
≥65 years	307	53	17.3	18.1	314	102	32.5	40.2	309	134	43.4	61.9
Race												
White	273	58	21.3	23.0	266	92	34.6	42.6	258	118	45.7	66.4
Asian	117	8	6.8	6.7	123	31	25.2	28.8	132	43	32.6	39.6
Black or African American	2	0	0	0	3	0	0	0	1	1	100.0	166.8
Ethnicity												
Not Hispanic or Latino	365	65	17.8	18.9	369	120	32.5	39.0	348	152	43.7	61.7
Hispanic or Latino	28	1	3.6	3.1	23	3	13.0	15.1	44	11	25.0	26.9
Baseline FVC % predicted												
≤70%	133	27	20.3	22.9	124	37	29.8	35.7	131	44	33.6	44.2
>70%	260	39	15.0	15.1	268	86	32.1	38.5	261	119	45.6	63.4
Background AF therapy												
No background therapy	87	7	8.1	7.8	88	15	17.1	17.9	87	23	26.4	30.2
Nintedanib	173	48	27.8	32.7	184	92	50.0	80.0	178	110	61.8	123.9
Pirfenidone	133	11	8.3	7.9	120	16	13.3	12.5	127	30	23.6	24.6
-9*Baseline body weight												
<65 kg	72	3	4.2	4.1	100	37	37.0	49.6	83	34	41.0	58.7
≥65 kg	321	63	19.6	20.8	292	86	29.5	34.1	309	129	41.8	56.3

FVC: forced vital capacity, N: total number of patients, n: number of patients with an AE of diarrhoea, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Table *108*: Summary of AEs 'diarrhoea' overall and by background antifibrotic therapy over the whole trial up to DBL2 – TS (trial 1305-0014)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Overall	393		392		392	
Patients with at least 1 AE 'diarrhoea'	72	100.0	126	100.0	166	100.0
CTCAE grade[1]						
Grade 1 (increase of <4 stools/day)	42	58.3	66	52.4	86	51.8
Grade 2 (increase of 4 to 6 stools/day)	28	38.9	55	43.7	70	42.2
Grade 3 (increase of ≥7 stools/day)	2	2.8	5	4.0	10	6.0
Drug-related AE as assessed by the investigator	40	55.6	87	69.0	135	81.3
Permanent discontinuation of trial drug	2	2.8	7	5.6	24	14.5
Serious diarrhoea AE	1	1.4	0	0	1	0.6
No background AF therapy	87		88		87	
Patients with at least 1 AE 'diarrhoea'	7	100.0	15	100.0	24	100.0
CTCAE grade[1]						
Grade 1 (increase of <4 stools/day)	4	57.1	11	73.3	19	79.2
Grade 2 (increase of 4 to 6 stools/day)	3	42.9	4	26.7	5	20.8
Grade 3 (increase of ≥7 stools/day)	0	0	0	0	0	0
Drug-related AE as assessed by the investigator	3	42.9	9	60.0	21	87.5
Permanent discontinuation of trial drug	0	0	0	0	1	4.2
Serious diarrhoea AE	0	0	0	0	0	0
Nintedanib background AF therapy	173		184		178	
Patients with at least 1 AE 'diarrhoea'	54	100.0	93	100.0	111	100.0
CTCAE grade[1]						
Grade 1 (increase of <4 stools/day)	29	53.7	41	44.1	48	43.2
Grade 2 (increase of 4 to 6 stools/day)	23	42.6	49	52.7	53	47.7
Grade 3 (increase of ≥7 stools/day)	2	3.7	3	3.2	10	9.0
Drug-related AE as assessed by the investigator	30	55.6	68	73.1	93	83.8
Permanent discontinuation of trial drug	2	3.7	4	4.3	23	20.7
Serious diarrhoea AE[2]	1	1.9	0	0	1	0.9
Pirfenidone background AF therapy	133		120		127	
Patients with at least 1 AE 'diarrhoea'	11	100.0	18	100.0	31	100.0
CTCAE grade[1]						
Grade 1 (increase of <4 stools/day)	9	81.8	14	77.8	19	61.3
Grade 2 (increase of 4 to 6 stools/day)	2	18.2	2	11.1	12	38.7
Grade 3 (increase of ≥7 stools/day)	0	0	2	11.1	0	0
Drug-related AE as assessed by the investigator	7	63.6	10	55.6	21	67.7
Permanent discontinuation of trial drug	0	0	3	16.7	0	0
Serious diarrhoea AE	0	0	0	0	0	0

In case of multiple AE occurrences, a patient is counted only once with the worst severity, worst relationship, worst outcome, and worst clinical consequence. Calculations of percentages are based on the number of patients with at least 1 diarrhoea episode documented as such by the investigator, i.e. with a completed diarrhoea CRF specific page.
1 No Grade 4 (life threatening) or Grade 5 (fatal) instances of diarrhoea were reported.
2 The SAE in the placebo group and the SAE in the 18 mg bid nerandomilast were considered serious because they required or prolonged hospitalisation.

PPF pivotal trial 1305-0023

Table *109*: Summary of AEs 'diarrhoea' overall and by background nintedanib therapy over the whole trial up to DBL2 – TS (trial 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%
Overall						
Number of patients	392		393		391	
Patients with at least 1 AE 'diarrhoea'	102	100.0	128	100.0	145	100.0
CTCAE grade						
Grade 1 (increase of <4 stools/day)	54	52.9	63	49.2	75	51.7
Grade 2 (increase of 4 to 6 stools/day)	46	45.1	60	46.9	68	46.9
Grade 3 (increase of ≥7 stools/day)	2	2.0	5	3.9	2	1.4
Grade 4 (life threatening) or Grade 5 (fatal)	0	0	0	0	0	0
Drug-related AE as assessed by the investigator	53	52.0	86	67.2	106	73.1
Permanent discontinuation of trial drug	2	2.0	10	7.8	10	6.9
Serious diarrhoea AE	1	1.0	2	1.6	0	0
No background nintedanib therapy						
Number of patients	222		220		220	
Patients with at least 1 AE 'diarrhoea'	38	100.0	39	100.0	60	100.0
CTCAE grade						
Grade 1 (increase of <4 stools/day)	22	57.9	26	66.7	37	61.7
Grade 2 (increase of 4 to 6 stools/day)	16	42.1	11	28.2	23	38.3
Grade 3 (increase of ≥7 stools/day)	0	0	2	5.1	0	0
Grade 4 (life threatening) or Grade 5 (fatal)	0	0	0	0	0	0
Drug-related AE as assessed by the investigator	16	42.1	25	64.1	44	73.3
Permanent discontinuation of trial drug	0	0	2	5.1	3	5.0
Serious diarrhoea AE	0	0	1	2.6	0	0
Nintedanib background therapy						
Number of patients	170		173		171	
Patients with at least 1 AE 'diarrhoea'	64	100.0	89	100.0	85	100.0
CTCAE grade						
Grade 1 (increase of <4 stools/day)	32	50.0	37	41.6	38	44.7
Grade 2 (increase of 4 to 6 stools/day)	30	46.9	49	55.1	45	52.9
Grade 3 (increase of ≥7 stools/day)	2	3.1	3	3.4	2	2.4
Grade 4 (life threatening) or Grade 5 (fatal)	0	0	0	0	0	0
Drug-related AE as assessed by the investigator	37	57.8	61	68.5	62	72.9
Permanent discontinuation of trial drug	2	3.1	8	9.0	7	8.2
Serious diarrhoea AE	1	1.6	1	1.1	0	0

In case of multiple AE occurrences, a patient is counted only once with the worst severity, worst relationship, worst outcome, and worst clinical consequence.

Table *110*: Patients with diarrhoea AEs in subgroups over the whole trial up to DBL1 – TS (trial 1305-0023)

Subgroup	Placebo				Nera 9 mg bid				Nera 18 mg bid			
	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY
All patients	392	98	25.0	25.5	393	121	30.8	34.0	391	143	36.6	44.8
Sex												
Male	231	61	26.4	27.6	203	66	32.5	37.0	220	83	37.7	49.2
Female	161	37	23.0	22.6	190	55	29.0	30.9	171	60	35.0	39.9
Age												
<65 years	149	37	24.8	24.0	142	37	26.1	26.6	152	38	25.0	26.1
≥65 years	243	61	25.1	26.5	251	84	33.5	38.7	239	105	43.9	60.4
Race												
White	226	64	28.3	31.0	224	82	36.6	46.1	235	100	42.6	57.7
Asian	154	30	19.5	17.9	161	37	23.0	21.7	145	42	29.0	31.6
Black or African American	7	3	42.9	48.6	3	1	33.3	40.5	6	0	0	0
Ethnicity												
Not Hispanic or Latino	339	88	26.0	26.4	333	112	33.6	38.2	334	130	38.9	49.4
Hispanic or Latino	53	10	18.9	19.4	60	9	15.0	14.2	57	13	22.8	23.3
Baseline FVC % predicted												
≤70%	214	63	29.4	32.2	202	58	28.7	31.4	194	76	39.2	50.1
>70%	178	35	19.7	18.6	191	63	33.0	36.8	197	67	34.0	40.0
Background nintedanib therapy												
No background therapy	222	35	15.8	14.9	220	35	15.9	14.9	220	59	26.8	28.2
Nintedanib	170	63	37.1	42.3	173	86	49.7	71.0	171	84	49.1	76.7
Baseline body weight												
<65 kg	131	28	21.4	20.2	150	43	28.7	30.3	127	46	36.2	43.7
≥65 kg	261	70	26.8	28.4	243	78	32.1	36.5	264	97	36.7	45.4
Baseline HRCT pattern												
UIP or UIP-like fibrotic pattern	275	68	24.7	25.5	290	91	31.4	34.4	275	102	37.1	45.8
Other fibrotic pattern	117	30	25.6	25.6	103	30	29.1	32.8	116	41	35.3	42.5
Underlying clinical ILD diagnosis												
Idiopathic nonspecific interstitial pneumonia	73	14	19.2	17.4	73	22	30.1	33.9	82	26	31.7	37.4
Unclassifiable idiopathic interstitial pneumonia	82	25	30.5	33.8	76	23	30.3	33.6	73	27	37.0	48.1
Hypersensitivity pneumonitis	77	22	28.6	32.3	83	26	31.3	37.6	73	33	45.2	68.9
Autoimmune ILDs	100	22	22.0	20.9	112	31	27.7	28.1	113	35	31.0	33.1
Other ILDs	60	15	25.0	26.4	49	19	38.8	44.1	50	22	44.0	55.1

FVC: forced vital capacity, N: total number of patients, n: number of patients with an AE of diarrhoea, PY: patient years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

5.4.4.2.2. **Weight decrease**

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of AEs in the safety topic 'weight decrease' was numerically higher with nerandomilast treatment than with placebo.

Similar trends were observed for the population of patients not taking pirfenidone as background therapy. Two AEs in the safety topic 'weight decrease' were considered serious (both in trial 1305-0014). This comprised one patient in the 9 mg bid nerandomilast group and 18 mg bid nerandomilast group each. One (0.1%) patient in the placebo group, two patients (0.3%) in the 9 mg bid nerandomilast treatment group, and six patients (0.8%) in the 18 mg bid nerandomilast group were reported with AELDs of weight decrease. The AEs in this safety topic were of mild or moderate intensity except for 3 (0.4%) patients in the placebo group, 1 (0.1%) patient in the 9 mg bid nerandomilast group, and 2 (0.3%) patients in the 18 mg bid nerandomilast group with severe events. 'Weight decreased' AEs were considered drug-related by the investigator in 24 (3.1%) patients in the placebo group, 29 (3.7%) patients in the 9 mg bid nerandomilast group, and 48 (6.1%) patients in the 18 mg bid nerandomilast group.

In trials 1305-0014 and 1305-0023 pooled, similar trends in the weight decrease AE display by subgroup were observed as described for trials 1305-0014 and 1305-0023. The frequency of AEs in the 'weight decrease' safety topic was higher in patients with background nintedanib or pirfenidone treatment than in patients taking no background therapy.

Change in weight over the course of the trials 1305-0014 and 1305-0023 pooled

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, a decrease in mean body weight over the duration of the trials was observed in all treatment groups. Mean (SD) change in body weight from baseline to last value on treatment was -2.3 (4.9) kg for placebo, -2.6 (4.47) kg under 9 mg bid nerandomilast, and -3.3 (4.9) kg under 18 mg bid nerandomilast. The mean (SD) of the maximum relative decline from baseline in body weight over the whole trial was -5.1 (5.4) % in the placebo group, -5.7 (5.0) % in the 9 mg bid nerandomilast group, and -6.4 (5.4) % in the 18 mg bid nerandomilast group. Over the whole trial, 14.4% in the placebo group, 15.1% in the 9 mg bid nerandomilast group, and 18.7% in the 18 mg bid nerandomilast group lost more than 10% of their body weight.

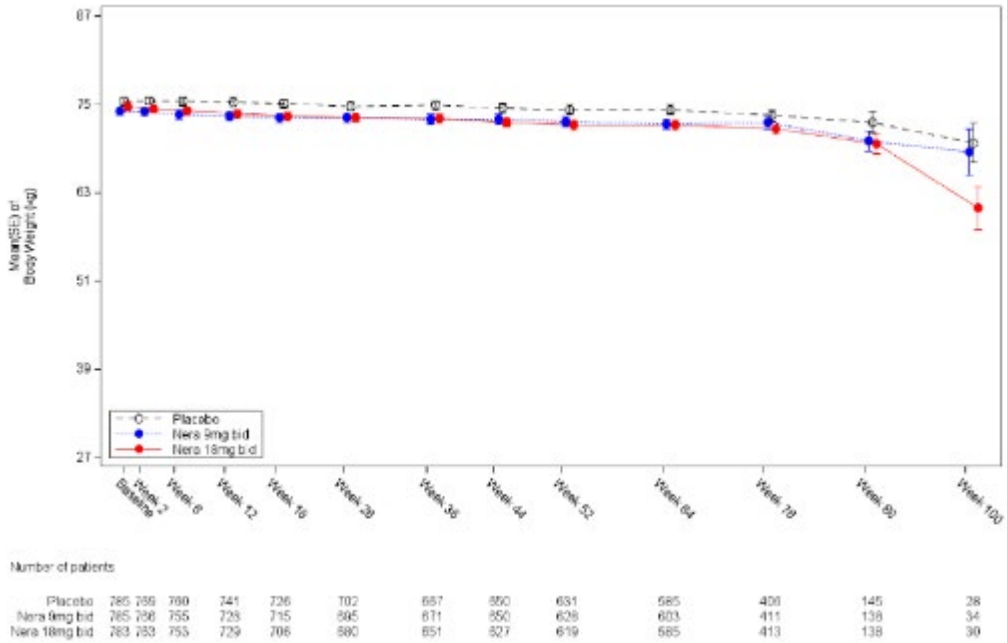

Figure *47*: Mean (standard error) change from baseline in body weight over time – TS-SAF

In trials 1305-0014 and 1305-0023 pooled, the change in body weight in subgroups by BMI category followed similar trends as described above for the overall patient population.

IPF pivotal trial 1305-0014

Table *111*: Patients with AEs in the safety topic 'weight decrease' in subgroups over the whole trial up to DBL1 – TS (trial 1305-0014)

Subgroup	Placebo				Nera 9 mg bid				Nera 18 mg bid			
	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY
All patients	393	33	8.4	8.0	392	40	10.2	9.6	392	44	11.2	11.0
Sex												
Male	337	29	8.6	8.3	317	36	11.4	10.6	323	39	12.1	11.7
Female	56	4	7.1	6.3	75	4	5.3	5.0	69	5	7.3	7.3
Age												
<65 years	86	6	7.0	6.3	78	6	7.7	11.1	258	4	4.8	4.3
≥65 years	307	27	8.8	8.5	314	34	10.8	10.4	309	40	12.9	13.0
Race												
White	273	22	8.1	7.6	266	31	11.7	11.1	258	26	10.1	10.0
Asian	117	9	7.7	7.3	123	8	6.5	5.9	132	18	13.6	12.8
Black or African American	2	1	50.0	76.4	3	1	33.3	32.2	1	0	0	0
Ethnicity												
Not Hispanic or Latino	365	30	8.2	7.8	369	39	10.6	9.8	348	42	12.1	11.9
Hispanic or Latino	28	3	10.7	10.0	23	1	4.4	4.7	44	2	4.6	4.2
Baseline FVC % predicted												
≤70%	133	16	12.0	12.4	124	14	11.3	11.1	131	16	12.2	12.8
>70%	260	17	6.5	6.0	268	26	9.7	8.9	261	28	10.7	10.1
Background nintedanib therapy												
No background therapy	87	5	5.8	5.4	88	2	2.3	2.1	87	7	8.1	7.3
Nintedanib	173	21	12.1	11.8	184	26	14.1	13.9	178	29	16.3	18.3
Pirfenidone	133	7	5.3	4.9	120	12	10.0	9.0	127	8	6.3	5.5
Baseline body weight												
<65 kg	72	7	9.7	9.8	100	13	13.0	12.7	83	12	14.5	14.5
≥65 kg	321	26	8.1	7.6	292	27	9.3	8.6	309	32	10.4	10.0

FVC: forced vital capacity, N: total number of patients, n: number of patients with an AE in safety topic 'weight decrease', PY: patient-years. Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

PPF pivotal trial 1305-0023

Table *112*: Patients with AEs in the safety topic 'weight decrease' in subgroups over the whole trial up to DBL1 – TS (trial 1305-0023)

Subgroup	Placebo				Nera 9 mg bid				Nera 18 mg bid			
	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY	N	n	%	Rate/ 100PY
All patients	392	26	6.7	5.7	393	36	9.2	8.0	391	49	12.5	11.5
Sex												
Male	231	16	6.9	6.1	203	14	6.9	5.9	220	32	14.6	14.1
Female	161	10	6.2	5.2	190	22	11.6	10.2	171	17	9.9	8.5
Age												
<65 years	149	10	6.7	5.5	142	10	7.0	6.0	152	11	7.2	6.1
≥65 years	243	16	6.6	5.9	251	26	10.4	9.1	239	38	15.9	15.3
Race												
White	226	10	4.4	3.9	224	12	5.4	4.8	235	24	10.2	9.5
Asian	154	15	9.7	8.2	161	24	14.9	12.5	145	25	17.2	15.4
Black or African American	7	1	14.3	12.3	3	0	0	0	6	0	0	0
Ethnicity												
Not Hispanic or Latino	339	25	7.4	6.3	333	34	10.2	8.9	334	48	14.4	13.4
Hispanic or Latino	53	1	1.9	1.7	60	2	3.3	2.8	57	1	1.8	1.5
Baseline FVC % predicted												
≤70%	214	22	10.3	9.3	202	23	11.4	10.3	194	26	13.4	12.3
>70%	178	4	2.3	1.8	191	13	6.8	5.7	197	23	11.7	10.7
Background nintedanib therapy												
No background therapy	222	11	5.0	4.3	220	18	8.2	6.9	220	28	12.7	11.3
Nintedanib	170	15	8.8	7.6	173	18	10.4	9.4	171	21	12.3	11.7
Baseline body weight												
<65 kg	131	11	8.4	7.2	150	22	14.7	13.0	127	18	14.7	13.2
≥65 kg	261	15	5.8	5.0	243	14	5.8	5.0	264	31	11.7	10.6
Baseline HRCT pattern												
UIP or UIP-like fibrotic pattern	275	19	6.9	6.0	290	29	10.0	8.6	275	38	13.8	12.7
Other fibrotic pattern	117	7	6.0	5.0	103	7	6.8	6.1	116	11	9.5	8.6
Underlying clinical ILD diagnosis												
Idiopathic nonspecific interstitial pneumonia	73	3	4.1	3.3	73	3	4.1	3.6	82	4	4.9	4.4
Unclassifiable idiopathic interstitial pneumonia	82	10	12.2	11.2	76	10	13.2	12.0	73	10	13.7	13.0
Hypersensitivity pneumonitis	77	3	3.9	3.4	83	6	7.2	6.7	73	6	8.2	7.7
Autoimmune ILDs	100	4	4.0	3.4	112	11	9.8	8.0	113	16	14.2	12.6
Other ILDs	60	6	10.0	9.1	49	6	12.2	10.6	50	13	26.0	24.2

FVC: forced vital capacity, N: total number of patients, n: number of patients with an AE in safety topic 'weight decrease', PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, trends in the decline of body weight over the whole trial and differences between treatment groups remained similar to those reported at DBL1.

Table *113*: Mean change and maximum relative decline from baseline in body weight over the whole trial up to DBL2 – TS (trial 1305-0023)

	Placebo		Nera 9 mg bid		Nera 18 mg bid	
Number of patients (N %)	392	100.0	393	100.0	391	100.0
Weight at baseline [kg] (mean SD)	73.4	17.9	72.1	17.5	73.2	17.1
Change from baseline to last value on treatment [kg] (mean SD)	-2.3	5.1	-2.3	4.9	-3.4	5.4
Maximum relative decline from baseline [%] (mean SD)	-5.4	5.8	-5.9	5.4	-6.6	5.8
Maximum relative decline from baseline in categories						
Decrease of >10% (N %)	66	16.8	69	17.6	78	19.9
Decrease of >5% to ≤10% (N %)	100	25.5	115	29.3	135	34.5
Decrease of >0% to ≤5% (N %)	163	41.6	163	41.5	130	33.2
Increase ≥0% (N %)	61	15.6	43	10.9	46	11.8

Only 390 placebo patients, 390 patients on 9 mg bid nerandomilast, and 389 patients on 18 mg bid nerandomilast were included in the calculation of change from baseline to last value on treatment (mean, SD).

Only 390 placebo patients, 390 patients on 9 mg bid nerandomilast, and 389 patients on 18 mg bid nerandomilast were included in the calculation of mean (SD) maximum relative weight decline from baseline and maximum relative weight decline from baseline in categories.

5.4.4.2.3. **Cardiovascular events**

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequencies of AEs in 'MACE' and 'QT prolongation' safety topics were similar across treatment groups. All AEs in the 'MACE' safety topic at the PT level were reported in 5 or fewer patients in any treatment group. A numerical increase in 'tachyarrhythmia' safety topic was observed for the 18 mg bid nerandomilast group. This was mostly attributed to the higher frequency of atrial fibrillation in the 18 mg bid nerandomilast group compared with placebo. At the PT level, most frequently reported AEs (i.e. reported in >2 patients in any treatment group) in 'tachyarrhythmia' safety topic were atrial fibrillation (placebo: 0.8%; 9 mg bid nerandomilast: 1.8%; 18 mg bid nerandomilast: 2.6%), supraventricular extrasystoles (0.5%; 0.5%; 0.6%), ventricular extrasystoles (0.9%; 0.3%; 0.5%), sinus tachycardia (0%; 0.5%; 0.9%), and supraventricular tachycardia (0.4%; 0%; 0.3%). Only one AELD was reported in 'tachyarrhythmia' safety topic (in the 18 mg bid nerandomilast group). Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Cardiovascular events ('MACE', 'QT prolongation', and 'tachyarrhythmia') (IPF 1305-0014)

Up to DBL2, the frequencies of 'MACE' AEs were similar across all treatment groups (placebo: 2.3%; 9 mg bid nerandomilast: 2.8%; 18 mg bid nerandomilast: 1.8%). All AEs in the 'MACE' safety topic at the PT level were reported in 3 or fewer patients in any treatment group.

The frequency of 'tachyarrhythmia' AEs in the 18 mg bid nerandomilast treatment group was numerically higher than in the other treatment groups (placebo: 13 patients [3.3%]; 9 mg bid nerandomilast: 13 patients [3.3%]; 18 mg bid nerandomilast: 20 patients [5.1%]). At the PT level, most frequently reported AEs (i.e. reported in >2 patients in any treatment group) in 'tachyarrhythmia' safety topic were atrial fibrillation (placebo: 1.3%; 9 mg bid nerandomilast: 1.8%; 18 mg bid nerandomilast: 2.6%), r extrasystoles (1.3%; 0.5%; 0.5%), sinus tachycardia (0%; 0%; 1.3%), and supraventricular extrasystoles (0%; 0.5%; 0.8%).

