Nerandomilast in idiopathic pulmonary fibrosis: data from the whole follow-up period of the FIBRONEER-IPF trial

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Abstract

Rationale: In the randomized placebo-controlled FIBRONEER-IPF trial in patients with idiopathic pulmonary fibrosis, both nerandomilast 9 mg bid and 18 mg bid met the primary endpoint of reducing decline in forced vital capacity at week 52. Patients continued to receive randomized treatment after week 52, until the last patient had completed an end-of-treatment visit.

Objectives: To assess the effects of nerandomilast over the full duration of follow-up in the FIBRONEER-IPF trial.

Methods: Time to first acute exacerbation, hospitalization for respiratory cause, or death (key secondary endpoint) and other time-to-event endpoints were assessed at final database lock.

Measurements and main results: 1177 patients were treated. Mean (SD) exposure to trial medication was 14.8 (5.0), 14.9 (5.0) and 14.7 (5.3) months in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively. Compared with placebo, the hazard ratio (95% CI) for the key secondary endpoint was 0.92 (0.69, 1.22) for nerandomilast 9 mg bid and 0.99 (0.75, 1.31) for nerandomilast 18 mg bid and the hazard ratio (95% CI) for death was 0.95 (0.61, 1.49) for nerandomilast 9 mg bid and 0.66 (0.41, 1.08) for nerandomilast 18 mg bid. Adverse events led to treatment discontinuation in 13.0%, 13.5% and 16.1% of the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively.

Conclusions: In the FIBRONEER-IPF trial, nerandomilast had no effect on the composite endpoint of time to first acute exacerbation, hospitalization for respiratory cause, or death, but nerandomilast 18 mg bid was associated with a numerically lower risk of death. Nerandomilast had a favorable safety profile, with a low rate of discontinuation due to adverse events.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease associated with progressive loss of lung function and high mortality (1). There are two approved drugs for IPF: nintedanib and pirfenidone. These treatments slow decline in lung function but have limited tolerability (2–5). There remains a need for therapies that improve clinical outcomes in patients with IPF and have a tolerability profile that enables patients to remain on treatment. Nerandomilast (BI 1015550) is an orally administered preferential inhibitor of phosphodiesterase 4B (PDE4B) that has antifibrotic and immunomodulatory properties (6–8). The Phase III randomized placebo-controlled FIBRONEER-IPF trial investigated the efficacy and safety of nerandomilast 9 mg bid and 18 mg bid, used as monotherapy or as add-on to background nintedanib or pirfenidone, in patients with IPF (9). The primary endpoint, change in forced vital capacity (FVC) (mL) at week 52, was met for both doses of nerandomilast, but a drug-drug interaction, which reduced plasma levels of nerandomilast by about 50% in patients taking pirfenidone, meant that the 9 mg twice daily dose of nerandomilast was not effective in patients taking pirfenidone (9).

In the FIBRONEER-IPF trial, patients continued to receive blinded randomized treatment after week 52. The results observed at the first database lock, which took place after the last patient had completed the week 52 visit and so the primary endpoint could be assessed, have been reported (9). The final database lock took place once all patients had completed an end-of-treatment visit. The data available at final database lock provide the longest period of follow-up for assessment of time-to-event endpoints, changes in FVC, and adverse events in patients treated with nerandomilast versus placebo. Here, we report the data from the final database lock.

Methods

Trial design

The design of the FIBRONEER-IPF trial has been described (10) and the protocol is publicly available (9). Briefly, eligible patients had IPF according to current guidelines (11), a usual interstitial pneumonia (UIP) or probable UIP pattern on high-resolution computed tomography (confirmed by central review), FVC ≥45% predicted and diffusion capacity of the lungs for carbon monoxide (DLco) (corrected for hemoglobin) ≥25% predicted. Patients who had taken a stable dose of nintedanib or pirfenidone for ≥12 weeks, and those who had not taken nintedanib or pirfenidone for ≥8 weeks, were eligible to participate.

Patients were randomized 1:1:1 to receive nerandomilast 9 mg bid, nerandomilast 18 mg bid, or placebo, stratified by background therapy (nintedanib/pirfenidone versus neither). Visits occurred at baseline, at weeks 2, 6, 12, 18, 26, 36, 44 and 52, and every 12 weeks thereafter, with a follow-up visit performed 7 days after the end of treatment. Patients continued to receive blinded randomized treatment until the end of the trial. The final database lock took place after all patients had completed an end-of-treatment visit. Patients who completed the trial on-treatment were eligible to enter an open-label study, in which all patients received nerandomilast (FIBRONEER-ON; NCT06238622).

The key secondary endpoint was time to first acute exacerbation of IPF, hospitalization for respiratory cause, or death, over the whole trial. Acute exacerbations were defined according to consensus criteria (12). Acute

exacerbations and hospitalizations for respiratory cause were reported by the investigators and not adjudicated. Secondary time-to-event endpoints were time to first acute exacerbation or death; time to first hospitalization for respiratory cause or death; time to absolute decline in FVC % predicted >10% or death; time to absolute decline in DLco % predicted >15% or death; and time to death, over the whole trial. Further time-to-event endpoints include time to first acute exacerbation and time to first hospitalization for respiratory cause over the whole trial. Time to respiratory-related death over the whole trial was analyzed post-hoc. All other analyses were pre-specified.

Safety was assessed via the recording of adverse events and clinical monitoring. Adverse events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) v27.1. Depression and suicidal ideation and behavior are adverse events associated with marketed PDE4 inhibitors (13, 14). Inhibitors of PDE4 have been associated with vasculitis in pre-clinical toxicology studies (15, 16). Thus, these adverse events were of interest in the FIBRONEER-IPF trial.

The trial was carried out in compliance with the protocol and in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization Harmonized Tripartite Guideline for Good Clinical Practice, applicable regulatory requirements and standard operating procedures. All patients provided written informed consent prior to entering the trial.

