ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 9 mg film-coated tablets

Jascayd 18 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jascayd 9 mg film-coated tablets

Each film-coated tablet contains 9 mg nerandomilast.

Excipient with known effect

Each film-coated tablet contains 81.1 mg of lactose (as monohydrate).

Jascayd 18 mg film-coated tablets

Each film-coated tablet contains 18 mg nerandomilast.

Excipient with known effect

Each film-coated tablet contains 162.2 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Jascayd 9 mg film-coated tablets

Light yellow, oval, biconvex, film-coated tablet debossed “F9” on one side and the Boehringer Ingelheim logo on the other (tablet length: 9.5 mm, tablet width: 4.6 mm).

Jascayd 18 mg film-coated tablets

Light red, oval, biconvex film-coated tablet debossed with “F18” on one side and the Boehringer Ingelheim logo on the other (tablet length: 12 mm, tablet width: 5.9 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic 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).

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the management of diseases for which Jascayd is approved.

Posology

The recommended dose is 18 mg twice daily, administered approximately 12 hours apart.

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.

Concomitant use with strong CYP3A inhibitors

If used concomitantly with strong CYP3A inhibitors, the dose must be reduced to 9 mg twice daily (see section 4.5).

Concomitant use with strong or moderate CYP3A inducers

If used concomitantly with strong or moderate CYP3A inducers, the recommended dose is 18 mg twice daily and must not be reduced to 9 mg twice daily (see section 4.5).

Concomitant use with pirfenidone

Concomitant use with pirfenidone decreased nerandomilast exposure by approximately 50% (see section 4.5). In patients using pirfenidone, the recommended dose is 18 mg twice daily and must not be reduced to 9 mg twice daily.

Missed dose

If a dose is missed, the next dose should be taken at the next scheduled time.
The patient should not take an additional dose. The recommended maximum dose of 18 mg twice daily should not be exceeded.

Special populations

Elderly

No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment

No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment (eGFR $\geq$ 15 and < 90 mL/min, based on CKD-EPI formula) (see section 5.2).

Treatment of patients with end stage renal disease (eGFR < 15 mL/min) is not recommended. The pharmacokinetics, safety and efficacy of nerandomilast in these patients have not been investigated.

Hepatic impairment

No dose adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment (see section 5.2).

Treatment of patients with severe hepatic impairment (Child-Pugh class C) is not recommended. The pharmacokinetics, safety and efficacy of nerandomilast in these patients have not been investigated.

Paediatric population

The safety and efficacy in paediatric patients have not yet been established.

No data are available.

Method of administration

Jascayd is for oral use. The tablets should be swallowed whole with water.

Jascayd can be taken with or without food (see section 5.2).

Alternative method of administration

For patients who have difficulty swallowing the whole tablet, a tablet may be dispersed in a glass with approximately 100 mL of non-carbonated, room temperature drinking water. No other liquids should be used. The tablet should be dropped in water without crushing it and stirred regularly for approximately 15-20 min until the tablet is dispersed into very small pieces (the tablets will not completely dissolve). The resultant dispersion should be drunk within 2 hours of mixing. If the dispersion is not drunk immediately, patients must stir again before drinking. The glass should be rinsed with approximately 100 mL of water which should also be drunk to ensure the full dose is administered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diarrhoea, nausea and decreased appetite

In clinical trials, diarrhoea, nausea and decreased appetite were frequently reported adverse reactions (see section 4.8) particularly in patients receiving nerandomilast in combination with nintedanib or pirfenidone. In most patients, these adverse reactions were of mild to moderate intensity. Patients should be monitored and adverse reactions managed with adequate symptomatic treatments such as hydration and anti-diarrhoeal or anti-emetic medicinal products, as applicable. Reduction in background therapy with nintedanib or pirfenidone should be managed in line with the advice in the respective SmPCs. Caution is advised in patients who are debilitated, have existing gastrointestinal symptoms, or have previously experienced significant gastrointestinal adverse reactions with nintedanib or pirfenidone. If patients with severe or persistent diarrhoea, nausea or decreased appetite do not respond to symptomatic treatment, dose reduction (see section 4.2) or treatment interruption, nerandomilast treatment should be discontinued.

Weight decrease

Treatment with nerandomilast has been associated with dose dependent weight loss particularly with concomitant use of nintedanib. Body weight should be monitored regularly during therapy. 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 (see section 4.8).

Psychiatric disorders

Psychiatric disorders can be a common comorbidity in patients with IPF and PPF. 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.

Excipients with known effect

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Based on *in vitro* assessment, nerandomilast is mainly metabolised by CYP3A and is a substrate of P-glycoprotein (P-gp).

Effects of other products on nerandomilast

Strong CYP3A inhibitors

Clinical Impact:	When a single dose of 6 mg nerandomilast was co-administered with multiple doses of itraconazole (a dual strong inhibitor of CYP3A and P-gp) in healthy volunteers, the exposure of nerandomilast increased by 2.2-times for AUC and by 1.3-times for C_{max}.
Intervention:	If used concomitantly with strong CYP3A inhibitors, the dose must be reduced to 9 mg twice daily (see section 4.2).
Examples:	Clarithromycin, itraconazole, ritonavir

Strong or moderate CYP3A inducers

Clinical Impact:	When a single dose of 18 mg nerandomilast was co-administered with multiple doses of carbamazepine (a strong CYP3A inducer) in healthy volunteers, the exposure of nerandomilast decreased by 51% for AUC and by 31% for C_{max}. When a single dose of 18 mg nerandomilast was co-administered with multiple doses of bosentan (a moderate CYP3A inducer) in healthy volunteers, the exposure of nerandomilast decreased by 41% for AUC and by 15% for C_{max}.
Intervention:	If used concomitantly with strong or moderate CYP3A inducers, the recommended dose is 18 mg twice daily and must not be reduced to 9 mg twice daily (see section 4.2).
Examples:	Carbamazepine, St. John's wort, rifampicin, phenytoin, bosentan, metamizole

Pirfenidone

Clinical Impact:	Concomitant use with pirfenidone decreased exposure of nerandomilast by approximately 50%, based on $C_{trough,ss}$ observed in the phase 3 study in patients with

	IPF. Based on *in vitro* data, pirfenidone may induce CYP3A activity, leading to decreased nerandomilast exposure. When nerandomilast was co-administered with pirfenidone in patients with IPF in this phase 3 trial, efficacy was not observed at the 9 mg dose but a reduction in Forced Vital Capacity (FVC) decline was observed with the 18 mg dose (see section 5.1).
Intervention:	In patients using pirfenidone, the recommended dose is 18 mg twice daily and must not be reduced to 9 mg twice daily (see section 4.2).

Nintedanib

Concomitant use with nintedanib did not alter the exposure of nerandomilast based on trough concentrations at steady state.

Effects of nerandomilast on other products

No clinically relevant differences in the pharmacokinetics of the following active substances were observed when used concomitantly with nerandomilast: pirfenidone, nintedanib, and oral midazolam (CYP3A4 substrate). Based on the results for concomitant use with midazolam, nerandomilast is not expected to decrease or increase the systemic exposure of other medicinal products that are mainly metabolised by CYP3A, e.g., oral contraceptives.

4.6 Fertility, pregnancy and lactation

Contraception

Based on findings in animal studies, nerandomilast may cause loss of pregnancy (see section Pregnancy below and section 5.3).

Women of childbearing potential should be advised to avoid becoming pregnant and to use effective contraceptive methods during treatment.

Pregnancy

There are no data from the use of nerandomilast in pregnant women. Based on findings in animal studies, nerandomilast may cause loss of pregnancy (see section 5.3).

Women of childbearing potential should be advised to avoid becoming pregnant while taking Jascayd. Jascayd is not recommended during pregnancy and in women of childbearing potential not using contraception.

Female patients should be advised to notify their health care provider if they become pregnant or suspect they may be pregnant during therapy with Jascayd. Pregnant women and women of childbearing potential should be advised of the potential risk of foetal loss.

Breast-feeding

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 evidence of excretion of nerandomilast in milk (see section 5.3).

A risk to the breast-fed infant cannot be excluded. Breast-feeding should be discontinued during treatment with Jascayd.

Fertility

There are no data on the impact of nerandomilast on human fertility. No adverse effects on fertility were observed in male and female rats at 4-times human exposure (see section 5.3).

4.7 Effects on ability to drive and use machines

Jascayd has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are diarrhoea and weight decreased.

Tabulated list of adverse reactions

Table 1 shows the frequencies of adverse reactions based on 52-week data from two randomised, placebo-controlled, double-blind Phase III clinical trials (FIBRONEER-IPF in IPF and FIBRONEER-ILD in PPF) with twice daily nerandomilast doses of 9 mg or 18 mg. Adverse reactions are listed by MedDRA System Organ Class (SOC).

Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions

System Organ Class	***Adverse reactions***	***Frequency category***	
		IPF[b]	***PPF***
Metabolism and nutrition disorders	Decreased appetite	Common	Common
Gastrointestinal disorders	Diarrhoea[a]	Very common	Very common
	Nausea	Common	Common
Musculoskeletal and connective tissue disorders	Back pain	Common	Common
Investigations	Weight decreased[a]	Common	Common

[a] see section *Description of selected adverse reactions*

[b] Frequencies were calculated excluding patients in the 9 mg dose group receiving concomitantly pirfenidone, as this combination is not recommended due to a clinically relevant drug-drug interaction (see section 4.2 and section 4.5).

Description of selected adverse reactions

Diarrhoea

In most patients treated with nerandomilast, diarrhoea was of mild to moderate intensity and generally occurred within the first 3 months of treatment.
Most cases were managed with symptomatic therapy with anti-diarrhoeal medication and, if applicable, with reduction in background therapy with nintedanib or pirfenidone.
Severe diarrhoea has been reported more frequently in patients receiving nerandomilast in combination with nintedanib.

The frequency of diarrhoea depended on the presence and type of background treatment (see Table 2).

Table 2. Frequencies of diarrhoea by background treatment subgroups over 52 weeks in the FIBRONEER-IPF trial (patients with IPF) and the FIBRONEER-ILD trial (patients with PPF).

	IPF (FIBRONEER-IPF)			PPF (FIBRONEER-ILD)		
	Placebo	Nerandomilast 9 mg bid	Nerandomilast 18 mg bid	Placebo	Nerandomilast 9 mg bid	Nerandomilast 18 mg bid
No background treatment	8%	17%	26%	16%	15%	27%
Nintedanib background therapy	27%	49%	62%	36%	48%	49%
Pirfenidone background therapy	8%	n.a.[a]	23%	n.a.[b]	n.a.[b]	n.a.[b]

[a] Not applicable, as 9 mg bid nerandomilast is not a recommended dose for patients receiving pirfenidone.

[b] Not applicable, as pirfenidone was not permitted as background treatment in FIBRONEER-ILD.

bid = twice daily

IPF

In patients treated in the FIBRONEER-IPF trial, without background IPF treatment, severe diarrhoea was not reported; with background nintedanib, it was reported in 5% in 18 mg, 2% in 9 mg and < 1% in placebo; with background pirfenidone, it was not reported.

Diarrhoea was the most common adverse reaction associated with treatment discontinuation and occurred most frequently with background nintedanib. Without background IPF treatment, discontinuations occurred in 1% in 18 mg and were not reported in 9 mg or placebo; with background nintedanib, in 13% in 18 mg, 2% in 9 mg and 1% in placebo; with background pirfenidone, no treatment discontinuations were reported in 18 mg or placebo.

PPF

In patients treated in the FIBRONEER-ILD trial, without background nintedanib treatment, severe diarrhoea was not reported; with background nintedanib, it was reported in 2% in 18 mg, 1% in 9 mg and < 1% in placebo.

Diarrhoea was the most common adverse reaction associated with treatment discontinuation and occurred most frequently with background nintedanib. Without background nintedanib treatment, discontinuations occurred in 1% in 18 mg and were not reported in 9 mg or placebo; with background nintedanib, in 4% in 18 mg, 3% in 9 mg and 1% in placebo.

Weight decrease

In clinical trials, weight decrease started after the second week of treatment and stabilised after 12 weeks of treatment.

IPF

In the FIBRONEER-IPF trial, the mean absolute change in body weight from baseline to week 52 was -2.6 kg for patients treated with nerandomilast 18 mg, -2.4 kg for patients treated with nerandomilast 9 mg, and -1.8 kg for patients receiving placebo.

The frequency of weight decrease depended on the presence and type of background IPF treatment: without background IPF treatment, 7% in 18 mg, 1% in 9 mg, and 6% in placebo; with background nintedanib, 16% in 18 mg, 13% in 9 mg and 11% in placebo; with background pirfenidone, 5% in 18 mg and in placebo.

PPF

In the FIBRONEER-ILD trial, the mean absolute change in body weight from baseline to week 52 was -3.2 kg for patients treated with nerandomilast 18 mg, -2.0 kg for patients treated with nerandomilast 9 mg and -2.0 kg for patients receiving placebo.

The frequency of weight decrease depended on the presence or absence of background nintedanib treatment: without background nintedanib, 10% in 18 mg, 5% in 9 mg and 4% in placebo; with background nintedanib, 11% in 18 mg, 9% in 9 mg and 8% in placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

In clinical trials, single doses of up to 48 mg of nerandomilast were studied in healthy volunteers without evidence of dose limiting toxicities. Cases of accidental overdose were reported in patients who received doses up to 72 mg/day for up to 17 days.

The observed adverse reactions were consistent with the known safety profile of nerandomilast.

Therapy

In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment is provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA61

Mechanism of action

Nerandomilast is a selective inhibitor of phosphodiesterase 4 (PDE4) with preferential inhibition of the PDE4B isoenzyme over PDE4A, C and D. There is a 9-fold selectivity over PDE4D, 24-fold selectivity over PDE4A and 870-fold selectivity over PDE4C based on *in vitro* data. At the recommended doses, inhibition of PDE4B and weaker inhibition of PDE4D can be expected. PDE4 hydrolyses and inactivates cyclic adenosine monophosphate (cAMP). Nerandomilast exerts both anti-

fibrotic and immunomodulatory effects as preferential PDE4B inhibition elevates intracellular cAMP levels and reduces the expression of pro-fibrotic growth factors and inflammatory cytokines, which are overexpressed in fibrotic lung disease.

Pharmacodynamic effects

Cardiac electrophysiology

At single doses of nerandomilast up to 48 mg (2.2-times the estimated $C_{max,ss}$ exposure at the maximum recommended human dose), clinically significant QTc interval prolongation was not observed.

Clinical efficacy and safety

Idiopathic Pulmonary Fibrosis (IPF)

A randomised, double-blind, placebo-controlled trial (FIBRONEER-IPF) evaluated the clinical efficacy and safety of nerandomilast in adult patients with IPF with or without receiving background treatment of nintedanib or pirfenidone. Patients were required to have a Forced Vital Capacity (FVC) greater than or equal to 45% of predicted and a diffusing capacity of the lungs for carbon monoxide (DLCO) greater than or equal to 25% of predicted normal corrected for haemoglobin (Hb).
1 177 patients were randomised in a 1:1:1 ratio to receive nerandomilast 9 mg twice daily, nerandomilast 18 mg twice daily, or placebo twice daily for at least 52 weeks. Randomisation was stratified by the presence of nintedanib or pirfenidone versus the absence of these background treatments at baseline. The primary endpoint of the trial was the absolute change from baseline in FVC in mL at 52 weeks compared with placebo. The key secondary endpoint was the time to the first occurrence of any of the components of the composite endpoint: first acute IPF exacerbation, first hospitalisation for respiratory cause, or death over the duration of the trial. 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.

The study population consisted of 83% men and 17% women with a mean age of 70 years (range: 42 to 90 years). 31% of patients were 75 years and older. 68% of the study population were White, 32% Asian and 0.5% Black/African American. Pulmonary hypertension was reported in 3% of patients at baseline. 78% of the patients were on stable treatment with nintedanib (46%) or with pirfenidone (32%) and 22% were on none of these treatments (15% of patients were treatment naïve and 8% previously discontinued treatment with nintedanib or pirfenidone). At baseline, the mean FVC was 2 843 mL and 78% of predicted normal. Patients receiving background treatment with nintedanib or pirfenidone had more advanced disease at baseline compared with patients not receiving background treatment, as reflected by a lower mean FVC % predicted (77% versus 82%), a lower mean DLCO % predicted (50% versus 55%), a longer mean time since first diagnosis (3.7 years versus 2.8 years), and more frequent use of supplemental oxygen (23% versus 16%).

Change from baseline in FVC

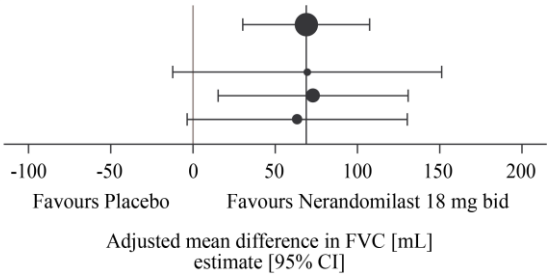
Overall, the primary endpoint of absolute change from baseline in FVC (in mL) at 52 weeks in patients receiving nerandomilast was statistically significantly improved compared with patients receiving placebo. The adjusted mean decline in patients receiving 18 mg or 9 mg nerandomilast twice daily was -115 mL and -139 mL, respectively, whereas in the placebo group, an adjusted mean decline of -183 mL was observed. The respective treatment difference compared with the placebo group was 69 mL (95% CI: 30, 107; p-value: 0.0005) and 45 mL (95% CI: 6, 83; p-value: 0.0222).

A drug-drug interaction was observed in patients receiving pirfenidone as background IPF treatment (see section 4.5). In these patients, no treatment effect was observed when receiving 9 mg nerandomilast twice daily.