Cardiovascular events ('MACE', 'QT prolongation', and 'tachyarrhythmia') (PPF 1305-0023)

The frequency of MACE AEs was similar across treatment groups. At the PT level, the most frequently reported AEs (i.e. >2 patients in any treatment group) in the 'MACE' safety topic were acute myocardial infarction (placebo: 0.3%, 9 mg bid nerandomilast: 0.3%, 18 mg bid nerandomilast: 0.8%) and cerebrovascular accident (0.8%, 0.3%, 0.3%).

There was a numerical increase in tachyarrhythmia in the nerandomilast groups. This was driven by the most frequently reported AE within this safety topic at PT level 'atrial fibrillation' (placebo: 0.3%; 8 mg bid nerandomilast: 1.8%; 18 mg bid nerandomilast: 2.6%). All other PTs except sinus tachycardia (0%, 0.8%, 0%) were reported in 2 patients or less in any treatment group. Nearly all cases of atrial fibrillation occurred in patients ≥65 years of age with baseline cardiac conditions or confounders.

Three (0.8%) patients in the 9 mg bid nerandomilast group and 2 patients (0.5%) in the 18 mg bid nerandomilast group were reported with an AE of QT prolongation and this is not considered a relevant imbalance.

Table *114*: Patients with AEs categorised as MACE and adjudication outcome over the whole trial up to DBL1 – TS (trial 1305-0023)

	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with an AE categorised as MACE	18	4.6	3.9	22	5.6	4.7	24	6.1	5.3
Adjudicated as MACE (fatal or non-fatal)	4	1.0	0.9	8	2.0	1.7	7	1.8	1.5
Adjudicated as fatal MACE	1	0.3	0.2	5	1.3	1.1	1	0.3	0.2
Sudden cardiac death	1	0.3	0.2	3	0.8	0.6	0	0	0
Cardiovascular procedures	0	0	0	1	0.3	0.2	1	0.3	0.2
Other cardiovascular causes	0	0	0	1	0.3	0.2	0	0	0
Adjudicated as non-fatal MACE	3	0.8	0.6	3	0.8	0.6	6	1.5	1.3
Myocardial infarction	1	0.3	0.2	2	0.5	0.4	3	0.8	0.7
Stroke	2	0.5	0.4	1	0.3	0.2	3	0.8	0.7
Haemorrhagic	0	0	0	0	0	0	1	0.3	0.2
Ischaemic	2	0.5	0.4	0	0	0	2	0.5	0.4
Undetermined	0	0	0	1	0.3	0.2	0	0	0
Adjudicated as not MACE	14	3.6	3.0	15	3.8	3.2	17	4.4	3.8

PY: patient years

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY. All AEs categories as MACE were referred for adjudication.

Up to DBL2, trends in AEs in the 'cardiovascular' safety topics were generally similar to those reported at DBL1. AEs confirmed as MACE by adjudication were balanced across treatment groups at DBL2. All AEs in the 'MACE' safety topic at the PT level were reported in 3 or fewer patients in any treatment group. In the 'tachyarrhythmia' safety topic, all AEs except for atrial fibrillation (placebo: 0.3%, 9 mg bid nerandomilast: 1.8%, 18 mg bid nerandomilast: 2.6%), sinus tachycardia (0%, 1.0%, 0.5%), and supraventricular extrasystoles (1.0%, 0.5%, 0.5%) were reported in 2 patients or less in any treatment group. As of DBL2, 1 additional patient in the 18 mg bid nerandomilast group was reported with an AE of QT prolongation, but no relevant imbalances were seen across treatment groups.

5.4.4.2.4. **Malignancies**

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of AEs (including SAEs and AELDs) in the safety topic 'malignancies' was balanced in the nerandomilast treatment groups and in the placebo group. At the PT level, most commonly reported AEs (i.e. reported in >3 patients in any treatment groups) were basal cell carcinoma (placebo: 0.3%; 9 mg bid nerandomilast: 0.9%; 18 mg bid nerandomilast: 0.9%), squamous cell carcinoma of skin (0.5%; 0.6%; 0.5%), and malignant lung neoplasm (0.4%; 0.6%; 0.5%). Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Malignancies: IPF pivotal study

Up to DBL2, the frequency of AEs (including SAEs and AELDs) in the safety topic 'malignancies' in the nerandomilast treatment groups was numerically lower than in the placebo group. At the PT level, most commonly reported AEs (i.e. reported in >2 patients in any treatment groups) were squamous cell carcinoma of skin (placebo: 1.0%; 9 mg bid nerandomilast: 1.0%; 18 mg bid nerandomilast: 0.3%), basal cell carcinoma (0.3%; 1.0%; 0.8%), and malignant lung neoplasm (0.8%; 1.0%; 0.8%)

Malignancies : PPF pivotal study

Up to DBL1, the frequency of AEs (including SAEs and AELDs) in the safety topic 'malignancies' in the nerandomilast treatment groups was numerically higher than in the placebo group.

At the PT level, most commonly reported AEs (i.e. reported in ≥2 patients in any treatment groups) were basal cell carcinoma (placebo: 0.3%; 9 mg bid nerandomilast: 0.8%; 18 mg bid nerandomilast: 0.5%), squamous cell carcinoma of the skin (0%; 0.3%; 0.8%), and small cell lung cancer (0%; 0%; 0.5%). There is no relevant pattern seen in specific types of malignancies.

Up to DBL2, trends in the AEs in the safety topic 'malignancies' were consistent with those reported up to DBL1.

Table *115*: Patients reported with SAEs and AELDs in the safety topic 'malignancies' over the whole trial up to DBL2 – TS (trial 1305-0014)

Safety topic[1]/ PT or HLT	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Malignancies (sub-SMQ narrow)	28	7.1	5.8	20	5.1	4.1	14	3.6	2.9
SAE	28	7.1	5.8	20	5.1	4.1	14	3.6	2.9
AELD	16	4.1	3.3	14	3.6	2.9	9	2.3	1.9

Table *116*: Patients reported with SAEs and AELDs in the safety topic 'malignancies' over the whole trial up to DBL2 – TS (trial 1305-0023)

Safety topic[1]/ PT or HLT	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Malignancies (sub-SMQ narrow)	8	2.0	1.6	11	2.8	2.2	15	3.8	3.1
SAE	8	2.0	1.6	11	2.8	2.2	15	3.8	3.1
AELD	5	1.3	1.0	6	1.5	1.2	11	2.8	2.3

Table *117*: Frequency [N(%)] of patients with adverse events by treatment, safety topic and preferred term – TS SAF1

Safety Topic/ Preferred Term	Placebo N	Placebo %	Placebo Time at risk [pt-yrs]	Placebo Rate/100 pt-yrs	Nera 9mg bid N	Nera 9mg bid %	Nera 9mg bid Time at risk [pt-yrs]	Nera 9mg bid Rate/100 pt-yrs	Nera 18mg bid N	Nera 18mg bid %	Nera 18mg bid Time at risk [pt-yrs]	Nera 18mg bid Rate/100 pt-yrs
Malignancies	36	4.59	981.21	3.67	31	3.95	981.51	3.16	29	3.70	961.21	3.02
Basal cell carcinoma	2	0.25	986.86	0.20	7	0.89	984.73	0.71	7	0.89	967.02	0.72
Squamous cell carcinoma of skin	4	0.51	986.36	0.41	5	0.64	987.97	0.51	4	0.51	970.26	0.41
Lung neoplasm malignant	3	0.38	988.49	0.30	5	0.64	990.37	0.50	4	0.51	971.80	0.41
Prostate cancer	2	0.25	988.63	0.20	3	0.38	990.19	0.30	1	0.13	972.54	0.10
Bowen's disease	3	0.38	986.59	0.30	1	0.13	989.51	0.10	1	0.13	972.38	0.10
Squamous cell carcinoma	2	0.25	988.41	0.20	0	0.00	990.52	0.00	2	0.26	971.31	0.21
Non-small cell lung cancer	1	0.13	988.64	0.10	1	0.13	990.37	0.10	1	0.13	972.24	0.10
Squamous cell carcinoma of lung	2	0.25	988.46	0.20	0	0.00	990.52	0.00	1	0.13	972.07	0.10
Colon cancer	1	0.13	988.64	0.10	1	0.13	990.49	0.10	0	0.00	972.56	0.00
Colorectal cancer	1	0.13	988.65	0.10	0	0.00	990.52	0.00	1	0.13	972.51	0.10
Hepatocellular carcinoma	0	0.00	988.67	0.00	2	0.25	990.37	0.20	0	0.00	972.56	0.00
Lung adenocarcinoma	2	0.25	988.57	0.20	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Metastases to liver	2	0.25	988.64	0.20	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Skin cancer	1	0.13	988.57	0.10	1	0.13	990.41	0.10	0	0.00	972.56	0.00
Small cell lung cancer	0	0.00	988.67	0.00	0	0.00	990.52	0.00	2	0.26	972.11	0.21
Transitional cell carcinoma	2	0.25	988.51	0.20	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Acute leukaemia	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.54	0.10
Adenosquamous cell carcinoma	0	0.00	988.67	0.00	1	0.13	990.46	0.10	0	0.00	972.56	0.00
Bladder cancer stage 0, with cancer in situ	0	0.00	988.67	0.00	1	0.13	990.43	0.10	0	0.00	972.56	0.00
Brain neoplasm malignant	1	0.13	988.66	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Cholangiocarcinoma	1	0.13	988.55	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Chronic myeloid leukaemia	1	0.13	988.62	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Clear cell renal cell carcinoma	0	0.00	988.67	0.00	1	0.13	990.43	0.10	0	0.00	972.56	0.00
Ductal adenocarcinoma of pancreas	1	0.13	988.65	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Extranodal marginal zone B-cell lymphoma (MALT type)	0	0.00	988.67	0.00	1	0.13	990.51	0.10	0	0.00	972.56	0.00
Gastric cancer	0	0.00	988.67	0.00	1	0.13	990.51	0.10	0	0.00	972.56	0.00
Hodgkin's disease	1	0.13	988.64	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Keratoacanthoma	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.48	0.10
Lip squamous cell carcinoma	1	0.13	988.35	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Localised melanoma	1	0.13	988.63	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Lung cancer metastatic	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.53	0.10
Metastases to bone	1	0.13	988.63	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Metastases to lung	1	0.13	988.65	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Neuroendocrine carcinoma of the skin	1	0.13	988.62	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Papillary thyroid cancer	1	0.13	988.61	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Rectal adenocarcinoma	0	0.00	988.67	0.00	1	0.13	990.50	0.10	0	0.00	972.56	0.00
Rectal cancer	1	0.13	988.64	0.10	0	0.00	990.52	0.00	0	0.00	972.56	0.00
Sarcomatoid carcinoma	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.54	0.10
Small intestine carcinoma	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.43	0.10
Squamous cell carcinoma of the cervix	0	0.00	988.67	0.00	0	0.00	990.52	0.00	1	0.13	972.37	0.10

5.4.5. Serious adverse events including deaths

Serious Adverse Events (Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data)

In the overall patient population, in trials 1305-0014 and 1305-0023 pooled, the frequency of patients with SAEs was lower in the nerandomilast groups than in the placebo group. SAEs were most frequently reported in the SOCs infections and infestations, respiratory, thoracic, and mediastinal disorders, and general disorders and administration site conditions. At the PT level, most frequently reported SAEs overall were condition aggravated, pneumonia, pulmonary hypertension, and respiratory failure. All other SAEs were reported in <2% of the patients in each of the treatment groups. Frequencies of all reported PTs were generally balanced for SAEs across treatment groups, with frequencies of condition aggravated SAEs being lower in the nerandomilast groups. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Table *118*: Patients with SAEs (frequency >1% in any treatment group at the PT level in the overall population) – TS (SAF1/SAF1c)

SOC PT	Overall population[1]						Non-pirfenidone population[2]					
	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Patients with at least 1 SAE	351	44.7	306	39.0	317	40.5	285	43.8	260	39.1	264	40.3
Infections and infestations	105	13.4	92	11.7	103	13.2	90	13.8	82	12.3	89	13.6
Pneumonia	51	6.5	46	5.9	46	5.9	40	6.1	41	6.2	41	6.3
COVID-19	11	1.4	9	1.2	7	0.9	10	1.5	8	1.2	5	0.8
Pneumonia bacterial	5	0.6	9	1.2	4	0.5	5	0.8	8	1.2	4	0.6
Respiratory, thoracic and mediastinal disorders	118	15.0	92	11.7	80	10.2	99	15.2	69	10.4	66	10.1
Pulmonary hypertension	25	3.2	17	2.2	23	2.9	20	3.1	12	1.8	17	2.6
Respiratory failure	17	2.2	10	1.3	9	1.2	15	2.3	9	1.4	9	1.4
Dyspnoea	15	1.9	12	1.5	7	0.9	10	1.5	9	1.4	5	0.8
Pneumothorax	11	1.4	10	1.3	12	1.5	11	1.7	8	1.2	10	1.5
Idiopathic pulmonary fibrosis	11	1.4	12	1.5	9	1.2	9	1.4	4	0.6	6	0.9
Pulmonary embolism	9	1.2	9	1.2	7	0.9	6	0.9	7	1.1	6	0.9
Interstitial lung disease	11	1.4	5	0.6	4	0.5	11	1.7	5	0.8	4	0.6
General disorders and administration site conditions	99	12.6	71	9.0	62	7.9	86	13.2	59	8.9	51	7.8
Condition aggravated	84	10.7	60	7.6	53	6.8	73	11.2	51	7.7	43	6.6
Cardiac disorders	43	5.5	36	4.6	43	5.5	33	5.1	29	4.4	33	5.0
Cardiac failure	7	0.9	2	0.3	9	1.2	7	1.1	2	0.3	6	0.9
Atrial fibrillation	2	0.3	5	0.6	8	1.0	1	0.2	4	0.6	8	1.2
Renal and urinary disorders	5	0.6	12	1.5	7	0.9	5	0.8	9	1.4	7	1.1
Acute kidney injury	4	0.5	8	1.0	4	0.5	4	0.6	7	1.1	4	0.6

1Data from all patients by randomised treatment

2Data from patients with no IPF or on nintedanib background treatment by randomised treatment

SAEs (IPF pivotal trial 1305-0014)

Up to DBL2, most frequently reported SAEs overall at the SOC level were respiratory, thoracic, and mediastinal disorders (placebo: 14.3%; 9 mg bid nerandomilast: 11.5%; 18 mg bid nerandomilast: 10.2%), infections and infestations (10.4%; 9.7%; 10.5%), and general disorders and administration site conditions (9.9%; 7.7%; 8.4%). At the PT level, these were condition aggravated, pneumonia, pulmonary hypertension, and IPF. All other SAEs were reported in <2% of the patients in each of the treatment groups.

Table *119*: Patients with SAEs (frequency >1% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0014)

System organ class	Placebo			Nerandomilast 9 mg bid			Nerandomilast 18 mg bid		
Preferred term	N	%	Rate/100PY	N	%	Rate/100PY	N	%	Rate/100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with at least 1 SAE	167	42.5	41.3	194	38.0	35.9	149	38.0	38.1
Respiratory, thoracic, and mediastinal disorders	56	14.3	12.0	45	11.5	9.5	40	10.2	8.7
Pulmonary hypertension	12	3.1	2.5	9	2.3	1.9	12	3.1	2.5
Idiopathic pulmonary fibrosis	11	2.8	2.3	12	3.1	2.5	9	2.3	1.9
Dyspnoea	7	1.8	1.4	6	1.5	1.2	5	1.3	1.0
Pulmonary embolism	7	1.8	1.4	5	1.3	1.0	4	1.0	0.8
Respiratory failure	8	2.0	1.7	4	1.0	0.8	2	0.5	0.4
Pneumothorax	1	0.3	0.2	3	0.8	0.6	7	1.8	1.5
Acute respiratory failure	2	0.5	0.4	4	1.0	0.8	3	0.8	0.6
Infections and infestations	41	10.4	8.8	38	9.7	8.0	41	10.5	9.0
Pneumonia	22	5.6	4.6	15	3.8	3.1	15	3.8	3.2
COVID-19	2	0.5	0.4	4	1.0	0.8	3	0.8	0.6
Pneumonia bacterial	1	0.3	0.2	6	1.5	1.2	1	0.3	0.2
Respiratory tract infection	2	0.5	0.4	1	0.3	0.2	4	1.0	0.8
General disorders and administration site conditions	39	9.9	8.2	30	7.7	6.3	33	8.4	7.1
Condition aggravated	32	8.1	6.7	24	6.1	5.0	28	7.1	6.0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	28	7.1	5.8	23	5.9	4.8	15	3.8	3.1
Lung neoplasm malignant	3	0.8	0.6	4	1.0	0.8	3	0.8	0.6
Squamous cell carcinoma of the skin	4	1.0	0.8	4	1.0	0.8	1	0.3	0.2
Basal cell carcinoma	1	0.3	0.2	4	1.0	0.8	3	0.8	0.6
Cardiac disorders	25	6.4	5.3	16	4.1	3.3	19	4.9	4.0
Cardiac failure	3	0.8	0.6	1	0.3	0.2	5	1.3	1.0
Renal and urinary disorders	3	0.8	0.6	7	1.8	1.4	4	1.0	0.8
Acute kidney injury	3	0.8	0.6	4	1.0	0.8	3	0.8	0.6

PY: patient-years. Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

On treatment AEs leading to death (IPF trial 1305-0014)

Deaths occurred in 104 patients enrolled in trial 1305-0014. The frequency of AEs resulting in fatal outcome was lowest in the 18 mg bid nerandomilast group (2.8%) compared with the placebo (6.6%) and 9 mg bid nerandomilast groups (5.4%). Condition aggravated was the most frequently reported fatal AE (placebo: 1.8%; 9 mg bid nerandomilast: 0.5%; 18 mg bid nerandomilast: 1.3%) (DBL2)

SAEs (PPF pivotal trial 1305-0023)

Up to DBL1, SAEs were most frequently reported in the SOC 'infections and infestations' (placebo: 15.6%; 9 mg bid nerandomilast: 13.0%; 18 mg bid nerandomilast: 13.8%), 'respiratory, thoracic, and mediastinal disorders' (14.8%; 10.4%; 8.4%), and 'general disorders and administration site conditions' (13.0%; 10.2%; 6.1%). At the PT level, most frequently reported SAEs overall were 'condition aggravated' (11.2%; 8.9%; 5.4%), and 'pneumonia' (7.1%; 7.6%, 6.9%). All other SAEs were reported in <3% of the patients in each of the treatment groups.

Frequencies of SAEs in the PT "condition aggravated" (coded term for 'suspected acute ILD exacerbations' and 'acute ILD exacerbations') were decreased under nerandomilast treatment compared with placebo, with the lowest numbers in the 18 mg group. Likewise, SAEs in the SOC "respiratory, thoracic, and

mediastinal disorders" were reported less frequently in both nerandomilast groups compared with placebo and were lowest in the 18 mg group. This is mirrored by the trends seen in PTs such as "dyspnoea" and "interstitial lung disease". Frequencies of other reported PTs were generally balanced for SAEs across treatment groups. All SAEs reported during the on-treatment period of the trial are shown in below.

The overall AE profile up to DBL2 was in line with that described for DBL1. The frequencies of severe AEs and SAEs were numerically lower for the nerandomilast groups than for the placebo group, with the lowest frequency of fatal AEs in the 18 mg bid nerandomilast group. Up to DBL2, the rate ratio [95% CI] of fatal AEs versus placebo was lower for 18 mg bid nerandomilast (0.3 [0.2, 0.6]) than for 9 mg bid nerandomilast (0.5 [0.3, 0.9]). The frequency of AELDs remained balanced across treatment groups up to DBL2.

At a PT level, all SAEs were reported in less than 3% of patients except for condition aggravated (placebo: 13.3%, 9 mg bid nerandomilast: 9.2%, 18 mg bid nerandomilast: 6.4%), pneumonia (7.4%, 7.9%, 7.9%), and pulmonary hypertension (3.3%, 2.0%, and 2.8%).

Table *120*: Patients with SAEs (frequency >1% in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0023)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 SAE	184	46.9	45.9	157	40.0	38.4	168	43.0	43.0
Infections and infestations	64	16.3	13.8	54	13.7	11.5	62	15.9	13.5
Pneumonia	29	7.4	6.0	31	7.9	6.4	31	7.9	6.6
COVID-19	9	2.3	1.8	5	1.3	1.0	4	1.0	0.8
Influenza	3	0.8	0.6	2	0.5	0.4	6	1.5	1.2
Pneumonia bacterial	4	1.0	0.8	3	0.8	0.6	3	0.8	0.6
Respiratory tract infection	1	0.3	0.2	4	1.0	0.8	2	0.5	0.4
COVID-19 pneumonia	0	0	0	0	0	0	4	1.0	0.8
Respiratory, thoracic, and mediastinal disorders	62	15.8	13.1	47	12.0	9.9	40	10.2	8.4
Pulmonary hypertension	13	3.3	2.6	8	2.0	1.6	11	2.8	2.3
Pneumothorax	10	2.6	2.0	7	1.8	1.4	5	1.3	1.0
Respiratory failure	9	2.3	1.8	6	1.5	1.2	7	1.8	1.4
Interstitial lung disease	10	2.6	2.0	4	1.0	0.8	4	1.0	0.8
Dyspnoea	8	2.0	1.6	6	1.5	1.2	2	0.5	0.4
Pulmonary embolism	2	0.5	0.4	4	1.0	0.8	3	0.8	0.6
Pulmonary fibrosis	5	1.3	1.0	6	1.5	1.2	1	0.3	0.2
Acute respiratory failure	4	1.0	0.8	3	0.8	0.6	4	1.0	0.8
Pneumomediastinum	4	1.0	0.8	2	0.5	0.4	5	1.3	1.0
General disorders and administration site conditions	60	15.3	12.4	41	10.4	8.4	29	7.4	6.1
Condition aggravated	52	13.3	10.7	36	9.2	7.3	25	6.4	5.2
Cardiac disorders	18	4.6	3.7	20	5.1	4.1	24	6.1	5.0
Atrial fibrillation	1	0.3	0.2	3	0.8	0.6	5	1.3	1.0
Cardiac failure	4	1.0	0.8	1	0.3	0.2	4	1.0	0.8
Coronary artery disease	2	0.5	0.4	5	1.3	1.0	1	0.3	0.2
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	9	2.3	1.8	14	3.6	2.8	16	4.1	3.3
Basal cell carcinoma	1	0.3	0.2	3	0.8	0.6	4	1.0	0.8
Renal and urinary disorders	2	0.5	0.4	5	1.3	1.0	3	0.8	0.6
Acute kidney injury	1	0.3	0.2	4	1.0	0.8	1	0.3	0.2

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

On treatment AEs leading to death (PPF trial 1305-0023)

The incidence of fatal AEs on treatment was presented by the applicant and are presented here. All deaths have not been presented in the safety review. These have been presented for the time-to-event analysis of all deaths over the duration of the trial as an efficacy endpoint.