Analyses

Analyses were conducted in patients who received ≥1 dose of trial medication. The key secondary endpoint and secondary time-to-event endpoints were analyzed using a Cox proportional hazards model adjusted for baseline background therapy (nintedanib/pirfenidone) (yes/no), age, FVC % predicted, DLco % predicted (corrected for hemoglobin) and treatment. The key secondary endpoint and time to death were analyzed in the overall population and in subgroups by background therapy (nintedanib, pirfenidone, none). In the subgroup analyses by background therapy, baseline background therapy use (yes/no) was replaced by type of baseline therapy (nintedanib, pirfenidone, none), treatment and type of baseline therapy−by−treatment interaction as covariates in the models. Interaction p-values were calculated as an indicator of the potential heterogeneity of the effect of nerandomilast versus placebo across subgroups.

Change from baseline in FVC (mL) over the whole trial was based on a mixed model for repeated measures, with fixed categorical effects of treatment at each visit, baseline therapy at each visit (yes/no), fixed continuous effects of baseline FVC (mL) at each visit and unstructured covariance for repeated measures. Unlike in the analysis of the primary endpoint, in which missing data due to death were imputed based on the tenth percentile of observed values across all treatment arms at the respective visit (9), in the analysis of change in FVC over the whole trial, missing data were not imputed. The mixed model for repeated measures implicitly handles missing data under an assumption that they are missing at random (*i.e.,* it assumes that missing data would follow the trend of the observed data within the same treatment group). ~~Missing data were not imputed and were assumed to be missing at random~~.

Results

Patients

A total of 1177 patients received trial medication (393 placebo, 392 nerandomilast 9 mg bid, 392 nerandomilast 18 mg bid). Of these, 535 (45.5%) were taking nintedanib, 380 (32.3%) pirfenidone and 262 (22.3%) neither nintedanib or pirfenidone. The baseline characteristics of the overall population and subgroups by use of background antifibrotic therapy have been described (9). Overall, mean (SD) age was 70.2 (7.7) years, FVC was 78.2 (17.3) % predicted and DLco was 50.9 (16.3) % predicted. Mean (SD) exposure to trial medication (time over which trial medication was taken irrespective of treatment interruptions) in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively was 13.3 (4.3) months, 13.4 (4.3) months and 13.2 (4.6) months up to the first database lock and 14.8 (5.0), 14.9 (5.0) and 14.7 (5.3) months up to the final database lock. Mean (SD) observation time (time over which endpoints were assessed) in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively was 14.4 (3.0) months, 14.6 (2.8) months and 14.6 (2.7) months up to the first database lock and 16.3 (3.5), 16.4 (3.2) and 16.4 (3.2) months up to the final database lock. Overall, 85.2% of patients completed the planned observation period up to the final database lock (Figure E1).

Changes in FVC

The FVC curves for nerandomilast and placebo continued to diverge beyond week 52 (Figure 1). At the final database lock, 650 patients had completed FVC assessments at week 76. Adjusted mean (SE) changes from baseline in FVC at

week 76 were −262.4 (17.6) mL in the placebo group, −165.1 (17.4) mL in the nerandomilast 9 mg bid group, and −138.3 (17.4) mL in the nerandomilast 18 mg bid group. Adjusted mean (95% CI) differences in change in FVC (mL) at week 76 versus placebo were 97.3 (48.9, 145.8) with nerandomilast 9 mg bid and 124.1 (75.7, 172.6) with nerandomilast 18 mg bid (Figure 2). Changes from baseline in FVC (mL) at week 76 in subgroups by use of background therapy are shown in Figure 2.

Key secondary endpoint and other secondary time-to-event endpoints

For all these endpoints, there was an increase in the number of events between the first and final database locks, with a smaller increase in the nerandomilast groups than in the placebo group (Table E1). The key secondary endpoint and secondary time-to-event endpoints up to the first and final database locks are shown in Figure E2. Up to the final database lock, the key secondary endpoint was met by 26.2%, 23.0% and 23.7% of patients in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively. Compared with placebo, the hazard ratio for this endpoint was 0.92 (95% CI: 0.69, 1.22) for nerandomilast 9 mg bid and 0.99 (95% CI: 0.75, 1.31) for nerandomilast 18 mg bid (Figure 3). Among patients not taking background therapy, the hazard ratio vs placebo was 0.47 (95% CI: 0.26, 0.88) for nerandomilast 9 mg bid and 0.62 (95% CI: 0.35, 1.10) for nerandomilast 18 mg bid (Figure 4 and Figure E3). Among patients taking background nintedanib, the hazard ratio vs placebo was 0.98 (95% CI: 0.63, 1.53) for nerandomilast 9 mg bid and 1.07 (95% CI: 0.70, 1.64) for nerandomilast 18 mg bid. Among patients taking background pirfenidone, the hazard ratio vs placebo was 1.30 (95% CI: 0.80, 2.12)

for nerandomilast 9 mg bid versus placebo and 1.28 (95% CI: 0.77, 2.12) for nerandomilast 18 mg bid.

Overall, 17.3%, 15.6% and 13.8% of patients in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, had an acute exacerbation or died. Compared with placebo, the hazard ratio was 0.97 (95% CI: 0.69, 1.38) for nerandomilast 9 mg bid and 0.87 (95% CI: 0.61, 1.24) for nerandomilast 18 mg (Figure 3). In total, 23.9%, 20.2% and 21.4% of patients in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, were hospitalized for a respiratory cause or died. The hazard ratio vs placebo was 0.89 (95% CI: 0.66, 1.20) for nerandomilast 9 mg bid and 0.97 (95% CI: 0.73, 1.31) for nerandomilast 18 mg bid (Figure 3). Findings on these endpoints in subgroups by background therapy are shown in Figure E4 and Figure E5. Data on the three individual components of the key secondary endpoint are shown in Table E2.