Results for the primary endpoint in the overall population and by background IPF treatment for the nerandomilast 18 mg and 9 mg doses versus matching placebo are presented in Figure 1 and Figure 2, respectively.

Figure 1. Absolute change from baseline in FVC (mL) at 52 weeks in the FIBRONEER-IPF study for patients receiving 18 mg nerandomilast compared to placebo.

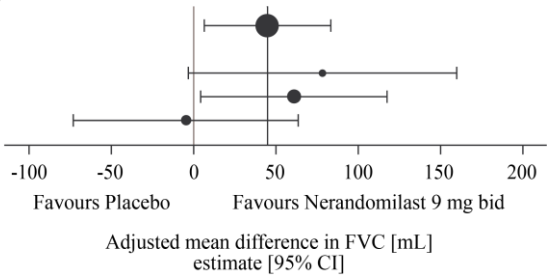
	Placebo		Nerandomilast 18 mg bid		Adjusted mean difference in FVC [mL] estimate [95% CI]
	N	FVC [mL] decline	N	FVC [mL] decline	
All patients	391	-183	392	-115	69 [30, 107]
Background treatment					
None	87	-149	87	-79	69 [-12, 151]
Nintedanib	172	-192	178	-119	73 [15, 131]
Pirfenidone	132	-197	127	-134	63 [-4, 130]



For patients who died before week 52, the 10th percentile change from baseline value was assigned.
bid = twice daily

Figure 2. Absolute change from baseline in FVC (mL) at 52 weeks in the FIBRONEER-IPF study for patients receiving 9 mg nerandomilast compared to placebo.

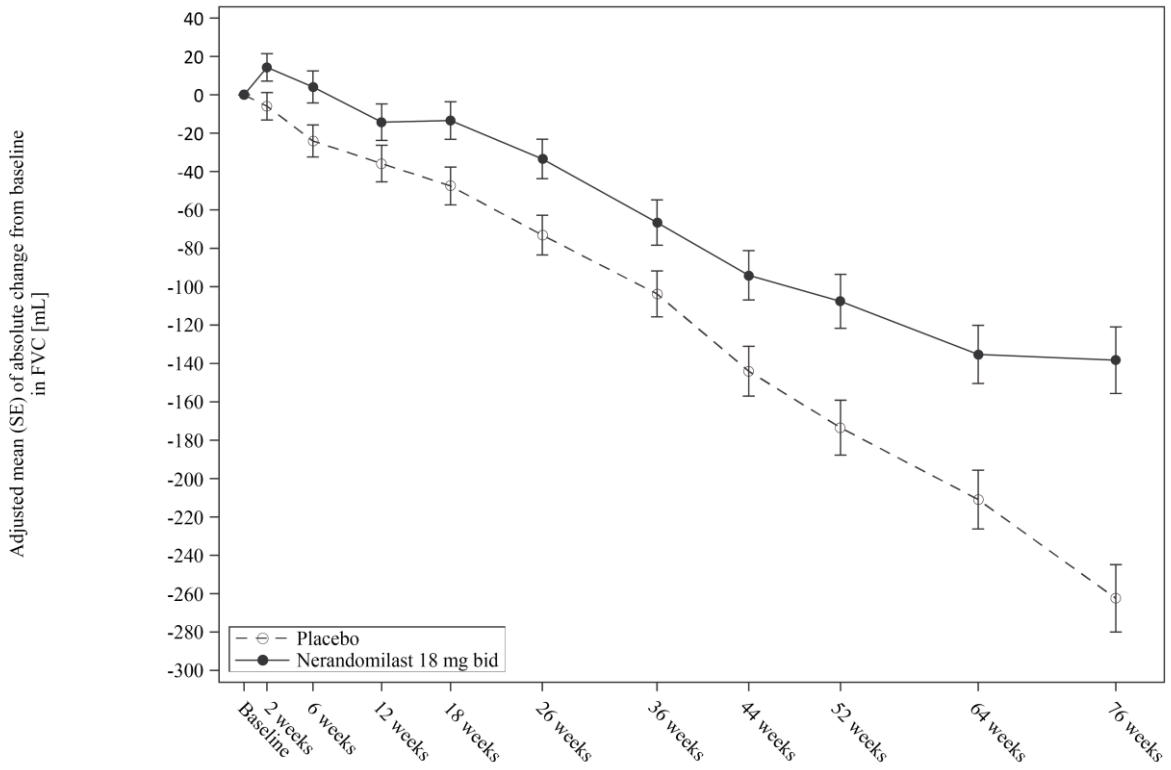
	Placebo		Nerandomilast 9 mg bid		Adjusted mean difference in FVC [mL] estimate [95% CI]
	N	FVC [mL] decline	N	FVC [mL] decline	
All patients	391	-183	390	-139	45 [6, 83]
Background treatment					
None	87	-149	86	-70	78 [-3, 160]
Nintedanib	172	-192	184	-131	61 [4, 117]
Pirfenidone	132	-197	120	-202	-5 [-73, 64]



For patients who died before week 52, the 10th percentile change from baseline value was assigned.
bid = twice daily

Figure 3 shows the change in FVC from baseline over time in patients receiving nerandomilast 18 mg twice daily compared to matching placebo. When the mean adjusted FVC change from baseline was plotted over time, the curves started to separate at week 2 and continued to diverge up to week 52 and beyond. This effect over time was consistently observed across the subgroups by background IPF treatment.

Figure 3. Change from baseline in FVC (mL) over time in the FIBRONEER-IPF study for patients receiving 18 mg nerandomilast compared to placebo.



Number of patients

Placebo	393	378	383	374	367	356	339	333	324	308	213
Nerandomilast 18 mg bid	392	382	384	374	376	359	352	332	342	313	218

bid = twice daily

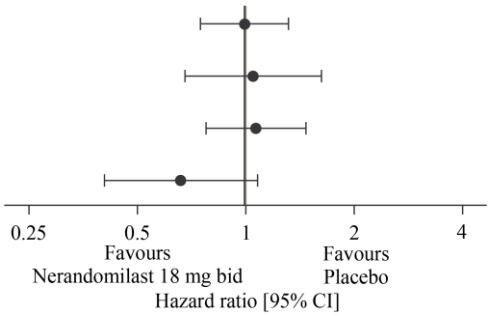
Time to first acute IPF exacerbation, first hospitalisation for respiratory cause, or death

The key secondary composite endpoint was the time to the first event of acute IPF exacerbation, hospitalisation for respiratory cause, or death over the duration of the trial. Acute IPF exacerbation was defined as acute worsening or development of dyspnoea typically less than 1 month duration, computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF, and deterioration not fully explained by cardiac failure or fluid overload. Neither acute IPF exacerbations nor respiratory hospitalisations were adjudicated. Overall, there was no statistically significant treatment difference for the nerandomilast 18 mg or 9 mg groups compared to placebo for the key secondary composite endpoint. At the time of main analysis, key secondary endpoint events occurred in 85 patients (22%) in the 18 mg group, in 79 patients (20%) in the 9 mg group, and in 80 patients (20%) in the placebo group. Compared with placebo, the hazard ratio (HR) for time to first event was 1.17 (95% CI: 0.86, 1.59; p = 0.3102) for the 18 mg dose and 1.03 (95% CI: 0.75, 1.41; p = 0.8568) for the 9 mg dose.

See Figure 4 and Figure 5 for results of nerandomilast 18 mg and 9 mg versus placebo for the key secondary endpoint and its components over the duration of the FIBRONEER-IPF study at the time of the end-of-trial analysis.

Figure 4. Acute IPF exacerbation, hospitalisation for respiratory cause or death over the duration of the FIBRONEER-IPF study for patients receiving 18 mg nerandomilast compared to placebo.

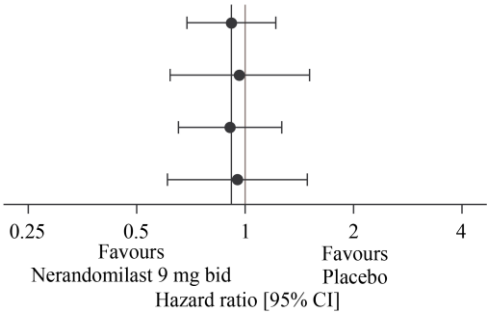
	N with event / N analysed		
	Placebo	Nerandomilast 18 mg bid	Hazard ratio [95% CI]
Key secondary endpoint	103/393	93/392	0.99 [0.75, 1.31]
Acute IPF exacerbation	42/393	40/392	1.05 [0.68, 1.62]
Hospitalisation for respiratory cause	76/393	75/392	1.07 [0.78, 1.47]
Death	42/393	26/392	0.66 [0.41, 1.08]



bid = twice daily

Figure 5. Acute IPF exacerbation, hospitalisation for respiratory cause or death over the duration of the FIBRONEER-IPF study for patients receiving 9 mg nerandomilast compared to placebo.