On treatment AEs leading to death (trials 1305-0014 and 1305-0023 pooled data)

In pooled data from trials 1305-0014 and 1305-0023, the frequency of fatal AEs was lower in the nerandomilast groups than in the placebo group, with rate ratios (95% CI) versus placebo of 0.62 (0.42, 0.92) for 9 mg bid nerandomilast and 0.37 (0.23, 0.59) for 18 mg bid nerandomilast. Condition aggravated (coded term for suspected acute/acute ILD exacerbation) was the most frequently reported fatal AE, with higher frequency in the placebo than the nerandomilast groups. All other PTs were reported for <1% of the patients in any treatment group. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Table *121*: Patients with AEs leading to death by SOC and PT (with ≥2 patients in any treatment group in the overall population at the PT level) – TS (SAF1/SAF1c)

	Overall population[1]						Non-pirfenidone population[2]					
SOC PT	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Patients with fatal AE	64	8.2	40	5.1	23	2.9	54	8.3	33	5.0	19	2.9
General disorders and administration site conditions	28	3.6	9	1.2	9	1.2	23	3.5	7	1.1	8	1.2
Condition aggravated	20	2.6	7	0.9	8	1.0	16	2.5	5	0.8	7	1.1
Death	3	0.4	2	0.3	0	0	3	0.5	2	0.3	0	0
Disease progression	4	0.5	0	0	1	0.1	3	0.5	0	0	1	0.2
Respiratory, thoracic, and mediastinal disorders	13	1.7	9	1.2	5	0.6	13	2.0	9	1.4	4	0.6
Respiratory failure	4	0.5	3	0.4	1	0.1	4	0.6	3	0.5	1	0.2
Interstitial lung disease	3	0.4	0	0	1	0.1	3	0.5	0	0	1	0.2
Dyspnoea	2	0.3	0	0	0	0	2	0.3	0	0	0	0
Infections and infestations	11	1.4	10	1.3	3	0.4	9	1.4	8	1.2	2	0.3
Pneumonia	5	0.6	4	0.5	1	0.1	5	0.8	2	0.3	1	0.2
Septic shock	1	0.1	2	0.3	0	0	0	0	2	0.3	0	0
Cardiac disorders	4	0.5	9	1.2	1	0.1	3	0.5	6	0.9	1	0.2
Cardiac arrest	3	0.4	1	0.1	0	0	2	0.3	1	0.2	0	0
Acute myocardial infarction	0	0	2	0.3	0	0	0	0	1	0.2	0	0
Cardiogenic shock	0	0	2	0.3	0	0	0	0	2	0.3	0	0
Ischaemic cardiomyopathy	0	0	2	0.3	0	0	0	0	1	0.2	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5	0.6	1	0.1	3	0.4	4	0.6	1	0.2	2	0.3
Vascular disorders	1	0.1	1	0.1	1	0.1	1	0.2	1	0.2	1	0.2
Nervous system disorders	1	0.1	1	0.1	0	0	0	0	1	0.2	0	0
Blood and lymphatic system disorders	1	0.1	0	0	0	0	1	0.2	0	0	0	0
Gastrointestinal disorders	0	0	1	0.1	0	0	0	0	1	0.2	0	0
Injury, poisoning and procedural complications	0	0	0	0	1	0.1	0	0	0	0	1	0.2

1 Data from all patients by randomised treatment

2 Data from patients with no IPF or on nintedanib background treatment by randomised treatment

On-treatment AEs leading to death IPF Trial 1305-0014

Table *122*: Patients with AEs leading to death by SOC and PT (with ≥2 patients in any treatment group at the PT level) over the whole trial up to DBL2 – TS]

SOC PT	Placebo N	 %	 Rate/ 100PY	Nera 9 mg bid N	 %	 Rate/ 100PY	Nera 18 mg bid N	 %	 Rate/ 100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with fatal AE	26	6.6	5.4	21	5.4	4.3	11	2.8	2.3
General disorders and administration site conditions	11	2.8	2.3	3	0.8	0.6	5	1.3	1.0
Condition aggravated	7	1.8	1.4	2	0.5	0.4	5	1.3	1.0
Disease progression	2	0.5	0.4	0	0	0	0	0	0
Infections and infestations	4	1.0	0.8	5	1.3	1.0	1	0.3	0.2
Pneumonia	2	0.5	0.4	3	0.8	0.6	0	0	0
Respiratory, thoracic, and mediastinal disorders	3	0.8	0.6	5	1.3	1.0	2	0.5	0.4
Cardiac disorders	2	0.5	0.4	6	1.5	1.2	0	0	0
Ischaemic cardiomyopathy	0	0	0	2	0.5	0.4	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	3	0.8	0.6	1	0.3	0.2	2	0.5	0.4
Nervous system disorders	1	0.3	0.2	1	0.3	0.2	0	0	0
Vascular disorders	1	0.3	0.2	0	0	0	1	0.3	0.2
Blood and lymphatic system disorders	1	0.3	0.2	0	0	0	0	0	0

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY

Table *123*: Frequency N (%) of patients with adjudicated cause of death – FAS [trial 1305-0014

Adjudicated cause of death/ Specific cause of death	Placebo N	 %	Nera 9mg bid N	 %	Nera 18mg bid N	 %
Number of patients	393	100.00	392	100.00	392	100.00
Number of patients with at least one adverse event categorized as leading to death	42	10.69	36	9.18	25	6.38
Respiratory	25	6.36	23	5.87	16	4.08
Underlying interstitial lung disease	18	4.58	17	4.34	13	3.32
Pneumonia	5	1.27	6	1.53	3	0.77
Other respiratory causes	2	0.51	0	0.00	0	0.00
Cardiovascular (fatal MACE)	6	1.53	6	1.53	3	0.77
Sudden cardiac death	6	1.53	4	1.02	3	0.77
Acute myocardial infarction	0	0.00	1	0.26	0	0.00
Hemorrhagic stroke	0	0.00	1	0.26	0	0.00
Undetermined	5	1.27	5	1.28	3	0.77
Undetermined	5	1.27	5	1.28	3	0.77
Non-cardiovascular/non-respiratory	6	1.53	2	0.51	3	0.77
Malignancy (new or worsening)	5	1.27	1	0.26	2	0.51
Infection (including sepsis)	1	0.25	0	0.00	1	0.26
Suicide	0	0.00	1	0.26	0	0.00

On-treatment AEs leading to death PPF trial 1305-0023

The frequency of fatal AEs was lower in patients receiving nerandomilast compared with placebo, and lowest in the 18 mg group (placebo: 9.7%; 9 mg bid nerandomilast group: 4.8%; 18 mg bid nerandomilast: 3.1%). Condition aggravated was the most frequently reported fatal AE (placebo: 3.3%; 9 mg bid nerandomilast: 1.3%; 18 mg bid nerandomilast: 0.8%). All other PTs were reported for less than 1% of the patients per treatment group.

Table *124*: Patients with AEs leading to death by SOC and PT (with ≥2 patients in any treatment group at the PT level) over the whole trial up to DBL2 – TS (trial 1305-0023) [Table 2: 71, SCS]

SOC PT	Placebo N	 %	 Rate/ 100PY	Nera 9 mg bid N	 %	 Rate/ 100PY	Nera 18 mg bid N	 %	 Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with fatal AE	38	9.7	7.6	19	4.8	3.8	12	3.1	2.5
General disorders and administration site conditions	17	4.3	3.4	6	1.5	1.2	4	1.0	0.8
Condition aggravated	13	3.3	2.6	5	1.3	1.0	3	0.8	0.6
Death	2	0.5	0.4	1	0.3	0.2	0	0	0
Disease progression	2	0.5	0.4	0	0	0	1	0.3	0.2
Respiratory, thoracic, and mediastinal disorders	10	2.6	2.0	4	1.0	0.8	3	0.8	0.6
Respiratory failure	3	0.8	0.6	3	0.8	0.6	1	0.3	0.2
Interstitial lung disease	2	0.5	0.4	0	0	0	1	0.3	0.2
Dyspnoea	2	0.5	0.4	0	0	0	0	0	0
Infections and infestations	7	1.8	1.4	5	1.3	1.0	2	0.5	0.4
Pneumonia	3	0.8	0.6	1	0.3	0.2	1	0.3	0.2
Septic shock	0	0	0	2	0.5	0.4	0	0	0
Cardiac disorders	2	0.5	0.4	3	0.8	0.6	1	0.3	0.2
Cardiac arrest	2	0.5	0.4	0	0	0	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2	0.5	0.4	0	0	0	1	0.3	0.2
Gastrointestinal disorders	0	0	0	1	0.3	0.2	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1	0.3	0.2
Vascular disorders	0	0	0	1	0.3	0.2	0	0	0

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Adjudication of all fatal AEs trial 1305-0023

An independent adjudication committee reviewed all fatal AEs and adjudicated them to cardiovascular, respiratory, or non-cardiovascular/non-respiratory causes. The majority of fatal AEs on-treatment based on TS were adjudicated as respiratory-related.

Table 125**: Patients with AEs leading to death by treatment and adjudicated cause of death up to DBL1 – TS (trial 1305-0023)**

Adjudicated cause of death	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 on-treatment fatal AE[1]	23	5.9	4.9	17	4.3	3.6	7	1.8	1.5
Respiratory	17	4.3	3.6	9	2.3	1.9	5	1.3	1.1
Cardiovascular (fatal MACE)	1	0.3	0.2	5	1.3	1.1	1	0.3	0.2
Non-cardiovascular/non-respiratory	2	0.5	0.4	3	0.8	0.6	1	0.3	0.2
Undetermined	3	0.8	0.6	0	0	0	0	0	0

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

1 Numbers of patients with at least 1 on-treatment fatal AE differ from numbers of patients with fatal AEs presented in Table 2: 68, as at the time of data cut-off for DBL1 adjudication was either still ongoing or not yet triggered for some patients.

Table *126*: **Frequency N (%) of patients with adjudicated cause of death – FAS (trial 1305-0023)**

Adjudicated cause of death/ Specific cause of death	Placebo		Nera 9mg bid		Nera 18mg bid	
	N	%	N	%	N	%
Number of patients	392	100.00	393	100.00	391	100.00
Number of patients with at least one adverse event categorized as leading to death	44	11.22	30	7.63	23	5.88
Respiratory	33	8.42	17	4.33	14	3.58
Underlying interstitial lung disease	22	5.61	9	2.29	7	1.79
Pneumonia	10	2.55	8	2.04	5	1.28
Other respiratory causes	1	0.26	0	0.00	2	0.51
Undetermined	7	1.79	3	0.76	5	1.28
Undetermined	7	1.79	3	0.76	5	1.28
Cardiovascular (fatal MACE)	2	0.51	5	1.27	3	0.77
Sudden cardiac death	2	0.51	3	0.76	2	0.51
Cardiovascular procedures	0	0.00	1	0.25	1	0.26
Other cardiovascular causes	0	0.00	1	0.25	0	0.00
Non-cardiovascular/non-respiratory	2	0.51	5	1.27	1	0.26
Malignancy (new or worsening)	0	0.00	3	0.76	0	0.00
Infection (including sepsis)	1	0.26	1	0.25	0	0.00
Gastrointestinal causes	0	0.00	1	0.25	0	0.00
Other non-cv/non-respiratory causes	1	0.26	0	0.00	0	0.00
Trauma	0	0.00	0	0.00	1	0.26

5.4.6. Discontinuation due to adverse events

Analyses including 1305-0014 DBL2 and 1305-0023 DBL2 pooled data

In the overall patient population of trials 1305-0014 and 1305-0023 pooled, the frequency of AELDs across treatment groups was similar, with rate ratios (95% CI) versus placebo of 1.00 (0.77, 1.30) for 9 mg bid nerandomilast and 1.11 (0.87, 1.43) for 18 mg bid nerandomilast. AELDs were most frequently reported in the SOCs gastrointestinal disorders, benign, malignant, and unspecified neoplasms (including cysts and polyps), and general disorders and administration site conditions. At the PT level, diarrhoea was the most common AELD overall as well as in both nerandomilast groups; the frequency was highest in the 18 mg bid nerandomilast group. Condition aggravated was the most frequent AELD under placebo, with a higher frequency in this group than under nerandomilast treatment. Dyspnoea AELDs were reported only in the placebo group except for 1 event in the 9 mg bid nerandomilast group. All other AELDs were generally balanced across treatment groups. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

Table *127*: Patients with AEs leading to permanent treatment discontinuation (with frequencies ≥1% in any treatment group in the overall population) – TS (SAF1/SAF1c)

	Overall population1						Non-pirfenidone population2					
SOC PT	Placebo		Nera 9 mg bid		Nera 18 mg bid		Placebo		Nera 9 mg bid		Nera 18 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	785	100.0	785	100.0	783	100.0	651	100.0	665	100.0	655	100.0
Patients with any AELD	100	12.7	100	12.7	111	14.2	84	12.9	90	13.5	97	14.8
Gastrointestinal disorders	9	1.2	26	3.3	39	5.0	7	1.1	23	3.5	36	5.5
Diarrhoea	4	0.5	17	2.2	34	4.3	4	0.6	14	2.1	34	5.2
Neoplasms benign, malignant, and unspecified[3]	21	2.7	22	2.8	20	2.6	16	2.5	22	3.3	16	2.4
General disorders and administration site conditions	26	3.3	12	1.5	17	2.2	25	3.8	11	1.7	14	2.1
Condition aggravated	21	2.7	9	1.2	12	1.5	20	3.1	8	1.2	9	1.4
Respiratory, thoracic, and mediastinal disorders	18	2.3	12	1.5	2	0.3	14	2.2	9	1.4	1	0.2
Dyspnoea	8	1.0	1	0.1	0	0	5	0.8	1	0.2	0	0
Infections and infestations	11	1.4	8	1.0	9	1.2	9	1.4	7	1.1	9	1.4
Psychiatric disorders[4]	3	0.4	8	1.0	9	1.2	3	0.5	8	1.2	8	1.2
Investigations	2	0.3	2	0.3	10	1.3	2	0.3	1	0.2	7	1.4

1 Data from all patients by randomised treatment

2 Data from patients not taking pirfenidone as background therapy by randomised treatment

3 This includes cysts and polyps. patients with a malignant neoplasm other than appropriately treated basal cell carcinoma, *in situ* squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix, had to permanently discontinue trial treatment.

4 As per CTP, patients with a new onset of severe depression (HADS >14) had to temporarily discontinue trial treatment. If the severe depression was not considered related to the trial medication and the patient had recovered, treatment could be restarted. Patients with suicidal behaviour/serious suicidality ideation (C-SSRS Type 4/5) had to permanently discontinue trial treatment.

Adverse events leading to temporary treatment interruption: Analyses including 1305-0014 DBL2 and 1305-0023 DBL1 pooled data

For pooled trials 1305-0014 and 1305-0023, similar trends for AEs leading to temporary treatment interruption were observed as described for trials 1305-0014 and 1305-0023.

IPF pivotal trial 1305-0014

Adverse events leading to permanent treatment discontinuation (IPF)

Table *128*: Patients with AEs leading to permanent treatment discontinuation by SOC and PT frequencies ≥1% in any treatment group) over the whole trial up to DBL2 – TS (1305-0014)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with at least 1 AE leading to treatment discontinuation	51	13.0	10.6	53	13.5	10.9	63	16.1	13.2
Gastrointestinal disorders	5	1.3	1.0	10	2.6	2.1	29	7.4	6.1
Diarrhoea	2	0.5	0.4	7	1.8	1.4	24	6.1	5.0
Nausea	2	0.5	0.4	1	0.3	0.2	4	1.0	0.8
Neoplasms benign, malignant, and unspecified (including cysts and polyps)[1]	16	4.1	3.3	15	3.8	3.1	9	2.3	1.9
Lung neoplasm malignant	2	0.5	0.4	4	1.0	0.8	3	0.8	0.6
General disorders and administration site conditions	10	2.5	2.1	5	1.3	1.0	10	2.6	2.1
Condition aggravated	7	1.8	1.4	3	0.8	0.6	6	1.5	1.2
Asthenia	0	0	0	0	0	0	4	1.0	0.8
Respiratory, thoracic, and mediastinal disorders	8	2.0	1.6	7	1.8	1.4	1	0.3	0.2
Idiopathic pulmonary fibrosis	1	0.3	0.2	4	1.0	0.8	0	0	0
Infections and infestations	4	1.0	0.8	5	1.3	1.0	3	0.8	0.6
Psychiatric disorders[2]	0	0	0	5	1.3	1.0	5	1.3	1.0
Nervous system disorders	4	1.0	0.8	2	0.5	0.4	2	0.5	0.4
Metabolism and nutrition disorders	1	0.3	0.2	1	0.3	0.2	4	1.0	0.8
Vascular disorders	1	0.3	0.2	0	0	0	4	1.0	0.8
Vasculitis[3]	0	0	0	0	0	0	4	1.0	0.8

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

1.]), patients with a malignant neoplasm other than appropriately treated basal cell carcinoma, in situ squamous cell carcinoma of the skin, or in situ carcinoma of uterine cervix, had to permanently discontinue trial treatment.

2. patients with a new onset of severe depression (HADS >14) had to temporarily discontinue trial treatment. If the severe depression was not considered related to the trial medication and the patient had recovered, treatment could be restarted. Patients with suicidal behaviour/serious suicidality ideation (C-SSRS type 4/5) had to permanently discontinue trial treatment.

3. treatment had to be temporarily discontinued in the case of events suspicious of vasculitis until the investigator could exclude a causal relationship. Cases of vasculitis in this table were as reported by the investigator and still had to undergo adjudication

Adverse events leading to temporary treatment interruption (IPF)

Table *129*: Patients with AEs leading to temporary treatment interruption (frequency ≥1% in any treatment group at the PT level) over the whole trial up to DLB1-TS (trial 1305-0014)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	393	100.0		392	100.0		392	100.0	
Patients with at least 1 AE leading to treatment interruption	63	16.0	15.8	77	19.6	20.0	83	21.2	21.9
Infections and infestations[1]	32	8.1	7.6	24	6.1	5.7	21	5.4	5.0
COVID-19	6	1.5	1.4	11	2.8	2.5	6	1.5	1.4
Pneumonia	9	2.3	2.1	3	0.8	0.7	8	2.0	1.9
Latent tuberculosis	5	1.3	1.2	1	0.3	0.2	1	0.3	0.2
Gastrointestinal disorders	6	1.5	1.4	23	5.9	5.5	27	6.9	6.5
Diarrhoea	1	0.3	0.2	17	4.3	4.0	20	5.1	4.8
Psychiatric disorders[2]	4	1.0	0.9	6	1.5	1.4	6	1.5	1.4
Depression	3	0.8	0.7	4	1.0	0.9	1	0.3	0.2
General disorders and administration site conditions	2	0.5	0.5	6	1.5	1.4	6	1.5	1.4
Condition aggravated	2	0.5	0.5	3	0.8	0.7	5	1.3	1.2

PY: patient years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.
1. treatment had to be interrupted in case of severe (CTCAE>2), serious, opportunistic or *M. tuberculosis* infections and could be restarted when the patient has recovered according to investigator's assessment.
2. patients with a new onset of severe depression (HADS >14) had to temporarily discontinue trial treatment. If the severe depression was not considered related to the trial medication and the patient had recovered, treatment could be restarted.

Up to DBL2, the trends in AEs leading to temporary treatment interruption were similar to DBL1.

PPF pivotal trial 1305-0023

Adverse events leading to permanent treatment discontinuation (PPF)

Table *130*: Patients with AEs leading to permanent treatment discontinuation by SOC and PT (frequencies ≥1% in any treatment group) over the whole trial up to DBL2 – TS (trial 1305-0023)

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 AE leading to treatment discontinuation	49	12.5	9.9	47	12.0	9.4	48	12.3	9.9
Gastrointestinal disorders	4	1.0	0.8	16	4.1	3.2	10	2.6	2.0
Diarrhoea	2	0.5	0.4	10	2.5	2.0	10	2.6	2.0
General disorders and administration site conditions	16	4.1	3.2	7	1.8	1.4	7	1.8	1.4
Condition aggravated	14	3.6	2.8	6	1.5	1.2	6	1.5	1.2
Neoplasms benign, malignant[1], and unspecified (including cysts and polyps)	5	1.3	1.0	7	1.8	1.4	11	2.8	2.3
Infections and infestations	7	1.8	1.4	3	0.8	0.6	6	1.5	1.2
Respiratory, thoracic, and mediastinal disorders	10	2.6	2.0	5	1.3	1.0	1	0.3	0.2
Dyspnoea	5	1.3	1.0	0	0	0	0	0	0
Psychiatric disorders[2]	3	0.8	0.6	3	0.8	0.6	4	1.0	0.8
Investigations	2	0.5	0.4	0	0	0	7	1.8	1.4

PY: patient years; Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

1 patients with a malignant neoplasm other than appropriately treated basal cell carcinoma, *in situ* squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix, had to permanently discontinue trial treatment.
2 patients with a new onset of severe depression (HADS >14) had to temporarily discontinue trial treatment. If the severe depression was not considered related to the trial medication and the patient had recovered, treatment could be restarted. Patients with suicidal behaviour/serious suicidality ideation (CSSRS Type 4/5) had to permanently discontinue trial treatment.

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 AE leading to treatment discontinuation	49	12.5	9.9	47	12.0	9.4	48	12.3	9.9
Gastrointestinal disorders	4	1.0	0.8	16	4.1	3.2	10	2.6	2.0
Diarrhoea	2	0.5	0.4	10	2.5	2.0	10	2.6	2.0
General disorders and administration site conditions	16	4.1	3.2	7	1.8	1.4	7	1.8	1.4
Condition aggravated	14	3.6	2.8	6	1.5	1.2	6	1.5	1.2
Neoplasms benign, malignant[1], and unspecified (including cysts and polyps)	5	1.3	1.0	7	1.8	1.4	11	2.8	2.3
Infections and infestations	7	1.8	1.4	3	0.8	0.6	6	1.5	1.2
Respiratory, thoracic, and mediastinal disorders	10	2.6	2.0	5	1.3	1.0	1	0.3	0.2
Dyspnoea	5	1.3	1.0	0	0	0	0	0	0
Psychiatric disorders[2]	3	0.8	0.6	3	0.8	0.6	4	1.0	0.8
Investigations	2	0.5	0.4	0	0	0	7	1.8	1.4

Adverse events leading to temporary treatment interruption (PPF)

Table *131*: Patients with AEs leading to temporary treatment interruption (frequency ≥1% in any treatment group at the PT level) over the whole trial up to DLB2-TS (trial 1305-0023) [Ref table 2:44, SCS]

SOC	Placebo			Nera 9 mg bid			Nera 18 mg bid		
PT	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Number of patients	392	100.0		393	100.0		391	100.0	
Patients with at least 1 AE leading to treatment interruption	72	18.4	16.0	76	19.3	17.1	81	20.7	19.0
Infections and infestations[1]	30	7.7	6.2	29	7.4	6.0	37	9.5	8.0
Pneumonia	8	2.0	1.6	8	2.0	1.6	15	3.8	3.1
COVID-19	10	2.6	2.0	8	2.0	1.6	8	2.1	1.7
Gastrointestinal disorders	14	3.6	2.9	24	6.1	4.9	24	6.1	5.1
Diarrhoea	6	1.5	1.2	14	3.6	2.8	20	5.1	4.2
General disorders and administration site conditions	5	1.3	1.0	5	1.3	1.0	7	1.8	1.4
Condition aggravated	4	1.0	0.8	4	1.0	0.8	6	1.5	1.2

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.
1 treatment had to be interrupted in case of severe (CTCAE>2), serious, opportunistic or *M. tuberculosis* infections and could be restarted when the patient has recovered according to investigator's assessment.

5.4.7. Safety in special populations

Safety in special populations

IPF pivotal trial 1305-0014 subgroup analysis:

Sex (IPF)

Table *132*: Overall summary of AEs over the whole trial up to DBL2 by sex – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Male	337	100.0		317	100.0		323	100.0	
Patients with any AE	331	98.2	392.8	300	94.6	370.3	313	96.9	467.8
Severe AEs (CTCAE grade >2)	112	36.2	34.8	110	34.7	31.6	110	34.1	33.2
Investigator-defined drug-related AEs	137	40.7	47.5	144	45.4	57.7	168	52.0	71.9
AELDs	50	14.8	12.3	44	13.9	11.2	47	14.6	11.8
AEs leading to treatment interruption	57	16.9	15.5	62	19.6	17.8	69	21.4	19.8
SAEs	152	45.1	45.5	129	40.7	38.8	131	40.6	40.7
Resulted in death	24	7.1	5.9	19	6.0	4.8	10	3.1	2.5
Female	56	100.0		75	100.0		69	100.0	
Patients with any AE	55	98.2	373.3	71	94.7	386.1	66	95.7	518.8
Severe AEs (CTCAE grade >2)	13	23.2	18.0	22	29.3	26.6	16	23.2	22.8
Investigator-defined drug-related AEs	13	23.2	21.3	35	46.7	62.9	40	58.0	93.9
AELDs	1	1.8	1.3	9	12.0	9.8	16	23.2	20.5
AEs leading to treatment interruption	11	19.6	15.4	21	28.0	27.3	19	27.5	28.0
SAEs	15	26.8	21.2	20	26.7	24.1	18	26.1	26.1
Resulted in death	2	3.6	2.6	2	2.7	2.2	1	1.5	1.3

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Age (IPF)

Table *133*: Overall summary of AEs over the whole trial up to DBL1 by age – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Age <65 years	86	100.0		78	100.0		83	100.0	
Patients with any AE	80	93.0	363.2	72	92.3	316.4	79	95.2	422.0
Severe AEs (CTCAE grade >2)	21	24.4	23.5	17	21.8	19.7	18	21.7	20.8
Investigator-defined drug-related AEs	29	33.7	41.3	33	42.3	54.0	40	48.2	66.6
AELDs	6	7.0	6.0	3	3.9	3.2	9	10.8	9.4
AEs leading to treatment interruption	11	12.8	11.8	20	25.6	25.2	11	13.3	12.2
SAEs	22	25.6	25.2	20	25.6	23.2	19	22.9	21.9
Resulted in death	2	2.3	2.0	2	2.6	2.1	2	2.4	2.1
Age ≥65 years	307	100.0		314	100.0		309	100.0	
Patients with any AE	295	96.1	379.0	296	94.3	401.1	294	95.2	483.1
Severe AEs (CTCAE grade >2)	91	29.6	30.7	97	30.9	31.6	96	31.1	34.1
Investigator-defined drug-related AEs	113	36.8	45.5	148	47.1	69.4	159	51.5	81.7
AELDs	39	12.7	11.6	45	14.3	13.2	51	16.5	15.4
AEs leading to treatment interruption	52	16.9	17.0	57	18.2	18.7	72	23.3	25.0
SAEs	118	38.4	41.6	114	36.3	38.9	112	36.3	41.0
Resulted in death	17	5.5	5.0	15	4.8	4.4	7	2.3	2.1

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by age exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by age subgroup at DBL1.