Deaths occurred in 10.7% of patients in the placebo group, 9.2% of patients in the nerandomilast 9 mg bid group and 6.6% of patients in the nerandomilast 18 mg bid group (Figure 5). Compared with placebo, the hazard ratio for death was 0.95 (95% CI: 0.61, 1.49) for nerandomilast 9 mg bid and 0.66 (95% CI: 0.41, 1.08) for nerandomilast 18 mg bid (Figure 3). Among patients not taking background therapy, the hazard ratio vs placebo for death was 0.56 (95% CI: 0.21, 1.49) for nerandomilast 9 mg bid and 0.26 (95% CI: 0.07, 0.91) for nerandomilast 18 mg bid (Figure 6 and Figure E6). Among patients taking background nintedanib, the hazard ratio vs placebo was 1.02 (95% CI: 0.51, 2.04) for nerandomilast 9 mg bid and 0.64 (95% CI: 0.30, 1.37) for nerandomilast 18 mg bid. Among patients taking background

pirfenidone, the hazard ratio vs placebo was 1.23 (95% CI: 0.58, 2.59) for nerandomilast 9 mg bid versus placebo and 1.12 (95% CI: 0.51, 2.47) for nerandomilast 18 mg bid.

Adjudication of causes of death indicated that 6.4%, 5.9% and 4.1% of patients in the placebo group, nerandomilast 9 mg bid group and nerandomilast 18 mg bid group, respectively, died from a respiratory-related cause (Table E3). Compared with placebo, the hazard ratio for respiratory-related death was 1.04 (95% CI: 0.59, 1.83) for nerandomilast 9 mg bid and 0.70 (95% CI: 0.37, 1.32) for nerandomilast 18 mg bid.

Overall, 38.9%, 33.7% and 29.6% of patients in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, had an absolute decline in FVC % predicted >10% or died. The hazard ratio vs placebo was 0.85 (95% CI: 0.67, 1.07) for nerandomilast 9 mg bid and 0.75 (95% CI: 0.59, 0.95) for nerandomilast 18 mg bid (Figure 3). A total of 22.9%, 20.9% and 19.9% of patients in the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, had an absolute decline in DLco % predicted >15% or died. The hazard ratio vs placebo was 0.90 (95% CI: 0.67, 1.22) for nerandomilast 9 mg bid and 0.84 (95% CI: 0.62, 1.15) for nerandomilast 18 mg bid. Findings on these endpoints in subgroups by background therapy are shown in Figure E7 and Figure E8.

Adverse events

Up to the final database lock, adverse events led to treatment discontinuation in 13.0%, 13.5% and 16.1% of patients in the placebo, nerandomilast 9 mg bid and

nerandomilast 18 mg bid groups, respectively. In these treatment groups, respectively, adverse events led to treatment discontinuation in 12.6%, 10.2% and 9.2% of patients not taking background therapy; 13.9%, 18.5% and 23.0% of patients taking background nintedanib; 12.0%, 8.3% and 11.0% of patients taking background pirfenidone.

The most frequently reported adverse event was diarrhea (Table E4). In the placebo, nerandomilast 9 mg bid and nerandomilast 18 mg bid groups, respectively, diarrhea was reported in 8.0%, 17.0% and 27.6% of patients not taking background therapy; 31.2%, 50.5% and 62.4% of patients taking background nintedanib; and 8.3%, 15.0% and 24.4% of patients taking background pirfenidone and led to treatment discontinuation in 0%, 0% and 1.1% of patients not taking background therapy; 1.2%, 2.2% and 12.9% of patients taking background nintedanib; and 0%, 2.5% and 0% of patients taking background pirfenidone. Among patients who had diarrhea adverse events, the worst event was rated as mild or moderate (CTCAE grade 1 or 2) in most patients (Table E5).

Serious adverse events were balanced across treatment groups (Table E6). There were no imbalances in psychiatric adverse events, vasculitis, or drug-induced liver injury across the treatment groups (Table E7).

Discussion

These analyses of data from the FIBRONEER-IPF trial showed continued efficacy of nerandomilast 9 mg bid and 18 mg bid in slowing the progression of IPF, as shown by continued divergence of the FVC curves up to week 76. As observed at the first

database lock, at the final database lock, nerandomilast had no effect on the key secondary endpoint of time to first acute exacerbation, hospitalization for respiratory cause, or death. This may reflect the challenges in identifying events such as acute exacerbation and hospitalization for respiratory cause in international trials (17). However, for both doses of nerandomilast, at the final database lock, there was a numerical reduction in the risk of this composite endpoint in patients not taking background therapy. Further, for nerandomilast 18 mg bid, there was a numerical reduction in the risk of death versus placebo (HR 0.66 [95% CI: 0.41, 1.08]), with a greater effect in patients not taking background therapy. The majority of deaths were adjudicated to have a respiratory cause. The reductions in FVC decline and death seen in this trial provide further support for decline in FVC as an indicator of mortality risk in patients with IPF (19–20). Nerandomilast 18 mg bid was also associated with a numerical reduction in the risk of an absolute decline in FVC % predicted >10% or death, which is generally regarded as indicating clinically significant disease progression in patients with IPF (21).

Of note, recruitment for the FIBRONEER-IPF trial was much faster than expected, with screening being completed in about 7 months rather than the planned 15 months. This reduced the follow-up time for time-to-event endpoints such as death and so hindered ascertainment of the effect of nerandomilast on these endpoints. Between the first and final database locks, the number of events included in the key secondary endpoint increased by 17% (from 244 to 286) and the number of deaths increased by 39% (from 75 to 104). This was accompanied by a shift in the hazard ratios for these endpoints to be more in favor of nerandomilast. These data suggest that while it may be possible to discern a difference between active treatment and

placebo groups in change in FVC at an early time-point in clinical trials, a greater observation time is needed to identify effects on clinically meaningful outcomes such as death.

The adverse event profile of nerandomilast with longer-term exposure was consistent with that observed over the first 52 weeks (9), with no additional safety concerns identified. Nerandomilast was well tolerated: in patients not taking background therapy, adverse events leading to treatment discontinuation were no more common in patients who received nerandomilast than placebo. Discontinuation of nerandomilast due to diarrhea was infrequent except in patients taking nerandomilast 18 mg bid with background nintedanib. Psychiatric adverse events, vasculitis and drug-induced liver injury were balanced across treatment groups.