	N with event / N analysed		
	Placebo	Nerandomilast 9 mg bid	Hazard ratio [95% CI]
Key secondary endpoint	103/393	90/392	0.92 [0.69, 1.22]
Acute IPF exacerbation	42/393	37/392	0.97 [0.62, 1.51]
Hospitalisation for respiratory cause	76/393	66/392	0.91 [0.65, 1.26]
Death	42/393	36/392	0.95 [0.61, 1.49]



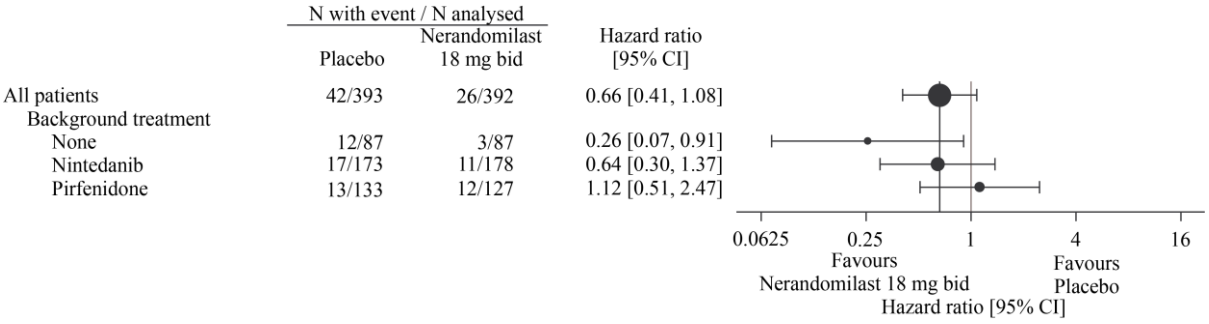
Results are shown for the overall population receiving nerandomilast 9 mg twice daily versus matching placebo.

bid = twice daily

At the end-of-trial analysis deaths occurred in 26 patients (7%) in the 18 mg group, in 36 patients (9%) in the 9 mg group, and 42 patients (11%) in the placebo group. Compared with placebo, the hazard ratio for time to death was 0.66 (95% CI: 0.41, 1.08) for the 18 mg dose and 0.95 (95% CI: 0.61, 1.49) for the 9 mg dose.

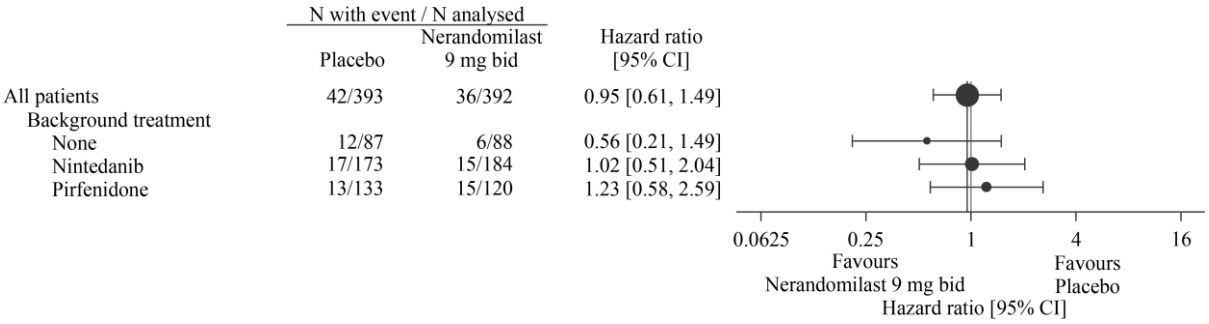
Figure 6 and Figure 7 show the analysis of time to death over the whole trial (end-of-trial analysis) in the nerandomilast 18 mg and 9 mg dose groups, respectively versus matching placebo for the subgroups by background treatment.

Figure 6. Time to death over the duration of the FIBRONEER-IPF study for patients receiving 18 mg nerandomilast compared to placebo.



bid = twice daily

Figure 7. Time to death over the duration of the FIBRONEER-IPF study for patients receiving 9 mg nerandomilast compared to placebo.



Results are shown for the overall population receiving nerandomilast 9 mg twice daily versus matching placebo.

bid = twice daily

Progressive Pulmonary Fibrosis (PPF)

A randomised, double-blind, placebo-controlled trial (FIBRONEER-ILD) evaluated the clinical efficacy and safety of nerandomilast in adult patients with PPF. Patients with PPF were selected if they had relevant fibrosis (greater than 10% fibrotic features) on high resolution computed tomography (HRCT) and presented with clinical signs of progression (defined as Forced Vital Capacity (FVC) decline greater than or equal to 10%, FVC decline greater than or equal to 5% and less than 10% with worsening of respiratory symptoms or imaging, or worsening of respiratory symptoms and worsening imaging all in the 24 months prior to screening). Patients were required to have an FVC greater than or equal to 45% of predicted and a diffusing capacity of the lungs for carbon monoxide (DLCO) greater than or equal to 25% of predicted normal corrected for haemoglobin (Hb). Eligible patients were or were not on stable background treatment with nintedanib. 1 178 patients were randomised in a 1:1:1 ratio to receive nerandomilast 9 mg twice daily, nerandomilast 18 mg twice daily, or placebo twice daily for at least 52 weeks. Randomisation was stratified by the presence or absence of background treatment with nintedanib and by high resolution computed tomography (HRCT) pattern (usual interstitial pneumonia (UIP) or UIP-like fibrotic pattern versus Other fibrotic patterns) using central review.

The primary endpoint of the trial was the absolute change from baseline in FVC in mL at 52 weeks compared with placebo. The key secondary endpoint was the time to the first occurrence of any of the components of the composite endpoint: the first acute Interstitial Lung Disease (ILD) exacerbation, first hospitalisation for respiratory cause, or death over the duration of the trial. Patients were followed for a median time of 15.4 months at the time of main analysis and 17.2 months at the end-of-trial analysis.

The study population consisted of 56% men and 44% women with a mean age of 66 years (range: 26 to 88 years). 20% of patients were 75 years and older. 58% of the study population were White, 39% Asian and 1% Black or African American. Pulmonary hypertension was reported in 5% of patients at baseline.

44% of the patients were on stable treatment with nintedanib and 56% not treated with nintedanib (44% of patients were treatment naïve and 12% previously discontinued nintedanib treatment). On baseline HRCT, 71% of the patients had UIP or UIP-like fibrotic pattern and 29% of the patients had other fibrotic patterns. The underlying clinical ILD diagnoses were autoimmune ILDs (28%), hypersensitivity pneumonitis (20%), unclassifiable idiopathic interstitial pneumonia (20%), idiopathic nonspecific interstitial pneumonia (19%), and other ILDs (14%). At baseline, the mean FVC was 2 353 mL and 70% of predicted normal. Patients receiving background treatment with nintedanib had more advanced disease at baseline compared with patients not receiving background treatment, as reflected by a slightly lower mean FVC % predicted (69% versus 71%), a lower mean DLCO % predicted (45% versus 52%), a slightly longer mean time since first ILD diagnosis (4.4 years versus 4.0 years), and more frequent use of supplemental oxygen (38% versus 19%).

Change from baseline in FVC

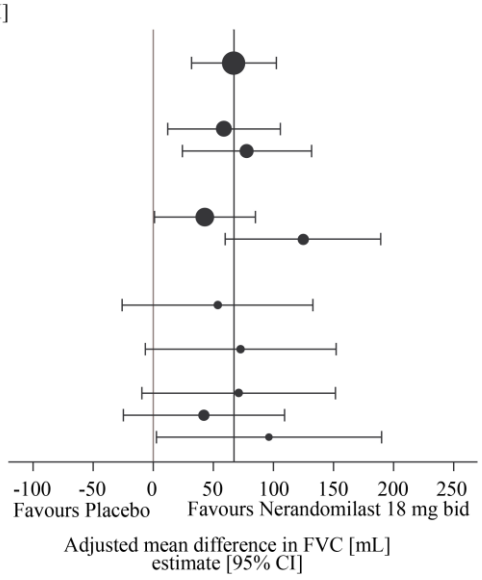
Overall, the primary endpoint of absolute change from baseline in FVC (in mL) at 52 weeks in patients receiving nerandomilast was statistically significantly improved compared with patients receiving placebo.

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 respective treatment difference compared with the placebo group was 67 mL (95% CI: 32, 102; p-value: 0.0002) and 81 mL (95% CI: 46, 116; p-value: < 0.0001).

The primary analysis was consistent across pre-specified subgroups by presence or absence of nintedanib background treatment, HRCT pattern, and underlying clinical ILD diagnoses. See Figure 8 and Figure 9.