Race (IPF)

Table 134**: Overall summary of AEs over the whole trial up to DBL1 by race – TS (1305-0014)**

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
White	273	100.0		266	100.0		258	100.0	
Patients with any AE	263	96.3	462.8	248	93.2	401.2	243	94.2	476.1
Severe AEs (CTCAE grade >2)	81	29.7	30.3	76	28.6	28.6	72	27.9	29.6
Investigator-defined drug-related AEs	109	39.9	51.2	129	48.5	48.5	136	52.7	85.2
AELDs	28	10.3	9.2	35	13.2	13.2	42	16.3	15.2
AEs leading to treatment interruption	40	14.7	14.2	57	21.4	21.4	59	22.9	24.4
SAEs	96	35.2	37.2	91	34.2	34.2	81	31.4	34.0
Resulted in death	15	5.5	4.9	15	5.6	5.6	9	3.5	3.2
Asian	117	100.0		123	100.0		132	100.0	
Patients with any AE	110	94.0	263.5	118	95.9	359.6	138	97.0	448.8
Severe AEs (CTCAE grade >2)	31	26.5	27.1	38	30.9	31.5	42	31.8	33.9
Investigator-defined drug-related AEs	31	26.5	29.7	51	41.5	54.3	61	46.2	64.1
AELDs	17	14.5	13.4	13	10.6	9.4	17	12.9	11.4
AEs leading to treatment interruption	23	19.7	20.2	20	16.3	16.3	24	18.2	17.8
SAEs	44	37.6	40.3	43	35.0	36.3	49	37.1	40.7
Resulted in death	4	3.4	3.1	2	1.6	1.4	0	0	0
Black or African American	2	100.0		3	100.0		1	100.0	
Patients with any AE	1	50.0	87.6	2	66.7	103.6	1	100.0	9131.3
Severe AEs (CTCAE grade >2)	0	0	0	0	0	0	0	0	0
Investigator-defined drug-related AEs	1	50.0	87.6	1	33.3	32.3	1	100.0	9131.3
AELDs	0	0	0	0	0	0	1	100.0	166.8
AEs leading to treatment interruption	0	0	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0	0	0
Resulted in death	0	0	0	0	0	0	0	0	0

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by race exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by race subgroup at DBL1.

Ethnicity (IPF)

Table *135*: Overall summary of AEs over the whole trial up to DBL1 by ethnicity – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Not Hispanic or Latino	365	100.0		369	100.0		348	100.0	
Patients with any AE	349	95.6	372.2	350	94.9	393.0	334	96.0	517.5
Severe AEs (CTCAE grade >2)	105	28.8	29.4	106	28.7	28.4	100	28.7	30.8
Investigator-defined drug-related AEs	135	37.0	45.9	175	47.4	67.5	186	53.5	85.8
AELDs	44	12.1	11.0	48	13.0	11.6	55	15.8	14.6
AEs leading to treatment interruption	59	16.2	15.9	75	20.3	20.5	70	20.1	20.8
SAEs	131	35.9	38.1	126	34.2	35.1	117	33.6	37.0
Resulted in death	17	4.7	4.2	13	3.5	3.1	6	1.7	1.6
Hispanic or Latino	28	100.0		23	100.0		44	100.0	
Patients with any AE	26	92.9	426.0	18	78.3	240.0	39	88.6	259.5
Severe AEs (CTCAE grade >2)	7	25.0	25.4	8	34.8	39.3	14	31.8	32.1
Investigator-defined drug-related AEs	7	25.0	28.5	6	26.1	40.4	13	29.6	34.2
AELDs	1	3.6	3.1	0	0	0	5	11.4	9.9
AEs leading to treatment interruption	4	14.3	13.9	2	8.7	10.3	13	29.6	31.2
SAEs	9	32.1	33.2	8	34.8	39.5	14	31.8	31.8
Resulted in death	2	7.1	6.2	4	17.4	18.6	3	6.8	6.0

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Overall AE profile as assessed by ethnicity showed trends generally consistent with the overall AE profile both DBL1 and DBL2

Baseline FVC % predicted (IPF)

Table *136*: Overall summary of AEs over the whole trial up to DBL1 by baseline FVC % predicted – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Baseline FVC % predicted ≤70%	133	100.0		124	100.0		131	100.0	
Patients with any AE	129	97.0	443.2	121	97.6	436.9	127	97.0	554.0
Severe AEs (CTCAE grade >2)	43	32.3	36.1	42	33.9	34.4	47	35.9	42.9
Investigator-defined drug-related AEs	48	36.1	47.8	52	41.9	60.4	62	47.3	71.2
AELDs	18	13.5	13.0	18	14.5	13.6	23	17.6	17.3
AEs leading to treatment interruption	21	15.8	16.5	27	21.8	23.1	27	20.6	23.2
SAEs	54	40.6	47.0	51	41.1	44.1	57	43.5	53.8
Resulted in death	7	5.3	5.0	11	8.9	8.3	6	4.6	4.4
Baseline FVC % predicted >70%	260	100.0		268	100.0		261	100.0	
Patients with any AE	246	94.6	347.6	247	92.2	358.7	246	94.3	434.2
Severe AEs (CTCAE grade >2)	69	26.5	25.9	72	26.9	26.5	67	25.7	25.9
Investigator-defined drug-related AEs	94	36.2	43.1	129	48.1	68.6	137	52.5	81.7
AELDs	27	10.4	9.1	30	11.2	9.9	37	14.2	12.6
AEs leading to treatment interruption	42	16.2	15.4	50	18.7	18.7	56	21.5	21.4
SAEs	86	33.1	33.6	83	31.0	31.5	74	28.4	29.1
Resulted in death	12	4.6	4.0	6	2.2	2.0	3	1.2	1.0

AELDs: AEs leading to treatment discontinuation, FVC: forced vital capacity, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by baseline FVC% predicted category subgroups showed trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by baseline FVC% predicted category subgroups at DBL1.

Baseline body weight (IPF)

Table *137*: Overall summary of AEs over the whole trial up to DBL1 by baseline body weight – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Baseline body weight <65 kg	72	100.0		100	100.0		83	100.0	
Patients with any AE	68	94.4	286.3	96	96.0	527.1	81	97.6	640.5
Severe AEs (CTCAE grade >2)	20	27.8	29.4	27	27.0	28.0	31	37.4	41.1
Investigator-defined drug-related AEs	19	26.4	30.3	52	52.0	85.5	44	53.0	83.5
AELDs	9	12.5	11.9	14	14.0	12.9	16	19.3	17.7
AEs leading to treatment interruption	9	12.5	13.0	19	19.0	20.2	19	22.9	23.5
SAEs	25	34.7	38.0	31	31.0	32.9	32	38.6	43.2
Resulted in death	4	5.6	5.3	1	1.0	0.9	1	1.2	1.1
Baseline body weight ≥65 kg	321	100.0		292	100.0		309	100.0	
Patients with any AE	307	95.6	403.3	272	93.2	347.2	292	94.5	436.3
Severe AEs (CTCAE grade >2)	92	28.7	29.0	87	29.8	29.3	83	26.9	28.3
Investigator-defined drug-related AEs	123	38.3	48.1	129	44.2	60.5	155	50.2	76.7
AELDs	36	11.2	10.0	34	11.6	10.4	44	14.2	13.1
AEs leading to treatment interruption	54	16.8	16.4	58	19.9	20.0	64	20.7	21.5
SAEs	115	35.8	37.7	103	35.3	36.1	99	32.0	34.6
Resulted in death	15	4.7	4.2	16	5.5	4.9	8	2.6	2.3

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

For both DBL1 and DBL2, the overall AE profile as assessed by baseline body weight category subgroups was similar and generally consistent with the overall AE profile in all patients

Baseline eGFR (IPF)

Table *138*: AEs up to DBL1 by baseline eGFR – TS (1305-0014)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
eGFR ≥90 mL/min/1.73 m²	99	100.0		96	100.0		93	100.0	
Any AE	94	95.0	370.6	89	92.7	312.2	88	94.6	439.8
Severe AEs (CTCAE grade >2)	26	26.3	26.7	23	24.0	22.5	25	26.9	27.6
Investigator-defined drug-related AEs	37	37.4	47.7	40	41.7	56.0	43	46.2	63.8
AELDs	9	9.1	8.2	5	5.2	4.5	11	11.8	10.6
AEs leading to treatment interruption	16	16.2	15.9	21	21.9	21.3	16	17.2	16.9
SAEs	31	31.3	33.2	28	29.2	28.1	30	32.3	34.3
Resulted in death	2	2.0	1.8	2	2.1	1.8	1	1.1	1.0
eGFR 60 to <90 mL/min/1.73 m²	254	100.0		254	100.0		244	100.0	
Any AE	244	96.1	379.4	238	93.7	411.7	233	95.5	470.2
Severe AEs (CTCAE grade >2)	72	28.4	28.9	77	30.3	30.9	72	29.5	31.4
Investigator-defined drug-related AEs	90	35.4	42.6	125	49.2	73.9	129	52.9	83.8
AELDs	28	11.0	10.0	37	14.6	13.3	39	16.0	14.6
AEs leading to treatment interruption	40	15.8	15.4	49	19.3	20.1	50	20.5	21.1
SAEs	94	37.0	39.2	86	33.9	35.7	79	32.4	34.7
Resulted in death	13	5.1	4.6	12	4.7	4.3	6	2.5	2.2
eGFR <60[1] mL/min/1.73 m²	40	100.0		42	100.0		55	100.0	
Any AE	37	92.5	363.0	41	97.6	400.1	52	94.6	518.9
Severe AEs (CTCAE grade >2)	14	35.0	36.3	14	33.3	33.3	17	30.9	35.3
Investigator-defined drug-related AEs	15	37.5	50.6	16	38.1	47.7	27	49.1	80.6
AELDs	8	20.0	18.5	6	14.3	13.1	10	18.2	17.9
AEs leading to treatment interruption	7	17.5	17.8	7	16.7	16.5	17	30.9	36.2
SAEs	15	37.5	39.9	20	47.6	51.4	22	40.0	48.8
Resulted in death	4	10.0	9.2	3	7.1	6.5	2	3.6	3.5

1 Patients with eGFR ≤30 mL/min/1.73m2 at baseline were not allowed to enter the trial. Please note that 2 patients with a baseline eGFR <30 were included in trial 1305-0014.

Up to DBL2, the AE profile by eGFR subgroups followed the same trends as described for DBL1.

PPF pivotal trial 1305-0023 subgroup analysis:

Sex (PPF)

Table *139*: Overall summary of AEs over the whole trial up to DBL1 by sex – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Male	231	100.0		203	100.0		220	100.0	
Patients with any AE	218	94.4	360.0	191	94.1	368.7	208	94.6	546.3
Severe AEs (CTCAE grade >2)	88	38.1	37.1	82	40.4	41.1	82	37.3	39.2
Investigator-defined drug-related AEs	74	32.0	35.4	85	41.9	52.8	101	45.9	65.4
AELDs	34	14.7	12.4	24	11.8	9.8	24	10.9	9.6
AEs leading to treatment interruption	38	16.5	15.0	42	20.7	19.4	42	19.1	18.7
SAEs	104	45.0	46.4	85	41.9	42.5	91	41.4	45.1
Resulted in death	19	8.2	6.9	12	5.6	4.9	6	2.7	2.4
Female	161	100.0		190	100.0		171	100.0	
Patients with any AE	151	93.8	341.0	178	93.7	402.9	156	91.2	366.0
Severe AEs (CTCAE grade >2)	58	36.0	34.1	57	30.0	28.4	63	36.8	36.4
Investigator-defined drug-related AEs	54	33.5	37.5	72	37.9	46.9	77	45.0	57.0
AELDs	12	7.5	6.1	15	7.9	6.5	20	11.7	9.6
AEs leading to treatment interruption	29	18.0	16.6	36	19.0	17.6	37	21.6	20.5
SAEs	64	39.8	39.7	65	34.2	33.7	63	36.9	36.4
Resulted in death	10	6.2	5.1	6	3.2	2.6	2	1.2	0.9

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by sex exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by sex subgroup at DBL1.

Age (PPF)

Table *140*: Overall summary of AEs over the whole trial up to DBL1 by age – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Age <65 years	149	100.0		142	100.0		152	100.0	
Patients with any AE	139	93.3	328.3	130	91.6	359.4	133	87.5	334.5
Severe AEs (CTCAE grade >2)	46	30.9	27.5	41	28.9	27.0	48	31.6	30.3
Investigator-defined drug-related AEs	42	28.2	28.9	53	37.3	44.4	57	37.5	45.3
AELDs	13	8.7	6.9	12	8.5	6.9	12	7.9	6.5
AEs leading to treatment interruption	27	18.1	16.0	27	19.0	17.6	26	17.1	15.8
SAEs	56	37.6	35.5	43	30.3	28.8	49	32.2	30.6
Resulted in death	5	3.4	2.6	5	3.5	2.9	3	2.0	1.6
Age ≥65 years	243	100.0		251	100.0		239	100.0	
Patients with any AE	230	94.7	368.1	239	95.2	399.6	231	96.7	564.3
Severe AEs (CTCAE grade >2)	100	41.2	41.6	98	39.0	39.5	97	40.6	43.4
Investigator-defined drug-related AEs	86	35.4	41.5	104	41.4	53.3	121	50.6	73.9
AELDs	33	13.4	11.7	27	10.8	9.0	32	13.4	11.6
AEs leading to treatment interruption	40	16.5	15.4	51	20.3	19.1	53	22.2	21.9
SAEs	112	46.1	49.2	107	42.6	43.9	105	43.9	48.9
Resulted in death	24	9.9	8.5	13	5.2	4.3	5	2.1	1.8

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by age exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by age subgroup at DBL1.

Race (PPF)

Table *141*: Overall summary of AEs over the whole trial up to DBL1 by race – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
White	226	100.0		224	100.0		235	100.0	
Patients with any AE	212	93.8	368.9	206	92.0	384.8	217	92.3	427.1
Severe AEs (CTCAE grade >2)	75	33.2	31.7	68	30.4	30.3	82	34.9	36.0
Investigator-defined drug-related AEs	74	32.7	37.7	94	42.0	57.4	106	45.1	63.1
AELDs	30	13.3	11.4	22	9.8	8.5	29	12.3	10.8
AEs leading to treatment interruption	34	15.0	14.1	43	19.2	18.9	48	20.4	20.0
SAEs	86	38.1	37.9	75	33.5	33.7	87	37.0	39.2
Resulted in death	16	7.1	6.0	12	5.4	4.6	6	2.6	2.2
Asian	154	100.0		161	100.0		145	100.0	
Patients with any AE	145	94.2	314.3	155	96.3	379.5	136	93.8	493.4
Severe AEs (CTCAE grade >2)	67	43.5	42.4	70	43.5	42.1	57	39.3	39.3
Investigator-defined drug-related AEs	50	32.5	34.0	60	37.3	41.6	67	46.2	59.7
AELDs	15	9.7	7.8	17	10.6	8.2	14	9.7	7.9
AEs leading to treatment interruption	31	20.1	17.8	35	21.7	19.1	30	20.7	19.6
SAEs	77	50.0	52.2	73	45.3	45.2	64	44.1	45.4
Resulted in death	11	7.1	5.6	6	3.7	2.9	2	1.4	1.1
Black or African American	7	100.0		3	100.0		6	100.0	
Patients with any AE	7	100.0	1141.4	3	100.0	1461.0	6	100.0	477.5
Severe AEs (CTCAE grade >2)	2	28.6	23.9	1	33.3	32.8	3	50.0	51.6
Investigator-defined drug-related AEs	3	42.9	57.0	1	33.3	40.5	1	16.7	13.0
AELDs	0	0	0	0	0	0	1	16.7	13.0
AEs leading to treatment interruption	2	28.6	25.6	0	0	0	0	0	0
SAEs	2	28.6	24.4	2	66.7	77.1	2	33.3	28.2
Resulted in death	0	0	0	0	0	0	0	0	0

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by race exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by race subgroup at DBL1.

Ethnicity (PPF)

Table *142*: Overall summary of AEs over the whole trial up to DBL1 by ethnicity – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Not Hispanic or Latino	339	100.0		333	100.0		334	100.0	
Patients with any AE	320	94.4	363.1	314	94.3	401.4	316	94.6	557.5
Severe AEs (CTCAE grade >2)	129	38.1	36.6	125	37.5	37.3	129	38.6	39.9
Investigator-defined drug-related AEs	116	34.2	38.4	145	43.5	56.9	161	48.2	67.3
AELDs	38	11.2	9.2	35	10.5	8.7	42	12.6	10.8
AEs leading to treatment interruption	62	18.3	16.7	73	21.9	20.7	70	21.0	20.4
SAEs	149	44.0	44.8	132	39.6	40.1	139	41.6	44.3
Resulted in death	20	5.9	4.8	13	3.9	3.2	6	1.8	1.5
Hispanic or Latino	53	100.0		60	100.0		57	100.0	
Patients with any AE	49	92.5	293.2	55	91.7	309.7	48	84.2	199.9
Severe AEs (CTCAE grade >2)	17	32.1	30.9	14	23.3	21.4	16	28.1	27.1
Investigator-defined drug-related AEs	12	22.6	23.6	12	20.0	20.1	17	29.8	33.7
AELDs	8	15.1	13.5	4	6.7	5.6	2	3.5	2.9
AEs leading to treatment interruption	5	9.4	8.8	5	8.3	7.4	9	15.8	14.3
SAEs	19	35.9	35.9	18	30.0	28.2	15	26.3	24.6
Resulted in death	9	17.0	15.1	5	8.3	7.0	2	3.5	2.9

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by ethnicity exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by ethnicity subgroup at DBL1.

Baseline FVC % predicted (PPF)

Table *143*: Overall summary of AEs over the whole trial up to DBL1 by baseline FVC % predicted – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Baseline FVC % predicted ≤70%	214	100.0		202	100.0		194	100.0	
Patients with any AE	201	93.9	368.5	189	93.6	378.7	177	91.2	433.4
Severe AEs (CTCAE grade >2)	94	43.9	44.3	74	36.6	36.8	79	40.7	42.5
Investigator-defined drug-related AEs	73	34.1	39.8	80	39.6	50.9	84	43.3	58.0
AELDs	30	14.0	11.9	20	9.9	8.4	19	9.8	8.3
AEs leading to treatment interruption	38	17.8	16.8	40	19.8	19.0	39	20.1	19.4
SAEs	109	50.9	55.7	82	40.6	42.3	82	42.3	44.4
Resulted in death	23	10.8	9.1	11	5.5	4.6	3	1.6	1.3
Baseline FVC % predicted >70%	178	100.0		191	100.0		197	100.0	
Patients with any AE	168	94.4	334.0	180	94.2	390.7	187	94.9	469.2
Severe AEs (CTCAE grade >2)	52	29.2	26.7	65	34.0	32.7	66	33.5	33.6
Investigator-defined drug-related AEs	55	30.9	32.4	77	40.3	49.0	94	47.7	65.0
AELDs	16	9.0	7.3	19	10.0	8.0	25	12.7	10.8
AEs leading to treatment interruption	29	16.3	14.4	38	19.9	18.1	40	20.3	19.5
SAEs	59	33.2	31.1	68	35.6	34.1	72	36.6	37.9
Resulted in death	6	3.4	2.7	7	3.7	2.9	5	2.5	2.2

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by baseline FVC% predicted exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by baseline FVC% predicted subgroup at DBL1.

Baseline body weight (PPF)

Table 144**: Overall summary of AEs over the whole trial up to DBL1 by baseline body weight – TS (1305-0023)**

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Baseline body weight <65 kg	131	100.0		150	100.0		127	100.0	
Patients with any AE	123	93.9	318.4	139	92.7	351.8	119	93.7	493.3
Severe AEs (CTCAE grade >2)	57	43.5	42.4	58	38.7	36.7	50	39.4	42.8
Investigator-defined drug-related AEs	41	31.3	33.4	60	40.0	51.2	62	48.8	68.1
AELDs	14	10.7	8.9	18	12.0	9.9	17	13.4	11.7
AEs leading to treatment interruption	25	19.1	17.5	31	20.7	19.2	30	23.6	23.9
SAEs	63	48.1	50.8	67	44.7	45.8	57	44.9	50.9
Resulted in death	12	9.2	7.5	11	7.3	6.0	3	2.4	2.0
Baseline body weight ≥65 kg	261	100.0		243	100.0		264	100.0	
Patients with any AE	246	94.3	371.6	230	94.7	407.3	245	92.8	433.1
Severe AEs (CTCAE grade >2)	89	34.1	32.6	81	33.3	33.4	95	36.0	35.8
Investigator-defined drug-related AEs	87	33.3	37.8	97	39.9	49.2	116	43.9	58.4
AELDs	32	12.3	10.2	21	8.6	7.2	27	10.2	8.6
AEs leading to treatment interruption	42	16.1	14.7	47	19.3	18.1	49	18.6	17.5
SAEs	105	40.2	40.2	83	34.2	33.6	97	36.7	36.9
Resulted in death	17	6.5	5.4	7	2.9	2.4	5	1.9	1.6

AELDs: AEs leading to treatment discontinuation, PY: patient-years
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by baseline body weight exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by baseline body weight subgroup at DBL1.

Baseline eGFR (PPF)

Table *145*: AEs up to DBL1 by baseline eGFR – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
eGFR ≥90 mL/min/1.73 m²	123	100.0		134	100.0		135	100.0	
Any AE	114	92.7	358.3	124	92.5	411.4	121	89.6	368.9
Severe AEs (CTCAE grade >2)	39	31.7	29.2	39	29.1	28.0	52	38.5	40.2
Investigator-defined drug-related AEs	36	29.3	30.7	53	39.6	50.7	59	43.7	58.2
AELDs	10	8.1	6.6	7	5.2	4.4	5	3.7	3.1
AEs leading to treatment interruption	21	17.1	15.1	24	17.9	17.1	29	21.5	20.6
SAEs	41	33.3	31.5	45	33.6	33.4	48	35.6	35.2
Resulted in death	6	4.9	4.0	7	5.2	4.4	2	1.5	1.2
eGFR 60 to <90 mL/min/1.73 m²	231	100.0		219	100.0		214	100.0	
Any AE	217	93.9	331.7	206	94.1	358.2	202	94.4	484.4
Severe AEs (CTCAE grade >2)	86	37.2	35.3	84	38.4	37.8	76	35.5	35.5
Investigator-defined drug-related AEs	77	33.3	37.3	88	40.2	49.3	101	47.2	64.9
AELDs	29	12.6	10.3	28	12.8	10.5	32	15.0	12.7
AEs leading to treatment interruption	36	15.6	14.1	51	23.3	21.8	45	21.0	20.1
SAEs	100	43.3	43.7	89	40.6	40.6	88	41.1	43.8
Resulted in death	16	6.9	5.7	11	5.0	4.1	5	2.3	2.0
eGFR <60[1] mL/min/1.73 m²	38	100.0		40	100.0		42	100.0	
Any AE	38	100.0	500.5	39	97.5	468.7	41	97.6	661.7
Severe AEs (CTCAE grade >2)	21	55.3	68.9	16	40.0	40.9	17	40.5	43.7
Investigator-defined drug-related AEs	15	39.5	51.5	16	40.0	51.5	18	42.9	55.2
AELDs	7	18.4	17.8	4	10.0	8.5	7	16.7	15.3
AEs leading to treatment interruption	10	26.3	28.8	3	7.5	6.5	5	11.9	12.0
SAEs	27	71.1	101.8	16	40.0	40.9	18	42.9	47.7
Resulted in death	7	18.4	17.6	0	0	0	1	2.4	2.2

1 Patients with eGFR ≤30 mL/min/1.73m² at baseline were not allowed to enter the trial (see exclusion criterion #9 in the CTP [c43862464, Appendix 16.1.1.2]). Please note that 2 patients with a baseline eGFR <30 were included in trial 1305-0023.