Limitations of these analyses include the limited trial duration, which restricted the numbers of events, particularly deaths, in subgroups by background therapy. Acute exacerbations and hospitalizations for respiratory cause were not adjudicated. The interaction between nerandomilast and pirfenidone, which reduced plasma levels of nerandomilast in patients taking pirfenidone (9), needs to be considered in the interpretation of the data from this trial. The size of certain subgroups was small, e.g. patients not on background therapy, which limits the reliability of the observed effect on events with lower prevalence such as mortality. P-values were not adjusted for multiple testing.

In conclusion, data from the FIBRONEER-IPF trial showed that FVC curves for nerandomilast and placebo continued to diverge up to week 76. Nerandomilast had

no effect on time to first acute exacerbation, hospitalization for respiratory cause, or death, but nerandomilast 18 mg bid was associated with a numerically lower risk of death, and of decline in FVC % predicted >10% or death. Nerandomilast had a favorable safety and tolerability profile.

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Data sharing statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically one year after the approval has been granted by major regulatory authorities or after termination of the development program. Researchers should use https://vivli.org/ to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Figure legends

Figure 1. Change from baseline in FVC (mL) over 76 weeks.

Figure 2. Change from baseline in FVC (mL) over 76 weeks in A) all patients, B) patients not taking background therapy, C) patients taking background nintedanib and D) patients taking background pirfenidone.

Figure 3. Key secondary and secondary time-to-event endpoints up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo.

Figure 4. Key secondary endpoint (time to first acute exacerbation, hospitalization for respiratory cause, or death) up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo by background therapy.

Figure 5. Time to death up to final database lock.

Figure 6. Time to death up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo by background therapy.

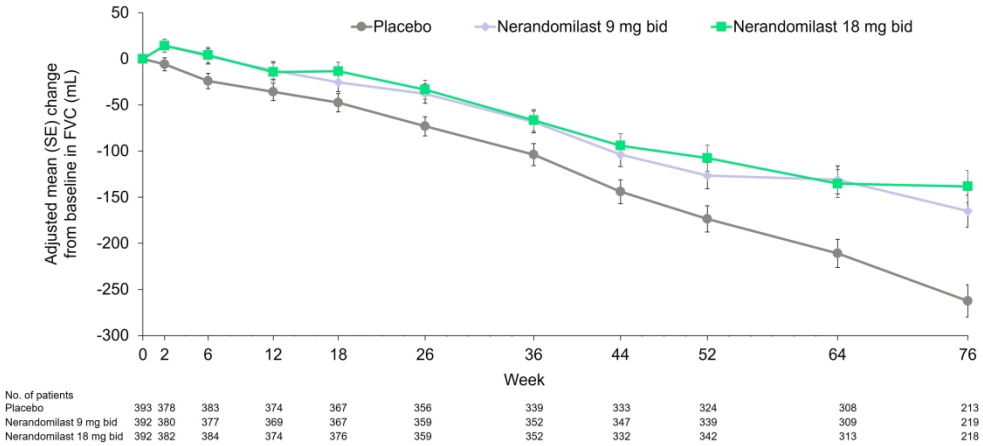


Figure 1. Change from baseline in FVC (mL) over 76 weeks.

349x156mm (300 x 300 DPI)

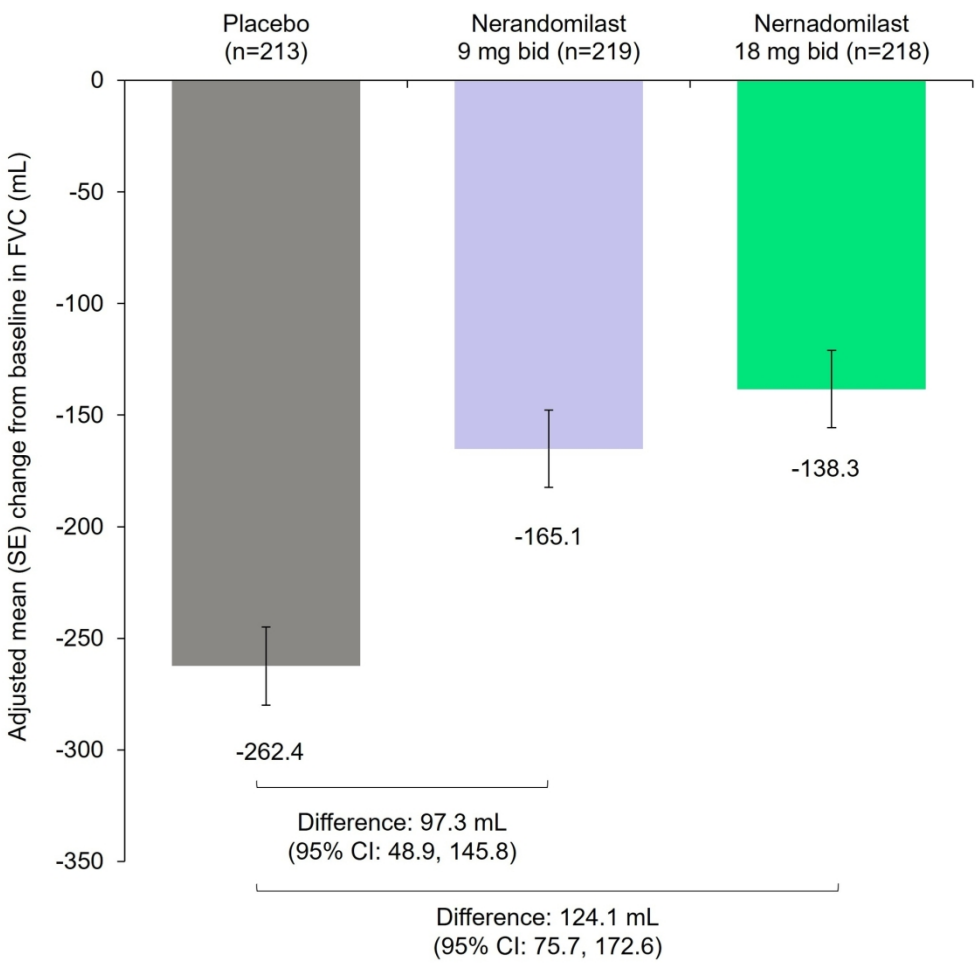


Figure 2. Change from baseline in FVC (mL) over 76 weeks in A) all patients, B) patients not taking background therapy, C) patients taking background nintedanib and D) patients taking background pirfenidone.