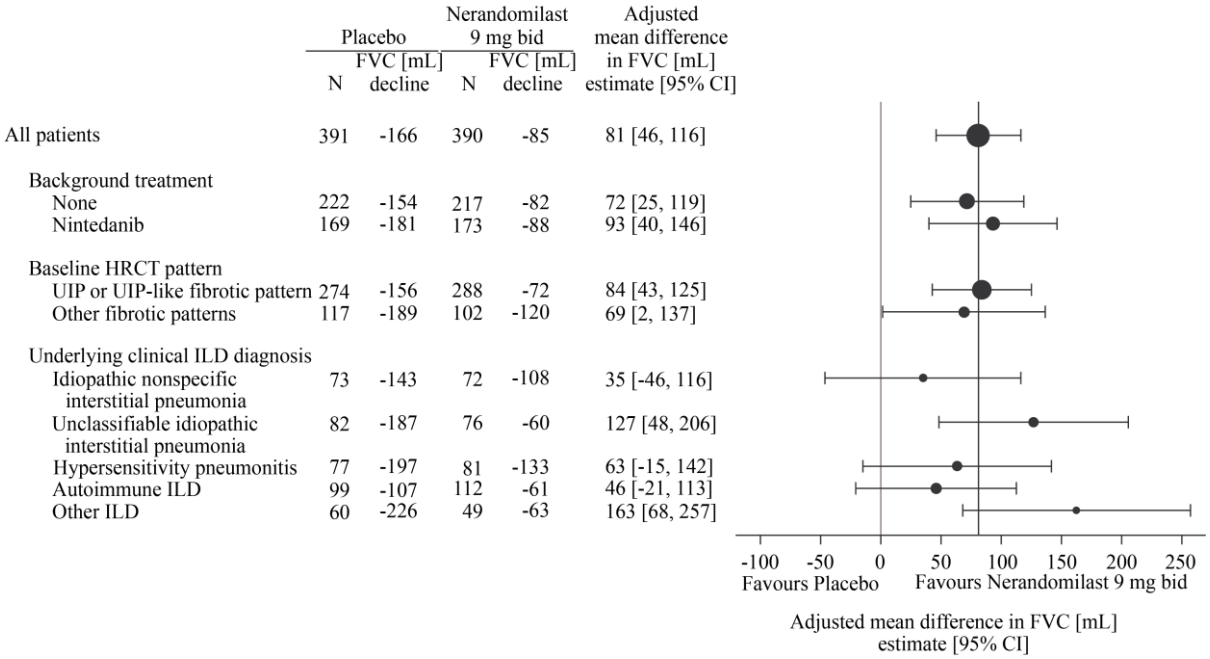
Figure 8. Absolute change from baseline in FVC (mL) at 52 weeks in the FIBRONEER-ILD study for patients receiving 18 mg nerandomilast compared to placebo.

	Placebo		Nerandomilast 18 mg bid		Adjusted mean difference in FVC [mL]
	N	FVC [mL] decline	N	FVC [mL] decline	estimate [95% CI]
All patients	391	-166	390	-99	67 [32, 102]
Background treatment					
None	222	-154	220	-95	59 [12, 106]
Nintedanib	169	-181	170	-103	78 [24, 132]
Baseline HRCT pattern					
UIP or UIP-like fibrotic pattern	274	-156	274	-113	43 [1, 85]
Other fibrotic patterns	117	-189	116	-64	125 [60, 189]
Underlying clinical ILD diagnosis					
Idiopathic nonspecific interstitial pneumonia	73	-143	82	-89	53 [-26, 133]
Unclassifiable idiopathic interstitial pneumonia	82	-187	73	-114	73 [-7, 152]
Hypersensitivity pneumonitis	77	-197	72	-126	71 [-9, 152]
Autoimmune ILD	99	-107	113	-65	42 [-25, 109]
Other ILD	60	-226	50	-129	96 [3, 190]



For patients who died before week 52, the 10th percentile change from baseline value was assigned.
bid = twice daily

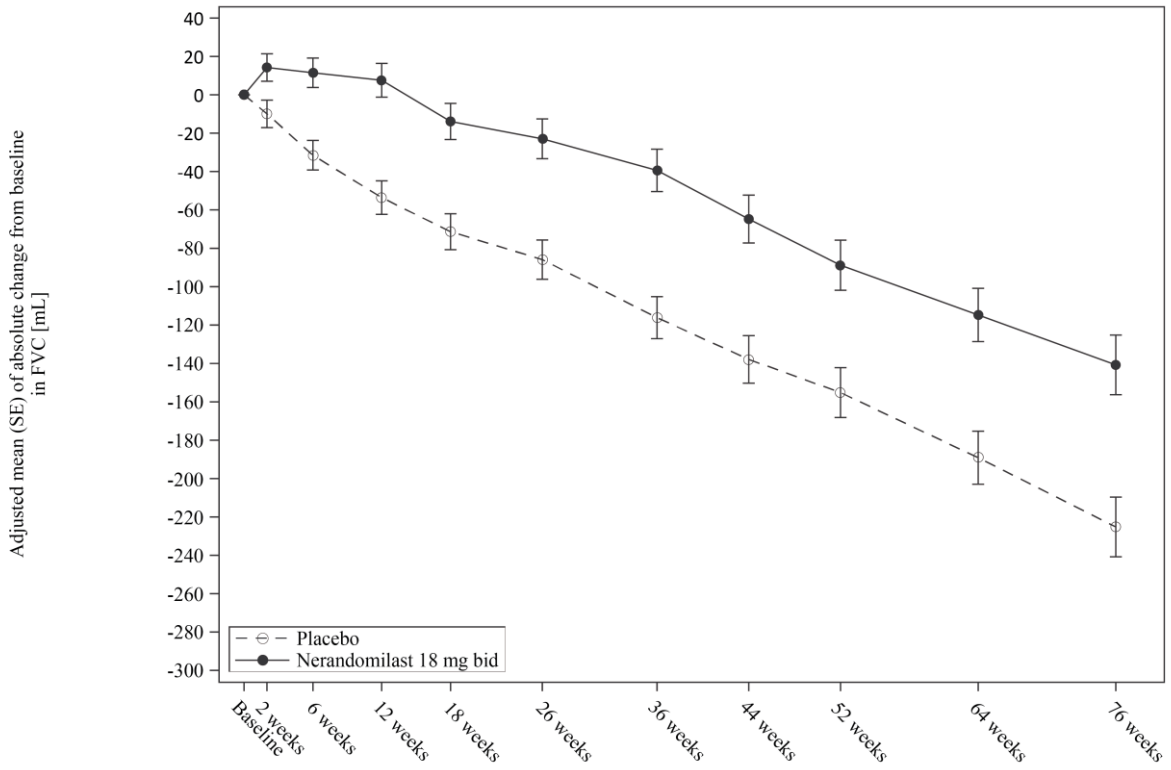
Figure 9. Absolute change from baseline in FVC (mL) at 52 weeks in the FIBRONEER-ILD study for patients receiving 9 mg nerandomilast compared to placebo.



For patients who died before week 52, the 10th percentile change from baseline value was assigned.
bid = twice daily

Figure 10 shows the change in FVC from baseline over time in patients receiving nerandomilast 18 mg twice daily compared to matching placebo. When the mean adjusted FVC change from baseline was plotted over time, the curves started to separate at week 2 and separation was maintained up to week 52 and beyond. This effect over time was consistently observed regardless of background nintedanib treatment.

Figure 10. Change from baseline in FVC (mL) over time in the FIBRONEER-ILD study for patients receiving 18 mg nerandomilast compared to placebo.



Number of patients

Placebo	392	378	374	369	358	355	337	326	327	293	202
Nerandomilast 18 mg bid	391	379	380	364	349	338	330	321	324	292	205

bid = twice daily

Time to first acute ILD exacerbation, first hospitalisation for respiratory cause, or death

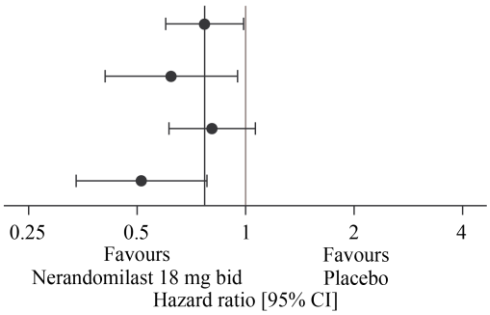
The key secondary composite endpoint was the time to the first event of acute ILD exacerbation, hospitalisation for respiratory cause, or death over the duration of the trial. Acute ILD exacerbation was defined as acute worsening or development of dyspnoea typically less than 1 month duration, computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD, and deterioration not fully explained by cardiac failure or fluid overload. Neither acute ILD exacerbations nor respiratory hospitalisations were adjudicated.

The risk for the key secondary endpoint was numerically lower for both nerandomilast dose groups compared to placebo. At the time of the main analysis, key secondary endpoint events occurred in 95 patients (24%) in the 18 mg group, 110 patients (28%) in the 9 mg group, and 122 patients (31%) in the placebo group. Compared with placebo, the hazard ratio for time to first event was 0.77 (95% CI: 0.59, 1.01; p-value: 0.0602) for the 18 mg dose and 0.88 (95% CI: 0.68, 1.14; p-value: 0.3398) for the 9 mg dose.