Up to DBL2, the AE profile by eGFR subgroups followed the same trends as described for DBL1.

Baseline HRCT pattern (PPF)

Table *146*: AEs over the whole trial up to DBL1 by baseline HRCT pattern – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
UIP or UIP-like fibrotic pattern	275	100.0		290	100.0		275	100.0	
Patients with any AE	260	94.6	362.3	269	92.8	372.3	257	93.5	469.7
Severe AEs (CTCAE grade >2)	106	38.6	37.9	96	33.1	31.7	105	38.2	39.3
Investigator-defined drug-related AEs	99	36.0	41.6	119	41.0	52.1	129	46.9	65.5
AELDs	36	13.1	11.0	30	10.3	8.4	34	12.4	10.5
AEs leading to treatment interruption	51	18.6	17.2	60	20.7	19.0	57	20.7	20.1
SAEs	117	42.6	43.6	106	36.6	35.5	116	42.2	45.1
Resulted in death	18	6.6	5.5	12	4.1	3.4	8	2.9	2.4
Other fibrotic patterns	117	100.0		103	100.0		116	100.0	
Patients with any AE	109	93.2	329.5	100	97.1	421.4	107	92.2	411.9
Severe AEs (CTCAE grade >2)	40	34.2	31.3	43	41.8	44.2	40	34.5	34.7
Investigator-defined drug-related AEs	29	24.8	25.2	38	36.9	44.2	49	42.2	52.9
AELDs	10	8.6	7.0	9	8.7	7.6	10	8.6	7.4
AEs leading to treatment interruption	16	13.7	12.2	18	17.5	17.2	22	19.0	18.0
SAEs	51	43.6	43.5	44	42.7	46.6	38	32.8	32.2
Resulted in death	11	9.4	7.7	6	5.8	5.1	0	0	0

AELDs: AEs leading to treatment discontinuation, PY: patient-years, UIP: usual interstitial pneumonia
Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by baseline HRCT pattern exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by baseline HRCT pattern subgroup at DBL1.

Underlying clinical ILD diagnosis (PPF)

Table *147*: AEs over the whole trial up to DBL1 by underlying clinical ILD diagnosis – TS (1305-0023)

Category of AEs	Placebo			Nera 9 mg bid			Nera 18 mg bid		
	N	%	Rate/ 100PY	N	%	Rate/ 100PY	N	%	Rate/ 100PY
Idiopathic nonspecific interstitial pneumonia	73	100.0		73	100.0		82	100.0	
Patients with any AE	68	93.2	278.8	70	95.9	340.4	73	89.0	326.5
Severe AEs (CTCAE grade >2)	25	34.3	30.5	27	37.0	36.2	27	32.9	32.3
Investigator-defined drug-related AEs	18	24.7	22.9	25	34.3	40.1	33	40.2	50.7
AELDs	8	11.0	8.7	7	9.6	8.1	11	13.4	11.8
AEs leading to treatment interruption	9	12.3	10.4	12	16.4	15.3	14	17.1	16.3
SAEs	30	41.1	38.9	28	38.4	36.9	31	37.8	38.4
Resulted in death	3	4.1	3.2	6	8.2	6.9	2	2.4	2.1
Unclassifiable idiopathic interstitial pneumonia	82	100.0		76	100.0		73	100.0	
Patients with any AE	77	93.9	343.7	74	97.4	557.3	71	97.3	697.9
Severe AEs (CTCAE grade >2)	38	46.3	46.9	29	38.2	40.3	21	28.8	28.5
Investigator-defined drug-related AEs	29	35.4	43.1	33	43.4	57.1	39	53.4	84.4
AELDs	9	11.0	9.2	10	13.2	11.2	7	9.6	8.3
AEs leading to treatment interruption	16	19.5	18.0	19	25.0	24.8	11	15.1	14.5
SAEs	45	54.9	59.0	31	40.8	44.2	30	41.1	44.5
Resulted in death	10	12.2	10.2	0	0	0	0	0	0
Hypersensitivity pneumonitis	77	100.0		83	100.0		73	100.0	
Patients with any AE	74	96.1	384.2	74	89.2	339.7	67	91.8	476.4
Severe AEs (CTCAE grade >2)	26	33.8	34.2	33	39.8	45.3	25	34.3	38.2
Investigator-defined drug-related AEs	24	31.2	34.5	31	37.4	49.9	36	49.3	74.1
AELDs	7	9.1	7.8	11	13.3	11.8	5	6.9	6.1
AEs leading to treatment interruption	12	15.6	14.8	14	16.9	16.5	17	23.3	23.6
SAEs	27	35.1	36.4	37	44.6	52.1	25	34.3	37.7
in death	5	6.5	5.6	4	4.8	4.3	2	2.7	2.4
Autoimmune ILDs	100	100.0		112	100.0		113	100.0	
Patients with any AE	93	93.0	347.7	105	93.8	330.6	104	92.0	376.3
Severe AEs (CTCAE grade >2)	36	36.0	33.9	33	29.5	25.6	48	42.5	43.9
Investigator-defined drug-related AEs	31	31.0	33.7	44	39.3	46.1	43	38.1	44.8
AELDs	11	11.0	9.0	7	6.3	4.8	12	10.6	8.8
AEs leading to treatment interruption	18	18.0	16.3	20	17.9	15.5	26	23.0	22.1
SAEs	39	39.0	38.2	37	33.0	29.6	45	39.8	41.3
Results in death	8	8.0	6.5	6	5.4	4.1	3	2.7	2.2
Other ILDs	60	100.0		49	100.0		50	100.0	
Patients with any AE	57	95.0	474.0	46	93.9	535.4	49	98.0	758.4
Severe AEs (CTCAE grade >2)	21	35.0	33.7	17	34.7	32.7	24	48.0	47.8
Investigator-defined drug-related AEs	26	43.3	57.2	24	49.0	65.4	27	54.0	80.1
AELDs	11	18.3	16.0	4	8.2	6.6	9	18.0	14.2
AEs leading to treatment interruption	12	20.0	19.6	13	26.5	25.2	11	22.0	20.0
SAEs	27	45.0	48.3	17	34.7	33.4	23	46.0	45.0
Results in death	3	5.0	4.3	2	4.1	3.3	1	2.0	1.6

Incidence rates were calculated using the number of patients with the respective events per treatment divided by time at risk expressed as 100 PY.

Up to DBL2, the overall AE profile as assessed by underlying clinical ILD diagnosis exhibited trends generally consistent with the overall AE profile in all patients in the trial and also with trends reported by underlying clinical ILD diagnosis subgroup at DBL1.

Pregnancy and breastfeeding (IPF and PPF)
In clinical trials for nerandomilast, women who were pregnant or planning to become pregnant and women who were breast-feeding were not allowed to participate. Women of childbearing potential were allowed to participate provided they use a highly effective method of contraception.

There were no reported cases of pregnancy of trial participants in any of the Phase I or II trials with nerandomilast or in the Phase III trials 1305-0014 (up to DBL2) and 1305-0023 (up to DBL2).

5.4.8. Safety related to drug-drug interactions and other interactions

Please refer to AE section above where data on AEs with use of background AF treatments in both IPF and PPF clinical trials is presented. See also Pharmacokinetics section for further discussion on drug-drug interaction studies.

5.4.9. Vital signs and laboratory findings

Trials 1305-0014 and 1305-0023 pooled (SAF1/SAF1C).

The same trends in safety laboratory assessment as described for individual trials 1305-0014 and 1305-0023 were observed, with no new findings in the pooled analysis results. No analyses of the clinical laboratory data based on the SAF1c grouping were carried out as part of the analyses prepared for the SCS.

Vital sign results for SAF1 (SAF1/SAF1C)

The same trends in vital signs as described for individual trials 1305-0014 and 1305-0023 were observed, with no new findings in the pooled analysis results.

5.4.10. Overall discussion and conclusions on clinical safety

5.4.10.1. Discussion

Safety data collection

Individual and pooled safety data from the clinical development program for IPF and PPF were presented in order to have a larger sample size for the evaluation of safety events, especially infrequent events. Two DBL were presented DBL1 and DBL2 including outstanding safety data for the pivotal PPF trial 1305-0023 (DBL2).

For the pooled analysis of the 2 pivotal trials (SAF1) and of all trials in patients with IPF (SAF2-IPF) and with IPF or PPF (SAF2), it was predefined to pool by randomised treatment (placebo, 9 mg bid nerandomilast, 18 mg bid nerandomilast). However, in trial 1305-0014 nerandomilast plasma trough exposure was decreased by approximately 50% in patients with pirfenidone background therapy. The Applicant therefore performed a post hoc safety grouping (SAF1c) excluding patients on pirfenidone as including data from patients treated with nerandomilast and pirfenidone group in pooled analyses could dilute or mask safety signals seen at full exposure.

While the pooled safety analysis can be supported on the basis that IPF and PPF have some shared clinical and pathobiological features, including common fibrotic mechanisms, differences in disease aetiology for IPF and PPF, comorbidities, baseline treatments, and study design, in particular inclusion/exclusion criteria (age profile, background disease and permitted

immunosuppressive therapies in the PPF population), impact the interpretation of safety outcomes. This supported the decision to reflect safety data in section 4.8 by indication.

A comprehensive overview of AEs, SAEs, AESIs, and subgroup analyses was presented by dose and by background therapy. Background therapy groups included nintedanib versus no background therapy in IPF and PPF populations, and pirfenidone versus no pirfenidone in IPF patients. Patients without background therapy were further stratified into those who were truly AF-treatment naïve and those previously treated with AF therapy, but who had discontinued treatment for the required period prior to study entry.

Exposure

The applicant submitted an extensive safety package covering Phase I, II and III studies with 3226 patients exposed overall (to any dose). In the pivotal trials 1568 patients were treated with nerandomilast 9mg bid or 18mg bid with 1387 patients treated for ≥6 months and 1259 patients treated for ≥12 months. For the pooled set SAF1, 1904 patients (80.9%) completed planned treatment up to Week 52 and 2147 patients (91.2%) completed planned observation for the primary endpoint assessment. Mean exposure to trial medication was between 14 and approximately 15 months (SD: approximately 5 months) for all treatment groups, with more than 70% of patients treated for at least 15 months. Mean observation time was about 17 months (SD: approximately 4 months) for all treatment groups. The total exposure to nerandomilast across the pivotal trials in PYs was 1953.43.

700 patients received a dose of nerandomilast 9 mg bid and 687 patients received a dose of 18 mg bid for >6 months and 636 patients received a dose of 9 mg bid and 623 patients received a dose of 18mg bid >12 months. Overall, 1259 patients were exposed to nerandomilast for >52 weeks in the pivotal studies.

In addition, as per DBL2, 1635 patients have been treated with 18 mg nerandomilast for a duration of up to about 7 months in the open-label extension trial 1305 0031. All patients included in this 1305-0031 snapshot were rolled over from trials 1305-0014 and 1305-0023.

Disposition

The most common reason for premature discontinuation of study medication was an adverse event (13.3%), followed by withdrawal by patient (6.8%) and "other" (6.5%). Clinical worsening (death/transplant) accounted for a substantial share of the "other" group. Overall, the discontinuations due to 'withdrawal of patient' or 'other' reasons reflect treatment issues, patient preferences, or disease severity/progression rather than safety or tolerability issues.

Adverse events leading to temporary treatment interruptions were most frequently reported in the nerandomilast 18 mg bd group (21.6%) compared with 20.3% of the 9 mg bd group and 17.8% of the placebo group.

Background treatment

The impact of background AF treatment was evaluated in two ways. Firstly, to account for the observed DDI with pirfenidone which results in a 50% reduction in exposure to nerandomilast, safety results excluding patients with background pirfenidone treatment ("non-pirfenidone population") were also shown, for trial 1305-0014 individually and trials 1305-0014/1305-0023

pooled. Secondly, at trial level a limited subgroup analysis by background treatment (pirfenidone, nintedanib or no treatment) was presented.

At baseline (study 1305-0014), 22.3% of the patients had no IPF background AF treatment, whereas 45.5% received nintedanib and 32.3% pirfenidone. In Study 1305-0023, 56.3% of the patients had neither nintedanib nor pirfenidone at baseline; 43.5% received nintedanib as the only currently approved therapy for PPF and 2 patients (0.2%) received background pirfenidone treatment.

Adverse events

An increased frequency of severe adverse events (AEs), investigator-assessed drug-related AEs, AEs leading to temporary treatment interruption, AEs leading to discontinuation, and serious adverse events resulting in death was observed in IPF and PPF patients receiving background antifibrotic therapy and in PPF patients on background nintedanib who were treated with either 9 mg bid or 18 mg bid nerandomilast when compared with nerandomilast monotherapy.

IPF:

In the IPF population safety data from DBL2 adverse events were most frequently reported in the SOCs: 'infections and infestations', 'gastrointestinal disorders', and 'respiratory, thoracic, and mediastinal disorders'. Overall, AE frequencies were similar across placebo, nerandomilast 9 mg bid, and 18 mg bid groups (98.2%, 94.6%, and 96.7%, respectively), consistent with expectations for a progressive disease like idiopathic pulmonary fibrosis. The most common AEs were diarrhoea, cough, and COVID-19. Diarrhoea incidence increased with dose: 18.3% (placebo), 32.1% (9 mg), and 42.4% (18 mg). Other AEs such as weight loss, nausea, back pain, and decreased appetite also showed a dose-dependent trend. While overall AE, SAE, and severe AE rates were balanced, AEs leading to treatment interruption or discontinuation and drug-related AEs were most frequent in the 18 mg bid group. These effects were most frequently reported in patients receiving background treatment with nintedanib compared to those on pirfenidone or no background therapy.

PPF:

For trial 1305-0023 up to DBL2 similar adverse events patterns to the IPF pivotal trial were observed. Adverse events were most frequently reported in the SOCs "infections and infestations", "gastrointestinal disorders", and "respiratory, thoracic, and mediastinal disorders". Diarrhoea was the most frequent AE, increasing from 26.0% (placebo) to 32.6% (9 mg) and 37.1% (18 mg). Dose-related increases were also noted for weight loss, nausea, and back pain. Although severe AEs and AEs leading to discontinuation were generally balanced across groups, they were more frequent in patients receiving nerandomilast with background treatment nintedanib.

Pooled:

The pooled incidence of treatment-emergent adverse events (TEAEs) was highest overall for placebo groups for the overall population and the non-pirfenidone population. Similar to the pivotal studies, there was a small trend of dose-dependent increases in AEs relating to GI disorders with nerandomilast in the overall population and the non-pirfenidone population. Diarrhoea, nausea, weight loss, and decreased appetite were reported more frequently in the nerandomilast treatment groups. The majority of cases reported with nerandomilast were mild to moderate in severity. In the pooled analysis, dose dependent increases across the nerandomilast

9 mg bid and 18 mg bid treatment arms were also observed for the following PTs: pneumonia, anxiety, RTI, back pain, atrial fibrillation.

Both pivotal trials demonstrated a small but consistent, dose-dependent increase with nerandomilast treatment in gastrointestinal AEs, particularly diarrhoea. The 18 mg bid dose in both IPF and PPF patients was associated with the highest incidence of diarrhoea and treatment-limiting AEs, especially when combined with nintedanib background treatment. This finding appeared to relate to an additive effect on AEs when nerandomilast and nintedanib are used concomitantly, rather than a formal clinical interaction.

The observed frequency of AEs with severe outcomes and AELDs in the background antifibrotic population is likely to reflect characteristics of the underlying disease and is explained by differences in baseline disease severity and comorbidity profile of patients in the background-treatment cohorts, rather than by any new or drug related safety signal associated with nerandomilast. The known safety profiles of nintedanib and pirfenidone are likely to have resulted in some additive AEs when combining antifibrotics. The impact of concomitant treatment with antifibrotic treatment either as previous treatment (no background treatment subgroup) or as concomitant treatment (with background treatment subgroup) is not consistent across the IPF and PPF population and this has been reflected in the Sections 4.8 Undesirable effects and 4.4 Special precautions and warnings.

AEs leading to permanent treatment discontinuation and drug interruption

IPF:

For IPF populations, AEs leading to permanent treatment discontinuation (AELDs) were more frequently reported with nerandomilast 9mg bid and 18 mg bid treatment compared with placebo and were most frequently reported in the 18 mg bid nerandomilast group. AEs resulting in discontinuation of treatment were most frequently reported in 'Gastrointestinal' SOC. Diarrhoea was the most frequently reported AELD. The reporting rates were highest in the 18 mg bid nerandomilast group.

PPF:

Up to DBL2, trends in AEs leading to permanent treatment discontinuation across SOCs and PTs were generally similar to those reported up to DBL1. For the PPF population, AELDs were more common in the placebo group, and were most frequently reported in 'General disorders and administration site conditions' SOC: with the PT 'Condition aggravated'. Treatment interruptions due to diarrhoea were more frequent with nerandomilast, with comparable reporting rates for the 9 mg bid and 18 mg bid treated groups.

Pooled:

In the pivotal trials 1305-0014 and 1305-0023 pooled (SAF1), the proportion of patients with adverse events leading to temporary treatment interruptions was higher with nerandomilast treatment (9 mg bid: 20.3%; 18 mg bid: 21.6%) than with placebo (17.8%). For the pooled data, AEs resulting in interruption were most frequently reported in 'infections and infestations' SOC and 'Gastrointestinal Disorders' SOC AEs leading to temporary treatment interruption overall were most frequently reported for Covid-19 and pneumonia. Diarrhoea was the most frequently reported AE in the Gastrointestinal Disorders SOC. Treatment interruptions due to diarrhoea were more frequent with nerandomilast, with comparable reporting rates for the 9 mg bid and 18 mg bid treated groups.

reatment interruptions were more frequently reported with nerandomilast plus bbackground AF herapy than with either placebo plus AF therapy or nerandomilast alone.

verall, diarrhoea was the commonest reason for drug discontinuation. The reporting rates were w but were highest in the 18 mg bid nerandomilast group (9 mg bid: 1.7%; 18 mg bid: 4.3%) ompared with placebo (0.5%). Rare but notable events like vasculitis and suicidal ideation esulting in discontinuation occurred mostly in the nerandomilast treatment arms.

olerability and proposed dose reduction

he applicant proposed dose reduction from nerandomilast 18mg bid to 9mg bid based on ndividual patient tolerability, although the applicant acknowledged that dose reduction from 18 mg id nerandomilast to 9 mg bid nerandomilast was not foreseen in the trial designs for the pivotal tudies in IPF and PPF.

olerability was most impacted by gastrointestinal side effects in the pivotal trials. This was mainly riven by AEs under the PT diarrhoea. Diet treatment, symptomatic treatment, antidiarrheal nedication, and dose reduction of background AF treatment were predefined in the pivotal trials or management of diarrhoea, according to severity of diarrhoea. Temporary interruption of trial reatment was recommended to be considered. Re-initiation of trial treatment was advised to be onsidered once the patient had sufficiently recovered, based on the investigator's clinical udgment and documented assessment. For the overall pooled population, dose interruptions due o diarrhoea AEs were low and comparable between the nerandomilast 18mg bid dose and the 9mg id dose (placebo: 0.8%; 9 mg bid nerandomilast: 4.1%; 18 mg bid nerandomilast: 5.2%). iscontinuations due to AE diarrhoea were also low overall (<5%) with the highest frequency in he 18 mg bid nerandomilast group (placebo: 0.5%; 9 mg bid nerandomilast: 2.2%; 18 mg bid erandomilast: 4.3%).

/hen reviewed by subgroup the reporting rates of grade 2/3 diarrhoea and rates of iscontinuations due to diarrhoea, varied across IPF and PPF indications, dose of nerandomilast and ackground antifibrotic therapy. A high discontinuation rate was noted in the 18 mg bid dose ubgroup in IPF patients treated with nintedanib (21%) with a similarly high discontinuation rate 17%) was noted in the IPF population on 9mg bid plus pirfenidone. No consistent safety dvantage in terms of reports of diarrhoea was evident for the 9mg bid dose across the IPF and PF subgroups with and without background therapy.

xposure–response analyses (ER) show a positive correlation between exposure and the key AEs, iarrhoea and weight loss. This ER analysis found only a small increase in the chance of getting iarrhoea with increased nerandomilast exposure. For weight loss, this small increase in risk was een only with the initial increase in exposure to nerandomilast. The most significant predictor of iarrhoea events was concomitant use of nintedanib. Similarly, weight loss was associated with reatment with nerandomilast with other concomitant therapies.

verall, the clinical data supporting the proposed dose reduction of nerandomilast from 18 mg bid o 9 mg bid are limited and are primarily based on a trend toward increased AEs and higher iscontinuation rates at the 18 mg bid dose. With respect to gastrointestinal safety, overall olerability was improved at the 9 mg bid dose.

Nevertheless the applicant's recommendation for dose decrease from 18mg bid to 9 mg bid based on patient tolerability as described in section 4.2 were considered acceptable with additional strengthening of information to specify management of diarrhoea and weight loss side effects with cross reference to sections 4.4 and 5.1.

Further evaluation of nerandomilast dose reduction and tolerability including dose decrease from 18 mg bid to 9 mg will be captured through postmarketing data from the ongoing and planned clinical trials with nerandomilast, including planned placebo-controlled trials This is considered broadly acceptable by CHMP. The applicant also committed to providing a focused evaluation of the 18 mg bid to 9 mg bid dose reduction as a Topic of Special Interest in the PSURs to further characterise dose-related safety trends in clinical studies and the potential impact of dose adjustment on overall benefit–risk of nerandomilast.

Serious Adverse events

IPF:

SAEs were numerically lower in IPF patients receiving 9mg bid (38.0%) and 18 mg bid (38%) nerandomilast than in patients on placebo (42.5%) respectively.

PPF:

A similar profile was identified for PPF with SAEs reported for 40.0% of 9 mg bid and 43.0% of 18 mg bid nerandomilast patients compared to 45.9% patients on placebo. The most frequently reported SAEs were 'condition aggravated' (coded term for suspected acute/acute ILD exacerbation), 'pneumonia', 'pulmonary hypertension', and 'idiopathic pulmonary fibrosis'.

By background treatment subgroup, SAE frequencies with nerandomilast were highest in the subgroup of patients with nintedanib background therapy (placebo 35.3%, 9 mg nerandomilast bid 39.1%, nerandomilast 18 mg bid 38.8% for the IPF population and 41.2%, 37.6%, 43.3% respectively in the PPF population). Up to DBL2 in the PPF pivotal study, the overall AE profile as assessed by background nintedanib therapy was generally consistent with trends exhibited in the entire trial population and also with trends reported by background nintedanib subgroup at DBL1. A decrease in SAE frequencies with nerandomilast compared to placebo was observed for the no background IPF and PPF treatment subgroup and the IPF pirfenidone subgroup.

Pooled:

In the pooled analysis, frequencies of SAEs were numerically lower in patients receiving nerandomilast than in patients on placebo, both in the overall pooled patient population (SAF1) as well as the pooled non-pirfenidone population (SAF1c). SAEs were most frequently reported in the SOCs 'infections and infestations', 'respiratory, thoracic, and mediastinal disorders', and 'general disorders and administration site conditions'. At the PT level, most frequently reported SAEs overall were condition aggravated, pneumonia, pulmonary hypertension, and respiratory failure.

All deaths in both 1305-0014 and 1305-0023 trials up to DBL2 were adjudicated by an independent blinded committee to determine the primary cause of death.

IPF:

Fatal AEs were observed least frequently in the 18 mg bid (2.8%) compared to 9mg nerandomilast group bid (5.4%) and placebo (6.6%). The Applicant has highlighted that the lowest incidence of fatal AEs was observed in the 18 mg bid nerandomilast group. This effect was also seen in the 18 mg bid nerandomilast treatment group when stratified by background AF therapy. However, there was an overall higher incidence of fatal AEs in patients receiving nerandomilast treatment with nintedanib (placebo: 4.6%, 9 mg bid nerandomilast: 6.0%, 18 mg bid nerandomilast: 2.8%), and pirfenidone (7.5%, 5.8%, 3.2%) compared to those with no background IPF treatment (9.2%, 3.4%, 2.8%) this likely due to the patients on background AF therapy at baseline having greater disease severity.