175x171mm (300 x 300 DPI)

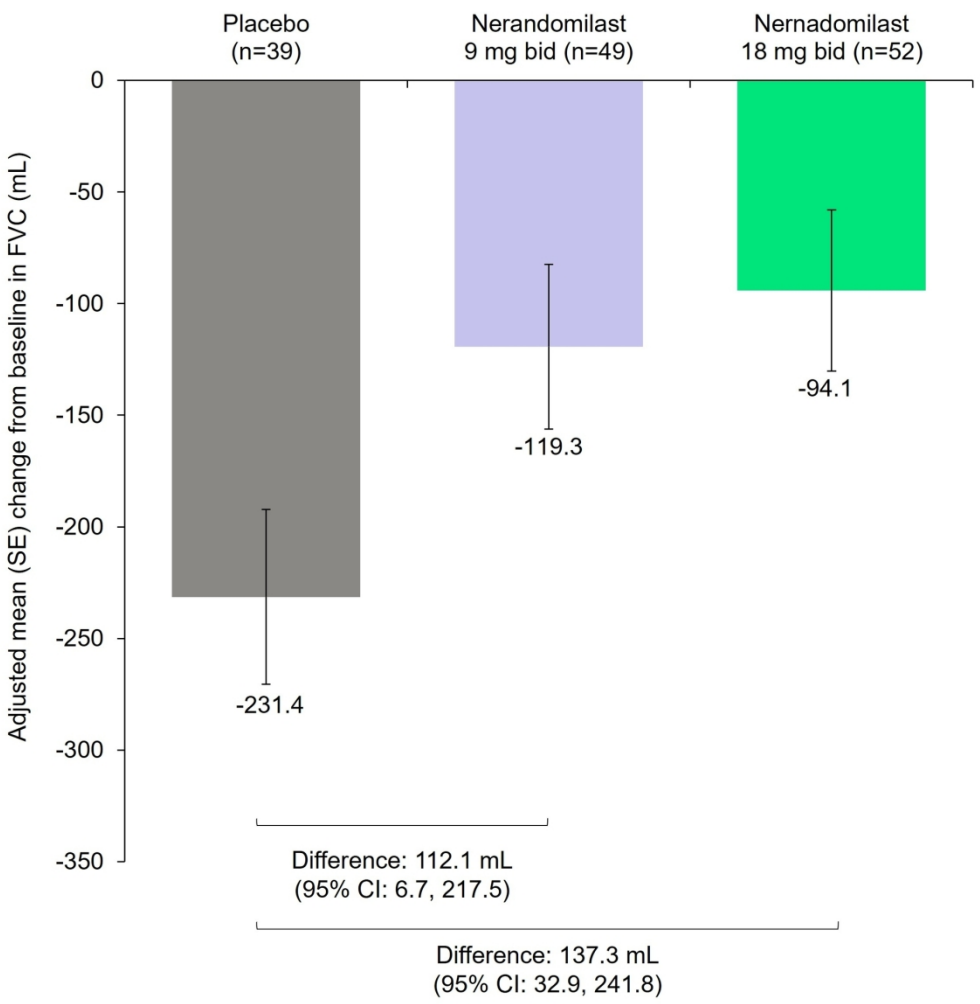
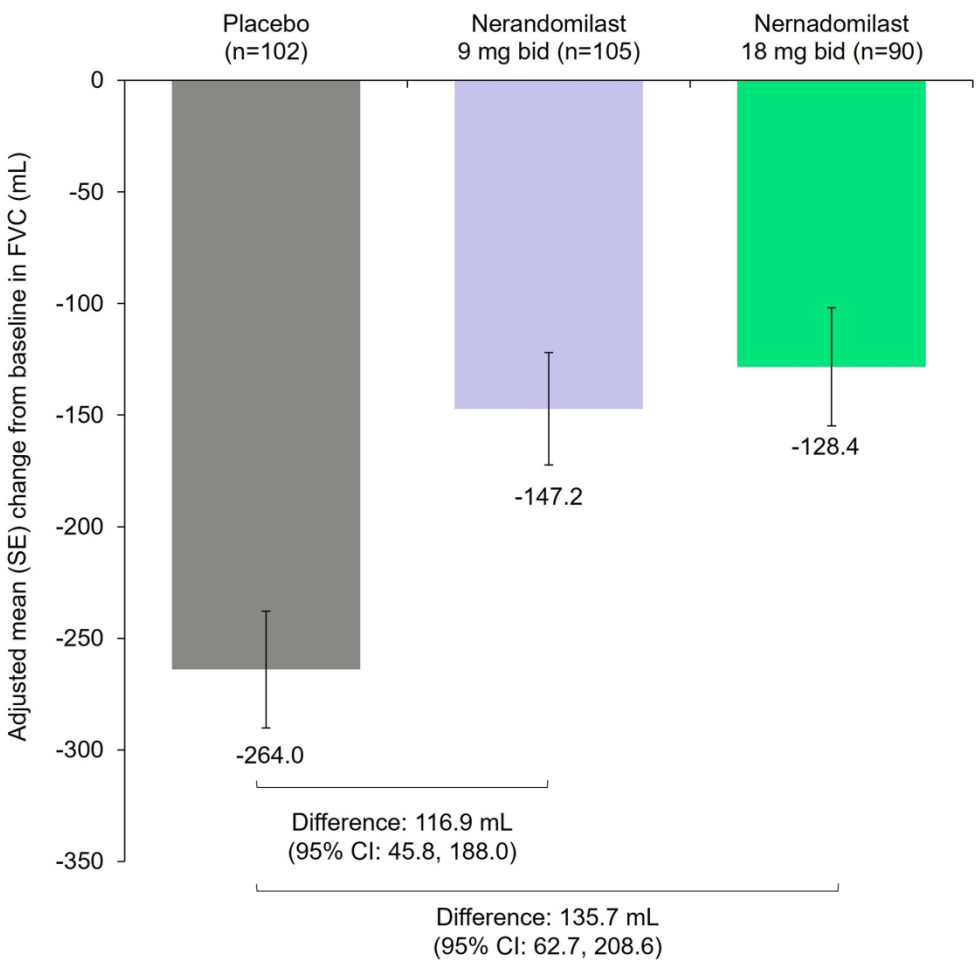