See Figure 11 and Figure 12 for results of nerandomilast 18 mg and 9 mg versus placebo for the key secondary endpoint and its components over the duration of the FIBRONEER-ILD study at the end-of-trial analysis.

Figure 11. Acute ILD exacerbation, hospitalisation for respiratory cause or death over the duration of the FIBRONEER-ILD study for patients receiving 18 mg nerandomilast compared to placebo.

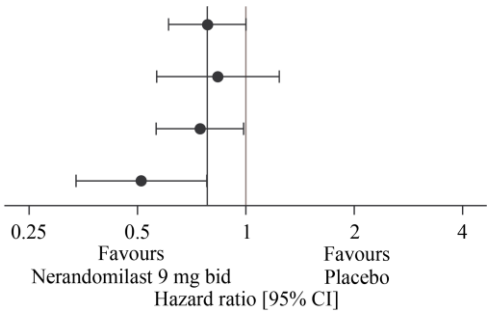
	N with event / N analysed		
	Placebo	Nerandomilast 18 mg bid	Hazard ratio [95% CI]
Key secondary endpoint	143/392	113/391	0.77 [0.60, 0.99]
Acute ILD exacerbation	57/392	35/391	0.62 [0.41, 0.95]
Hospitalisation for respiratory cause	113/392	94/391	0.81 [0.61, 1.06]
Death	64/392	34/391	0.51 [0.34, 0.78]



bid = twice daily

Figure 12. Acute ILD exacerbation, hospitalisation for respiratory cause or death over the duration of the FIBRONEER-ILD study for patients receiving 9 mg nerandomilast compared to placebo.

	N with event / N analysed		
	Placebo	Nerandomilast 9 mg bid	Hazard ratio [95% CI]
Key secondary endpoint	143/392	116/393	0.78 [0.61, 1.00]
Acute ILD exacerbation	57/392	46/393	0.84 [0.57, 1.24]
Hospitalisation for respiratory cause	113/392	90/393	0.75 [0.56, 0.99]
Death	64/392	36/393	0.51 [0.34, 0.78]



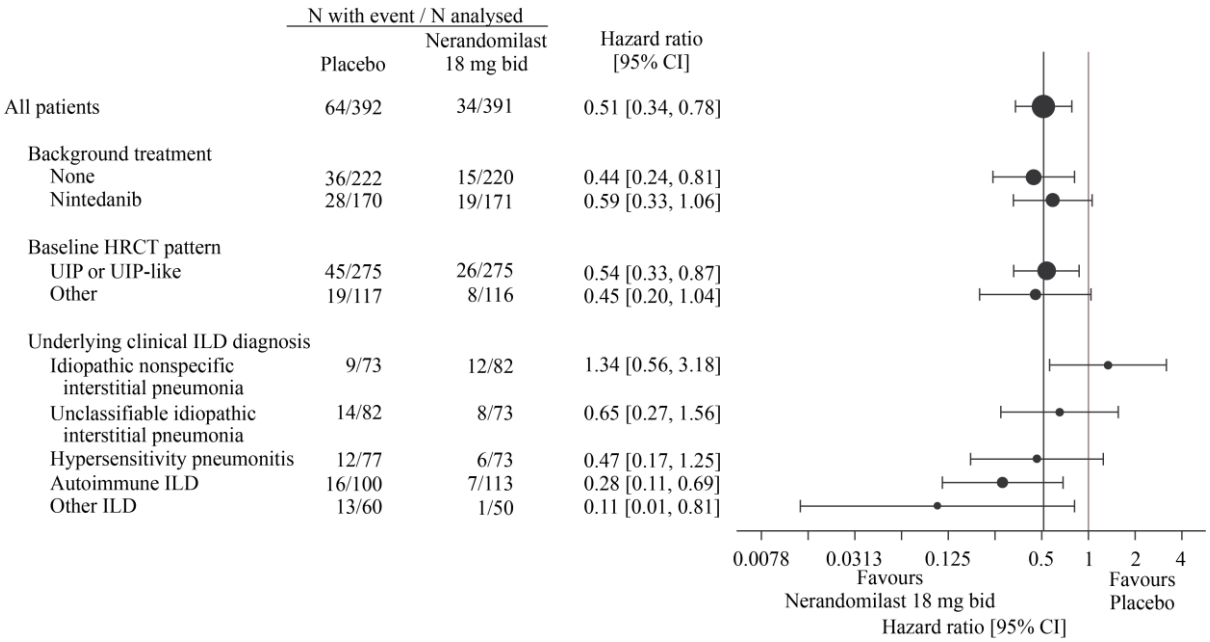
bid = twice daily

The results of the key secondary endpoint were generally consistent regardless of background nintedanib treatment or HRCT pattern.

At the end-of-trial analysis deaths occurred in 34 patients (9%) in the 18 mg group, in 36 patients (9%) in the 9 mg group, and 64 patients (16%) in the placebo group. Compared with placebo, the hazard ratio for time to death was 0.51 (95% CI: 0.34, 0.78) for the 18 mg dose and 0.51 (95% CI: 0.34, 0.78) for the 9 mg dose.

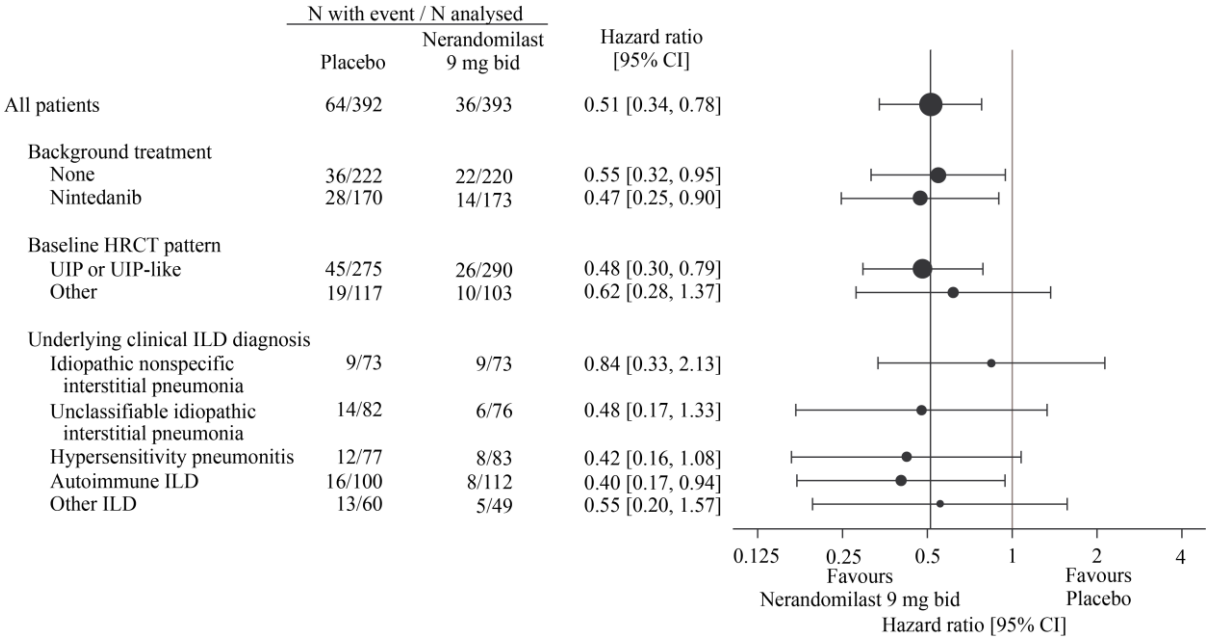
Figure 13 and Figure 14 show the analysis of time to death over the whole trial (end-of-trial analysis) in the nerandomilast 18 mg and 9 mg dose groups, respectively versus matching placebo for the subgroups by background treatment and HRCT pattern, as well as by underlying clinical ILD diagnosis.

Figure 13. Time to death over the duration of the FIBRONEER-ILD study for patients receiving 18 mg nerandomilast compared to placebo.



bid = twice daily

Figure 14. Time to death over the duration of the FIBRONEER-ILD study for patients receiving 9 mg nerandomilast compared to placebo.



bid = twice daily

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Jascayd in one or more subsets of the paediatric population in fibrosing interstitial lung disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of nerandomilast have been characterised in healthy volunteers, patients with IPF and patients with PPF. No clinically relevant differences in pharmacokinetics of nerandomilast were noted between these populations.

Absorption

Nerandomilast reached peak plasma concentrations (C_{max}) at a median time (T_{max}) of 1.00-1.25 h (range between 0.5-4 hours) after oral administration of 9 mg and 18 mg doses. The absolute oral bioavailability of nerandomilast was 73% (90% CI: 67-79%).

Administration of 18 mg nerandomilast with a high-fat and high caloric meal did not change nerandomilast exposure to a clinically relevant extent (AUC increased by approximately 15% while C_{max} decreased by approximately 14%).

Distribution

After single intravenous administration of nerandomilast, the geometric mean volume of distribution V_{ss} was approximately 94 L (gCV 32.0%). *In vitro*, nerandomilast was a substrate of the transporter protein P-gp, but not of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2.