PPF:

Similar to the IPF population, fatal AEs were observed least frequently in the 18 mg bid (3.1%) compared to 9 mg nerandomilast bid group (4.8%) and placebo (9.7%) overall at DLB2 of the pivotal PPF study. In the PPF population, the pattern observed in patients on background AF therapy was different to the general PPF population. The incidence of fatal AEs in patients receiving nerandomilast treatment with nintedanib (placebo: 7.7%, 9 mg bid nerandomilast: 2.3%, 18 mg bid nerandomilast: 1.8%) was lower than in patients without background nintedanib therapy (7.2%, 6.4%, 2.3%) with similar trends observed in the DLB2.

Pooled:

For the pooled populations, the overall frequency of patients with AEs with an outcome of death was numerically higher in the placebo group compared with nerandomilast 9mg and 18 mg bd groups (8.2% vs 5.1% vs 2.9% respectively) for the overall population with a similar picture evident for the non-pirfenidone populations.

For the IPF, PPF and pooled populations, fatal AEs were most frequently reported in the SOCs 'general disorders and administration site conditions', 'respiratory, thoracic, and mediastinal disorders', 'infections and infestations' and 'cardiac disorders'. The most frequently reported fatal AE was 'condition aggravated' which was numerically higher in the placebo group compared with nerandomilast 9 mg and 18 mg bd groups (pooled SAF1 population: 2.6% vs 0.9% vs 1.0% respectively overall). None of these cases were reported as related to study medication and are most likely due to suspected/acute exacerbation of the underlying interstitial lung disease rather than directly related to the investigational product. The majority of the observed deaths were generally consistent with underlying disease and the patient population (i.e. respiratory failure, ILD, dyspnoea).

There were 13 fatal Cardiac disorders events reported in the nerandomilast group (9 in the nerandomilast 9 mg bd group and 1 in the 18 mg bd group) compared with 3 in the placebo group. Otherwise, no clinically meaningful imbalances or safety signals were identified.

Pooled Topics of Special interest

Five topics were specified as AESIs (potential severe DILI, vasculitis, severe infections, new onset severe depression and severe anxiety). Additional information was collected on eCRF for suicidality, malignancies, gastrointestinal disorders including diarrhoea, and weight loss. Some events were adjudicated by an independent, blinded endpoint adjudication committee (MACE, vasculitis).

Gastrointestinal symptoms

Gastrointestinal symptoms were evaluated using PTs/HLTs diarrhoea, nausea, vomiting, and abdominal pain. The overall frequency of patients with AEs reported in the safety topic 'gastrointestinal symptoms' was higher with nerandomilast treatment than with placebo, with highest frequency in the 18 mg bid nerandomilast group. This pattern was evident in the two pivotal trials (1053-0014 for IPF and 1053-23 for PPF) and in the overall population (pool SAF1) as well as the non-pirfenidone population (pool SAF1c).

Diarrhoea was most frequently reported PT with the highest frequency of reports in the nerandomilast 18 mg bid (42.4%) compared to the 9mg bid (32.1%) or placebo group (18.3%). The majority of diarrhoea AEs were non-serious with only one serious adverse event report of diarrhoea. The majority of diarrhoea events were mild or moderate. Moderate cases were described as having an increase of 4-6 stools /day which is still a significant burden for a patient.

Severe diarrhoea (>7 stools per day) was reported in 0.5% of the placebo group, 1.3% of the 9 mg bid group and 1.7% of the 18 mg bid group. The majority of severe events were observed in patients receiving 18 mg bid nerandomilast together with nintedanib. Most diarrhoea symptoms started within the first 3 months of trial treatment with most people experiencing 1-2 episodes lasting approximately 3-4 weeks.

Diarrhoea was the most frequently reported AE causing treatment discontinuation (18 mg bid: 4.3%, 9 mg bid: 2.2%, placebo: 0.5%) and interruption (18 mg bid: 5.2%, 9 mg bid: 4.1%, placebo: 0.5%). Discontinuation rates for diarrhoea varied by background condition, background AF therapy and by nerandomilast dose. AELDs were highest in IPF patients treated with nerandomilast 18mg bid plus nintedanib (23/178 = 13%) i.e., over 1 in 10 patients with IPF treated with nerandomilast 18mg bid with nintedanib stopped treatment due to diarrhoea.

In the pooled dataset, the frequency of nausea was numerically higher in the nerandomilast groups than in the placebo group (18 mg bid: 10.3%, 9 mg bid: 9%, placebo: 7.1%). Nausea-related AELDs were reported in <1% of patients across all treatment arms and doses. There was 1 SAE of nausea) and 1 severe AE of nausea, both reported in the 18 mg bid nerandomilast group. The onset of nausea AEs was mostly observed in the first 3 months of trial treatment. The incidence of nausea was higher in patients receiving background nintedanib than in patients on monotherapy.

The increased frequency and severity of diarrhoea seen in patients on nintedanib background treatment did not translate into more clinically relevant consequences such as serious hypokalaemia, serious dehydration, or acute kidney injury. The impact on dose selection and the possible requirement for titration strategies to balance efficacy and tolerability is considered a remaining uncertainty but further data from planned and ongoing clinical trials will be reviewed in the PSURs.

Although there is a dose-dependent increase in gastrointestinal tolerability issues associated with nerandomilast particularly at the higher 18 mg bid dose with background nintedanib treatment, serious events were infrequent. However, gastrointestinal symptoms should be closely monitored, especially during the initial weeks of combined therapy. Exposure-response data shows a correlation between nerandomilast dose and the AEs diarrhoea and weight loss. The proposal to include diarrhoea, weight loss and nausea as ADRs and additional information in section 4.8 outlining the severity profile for diarrhoea for IPF and PPF populations based on presence and type of background therapy is endorsed (see Adverse drug reactions).

Warnings have been included in section 4.4 regarding the increased risk of gastrointestinal side effect profile (diarrhoea, nausea, reduced appetite) with nerandomilast monotherapy and when used together with pirfenidone or nintedanib, and advice on caution when prescribing nerandomilast to patients who are debilitated, already experiencing gastrointestinal symptoms and previously intolerant of antifibrotic GI side effects.

Weight decrease

There was a numerically higher reporting rate of weight decrease in the pivotal IPF and PPF studies in patients treated with nerandomilast compared with placebo. This was dose dependent, with the highest frequency observed at the nerandomilast 18 mg bid dose. In the pooled analysis, AE 'weight decrease' was reported by 13.5% vs 10.5% vs 8.9% respectively of patients treated with nerandomilast 18 mg and 9 mg bid compared with placebo. Of these, <0.5% reported severe events.

Overall, for patients on no baseline antifibrotic therapy (Pool SAF1) there was a dose dependent increase of weight loss evident across the placebo and nerandomilast 9mg bid and 18 mg bid treatment arms (5.8% vs 6.5% vs 11.7% respectively). In patients on antifibrotic therapy, 9.7% vs 12.4% vs 12.8% respectively reported weight decrease. In patients with IPF, weight decrease was most pronounced in patients treated with nintedanib plus nerandomilast 18mg bid (13.3% vs 14.1% vs 16.9% respectively). In patients with PPF weight loss was comparable between patients on nerandomilast alone and on nerandomilast with nintedanib. Differences with placebo were small suggesting that weight loss may be an additive effect to other factors such as background AF treatment or disease progression. Similar trends were observed for the population of patients not taking pirfenidone as background therapy.

For the SAF1 pooled population, mean reduction in body weight from baseline to last value on treatment and mean largest percentage drop in body weight from baseline was also highest in the 18 mg bid group suggesting a dose related weight loss with nerandomilast that was sustained over the duration of the study. In the IPF population the mean weight loss was -3.0 kg for the nerandomilast 18mg bid group compared with -2.7 kg for the 9 mg bid group and -2.1 kg for the placebo group.

Maximum relative decline from baseline in weight was more pronounced in the 18 mg nerandomilast group. Of particular note, the percentage of patients with >10% maximum relative decline in body weight was numerically higher in the 18 mg bid nerandomilast group compared with placebo and 9 mg bid nerandomilast over the whole trial: 13.5% in the placebo group, 13.7% in the 9 mg bid nerandomilast group and 17.7% in the 18 mg bid nerandomilast group lost more than 10% of their body weight. Patients with a BMI under 18.5 kg/m² experienced slightly smaller reductions in body weight during the trials, and fewer of them lost more than 10% of their body weight compared to other BMI groups. Weight loss has been identified as a strong prognostic marker for mortality and hospitalisation in IPF. In view of the potential clinical significance of weight loss on the overall prognosis in this population, warnings have been included in section 4.4 regarding the increased risk of weight decrease with nerandomilast particularly when used with nintedanib, and advice on caution when prescribing nerandomilast in patients who are debilitated. Weight decrease will also be presented as topic of special interest in future PSURs.

Vasculitis

As vasculitis is a known preclinical effect of PDE 4 inhibitors, it was predefined as an AESI by the applicant in trials 1305-0014 and 1305-0023. A preclinical signal for vasculitis was identified in repeat-dose toxicity studies in rats and minipigs but not in primates (see Nonclinical section).

Across both pivotal trials, 19 cases of vasculitis were identified using the broad SMQ 'vasculitis' while 17 AE were identified using the narrow SMQ 'vasculitis' safety topic, with slightly higher incidence in the nerandomilast treatment groups (0.9% in 9 mg BID and 0.8% in 18 mg bid) compared to placebo (0.5%). Four drug-related AEs were reported exclusively in the 18 mg bid group, and six patients discontinued treatment permanently, 5 of whom were treated with nerandomilast. Eleven of the 17 AEs were classified as serious (SAEs), again with higher rates reported in the nerandomilast groups. Seven of the SAEs were reported in patients treated with nerandomilast in the IPF population compared with 2 reports in the PPF population (9mg bid group).

An independent adjudication committee confirmed 10 vasculitis cases. The majority of the confirmed cases of vasculitis (8/10) occurred in nerandomilast-treated patients (0.3% placebo vs 0.4% 9mg bid and 0.6% 18mg bid groups overall). Causality assessment was complicated by

confounding factors such as infections, concomitant medications, and underlying diseases and the decreased exposure in the pirfenidone-treated patients (due to the DDI) with IPF.

Six of the 10 cases were adjudicated as MPO ANCA vasculitis or microscopic polyangiitis, 2 of which were in the placebo group and 4 cases in the nerandomilast treated groups (1 nerandomilast 9 mg bid and 3 in the 18 mg bid group). In both placebo cases and three of the four nerandomilast cases, the patients were MPO-ANCA positive at baseline. The overall frequency of MPO□ANCA positivity was consistent with published literature in pulmonary fibrosis, and the available evidence does not support a causal relationship between vasculitis and nerandomilast treatment.

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. It is acknowledged that no signal for vasculitis has been identified in the ongoing apremilast PASS. Although vasculitis may emerge independently in this population, the clustering of cases in the nerandomilast treated population, in particular in the IPF population requires further monitoring. Vasculitis will be monitored via routine pharmacovigilance activities (signal detection, adverse reaction reporting) and will be discussed as safety concern of special interest in the PSURs.

Psychiatric events

Across the pooled SAF1/SAF1c dataset frequencies of severe depression and severe anxiety were broadly comparable across the treatment groups. These AESIs were reported in <2% of subjects across all treatment groups. Reporting rates were comparable in the overall population compared to the non-pirfenidone population.

There is a slight upward trend in suicidal ideation and behaviour rates with increasing dose of nerandomilast. There was an increase from 0.5% in the placebo group to 0.8% in the nerandomilast 18 mg bd group. Although numerically small, the point estimates suggest a numerical increase at the higher dose. This pattern could suggest a dose-response relationship. The prevalence of depression and anxiety are high in ILD patients compared to the general population. No statistically significant increase in suicidal ideation was observed with either nerandomilast dose, however the wide confidence intervals make it difficult to draw firm conclusions. Although 0.3% increase is small, this is potentially clinically relevant in the context of suicidal ideation.

Confounders in the form of event triggers and concomitant medications were reported in all cases except 1 patient (on nerandomilast 18 mg bid with nintedanib) in whom the AE was reported as related by the investigator. Six cases in the nerandomilast treated group (3 each in the 9 mg bd and 18 mg bd groups respectively) compared with 2 in the placebo group were reported as related to study medication by the investigator.

One attempted suicide occurred. This SAE of 'suicide attempt' (CTCAE Grade 4) which occurred on the 260th day after start of trial medication, was assessed as drug-related by the investigator. The patient had attempted suicide by medication overdose. Worsening functional status was a trigger for the event assessed by a psychiatrist. One completed suicide occurred in a nerandomilast 9 mg bd recipient (not on any other antifibrotic treatment during the testing programme): 3 months after experiencing a SAE of serious suicidal ideation the patient underwent a physician-assisted suicide. The suicidal ideation was reported as being triggered by declining physical health.

Suicidal ideation and depression are established side effects for the other currently licensed PDE4 inhibitors. Non-selective PDE4 inhibitors like roflumilast and apremilast include specific warnings

in their SmPCs that treatment should be carefully considered in patients with a history of psychiatric symptoms, especially depression or suicidal ideation/behaviour. Suicidality is an important identified risk for apremilast and Psychiatric disorders (depression, suicidal ideation, and behaviour) are listed as important identified risks for roflumilast. Both products have long-term post-marketing observational studies evaluating suicidality and depression.

Of note, pirfenidone is associated with psychiatric adverse effects such as insomnia (common), depression, and anxiety (both uncommon), while nintedanib does not list any psychiatric adverse reactions in its EMA product information. Psychiatric events will be subject to targeted follow-up and enhanced medical assessment as part of routine pharmacovigilance activities. Further opportunities to provide additional safety insights and collect and evaluate safety data will follow as part of the ongoing and planned interventional clinical trials. The applicant will also evaluate data from post-marketing data sources (spontaneous reporting, literature review, non-interventional studies as applicable). This approach is agreed. Psychiatric disorders will be presented as a safety topic of interest in the PSURs.

Considering the EU and global context where information relating to psychiatric events is included in the PI for several other medicines approved in this class, a warning regarding suicidal ideation and behaviour has been included in section 4.4 of SmPC.

Cardiovascular events (MACE [investigator-reported as well as adjudicated])

While overall AEs in 'MACE' and 'QT prolongation' safety topics were generally balanced between the nerandomilast and placebo groups, in the cases that were adjudicated as fatal MACE, 5 patients in the placebo group reported AEs compared with 13 in total in the nerandomilast treated group. The majority of these were reported in the nerandomilast 9 mg bd group (10 cases) versus 3 in the nerandomilast 18 mg bd group. Sudden cardiac death was reported for the 5 placebo cases. Six of the 10 cases in the nerandomilast 9 mg bd group and 2 of the 3 cases in the 18 mg bd group were due to sudden cardiac death. All other cardiac causes of death were reported once. There was no consistent pattern that supported a causal association between nerandomilast treatment and MACE with fatal outcome.

There was a numerically higher rate of tachyarrhythmia compared to placebo in the nerandomilast 18 mg bid treatment groups in both the IPF and PPF pivotal studies. 'Atrial fibrillation' was reported at a numerically higher frequency in both the nerandomilast 9 mg bid and 18 mg bid treatment groups when compared to placebo. A similar picture was evident in the pooled analysis (placebo: 0.8%; 8 mg bid nerandomilast: 1.8%; 18 mg bid nerandomilast: 2.6%). Serious adverse events followed a similar trend, with rates of 0.3% (placebo), 0.6% (9mg), and 1.02% (18mg). No patients discontinued treatment due to atrial fibrillation. In the majority of cases causality assessment was confounded by underlying conditions and background medications and time to onset varied. There was no consistent pattern that supported a causal association between nerandomilast treatment and atrial fibrillation. Cardiac events including tachyarrhythmia will be monitored as a topic of special interest in future PSURs.

Malignancy

Some small numerical imbalances between the nerandomilast and placebo groups for non-melanomatous skin cancers and lung neoplasm were noted in the PPF and pooled populations. There was no indication of a dose related trend in reports of malignancies and nerandomilast treatment.

In the PPF population, a small but numerically higher rate of malignancies were reported for the 9mg and 18mg bd nerandomilast treatment groups. On the basis of the applicant's evaluation of

this topic, the numerical imbalances observed in the PPF study are likely to reflect random findings. Indeed, a reverse trend was seen in the IPF pivotal trial. The lack of causality is supported by the absence of identified safety signals from nonclinical safety studies, in which no carcinogenic potential of nerandomilast was identified. It was also highlighted by the applicant that no safety signal for malignancy has been identified from extensive post-marketing experience for two approved products in the class, apremilast and roflumilast. No imbalances have been reported in relation to malignancy events across the treatment arms in the ongoing open label extension study for nerandomilast.

In this context, no additional risk minimisation measures are proposed by the applicant and on the basis of the response provided, this approach is considered broadly acceptable, at this time.

As lung cancer is a recognised risk in patients with both IPF and PPF due to underlying disease and risk factors and given the limited exposure to nerandomilast over longer-term treatment, the topic should be presented for review as a topic of special interest in future PSURs.

There were no relevant imbalances related to nerandomilast treatment in serious or opportunistic infections in the pooled safety analysis.

The incidence of potential severe drug-induced liver injury (DILI) was low and comparable across treatment groups, with no evidence of a dose-dependent increase in hepatic risk.

ADRs

Pooled data provide a comprehensive overview of AEs and SAEs up to DBL2 for 1305-0014 and 1305-0023. ADRs are presented for the week 52 analyses which coincide with the primary analysis timepoint. The methodology for identifying PTs for further thorough medical causality assessment was based on the total safety data base from completed and ongoing IPF and PPF trials, including safety data over the whole trial for both pivotal trials corresponding to a mean exposure to trial medication of 14-15 months.

The ADRs diarrhoea, weight loss, decreased appetite, nausea, and back pain, were identified for both IPF and PPF patients with and without background treatment.

Due to differences in background treatment regimens and patient characteristics between these two populations, ADR data is presented in an indication-specific format to include a comparative table that clearly displays the frequency rates of ADRs for IPF and PPF populations side by side.

While the safety profile identified is similar between the pivotal trials, some differences in safety profile have been identified in subgroup analyses by indication and particularly with regards to background treatment and by dose. The description of selected adverse events highlights any clinically meaningful differences that may be attributable to dose or background antifibrotic treatments by indication.

Separation of the safety data for the indications provides clarity for prescribers regarding the safety profile of nerandomilast with or without background treatment for patients with IPF or PPF and provides a practical basis for future indication-specific safety monitoring and safety updates should clinically meaningful divergences in safety across the IPF and PPF populations emerge.

Safety in special groups

Across demographic and baseline subgroups in the IPF and PPF pivotal studies, nerandomilast demonstrated a generally consistent safety profile without new or clinically meaningful safety signals.

In IPF, a higher proportion of male patients experienced severe AEs than females, while no gender-related imbalances were observed in PPF.

The overall data on the AE profiles are not suggestive of any meaningful trends or differences in safety profile by race although, given the low numbers of patients reported as Black or African American in the treatment groups, the interpretability of this subgroup analysis is limited.

The higher nerandomilast exposure observed in Asian patients is not expected to have a clinically relevant impact on safety. Adequate information on higher exposure (up to 47%) in Asian patients is included in section 5.2 of the SmPC.

Overall, SAEs, severe AEs and AELDs were reported more frequently in nerandomilast-treated patients ≥65 years compared to patients <65 years. No specific safety concerns were associated with nerandomilast treatment in patients ≥65 years old. Therefore, no specific warnings for elderly patients are considered warranted.

Baseline FVC % predicted:

Severe AEs, AELDs, and SAEs (including fatal AEs) were reported more frequently in the subgroup of patients with baseline FVC % predicted ≤70% subgroup across all treatment groups likely due to the more advanced disease state at baseline in those patients independent of nerandomilast treatment.

Baseline body weight:

The AE profile by body weight at baseline was in general comparable for both pivotal trials. The frequencies of drug-related AEs were higher for nerandomilast than for placebo in both pivotal trials for both body weight subgroups. The frequencies of AELDs tended to be higher for nerandomilast than for placebo mainly driven by gastrointestinal disorders, while frequencies across treatment groups (including a dose-dependent increase) were comparable for both body weight subgroups.

Results of PK modelling showed that patients with low body weight (<40 kg) are not anticipated to have a significant increase in exposure-related safety events (diarrhoea and weight loss ≥5%) over the general population.

Baseline eGFR:

Both pivotal trials included patients with mild (n=752 and n=664, respectively) and moderate renal impairment (n=127 and n=120). Frequencies of SAEs, fatal AEs, and AELDs were generally higher in patients with mild or moderate kidney function across all treatment groups, including the placebo groups in particular for PPF patients with moderate renal impairment. This is in line with the fact that patients with reduced kidney function have a higher disease burden and are more likely to experience AEs. However, no warning is necessary with respect to mild or moderate renal impairment.

Hepatic impairment:

Patients with severe hepatic impairment were not included in any of the pivotal trials. A dedicated hepatic impairment trial which included patients with Child Pugh A and B (mild and moderate hepatic impairment) showed that the impact of mild or moderate hepatic impairment on nerandomilast exposure was not substantial.. Therefore, no dose adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment (see

section 4.2 of SmPC). The pharmacokinetics,afety and efficacy has not been established in patients with severe hepatic impairment, which has been reflected in the SmPC.

Baseline HRCT pattern:

In patients with 'UIP or UIP-like fibrotic pattern' on HRCT, there was a dose-dependent overall increase in rates of AEs, severe AEs, SAEs and Investigator-defined drug-related AEs most notable in the 18 mg bid nerandomilast treatment group compared to placebo. The exception was in SAEs resulting in fatal outcome and AELDs which were higher in the placebo group compared to both nerandomilast treatment groups.

In patients with 'Other fibrotic patterns' on HRCT, the frequency of AEs, severe AEs, Investigator-defined drug-related AEs were higher in both nerandomilast treatment groups compared to placebo. No specific safety conclusions can be drawn from the data provided.

Pregnancy:

There is no clinical experience from clinical trials or post-marketing use regarding the use of nerandomilast in pregnant and breastfeeding women. Therefore, section 4.6 of the SmPC states that nerandomilast is not recommended for use during pregnancy or breastfeeding and women of childbearing potential have to use effective contraceptive methods due to the non-clinical observation of loss of pregnancy.

5.4.10.1.1. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed for inclusion in the SmPC are described below:

Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Common
Metabolism and nutrition disorders	
Decreased appetite	Common
Investigations	
Weight decreased	Common
Musculoskeletal and connective tissue disorders	
Back pain	Common

Reported frequencies over 52 weeks in trials 1305 0014 and 1305 0023 – TS

Due to differences in background treatment regimens and patient characteristics between the IPF and PPF populations, CHMP requested that ADRs for IPF and PPF should be presented separately in section 4.8 of the SmPC. The proposed ADRs diarrhoea, nausea, decreased appetite, weight decreased, and back pain are common to IPF and PPF and supported.

The description of selected adverse events clarifying any clinically meaningful differences based on background treatment was further supported with tabulated summaries to enhance clarity and facilitate interpretation.

5.4.10.2. Conclusions on clinical safety

Based on the safety data presented, most AEs reported with nerandomilast treatment were expected and manageable, aligning with the known profile of PDE4 inhibitors. Overall, the safety profile of nerandomilast is largely similar in IPF and PPF, although differences were observed in mortality and in the drivers of fatal AEs, as well as the frequency of diarrhoea AEs and treatment discontinuation due to diarrhoea. Both pivotal trials in IPF and PPF respectively demonstrated a consistent, dose-dependent increase in gastrointestinal AEs, particularly diarrhoea, with nerandomilast treatment. The nerandomilast 18 mg bid dose was associated with the highest incidence of diarrhoea and treatment-limiting AEs, especially when combined with background treatment with nintedanib.

IPF and PPF are distinct clinical entities with different aetiologies, comorbidities and treatments, in this context, the proposed ADRs have been presented separately for IPF and PPF and by background treatment in section 4.8 of the SmPC.