Figure 2. Change from baseline in FVC (mL) over 76 weeks in A) all patients, B) patients not taking background therapy, C) patients taking background nintedanib and D) patients taking background pirfenidone.

175x177mm (300 x 300 DPI)



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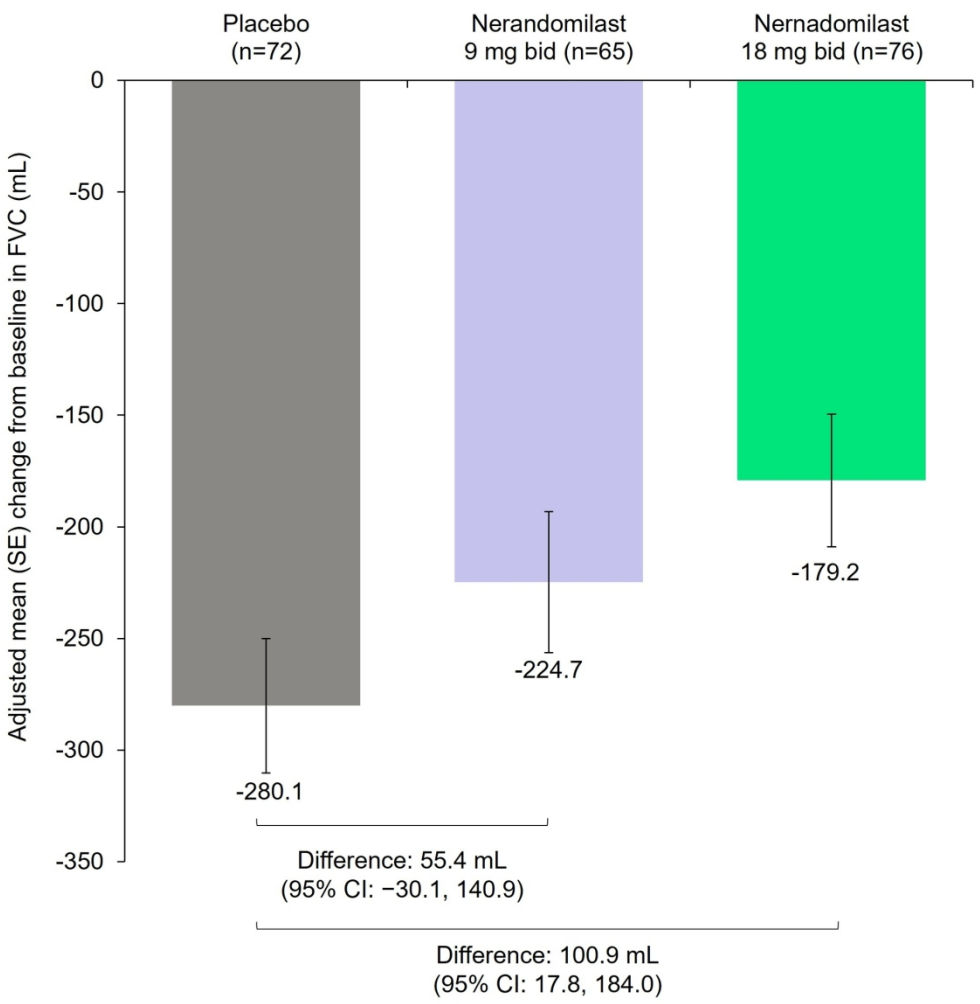
175x171mm (300 x 300 DPI)



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175x177mm (300 x 300 DPI)

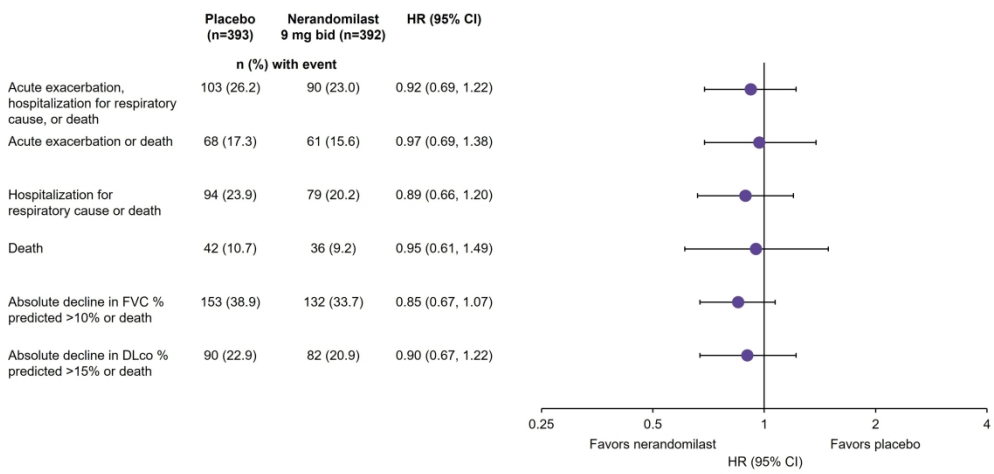


Figure 3. Key secondary and secondary time-to-event endpoints up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo.