In vitro human plasma protein binding of nerandomilast was 77% with no concentration dependence.

In healthy volunteers, nerandomilast was preferentially distributed in plasma with a blood-to-plasma ratio of 0.6-0.8.

Biotransformation

Nerandomilast is mainly metabolised via oxidation by CYP3A and glucuronidation by multiple uridine-5′-diphospho-glucuronosyltransferase enzymes.

Following single oral administration, nerandomilast was the primary circulating component representing approximately 50% of circulating radioactivity.

After multiple oral administrations of 12 mg nerandomilast twice daily, the only major metabolite identified in plasma at steady state was the di-oxidative metabolite BI 764333/M480(4). This pharmacologically inactive metabolite represented 12% of the total plasma material at steady state consisting of both parent compound and all its metabolites.

Nerandomilast has a chiral sulfur atom and Jascayd predominantly contains chirally pure nerandomilast (R-enantiomer). After oral administration of nerandomilast, chiral inversion from R-enantiomer to S-enantiomer occurs via metabolism. The S-enantiomer was identified as a minor (3% of total circulating radioactivity) metabolite of nerandomilast and is pharmacologically inactive. The pharmacologically active R-enantiomer remained as the predominant circulating enantiomer.

Elimination

Following multiple oral doses of 18 mg nerandomilast twice daily, the terminal half-life was approximately 10 to 17 h and the geometric mean apparent plasma clearance at steady state was 274 mL/min with inter-individual variability (gCV%) of 23.6%. After oral administration of a single 18 mg dose of radiolabelled nerandomilast, approximately 95% of the dose was recovered within 9 days after dosing, with 58% recovered in faeces (13% unchanged) and 36% recovered in urine (12% unchanged).

Linearity/non-linearity

Nerandomilast exhibited dose proportional pharmacokinetics following oral administration of both, single doses (0.06 to 48 mg) and multiple doses (1 to 18 mg twice daily).
Following oral administration of 18 mg nerandomilast twice daily, steady state was achieved within 4 days with an accumulation ratio of up to 1.38 based on AUC and Cmax.

PK in specific populations

Age, sex, ethnicity, renal or hepatic impairment

No clinically significant differences in the pharmacokinetics of nerandomilast were observed based on age (18-90 years), sex, ethnicity (Hispanic/Latino or not Hispanic/Latino), mild, moderate, and severe renal impairment (eGFR $\geq$ 15 and < 90 mL/min based on CKD-EPI formula), or mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Subjects with end stage renal disease and subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Race

Asian patients have up to 47% higher nerandomilast trough concentration compared to White patients. This effect is not expected to be clinically meaningful.

Body weight

A population PK analysis indicated higher nerandomilast exposure in patients with lower body weight and lower exposure in patients with higher body weight. The impact of body weight on nerandomilast plasma concentrations is not expected to be clinically meaningful.

Pharmacokinetic/pharmacodynamic relationship(s)

Increases in nerandomilast steady state trough concentrations were associated with better efficacy in patients with IPF and PPF, as indicated by a smaller reduction in absolute Forced Vital Capacity (FVC) from baseline over 52 weeks.

5.3 Preclinical safety data

General toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity. There is no evidence of phototoxic potential.

Repeat-dose toxicity studies were conducted in rats, minipigs, and monkeys. Vasculopathy (inflammation, haemorrhage, and blood vessel necrosis) was the primary finding observed in the rat and minipig. No adverse vascular effects were observed in monkeys administered up to 30 mg/kg/day (10-times human exposure based on AUC at the maximum recommended human dose (MRHD) (see section 4.2)). 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). The exposure margin in monkeys, considered the most relevant species to humans, suggests that primates are less sensitive to vascular effects than other species.

In toxicology studies in monkeys at exposures higher than 10-times human exposure based on AUC at the MRHD, emesis and heart findings (focal degeneration or necrosis not accompanied by vascular changes) were observed.

Reproductive and developmental toxicology

Fertility and early embryonic development

In a fertility study in male rats, nerandomilast administration at a dose of 6 mg/kg/day (approximately 4-times human exposure based on AUC at the MRHD) showed no effect on mating, fertility, or sperm indices.

In female rats, decreased indices for mating and fertility were observed at the highest tested dose of 9 mg/kg/day (approximately 9-times human exposure based on AUC at the MRHD) and were related to general toxicity. No such effects were observed at the No Observed Adverse Effects Level (NOAEL) dose of 6 mg/kg/day (approximately 4-times human exposure at the MRHD). In the fertility and early embryonic development and the embryo-foetal development studies, an increase in early resorptions was observed in rats at doses ≥ 6 mg/kg/day. No such effects were observed at the NOAEL dose of 3 mg/kg/day (approximately 3-times human exposure at the MRHD).

Sexually mature female monkeys administered nerandomilast for 39 weeks showed sporadic menstrual cycle prolongation at dose levels of 10 mg/kg/day and 30 mg/kg/day (approximately 3- or 10-times human exposure based on AUC at the MRHD). Menstrual cycles were not affected in monkeys at 3 mg/kg/day (equivalent to human exposure based on AUC at the MRHD).
No changes in oestrous cycles were observed in rats.

Embryo-foetal development

Following administration of radiolabelled nerandomilast to pregnant rats, radioactivity was detected in placenta, embryo-foetal blood and tissues, suggesting transfer across the placental barrier.

Embryo-foetal development studies in rats and rabbits showed no teratogenicity, no skeletal variations and no fetotoxicity up to the highest tested dose levels of 9 mg/kg/day and 15 mg/kg/day, equivalent to 7- and 4-times human exposure based on AUC at the MRHD, respectively. Embryo-foetal lethality due to post-implantation loss related to an increase in early resorptions was observed in rats at the dose of 6 mg/kg/day (5-times human exposure based on AUC at the MRHD) administered from gestation day 6 to 17. No embryo-foetal lethality was observed in rats and rabbits at the NOAEL dose of 3 mg/kg/day and 15 mg/kg/day (approximately 3- and 4-times human exposure based on AUC at the MRHD, respectively).

Pre- and postnatal development

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 exposure at the MRHD) from gestation day 6 to lactation day 6 resulted in lower pup weights. In the pivotal pre- and postnatal development study, nerandomilast administered to pregnant female rats from gestation day 6 to lactation day 20, had no adverse effects on maternal performance or toxicity or on F1 generation (offspring) development, behaviour, and reproductive performance up to the highest tested dose of 3 mg/kg/day (approximately 2-times human exposure based on AUC at the MRHD). In this study, nerandomilast was present in the plasma of rat pups during the lactation period.
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, with the maximum radioactive concentration observed at 1 hour post dose that was significantly reduced by 24 hours post dose. The concentration of total radioactivity in animal milk does not necessarily predict the concentration of the active substance in human milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

9 mg film-coated tablets

Lactose monohydrate
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate
Hypromellose 2910
Talc
Mannitol
Macrogol 8000
Iron oxide yellow (E172)

18 mg film-coated tablets

Lactose monohydrate
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate
Hypromellose 2910
Talc
Mannitol
Macrogol 8000
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

PVC/aluminium perforated unit dose blisters.
Pack sizes of 10 × 1, 30 × 1, or 60 × 1 film-coated tablets.

HDPE bottle with a child-resistant closure.
Pack sizes of 60 or 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal [and other handling]

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Jascayd 9 mg film-coated tablets

EU/1/26/2040/001
EU/1/26/2040/002
EU/1/26/2040/003
EU/1/26/2040/004
EU/1/26/2040/005

Jascayd 18 mg film-coated tablets

EU/1/26/2040/006
EU/1/26/2040/007
EU/1/26/2040/008
EU/1/26/2040/009
EU/1/26/2040/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 9 mg film-coated tablets
nerandomilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 9 mg of nerandomilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
10 × 1 film-coated tablets
30 × 1 film-coated tablets
60 × 1 film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2040/001 10 × 1 film-coated tablets
EU/1/26/2040/002 30 × 1 film-coated tablets
EU/1/26/2040/003 60 × 1 film-coated tablets
EU/1/26/2040/004 60 film-coated tablets
EU/1/26/2040/005 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jascayd 9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 9 mg tablets
nerandomilast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 9 mg film-coated tablets
nerandomilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 9 mg of nerandomilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2040/004 60 film-coated tablets
EU/1/26/2040/005 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 18 mg film-coated tablets
nerandomilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 18 mg of nerandomilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
10 × 1 film-coated tablets
30 × 1 film-coated tablets
60 × 1 film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2040/006 10 × 1 film-coated tablets
EU/1/26/2040/007 30 × 1 film-coated tablets
EU/1/26/2040/008 60 × 1 film-coated tablets
EU/1/26/2040/009 60 film-coated tablets
EU/1/26/2040/010 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jascayd 18 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 18 mg tablets
nerandomilast

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Jascayd 18 mg film-coated tablets
nerandomilast

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 18 mg of nerandomilast.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2040/009 60 film-coated tablets
EU/1/26/2040/010 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Jascayd 9 mg film-coated tablets
Jascayd 18 mg film-coated tablets
nerandomilast

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jascayd is and what it is used for

Jascayd contains the active substance nerandomilast.