Nerandomilast was associated with higher rates of adverse events leading to treatment interruption or discontinuation, particularly at higher doses and when used with background antifibrotic therapy, where gastrointestinal events such as diarrhoea were more frequent and severe. These risks are appropriately addressed in Section 4.4 and in section 4.2 of the SmPC to reduce nerandomilast dose of 18 mg bid to 9 mg bid to manage tolerability in patients not on background pirfenidone treatment. Additional data on tolerability and dose reduction is anticipated from the ongoing and planned clinical trials with nerandomilast and this topic will be presented as a topic of special interest in the PSURs.

The potential for additive ADRs with concomitant AF treatment and the clinical impact of weight loss and severe GIT/diarrhoea ADRs with real world use of nerandomilast, will be further characterised post marketing particularly in more clinically vulnerable subgroups of patients, where literature data indicates that patients with low baseline BMI and weight loss in the course of IPF may indicate a high risk of mortality.

Section 4.4 of the SmPC has been updated to further inform HCP/patients on psychiatric safety issues, noting the existing warnings in section 4.4 for currently approved PDE4 inhibitors.

In conclusion, the overall safety profile is considered to be generally favourable and a number of topics of special interest (weight loss, cardiac events including tachyarrhythmia, in particular atrial fibrillation, diarrhoea, psychiatric events, vasculitis, lung cancer and overall tolerability) will be monitored in the PSURs as safety concerns of interest.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 148: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

6.1.2. Discussion on proposed safety specification

The applicant has not proposed to include any 'important identified risks' or 'important potential risks' in the nerandomilast summary of safety concerns. This is agreed.

The applicant's initial proposal to include 'Paediatric use' under 'Missing information' in the Summary of Safety concerns was not justified. It was considered that paediatric use was not justified for inclusion as missing information in the nerandomilast summary of safety concerns in the RMP at this time since it is not approved for this population and low off label use is anticipated.

A causal association between nerandomilast and vasculitis, psychiatric side effects, including suicidal behaviour has not been confirmed from the available safety data. These AEs will be followed post marketing. In conclusion, the lack of safety concerns is endorsed.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

The applicant's proposed routine pharmacovigilance activities, this is agreed by PRAC.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The CHMP requested that the Applicant includes the following safety concerns in the PSURs as topics of special interest: weight loss, cardiac events including tachyarrhythmia, diarrhoea, pregnancy cases (missing information), malignancy including lung cancer, vasculitis, psychiatric events and tolerability/dose reduction.

The conclusion that pregnancy could be followed through PSURs, in light of the likely low exposure in women of child-bearing potential and proposed warnings in the product information, is agreed.

6.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are currently proposed by the applicant; this is agreed by PRAC and CHMP.

6.3. Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies imposed for Jascayd.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The applicant proposal is endorsed by PRAC and CHMP.

6.4.2.2. Additional risk minimisation measures

No additional risk minimisation measures are proposed by the applicant, which is agreed.

6.5. RMP summary and RMP annexes overall conclusion

Summary of the RMP is updated in accordance with the template provided in the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2, 31/10/2018), and thus it is considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

The applicant is reminded that in case of a positive opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the international birth date (IBD) to determine the forthcoming Data Lock Points.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

8. Product information

8.1. Summary of product characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The proposed wording for both indications is considered acceptable, following removal of the reference to section 5.1 and removal of outcome measures for the PPF indication.

8.1.1. SmPC section 4.2 justification

The recommended dose is 18 mg twice daily. The dose may be reduced to 9 mg twice daily (except in patients who concomitantly use pirfenidone or strong or moderate cytochrome P450 3A (CYP3A) inducers based on individual patient tolerability of the side effects of diarrhoea or weight decrease and based on the anticipated benefit of treatment.

Once the adverse reaction has resolved or is adequately controlled, treatment may be resumed at the recommended dose of 18 mg twice daily.

Clear guidelines and relevant recommendations regarding treatment interruption, discontinuation and when the treatment can resume in the case of AEs has been introduced upon CHMP request with appropriate cross reference to sections 4.4, 4.5, 4.8 and 5.1 of the SmPC.

8.1.2. SmPC section 5.1 justification

For the IPF indication, both DBL1 and DBL2 have been presented in section 5.1. However, it is highlighted that the main analysis remains on the DBL1 data, and DBL2 is exploratory in nature.

The baseline disease characteristics, inclusion/exclusion criteria and randomisation strategy have been mentioned to include an appropriate description of the more advanced disease symptoms of background antifibrotic patients compared to non-antifibrotic patients. Additionally pulmonary hypertension incidence rates, an important co-morbidity for IPF, have also been included.

As usual, results were limited to main analyses that were clinically relevant and statistically compelling. Only data from the main analysis was presented for the key secondary endpoints, with the exception of mortality end-of-trial analysis as this was considered valuable for the IPF indication.

8.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Jascayd (nerandomilast) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

The agreed indications are:

- The treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF)
- The treatment of adult patients with Progressive Pulmonary Fibrosis (PPF)

The posology is: 18 mg twice daily.

Based on individual patient tolerability of the side effects of diarrhoea or weight decrease and based on the anticipated benefit of treatment with nerandomilast, the dose may be reduced to 9 mg twice daily (except in patients who concomitantly use pirfenidone or strong or moderate cytochrome P450 3A (CYP3A) inducers. Once the adverse reaction has resolved or is adequately controlled, treatment may be resumed at the recommended dose of 18 mg twice daily.

9.1.1. Disease or condition, proposed therapeutic indication

Nerandomilast is an oral selective inhibitor of phosphodiesterase 4 (PDE4) with preferential inhibition of the PDE4B isoenzyme. The PDE4 enzyme inactivates the second messenger molecule cAMP, which can contribute to fibrotic and inflammatory processes. In humans, the PDE4B isoenzyme is highly expressed in the lung and plays an important role in fibrosis and inflammation in the lungs. Nerandomilast reduces the expression of pro-fibrotic growth factors and inflammatory cytokines, which are overexpressed in fibrotic lung disease.

IPF indication

IPF is specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring in adults and limited to the lungs resulting in a significant decline in lung function and in progression to respiratory failure and death, approximately four to five years after the initial diagnosis. However, there is great variability in disease course influenced by occurrence of acute exacerbations, and comorbid disease.

IPF is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). Both prevalence and incidence increase with advancing age, higher in males than females with presentation commonly occurring in the sixth and seventh decades; IPF is rare in patients less than 50 years of age.

Overall, the incidence of IPF is increasing worldwide and conservative estimates range from 0.9 to 13 per 100,000 persons; the prevalence ranges from 3.3 to 45 per 100,000 persons.

PPF indication

The term interstitial lung disease (ILD) encompasses a large group of over 200 pulmonary disorders and a large category of diseases that have either fibrosis, inflammation, or both, in the walls of the air sacs in the lung. While IPF is universally progressive, there is a group of patients with different underlying clinical

ILD diagnoses who develop a progressive phenotype (termed PPF) similar to patients with IPF during their disease (Wells et al. 2018).

Disease onset during adulthood is most common (Kang et al. 2023), but onset can range over multiple decades with some cases reported in the paediatric population (Rajan et al. 2023). The estimated prevalence for PPF were 2.2–20.0 per 100 000 in Europe and 28.0 per 100 000 in the USA (Olson et al. 2021). Non-IPF PF-ILD is associated with a considerable mortality risk with an average median survival rate of around 3-5 years varying by countries (Cottin et al. 2022).

The major abnormality across ILDs is the disruption of the distal lung parenchyma with some form of injury of the alveolar epithelial cells initiating an inflammatory response coupled with repair mechanisms and resulting in alterations and in restrictive ventilatory and gas exchange deficits on pulmonary function testing.

9.1.2. Available therapies and unmet medical need

IPF and PPF indication

Nintedanib and pirfenidone are the only drugs authorised in the EU for the treatment of IPF while only nintedanib is approved for the treatment of adults with PPF. No medication has been found to cure IPF/PPF, but nintedanib and pirfenidone (for IPF only), appear to slow disease progression and reduce the frequency of acute exacerbations but cannot stop or reverse fibrosis. Thus, despite existing treatments, significant morbidity and mortality remain in patients with IPF. Despite the availability of nintedanib and pirfenidone as antifibrotic therapies, there remains a high unmet medical need for more efficacious and better tolerated treatments for patients living with these diseases.

9.2. Main clinical studies

IPF indication

Study 1305-0014 (FIBRONEER-IPF) was the pivotal trial supporting the IPF indication. It was a multi-centre, multi-national, randomised, placebo-controlled, double-blind clinical trial in patients with IPF treated for period of at least 52 weeks and a 1-week follow-up. Patients were randomised 1:1:1 to receive nerandomilast 9 mg, 18 mg, or matching placebo twice daily. Randomisation was stratified by the presence or absence of antifibrotic treatment at baseline, allowing inclusion without altering ongoing standard of care. The trial had two parts: Period A until Week 52, followed by Period B with continued blinded treatment for a variable duration. A total of 1177 patients were randomised as follows: placebo (393 patients), nerandomilast 9 mg bid (392 patients), or nerandomilast 18 mg bid (392 patients).

The study included patients with or without stable background treatment approved for IPF and investigated the effect on the absolute change from baseline in FVC [mL] at Week 52 (primary efficacy outcome). The key secondary endpoint was a composite endpoint of first acute exacerbation, hospitalization for a respiratory cause, or death, assessed in a time-to-event analysis over the duration of the trial. The main analysis was performed at Week-52 (first database lock: DBL1 – 16 Aug 2024). For IPF study 0014, results of the final analysis (DBL2 – 3 Feb 2025) were also presented, i.e. when all patients completed the last study visit.

PPF indication

Study 1305-0023 (FIBRONEER-ILD) was the pivotal trial supporting the PPF indication. It was a multi-centre, multi-national, randomised, placebo-controlled, double-blind clinical trial in patients with PPF. Patients were randomised 1:1:1 to receive 9 mg nerandomilast, 18 mg nerandomilast, or matching

placebo twice daily. Randomisation was stratified the absence vs. presence of baseline antifibrotic treatment (nintedanib) and by the HRCT pattern ("UIP or UIP-like fibrotic pattern" vs "other fibrotic patterns"). The trial had two parts: Period A until Week 52, followed by Period B with continued blinded treatment for a variable duration. 1178 participants were enrolled with placebo (N=393), nerandomilast 9 mg (N=393) and nerandomilast 18 mg (N=392) patients randomized per group.

The study included patients with or without stable background treatment approved for PPF and investigated the effect on the absolute change from baseline in FVC [mL] at Week 52 (primary efficacy outcome). The key secondary endpoint was time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalisation for respiratory cause, or death (whichever occurred first) over the duration of the trial.

Patients in the IPF and PPF pivotal trials were allowed to remain on their background treatment (nintedanib or pirfenidone but not both simultaneously). The trial stratified patients based on whether they had been on stable nintedanib or pirfenidone therapy for at least 12 weeks prior to the first nerandomilast dose.

9.3. Favourable effects

IPF indication

The primary endpoint measuring the absolute change from baseline in FVC [mL] at Week 52 was met. Treatment with nerandomilast 9 mg and 18 mg bid resulted in a statistically significant decrease in the rate of FVC decline compared to placebo. The adjusted mean (95% CI) change from baseline in FVC [mL] at Week 52 was -183.5 (-210.9, -156.1) in the placebo group, -138.6 (-165.6, -111.6) in the 9 mg bid nerandomilast group, and -114.7 (-141.8, -87.5) in the 18 mg bid nerandomilast group. The adjusted mean difference (95% CI, p-value) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 44.9 (6.4, 83.3, p = 0.0222) and between 18 mg bid nerandomilast and placebo groups was 68.8 (30.3, 107.4, p = 0.0005).

The primary endpoint results were supported by other endpoints investigating the effect on FVC. The change from baseline in FVC % predicted at week 52, demonstrated similar efficacy as the primary endpoint. The adjusted mean difference (95% CI) in FVC % predicted change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 1.2 % (0.1%, 2.2%) and between 18 mg bid nerandomilast and placebo groups was 1.7% (0.7%, 2.8%). Further supporting evidence for efficacy of nerandomilast came from the DLCO related endpoints. The adjusted mean difference (95% CI) in DLCO % predicted (corrected for haemoglobin) change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 2.5% (0.8%, 4.2%) and between 18 mg bid nerandomilast and placebo groups was 1.7% (0.0%, 3.4%).

Effect on mortality

The cumulative incidence of deaths was numerically lower in the treatment groups as compared to the placebo group. For the higher dose, the decrease in the number of deaths was more pronounced and seen earlier. Over the whole trial up to DBL2, deaths occurred in 42 patients in the placebo group (10.7%), 36 patients in the 9 mg bid nerandomilast group (9.2%), and 26 patients in the 18 mg bid nerandomilast group (6.6%). For the 18 mg bid nerandomilast dose, a small numerical reduction in mortality (one of the composites of the key secondary endpoint) was observed, which slightly increased in time:

- DBL1: mortality n=21 (5.4%) vs. placebo n=28 (7.1%); HR: 0.81 (0.46, 1.43)

- DBL2: mortality n=26 (7.2%) vs. placebo n=42 (10.7%); HR: 0.66 (0.44, 1.08)

In a post hoc analysis excluding patients with pirfenidone background treatment, the HR (95% CI) vs. placebo were 0.84 (0.48, 1.48) for 9 mg bid and 0.47 (0.25, 0.90) for 18 mg bid nerandomilast

Favourable effect in subgroups

The positive treatment effect was also observed in subgroups. Results in subgroups depending on gender, age group, race, ethnicity, baseline FVC % predicted, baseline anti fibrotic treatment, baseline bodyweight and type of antifibrotic treatment were presented.

For the group of patients receiving monotherapy the adjusted mean difference (95% CI) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 78.3 (-3.2, 159.8) and between 18 mg bid nerandomilast and placebo groups was 69.4 (-12.3, 151.2) corresponding to 53% and 47% relative reduction, respectively.

For the group of patients treated in combination with nintedanib, the adjusted mean difference (95% CI) in FVC [mL] change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 60.9 mL (4.3, 117.5) and between 18 mg bid nerandomilast and placebo groups was 73.0 mL (15.3, 130.8) corresponding to 32% and 38% relative reduction respectively.

The 18 mg bid dose showed a decreased FVC decline in combination with pirfenidone; however, the relative reduction (32%) was smaller than seen in other subgroups.

In subgroups by AF background treatment, a numerical reduction in mortality was observed for patients receiving monotherapy for the 18 mg bid dose:

- DBL1: mortality n=1 (1.1%) vs. placebo n=9 (10.3%); HR of 0.12 (0.02, 0.96)
- DBL2: mortality n=14 (16.1%) vs. placebo n=24 (27.6%); HR 0.63 (0.32, 1.21)

PPF indication

The primary endpoint measuring the absolute change from baseline in FVC [mL] at Week 52 was met. Both nerandomilast doses of 9 mg and 18 mg bid showed statistically significant FVC change [mL] improvement compared to placebo for the primary endpoint. The adjusted mean decline in patients receiving 18 mg or 9 mg nerandomilast twice daily was -99 mL and -85 mL, respectively, whereas in the placebo group, an adjusted mean decline of -166 mL was observed. The difference to placebo in the adjusted mean (95% CI, p-value) change from baseline at Week 52 in FVC [mL] was 81.1 (46.0, 116.3, $p<0.0001$) in the nerandomilast 9 mg bid group and 67.2 (31.9, 102.5, $p = 0.0002$) in the nerandomilast 18 mg bid group.

The primary endpoint results were supported by other endpoints investigating the effect on FVC. The adjusted mean difference (95% CI) in FVC % predicted change from baseline at Week 52 between 9 mg bid nerandomilast and placebo groups was 2.19% (1.15%, 3.23%) and between 18 mg bid nerandomilast and placebo groups was 1.94% (0.90%, 2.98%). At DBL1, the risk of acute ILD exacerbations or deaths was reduced by 41% for the 18 mg bid nerandomilast group vs. placebo (HR 0.59, 95% CI 0.41, 0.84). The risk of hospitalisations for respiratory cause or deaths was reduced by 25% for the 18 mg bid nerandomilast group vs. placebo (HR 0.75, 95% CI 0.56, 1.00).

Over the duration of the trial up to DBL2, acute ILD exacerbations or deaths occurred in 24.7% of the patients in the placebo group, 17.8% in the 9 mg bid nerandomilast group, and 15.1% in the 18 mg bid nerandomilast group. Hospitalisations for respiratory cause or deaths over the duration of the trial up to

DBL2 occurred in 33.4% of the patients in the placebo group, 26.2% in the 9 mg bid nerandomilast group, and 26.3% in the 18 mg bid nerandomilast group.

At DBL2, deaths over the duration of the trial occurred in 64 patients in the placebo group (16.3%), 36 patients in the 9 mg bid nerandomilast (9.2%), and 34 patients in the 18 mg nerandomilast (8.7%). The risk of death was reduced by 49% for both doses (HR 0.51 [0.34, 0.78] for 9 mg bid nerandomilast and 0.51 [0.34, 0.78] for 18 mg bid nerandomilast.

Favourable effect in subgroups

The results in subgroups depending on gender, age group, race, ethnicity, baseline FVC % predicted, baseline anti fibrotic treatment, baseline bodyweight, baseline HRCT pattern and underlying clinical ILD diagnosis were presented.

The results in subgroups by fibrotic pattern showed a slightly stronger effect for the other fibrotic pattern, especially for the 18 mg dose (treatment by subgroup interaction p-value: 0.0384).

The results in subgroups by underlying ILD diagnosis noted some differences. Nerandomilast was slightly less effective in treating Idiopathic nonspecific interstitial pneumonia and autoimmune ILD (Adjusted Mean Difference in FVC: 34.94 mL (95% CI: -45.4, 116.27) and 45.86 mL (95% CI: -20.84, 112.57) for 9 mg twice daily and 53.48 mL (95% CI -25.89, 132.85) and 42.22 mL (95% CI: -24.85,109.30) for 18 mg twice daily for Idiopathic nonspecific interstitial pneumonia and autoimmune ILD) compared to the remaining underlying ILDs.

The positive treatment effect was also observed in patients treated in combination with nintedanib and with monotherapy.

Patients on monotherapy in the placebo group had a loss of FVC of 154.1 mL. The treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed reductions of 71.8 (95% CI: 24.9, 118.8) mL and 58.9 (95% CI: 12.1, 105.8) mL in this subgroup of patients respectively.

Patients receiving nerandomilast monotherapy had a reduction of the risk of acute ILD exacerbations, hospitalisation for respiratory causes combined with death and death alone. For first acute ILD exacerbation or death, the treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed a hazard ratio of 0.76 (95% CI: 0.49, 1.18) and 0.59 (95% CI: 0.37, 0.96), respectively. Regarding death, the treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed hazard ratios of 0.64 and 0.41 respectively.

Patients on nintedanib background therapy in the placebo group had a loss of FVC of 180.9 mL. The treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed reductions of 93.1 (95% CI: 39.9, 146.3) mL and 78 (95% CI: 24.2, 131.8) mL in this subgroup of patients respectively, suggesting a stronger effect of the low dose of nerandomilast on lung function as observed for the overall population.

At DBL1, patients treated in combination with nintedanib had a reduction of the risk of acute ILD exacerbations, hospitalisation for respiratory causes combined with death and death alone (HR 0.78 (CI 0.55, 1.11) for 9mg bid and HR 0.70 (0.49, 1.01) for 18mg bid). For first acute ILD exacerbation or death, the treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed a difference of hazard ratio of 0.80 (95% CI: 0.49, 1.31) and 0.58 (95% CI: 0.34, 0.99) respectively. Regarding time to death over the whole trial, the treatment effect of nerandomilast (9 and 18 mg bid) when compared to placebo showed hazard ratios of 0.55 (95% CI 0.27, 1.14) and 0.57 (95% CI 0.28, 1.15) respectively.

9.3.1. Uncertainties and limitations about favourable effects

IPF indication

Use of nerandomilast in combination with pirfenidone

Combination use with pirfenidone led to a 55% decrease in nerandomilast plasma exposure in the 9 mg bid group and 48% plasma exposure in the 18 mg group, compared to patients not taking pirfenidone. However, this assessment of reduced exposure was based on the PK data from the pivotal clinical study, and no formal drug-drug interaction study was performed. A clinical Drug-Drug Interaction (DDI) study in IPF patients will be performed and this will further inform the level of interaction between the two products. The Applicant has committed to submitting the results of this study in July 2027.

Nerandomilast 18 mg bid dose showed a statistically significant decrease in the absolute change from baseline in FVC [mL] at Week 52 in combination with pirfenidone. However, this was not supported by secondary endpoints capturing direct clinical benefits in particular there is no apparent reduction in mortality at DBL1 or DBL2 for this subgroup. At DBL2, no difference in the number of mortality events was observed in the placebo group (n=13 (9.8%)) compared to the nerandomilast 18 mg dose (n=12 (9.4%)) for this subgroup (HR 1.12 (95% CI 0.51, 2.47)). This is adequately reflected in section 5.1 of the SmPC.

Uncertainties regarding the effect on mortality in IPF population

There are uncertainties regarding the mortality results. Deaths (All) at the main analysis of DBL1, showed little difference with treatment, with 28 (7.1%) in placebo, 26 (6.6%) in 9 mg bid, and 21 patients (5.4%) in 18 mg bid. Although not multiplicity controlled, the positive effect seen on reduction in mortality was based on the analysis of DBL2 data.

PPF indication

Uncertainties regarding the effect on mortality in PPF population

Nerandomilast treatment, especially the higher 18 mg dose reduced the risk of acute ILD exacerbations, hospitalisation for respiratory causes combined with death and death alone. However, multiplicity adjustment was not applied, therefore the finding should be interpreted cautiously.

IPF and PPF indication

Monotherapy use in patients who are treatment naïve

While both studies employed placebo-controlled designs and enrolled patient subgroups with different background therapies, a non-inferiority design against authorised therapies would have enabled a more rigorous assessment of relative efficacy compared with nintedanib or pirfenidone.

Additionally, the subpopulations not receiving background antifibrotic therapy did not exclusively represent treatment-naïve patients, as they also included individuals with prior exposure to antifibrotic agents that had subsequently been discontinued prior nerandomilast administration. This is reflected in SmPC section 5.1 for both indications.

Uncertainties about the dose selection

No formal dose response study has been conducted with increasing doses, making it uncertain whether the proposed dosing regimen (18 mg and 9 mg) is ultimately the optimal regimen. However the overall clinical data programme supports the intended posology for both 18 and 9mg BID regimen in case of tolerability issues as recommended in section 4.2 of SmPC.

Uncertainties regarding the key secondary endpoint

The key secondary endpoint was a composite of the time to the first pulmonary exacerbation, hospitalization due to respiratory disease and death. In both studies, this endpoint failed to show statistical significance, but an improved effect was observed in the reduction of mortality events.

In the IPF population, this reduction was most pronounced in the stratified subgroup without AF background treatment, but over time the mortality events also improved in the subgroups with AF background treatment. The effect on mortality was smallest in the subgroup treated with pirfenidone and 18 mg nerandomilast, as at DBL1 the mortality numbers favoured placebo, but this effect had largely disappeared at DBL2.

In the PPF population, the idiopathic nonspecific interstitial pneumonia (iNSIP) subgroup did not show an improvement in mortality events for nerandomilast 18 mg bid at either DBL1 or DBL2.

No statistically significant effect has been demonstrated in the symptomatic improvement of the key symptoms of IPF/PPF i.e. cough, dyspnoea and fatigue for either indication.

The efficacy of nerandomilast in patients with severe to very severe lung impairment was not investigated; however, prespecified and additional subgroup analyses by baseline FVC % predicted and DLCO % predicted (as proxy for disease severity in the absence of a formal severity classification) for the primary endpoint showed consistent results for both doses of nerandomilast across both indications irrespective of FVC or DLCO impairment, supporting the extrapolation to very severe patients not included in the study. The applicant presented the efficacy data in patients with pulmonary hypertension and also for this subgroup the use of nerandomilast is considered as justified, despite the limited patient numbers exposed in the pivotal trials.