320x153mm (300 x 300 DPI)

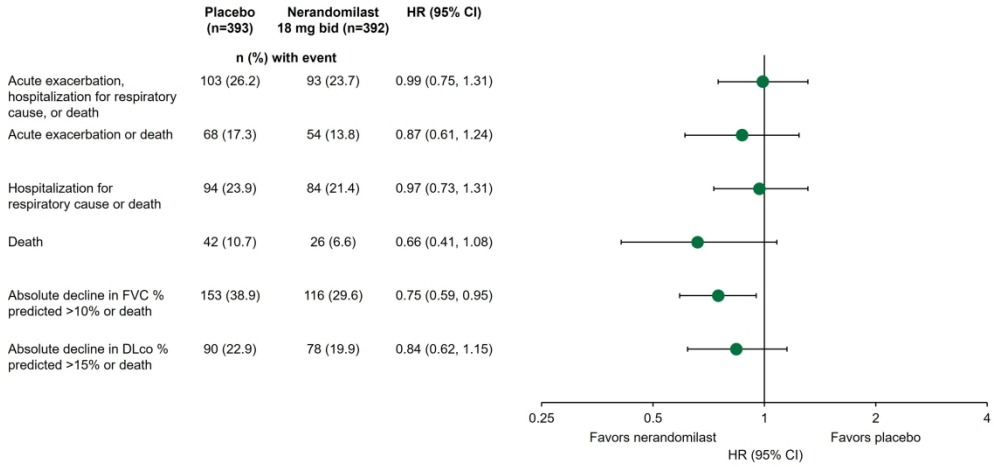


Figure 3. Key secondary and secondary time-to-event endpoints up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo.

319x160mm (300 x 300 DPI)

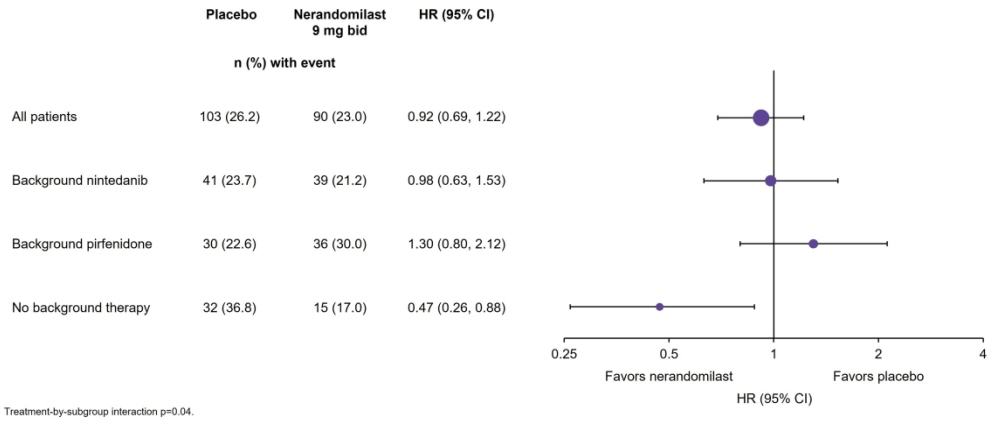
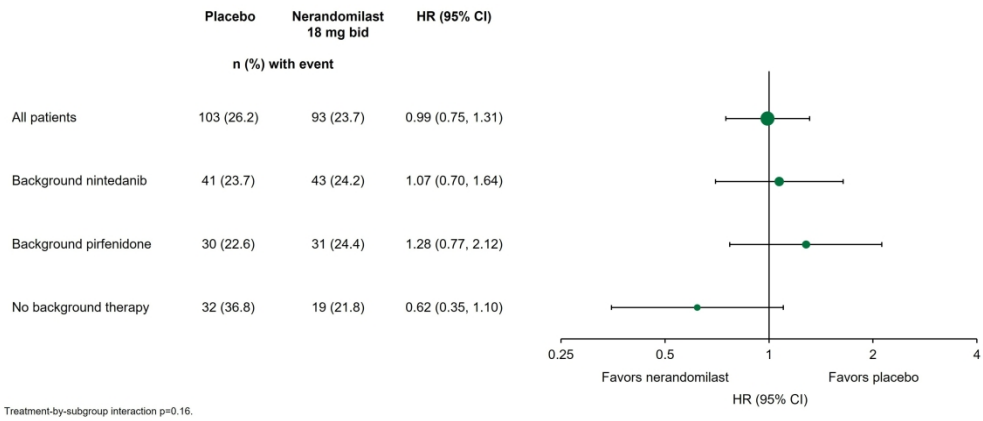


Figure 4. Key secondary endpoint (time to first acute exacerbation, hospitalization for respiratory cause, or death) up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo by background therapy.

317x136mm (300 x 300 DPI)