It is a medicine called phosphodiesterase 4B inhibitor, which helps to regulate the activity of your immune system and to reduce tissue scarring.

Jascayd is used:
- to treat idiopathic pulmonary fibrosis (IPF) in adults;
- to treat progressive pulmonary fibrosis (PPF) in adults.

IPF and PPF are lung diseases in which the tissue in the lungs becomes thickened, stiff and scarred over time. The scarring makes it difficult for oxygen to pass from the lungs into the bloodstream, making it hard to breathe deeply. Jascayd helps to reduce further scarring and stiffening of the lungs, thereby making it easier for you to breathe.

2. What you need to know before you take Jascayd

Do not take Jascayd

- if you are allergic to nerandomilast or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Jascayd:
- if you take nintedanib or pirfenidone as this can increase the risk of certain side effects;

- if you have stomach or gut problems;
- if you have, or had in the past, stomach or gut problems when taking nintedanib or pirfenidone;
- if you have mental health problems.

Talk to your doctor while taking Jascayd:
- if you get diarrhoea, feel sick (nausea) or lose your appetite;
- if you lose weight without meaning to.

Children and adolescents

Do not give this medicine to children or adolescents because it is not known if this medicine is safe and effective in this population.

Other medicines and Jascayd

Jascayd may affect the way other medicines work, and other medicines may affect how Jascayd works.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

This is especially important if you are taking pirfenidone (another medicine to treat IPF), as it can reduce how well Jascayd works.

Additionally, tell your doctor or pharmacist if you are taking any of the following medicines as they may reduce how well Jascayd works:
- carbamazepine: a medicine to treat epilepsy and certain nerve pain;
- St. John's wort: a herbal medicine used to help with mild depression, symptoms of menopause, and certain mood-related conditions such as anxiety;
- rifampicin: an antibiotic medicine to treat tuberculosis and other bacterial infections;
- phenytoin: a medicine to treat epilepsy;
- bosentan: a medicine to treat pulmonary arterial hypertension;
- metamizole: a medicine to relieve pain and reduce fever.

Also tell your doctor if you take any of the medicines listed below. Your doctor may reduce your dose of Jascayd if you take any of these, as they may increase the levels of Jascayd in your blood:
- clarithromycin: an antibiotic medicine to treat bacterial infections;
- itraconazole: a medicine to treat fungal infections;
- ritonavir: a medicine to treat COVID-19 and HIV infections.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

This medicine may cause loss of pregnancy (miscarriage). You should use effective contraception during treatment with Jascayd. If you become pregnant while being treated with this medicine, tell your doctor straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

It is not known if this medicine passes into breastmilk. Do not breastfeed during treatment with Jascayd.

Driving and using machines

This medicine is not expected to affect your ability to drive or to use machines.

Jascayd contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Jascayd contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Jascayd

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how much Jascayd to take and when to take it.

The recommended dose is 1 tablet of Jascayd 18 mg twice daily. Take the tablets approximately 12 hours apart.

Your doctor may decide to reduce your dose of Jascayd to 9 mg twice daily depending on:
- how well you tolerate Jascayd;
- any other medicines you are taking.

Taking this medicine

- Swallow the tablets whole with water.
- You can take the tablet with or without food.

<u>If you cannot swallow Jascayd tablets whole:</u>

- Fill a glass with about 100 mL of non-carbonated (still) water that is at room temperature. Do not use any other liquids.
- Drop the tablet into the water without crushing it.
- Stir regularly for approximately 15 to 20 minutes until the tablet has broken down into very small bits (it will not dissolve completely).
- Drink the Jascayd and water mixture within 2 hours of mixing.
- If you do not drink the mixture right away, stir the mixture again before drinking.
- Fill the glass with another 100 mL of water and drink it. This ensures you have taken the full dose.

If you take more Jascayd than you should

Contact your doctor or pharmacist immediately.

If you forget to take Jascayd

If you forget a dose, take your next dose at your regular time. **Do not** take the missed dose. **Do not** take more than 2 tablets of 18 mg Jascayd in 1 day.

If you stop taking Jascayd

You should continue taking Jascayd until your doctor tells you to stop.
Do not stop taking Jascayd without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to your doctor if you get any side effects.

Idiopathic pulmonary fibrosis (IPF)

Very common (may affect more than 1 in 10 people):

- diarrhoea.

Common (may affect up to 1 in 10 people):

- decreased appetite;
- feeling sick (nausea);
- back pain;
- weight loss.

Progressive pulmonary fibrosis (PPF)

Very common (may affect more than 1 in 10 people):

- diarrhoea.

Common (may affect up to 1 in 10 people):

- decreased appetite;
- feeling sick (nausea);
- back pain;
- weight loss.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jascayd

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister or bottle label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Jascayd contains

Jascayd 9 mg tablets

- The active substance is nerandomilast. Each tablet contains 9 mg nerandomilast.
- The other ingredients are:
  - lactose monohydrate;
  - microcrystalline cellulose;
  - hydroxypropylcellulose;
  - croscarmellose sodium;
  - magnesium stearate;
  - hypromellose 2910;
  - talc;
  - mannitol;
  - macrogol 8000;
  - iron oxide yellow (E172).

Jascayd 18 mg tablets

- The active substance is nerandomilast. Each tablet contains 18 mg nerandomilast.
- The other ingredients are:
  - lactose monohydrate;
  - microcrystalline cellulose;
  - hydroxypropylcellulose;
  - croscarmellose sodium;
  - magnesium stearate;
  - hypromellose 2910;
  - talc;
  - mannitol;
  - macrogol 8000;
  - iron oxide red (E172);
  - iron oxide black (E172).

What Jascayd looks like and contents of the pack

Jascayd 9 mg film-coated tablets are light yellow, oval and biconvex. They have “F9” on one side and the Boehringer Ingelheim logo on the other side. The tablets are 9.5 mm long and 4.6 mm wide.

Jascayd 18 mg film-coated tablets are light red, oval and biconvex. They have “F18” on one side and the Boehringer Ingelheim logo on the other side. The tablets are 12 mm long and 5.9 mm wide.

Jascayd tablets are available in:
- PVC/aluminium perforated unit dose blisters.
  The pack sizes are 10 × 1, 30 × 1 or 60 × 1 film-coated tablets.
- HDPE bottle with a child-resistant closure.
  The pack sizes are 60 or 180 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

Lietuva
Boehringer Ingelheim RCV GmbH & Co KG
Lietuvos filialas
Tel: +370 5 2595942

България
Бьорингер Ингелхайм РЦВ ГмбХ и Ко. КГ - клон България
Тел.: +359 2 958 79 98

Luxembourg/Luxemburg
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

Česká republika
Boehringer Ingelheim spol. s r.o.
Tel: +420 234 655 111

Magyarország
Boehringer Ingelheim RCV GmbH & Co KG
Magyarországi Fióktelepe
Tel.: +36 1 299 89 00

Danmark
Boehringer Ingelheim Danmark A/S
Tlf.: +45 39 15 88 88

Malta
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Deutschland
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 (0) 800 77 90 900

Nederland
Boehringer Ingelheim B.V.
Tel: +31 (0) 800 22 55 889

Eesti
Boehringer Ingelheim RCV GmbH & Co KG
Eesti filiaal
Tel: +372 612 8000

Norge
Boehringer Ingelheim Danmark A/S NUF
Tlf: +47 66 76 13 00

Ελλάδα
Boehringer Ingelheim Ελλάς Μονοπρόσωπη A.E.
Τηλ: +30 2 10 89 06 300

Österreich
Boehringer Ingelheim RCV GmbH & Co KG
Tel: +43 1 80 105-7870

España
Boehringer Ingelheim España, S.A.
Tel: +34 93 404 51 00

France
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

Hrvatska
Boehringer Ingelheim Zagreb d.o.o.
Tel: +385 1 2444 600

Ireland
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 5355 1

Κύπρος
Boehringer Ingelheim Ελλάς Μονοπρόσωπη A.E.
Τηλ: +30 2 10 89 06 300

Latvija
Boehringer Ingelheim RCV GmbH & Co KG
Latvijas filiāle
Tel: +371 67 240 011

Polska
Boehringer Ingelheim Sp. z o.o.
Tel.: +48 22 699 0 699

Portugal
Boehringer Ingelheim Portugal, Lda.
Tel: +351 21 313 53 00

România
Boehringer Ingelheim RCV GmbH & Co KG Viena - Sucursala Bucureşti
Tel: +40 21 302 28 00

Slovenija
Boehringer Ingelheim RCV GmbH & Co KG
Podružnica Ljubljana
Tel: +386 1 586 40 00

Slovenská republika
Boehringer Ingelheim RCV GmbH & Co KG
organizačná zložka
Tel: +421 2 5810 1211

Suomi/Finland
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 3102 800

Sverige
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.