9.4. Unfavourable effects

The applicant submitted an extensive patient exposure population covering Phase I, II and III studies with 2738 patients exposed overall (to any dose). In total 1568 patients were exposed to nerandomilast in the pivotal trials with 1387 patients treated for ⩾6 months and 1259 patients treated for ⩾12 months. For the pooled safety set SAF1, 1267 patients (80.8%) completed planned nerandomilast treatment up to Week 52. In the SAF1 pooled analysis, more than 71.4% (1119/1568) of patients were treated for at least 15 months and 25.9% (406/1568) for at least 18 months. The total exposure to nerandomilast across the pivotal trials in PYs was 1953.43. Of these, 700 patients received a dose of nerandomilast 9 mg bid and 687 patients received a dose of 18 mg bid for >6 months and 636 patients received a dose of 9 mg bid and 623 patients received a dose of 18 mg bid >12 months.

Gastrointestinal events, weight decrease and decreased appetite:

Diarrhoea was most frequently reported in the nerandomilast 18 mg bid compared to the 9 mg bid or placebo group and in patients with background nintedanib or pirfenidone treatment compared to no treatment. Events occurred within the first 3 months of the trial and were of 2 weeks duration. Although the large majority of diarrhoea events were mild, most moderate/severe events were observed in patients receiving 18 mg bid nerandomilast together with nintedanib.

In the SAF1 pooled analysis, nausea was reported most frequently in the 18 mg bid nerandomilast group (placebo: 7.1%, 9 mg bid nerandomilast: 9.0%, 18 mg bid nerandomilast: 10.3%).

There was a numerically higher reporting rate of weight decrease AEs in the pivotal IPF and PPF studies in patients treated with nerandomilast compared with placebo. This was dose dependent with the highest frequency observed with nerandomilast 18 mg bid dosing. In the pooled analysis AE 'weight decreased' was reported by 8.9% vs 10.3% vs 13.3% respectively of patients treated with placebo and nerandomilast 9 mg and 18 mg bid.

Overall, for patients not receiving baseline antifibrotic therapy (Pool SAF1), a dose-dependent increase in the incidence of weight loss was observed across the placebo, nerandomilast 9 mg bid, and nerandomilast 18 mg bid treatment arms (6.8%, 7.1%, and 13.0%, respectively). In patients on background antifibrotic therapy, 10.3% vs 12.4% vs 13.5% respectively reported weight decrease. In patients with IPF, weight decrease was most pronounced in patients treated with nintedanib plus nerandomilast 18 mg bid (13.3% vs 14.1% vs 16.9% respectively). In patients with PPF weight loss was comparable between patients on nerandomilast alone and on nerandomilast with nintedanib.

Decreased appetite (PT) was reported most frequently in the 18 mg bid nerandomilast group (placebo: 7.5%, 9 mg bid nerandomilast: 8.3%, 18 mg bid nerandomilast: 9.7%; SAF1 pooled analysis).

Other events:

Back pain was reported most frequently in the 18 mg bid nerandomilast group (placebo: 3.6 %, 9 mg bid nerandomilast: 5.2%, 18 mg bid nerandomilast: 6.9 % (Pool SAF1).

Vasculitis (SMQ narrow): In IPF patients, a higher incidence was observed in the nerandomilast treatment groups (1.0% in 9 mg bid and 1.3% in 18 mg bid) compared to placebo (0.8%). In the PPF study vasculitis was reported in 0.3% of the placebo population vs 0.8% of the 9 mg bid and 0.3% of the 18mg bid population.

Suicidal ideation and behaviour (SMQ narrow): There was a slight upward trend in suicidal ideation and behaviour rates with increasing dose of nerandomilast (0.5% in the placebo group to 0.8% in the nerandomilast 18 mg bd group (Pool SAF 1)).

9.4.1. Uncertainties and limitations about unfavourable effects

Tolerability: Section 4.2 of the SmPC allows for dose reduction to 9 mg bid based on individual tolerability. However, the pivotal IPF and PPF studies did not specify dose modification criteria. There was no within-trial switching of dose from 18 mg bid to 9 mg bid. Further evaluation of dose reduction in the post authorisation setting together with data relating to tolerability are anticipated from the dedicated drug-drug interaction study planned to be completed in July 2027. This will be monitored post marketing in the PSURs.

Nerandomilast in combination with nintedanib/pirfenidone was only studied in patients who tolerate nintedanib/pirfenidone. Tolerability of starting combination therapy in treatment-naïve patients is not known.

Weight decrease/loss: Weight loss has been identified as a strong prognostic marker for mortality and hospitalisation in IPF (Xing He et al 2024; Kalinsky et al 2022). Treatment with nerandomilast has been associated with dose dependent weight loss particularly with concomitant use of nintedanib and body weight should be monitored regularly during therapy. There is uncertainty regarding need for and impact of dose titration, therefore additional warnings have been added to the SmPC section 4.4. If unexplained weight loss becomes progressive or clinically concerning, treatment should be reassessed and dose reduction or discontinuation of treatment should be considered. Nerandomilast should be used with caution in patients who are underweight or have conditions in which additional weight loss may be medically undesirable. Weight decrease/ loss will be monitored as a topic of special interest in the PSURs.

Vasculitis: Although vasculitis may emerge independently in the IPF and PPF population, vasculitis is a known preclinical effect of PDE 4 inhibitors. A signal for vasculitis was identified in nonclinical toxicity studies and higher incidence observed in nerandomilast groups although numbers are low, and many cases were confounded limiting causality assessment. Vasculitis will be reviewed as a topic of special interest post marketing in the PSURs.

Tachyarrhythmia/Atrial fibrillation: Major adverse cardiac events (MACE) and tachyarrhythmia are included as important potential risks in other non-selective PDE4 inhibitors. There was a dose dependent increase in reports of tachyarrhythmias with nerandomilast. The majority of cases were confounded by a relevant medical/cardiac history and no clear trends identified. The topic will be closely monitored as a topic of special interest in the PSURs.

Malignancy: Some small numerical imbalances between the nerandomilast and placebo groups for non-melanomatous skin cancers and lung neoplasm were noted in the PPF and pooled populations. There was no indication of a dose related trend with nerandomilast. Malignancy including lung cancer will continue to be closely monitored as a topic of special interest in the PSURs.

Suicidal ideation and behaviour (SIB): Psychiatric disorders can be a common comorbidity in patients with IPF and PPF. All suicidal ideation SAEs in the nerandomilast group were slightly higher with nerandomilast compared to placebo, although numerically small, point estimates indicate a potential dose-response relationship. For the higher dose (nerandomilast 18mg bid) the risk ratio was 1.5 (0.43, 5.3) and the risk difference was 0.21 (−0.42, 0.85). For the 9 mg bid group the risk ratio was the same as placebo on average.

Although confounding factors were noted in some cases, two patients in the PPF population with suicidal ideation had no confounding factors. The 0.3% increase in SIB noted in the pooled data; although small is clinically relevant in the context of suicidal ideation. Therefore, a warning was added to section 4.4 of SmPC to inform prescribers that psychiatric events, including very rare instances of suicidal ideation and behaviour, have been reported in clinical studies of nerandomilast across treatment groups. Routine monitoring for psychiatric disorders is recommended and psychiatric events will be followed up as a topic of special interest in PSURs.

9.5. Effects table

Table 149: Effects table

Effects Table for Jascayd indicated for the treatment of adult patients with IPF (data cut-off: 28 November 2024 (main analysis at DBL1), 31 Mar 2025 (final analysis at DBL2)).

Effects Table for Jascayd indicated for the treatment of adult patients with PPF until DBL1 (data cut-off: 11 Dec 2024 (main analysis at DBL1), 28 APR 2025 (final analysis at DBL2)).

Effect (short description)	*Treatment*		*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable effects					
IPF indication					
	Nerandomilast 9 mg bid	Nerandomilast 18 mg bid	Placebo		
Primary endpoint Absolute change from baseline in FVC [mL] at Week 52	-138.6	-114.7	-183.5	**SoE:** PE; mean difference vs placebo 9mg 44.9 ml (6.4, 83.3, p = 0.0222), 18 mg 68.8 ml (30.3, 107.4, p = 0.0005) **Unc:** Surrogate endpoint only, results confounded by pirfenidone	Study 1305-0014 **DBL1)**

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Key secondary endpoint Time to the first event in the key secondary composite endpoint (acute IPF exacerbation, first hospitalisation for respiratory cause, or death) over the duration of the trial	90 (23.0%)	93 (23.7%)	103 (26.2%)	**SoE:** HRs (95% CI) vs. placebo was 0.92 (0.69, 1.22) for 9 mg bid nerandomilast (p = 0.5443) and 0.99 (0.75, 1.31) for 18 mg bid nerandomilast (p = 0.9512). **Unc:** It should be ensured that no non-detrimental effect has been robustly demonstrated for components of the key secondary endpoint	Study 1305-0014 **(DBL2)**
Deaths over the whole trial	36 (9.2%)	26 (6.6%)	42 (10.7%)	**SoE:** SE; HRs (95% CI) vs. placebo 0.95 (0.61, 1.49) for 9 mg bid, 0.66 (0.41, 1.08) for 18 mg bid nerandomilast **Unc:** Nominal significance only, DBL2 data	Study 1305-0014 **(DBL2)**
Time to absolute decline from baseline in FVC % predicted of >10% or death over the duration of the trial	132 (33.7%)	116 (29.6%)	153 (38.9%)	**SoE:** SE; HRs (95% CI) vs. placebo 0.85 (0.67, 1.07, p = 0.1580) for 9 mg bid, 0.75 (0.59, 0.95, p = 0.0180) for 18 mg bid nerandomilast **Unc:** Not independent endpoint, Nominal significance only, DBL2 data	Study 1305-0014 **(DBL2)**
Absolute change from baseline in DLCO % predicted (corrected for haemoglobin) at Week 52	2.5	1.7	-	**SoE:** SE; change vs. placebo 2.5 (0.8, 4.2, p = 0.0042) for 9 mg bid, 1.7 (0, 3.4, p = 0.0530) for 18 mg bid nerandomilast **Unc:** Nominal significance only	Study 1305-0014
PPF indication					
Primary endpoint: Absolute change from baseline in FVC [mL] at Week 52	-84.6	-98.6	-165.8	**SoE:** PE; (Nerandomilast vs Placebo) 9mg: 81.1 (95% CI 46.0, 116.3, p<0.0001); 18mg: 67.2 (95% CI 31.9, 102.5, p = 0.0002) **Unc:** surrogate endpoint, clinical relevance associated with mortality	Study 1305-0023 **(DBL1)**
Key secondary endpoint Time to the first event in the key secondary composite endpoint (acute IPF exacerbation, first hospitalisation for respiratory cause, or death) over the duration of the trial	110 (28.0%)	95 (24.3%)	122 (31.1%)	**SoE:** HR vs. placebo for 9 mg bid 0.88, 95% CI 0.68, 1.14, p = 0.3398; for 18 mg bid 0.77, 95% CI 0.59, 1.01, p = 0.0602 **Unc:** statistical significance was not reached	Study 1305-0023 **(DBL1)**
FVC absolute change from baseline in FVC % predicted at Week 52 (%)	-2.69	-2.94	-4.88	**SoE:** (Nerandomilast vs Placebo) 9mg: 2.19 (1.15, 3.23); 18mg: 1.94 (0.90, 2.98) **Unc:** Secondary endpoint not under multiplicity adjustment	Study 1305-0023 **(DBL1)**

Effect (short description)	*Treatment*		*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Mortality (DBL2) (%)	9.2	8.7	16.3	**SoE:** (Nerandomilast vs Placebo) 18mg: HR 0.51, 95% CI 0.34, 0.78; 9mg: HR 0.51, 95% CI 0.34, 0.78. **Unc:** For patients with iNSIP, no numerical improvement in mortality was observed.	Study 1305-0023 (**DBL2**)
Unfavourable effects					
	Nerandomilast 9mg bid	Nerandomilast 18mg bid	Placebo		
Diarrhoea: **frequency of AEs in the safety topic**					
IPF:					
No background AF treatment	n=15 (17.1%)	n=23 (26.4%)	n=7 (8.1%)	**SoE:** evidence of dose dependent effect, which is more marked when used with nintendanib. **Unc:** probable additive effects with combined AF	Study 1305-0014 (DBL1 – TS)
+nintedanib	n=92 (50.0%)	n=110 (61.8%)	n=48 (27.8%)		
+pirfenidone	n=16 (13.3%)	n=30 (23.6%)	n=11 (8.3%)		
PPF:				Data on dose titration and warnings on management of this ADR have been added to the PI to reflect the current data.	
No background AF	n=39 (17.7%)	n=60 (27.3%)	n=38 (17.1%)		Study 1305-0023 (DBL2)
+nintedanib	n=89 (51.5%)	n=85 (49.7%)	n=64 (37.7%)		
Weight decrease:	**Frequency of AEs in the safety topic of interest**				
IPF:				**SoE:** Pooled analysis showed decrease in mean body weight from baseline to last value on treatment was observed in all treatment groups and was numerically larger with nerandomilast 9mg bid and 18mg bid compared to placebo. **Unc:** uncertainty re clinical outcomes in PPF/IPF patients, dose titration, need for additional warnings acknowledged and added to the PI and future monitoring as a topic of interest in PSURs recommended.	
No background AF treatment	n=2 (2.3%)	n=7 (8.1%)	n=5 (5.8%)		Study 1305-0014 (DBL1 – TS)
+nintedanib	n=26 (14.1%)	n=29 (16.3%)	n=21 (12.1%)		
+pirfenidone	n=12 (10.0%)	n=8 (6.3%)	n=7 (5.3%)		
PPF:					
No background AF	n=20 (9.1%)	n=32 (14.6%)	n=14 (6.3%)		Study 1305-0023 (DBL2)
+nintedanib	n=18 (10.4%)	n=25 (14.6%)	n=18 (10.6%)		
Pooled:	n=82 (10.5%)	n=106 (13.5%)	n=70 (8.9%)		Study 1305-0014 (DBL1 – TS) Study 1305-0023 (DBL2 – TS)
Vasculitis:	**Frequency of AEs in the safety topic of interest**				

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
IPF:	Total:n=4 (1.0%) Adjudicated: n=1	Total:n=5 (1.3%) Adjudicated: n=4	Total:n=3 (0.8%) Adjudicated: n=1	**SoE:** Vasculitis is a known preclinical effect of PDE 4 inhibitors. A preclinical signal for vasculitis was identified in repeat-dose toxicity studies in rats and minipigs. Higher incidence in the nerandomilast treatment groups although numbers are low. In pooled trials, 17 patients overall were reported with AEs in the vasculitis safety topic. This comprised 4 (0.5%) patients in the placebo group, 7 (0.9%) patients in the 9 mg bid nerandomilast group, and 6 (0.8%) patients in the 18 mg bid nerandomilast group. **Unc:** confounding factors limit causality. There is uncertainty as to whether nerandomilast may act as a trigger in a susceptible subpopulation. Ongoing monitoring has been recommended.	Study 1305-0014 (DBL2 – TS)
PPF:	Total:n=3 Adjudicated: n=2	Total:n=1 Adjudicated: n=1	Total:n=1 Adjudicated: n=1		Study 1305-0023 (DBL2)
Pooled data:	Total: n=7 (0.9%) Adjudicated: n=3 (0.4%)	Total: n=6 (0.8%) Adjudicated: n=5 (0.6%)	Total: n=4 (0.5%) Adjudicated: n=2 (0.3%)		Study 1305-0014 (DBL2 – TS) Study 1305-0023 (DBL2)
Suicidal ideation (SI):	**Frequency of AEs in the safety topic of interest**				
IPF	Total SAE: n=3 (0.8%)	Total SAE: n=3 (0.8%)	Total SAE: n=2 (0.5%)		Study 1305-0014 (DBL2 – TS)
PPF	n=2 (0.5%)	n=3 (0.8%)	n=2 (0.5%)		DBL2 (trial 1305-0023)

Effect (short description)	Treatment		Control	Uncertainties/ Strength of evidence	Ref
Pooled	Total SAEs: n=5 (0.6%)	Total SAEs: n=6 (0.8%)	Total SAEs: n=4(0.5%)	**SoE:** SI AEs in the nerandomilast group slightly higher than in placebo, although numerically small, point estimates indicate a potential dose-response relationship. The risk ratio for Suicidal ideation suggests that the rate of suicidal ideation is the same as placebo on average for the nerandomilast 9mg bid group. For the higher dose (nerandomilast 18mg compared to placebo) the risk ratio was 1.5 (0.43, 5.3) and the risk difference was 0.26 (−0.53, 1.30) **Unc**: although confounding/background factors noted, a possible association with nerandomilast needs to be closely monitored. 2 patients in the PPF population had no confounding factors. The 0.3% increase noted in the pooled data although small is clinically relevant in the context of suicidal ideation. Further monitoring proposals for this safety issue were agreed and a warning was added to section 4.4 to reflect the uncertainty.	DBL2 – TS (trial 1305-0014) DBL2 (trial 1305-0023)

Abbreviations: DBL1: Data base lock one; DBL2: Data base lock two; Ref: reference; Unc: uncertainties; SoE: strength of evidence; PE: primary endpoint; SE: secondary endpoint, SAE : serious adverse event; TS: treated set

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

IPF indication

A statistically significant reduction in absolute change from baseline in FVC [mL] at Week 52 relative to placebo was reported with nerandomilast treatment in the overall FIBRONEER-IPF study population. The observed reductions in the rate of decline relative to placebo are considered as both statistically and clinically relevant. The clinical relevance of the results on this surrogate endpoint was primarily supported by a reduction in mortality. A numerical reduction in the risk of death was observed for the 18 mg bid dose vs placebo at the time of the primary analysis at DBL1. However, the composite key secondary endpoint was not met in the FIBRONEER-IPF study and there was no reduction in the risk of acute IPF exacerbation or hospitalisation for respiratory cause at this time point. Further, nerandomilast 9 mg was not associated with a reduction in the risk of death at this time point. More positive results on these endpoints were observed for both the 18 mg bid and 9 mg bid doses vs placebo at the time of the final analysis at DBL2.

The observed numerical improvement in mortality is considered an important outcome, even if the observed improvement in mortality was not consistently observed across the various (non-stratified)

subgroups. As event numbers were limited in these subgroups and results should be interpreted with caution. For patients on concomitant treatment with pirfenidone no numerical improvement in mortality could be observed at DBL1 and DBL2 and no clear numerical detrimental effect observed either. Since mortality is the main patient derived outcome, health care providers are informed about these differential effects in these subgroups in SmPC section 5.1.

PPF indication

Treatment with nerandomilast 9 mg and 18 mg bid resulted in a statistically significant decrease in the rate of FVC decline compared to placebo. The observed reductions in the rate of decline relative to placebo are both statistically and clinically relevant. The primary endpoint results were supported by the secondary endpoints which showed a clinically relevant reduction in mortality rate for both 9 mg and 18 mg nerandomilast.

For subgroups of patients with idiopathic nonspecific interstitial pneumonia, no numerical improvement in mortality could be observed at DBL1 and DBL2 with no clear numerical detrimental effect either. Consistent with the subgroup receiving background pirfenidone therapy in the IPF trial, the mortality results for this subgroup are presented in SmPC section 5.1 to inform prescribers.

Safety IPF and PPF

Overall, nerandomilast demonstrated a safety profile consistent with PDE4 inhibition, with gastrointestinal adverse events, particularly diarrhoea, and weight loss occurring in a dose-dependent manner and more frequently in IPF than PPF. The 18mg bid dose, was associated with higher rates of treatment interruption and discontinuation, largely driven by diarrhoea particularly when combined with nintedanib. In this subgroup, >1 in 2 patients experienced at least one diarrhoea AE and >1 in 10 patients discontinued treatment due to diarrhoea.

Weight loss has been identified as a strong prognostic marker for mortality and hospitalisation in these patients. Weight loss, especially ⩾5 – 10% of body weight in patients with pulmonary fibrosis, is a significant clinical concern and is associated with worse outcomes. Monitoring changes in BMI and weight may serve as an early indicator of poor drug tolerance or worsening disease especially in older or frail patients. Providing early and effective intervention could potentially improve drug adherence and outcomes. These risks are addressed with warnings in section 4.4 SmPC, including strengthened warnings on gastrointestinal toxicity, weight loss, and concomitant antifibrotic use, with additional safety concerns to be monitored post approval. Section 4.2 of the SmPC has been updated to include advice on dose reduction based on individual tolerability of the side effects of diarrhoea or weight decrease.

Psychiatric events, including suicidality-related adverse events, were reported in very low numbers in the clinical studies in patients who received nerandomilast. SmPC warnings were added to further inform HCP/patients on psychiatric events in line with information of currently approved PDE4 inhibitors. This topic will be closely monitored post-marketing through the PSURs.

There were reports of vasculitis in patients who received nerandomilast. This event will be further evaluated as a topic of special interest in the PSURs.

Major adverse cardiac events (MACE) and tachyarrhythmia are included as important potential risks in other non-selective PDE4 inhibitors. No trends were noted in the reported cases of tachyarrhythmias and most cases presented were confounded by a relevant medical/cardiac history. This topic will be closely monitored in the PSURs.

The ADRs diarrhoea, nausea, decreased appetite, weight decreased, and back pain are common to IPF and PPF. Due to differences in background treatment regimens and patient characteristics between these

two populations, ADR data have been presented in an indication-specific format in the SmPC section 4.8. The description of selected adverse events highlights further clinically meaningful differences for the ADRs of diarrhoea and weight decrease by indication, dose, and background treatment.

Overall, the safety profile of nerandomilast in the treatment of IPF and PPF as monotherapy or with background AF therapy is considered favourable and manageable with the implemented risk minimisations.

Posology recommendations

Recommendations relating to dose adjustments are in place based on individual patient tolerability. Due to the decrease observed in exposure for patients taking concomitantly nerandomilast and pirfenidone, the 18 mg dose is considered justified. The recommended posology is adequately reflected in the SmPC section 4.2 as follows:

Based on individual patient tolerability of the side effects of diarrhoea or weight decrease (see section 4.4 and section 4.8) and based on the anticipated benefit of treatment with nerandomilast (see section 5.1), the dose may be reduced to 9 mg twice daily (except in patients who concomitantly use pirfenidone or strong or moderate cytochrome P450 3A (CYP3A) inducers, see section 4.5). Once the adverse reaction has resolved or is adequately controlled, treatment may be resumed at the recommended dose of 18 mg twice daily.

9.6.2. Balance of benefits and risks

For both IPF and PPF indications treatment with nerandomilast 9 mg and 18 mg bid resulted in a statistically significant and clinically relevant decrease in the rate of FVC decline compared to placebo. Further, some positive treatment effect was observed in respect to mortality for some patient subpopulations.

A numerical improvement in mortality is observed for both indications, except for some non-stratified subgroups of patients (the subgroup of IPF patients on pirfenidone using 18 mg nerandomilast as well as the subgroup of patients with iNSIP). SmPC section 5.1 includes the outcomes for these subgroups and mortality results by background IPF therapy, background nintedanib therapy and background pirfenidone therapy.

Nerandomilast with background AF treatment is associated with more adverse effects than as monotherapy. Based on the safety data presented, most AEs reported with nerandomilast treatment were expected and manageable, aligning with the known safety profile of PDE4 inhibitors.

Clinically significant safety findings associated with diarrhoea, weight loss and other gastrointestinal adverse reactions in IPF and PPF patients, particularly patients receiving concomitant antifibrotic therapy with nintedanib have been identified. The product information has been further strengthened to include relevant safety warnings on diarrhoea, nausea and decreased appetite, weight decrease and psychiatric disorders for patients and HCPs. Malignancy, vasculitis, cardiac events including tachyarrhythmia will also be monitored in the post-marketing setting and further evaluated as topics of interest in the PSURs. Overall, the safety profile is considered acceptable.

Based on these considerations, the benefit risk of nerandomilast in the treatment of adult patients with IPF or PPF is considered positive.

9.6.3. Additional considerations on the benefit-risk balance

Not applicable

9.6.3.1. Areas for further treatment optimisation

Table 150: Areas for further development

Problem statement	*Objectives of study or further research*
For treatment naïve IPF and PPF patients, the placebo-controlled design of the pivotal trials does not allow conclusions on the preferred antifibrotic therapy for first line treatment.	A randomized controlled trial with existing therapies as control treatment, would allow conclusions on the preferred antibiotic therapy for first line treatment.

9.7. Benefit-risk conclusions

The benefit risk balance for nerandomilast is positive for the treatment of adult patients with idiopathic pulmonary fibrosis (IPF).

The benefit risk balance for nerandomilast is positive for the treatment of adult patients with progressive pulmonary fibrosis (PPF).