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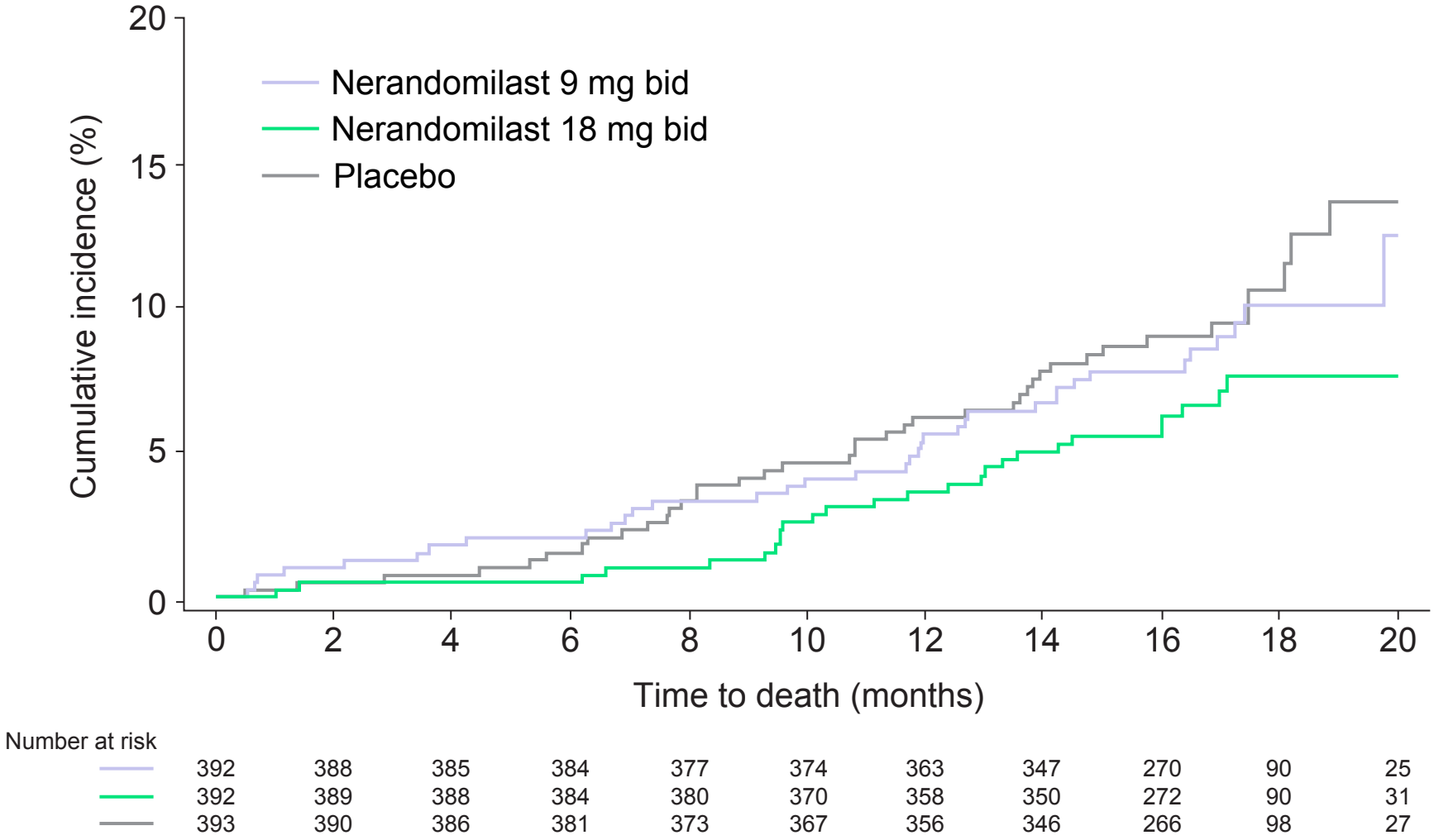
318x133mm (300 x 300 DPI)



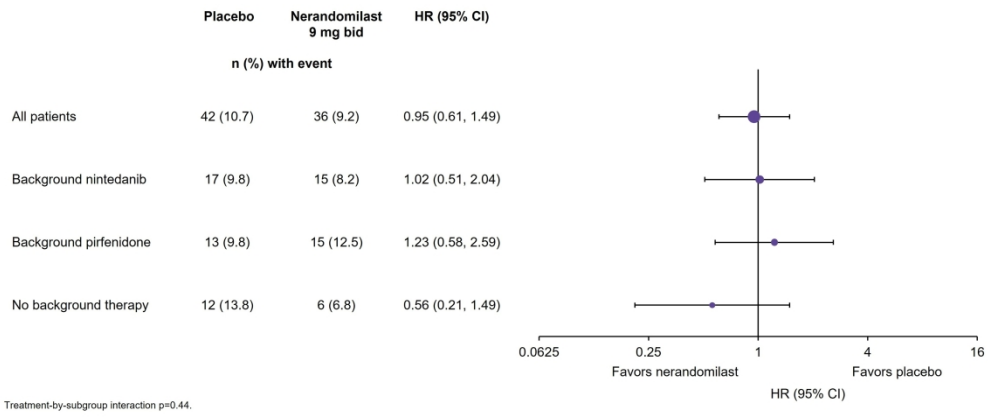


Figure 6. Time to death up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo by background therapy.

320x132mm (300 x 300 DPI)

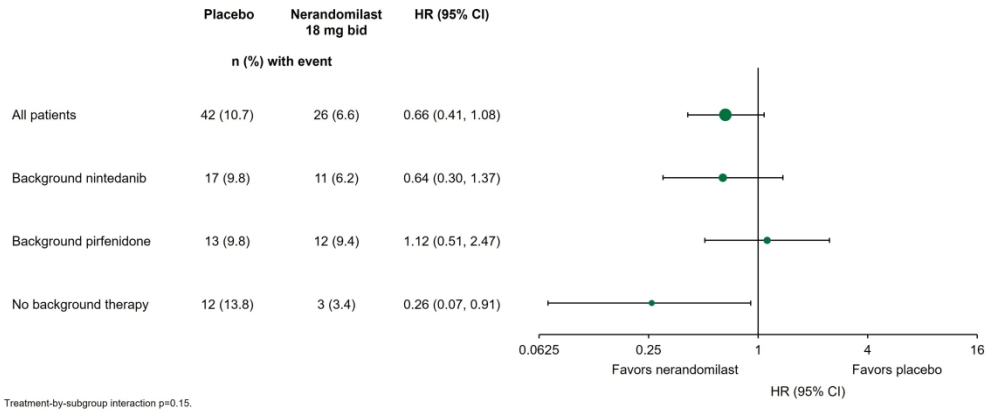


Figure 6. Time to death up to final database lock for nerandomilast 9 mg bid (A) and nerandomilast 18 mg bid (B) versus placebo by background therapy.

320x132mm (300 x 300 DPI)