Matteson Eric L. (Orcid ID: 0000-0002-9866-0124)
Distler J;rg H.W. (Orcid ID: 0000-0001-7408-9333)
Aringer Martin (Orcid ID: 0000-0003-4471-8375)
Pope Janet E (Orcid ID: 0000-0003-1479-5302)
Distler Oliver (Orcid ID: 0000-0002-2413-1959)

Short title: Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases

Title: Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial

Eric L. Matteson, MD[1] Clive Kelly, MD,[2] Jörg H.W. Distler, MD,[3] Anna Maria Hoffmann-Vold, MD,[4] James R. Seibold, MD,[5] Shikha Mittoo, MD,[6] Paul F. Dellaripa, MD,[7] Martin Aringer, MD,[8] Janet Pope, MD,[9] Oliver Distler, MD,[10] Alexandra James, MSc,[11] Rozsa Schlenker-Herceg, MD,[12] Susanne Stowasser, MD,[13] Manuel Quaresma, Lic,[13] Kevin R. Flaherty, MD[14] on behalf of the INBUILD trial investigators

[1]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA; [2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; [3]Department of Internal Medicine 3 - Rheumatology and Immunology, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany; [4]Department of Rheumatology, Oslo University Hospital, Oslo, Norway; [5]Scleroderma Research Consultants LLC, Aiken, SC, USA; [6]Division of Rheumatology, Department of Medicine, University of Toronto, Toronto, ON, Canada; [7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA; [8]Division of Rheumatology, Department of Medicine III, University Medical Center and Faculty of Medicine Carl Gustav Carus, TU Dresden, Dresden, Germany; [9]Division of Rheumatology, University of Western Ontario, Schulich School of Medicine, London, Ontario, Canada; [10]Department of

Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [11]elderbrook solutions GmbH, Bietigheim-Bissingen, Germany; [12]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [13]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany;[14]Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.

Corresponding author:

Eric L. Matteson, M.D., M.P.H., Division of Rheumatology and Internal Medicine, Mayo Clinic College of Medicine and Science, 200 First St. SW, Rochester, MN, USA. Tel: +1 507 284 2511

Email: matteson.eric@mayo.edu

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ABSTRACT

Objective: To analyze the efficacy and safety of nintedanib in patients with fibrosing autoimmune disease-related interstitial lung diseases (ILDs) with a progressive phenotype.

Methods: The INBUILD trial enrolled subjects with a fibrosing ILD other than idiopathic pulmonary fibrosis, with diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography, forced vital capacity (FVC) ≥45% predicted and diffusing capacity of the lungs for carbon monoxide ≥30%–<80% predicted. Subjects fulfilled protocol-defined criteria for progression of ILD within the 24 months before screening, despite management deemed appropriate in clinical practice. Subjects were randomized to receive nintedanib or placebo. We assessed the rate of decline in FVC (mL/year) and adverse events over 52 weeks in the subgroup with autoimmune disease-related ILDs.

Results: Among 170 subjects with autoimmune disease-related ILDs, the rate of decline in FVC over 52 weeks was -75.9 mL/year with nintedanib versus -178.6 mL/year with placebo (difference 102.7 mL/year [95% CI 23.2, 182.2]; nominal *P*=0.012). No heterogeneity was detected in the effect of nintedanib versus placebo across subgroups by ILD diagnosis (*P*=0.91). The most frequent adverse event was diarrhea, reported in 63.4% and 27.3% of subjects in the nintedanib and placebo groups, respectively. Adverse events led to permanent discontinuation of trial drug in 17.1% and 10.2% of subjects in the nintedanib and placebo groups, respectively.

Conclusion: In the INBUILD trial, nintedanib slowed the rate of decline in FVC in subjects with progressive fibrosing autoimmune disease-related ILDs, with adverse events that were manageable for most subjects.

INTRODUCTION

Interstitial lung disease (ILD) is a common manifestation of systemic autoimmune diseases including rheumatoid arthritis (RA) (1), systemic sclerosis (SSc) (2), and mixed connective tissue disease (MCTD) (3). Some patients with autoimmune disease-related ILD develop a progressive fibrosing phenotype characterized by increasing lung fibrosis on high-resolution computed tomography (HRCT), decline in lung function, worsening symptoms and quality of life, and early mortality, despite immunomodulatory therapy (2-9). Decline in forced vital capacity (FVC) is a predictor of mortality in patients with autoimmune disease-associated ILDs (2, 10, 11).

Immunosuppressants and disease modifying anti-rheumatic drugs (DMARDs) are the standard of care for systemic autoimmune diseases, but their efficacy in slowing the progression of ILD remains uncertain. Tocilizumab, an antagonist of the interleukin-6 receptor, and nintedanib, an intracellular inhibitor of tyrosine kinases, have been approved by the US Food and Drug Administration for slowing lung function decline in patients with SSc-ILD. Data from a subgroup of patients with SSc-ILD from a randomized placebo-controlled trial in patients with diffuse cutaneous SSc and elevated markers of inflammation suggested that tocilizumab slowed decline in FVC (12). Nintedanib inhibits processes fundamental to the progression of lung fibrosis (13-18). In clinical trials, nintedanib had a consistent effect on reducing the rate of decline in FVC in patients with IPF (19), SSc-ILD (20) and progressive fibrosing ILDs other than IPF (21), with an adverse event profile characterized mainly by gastrointestinal events. No significant effect of nintedanib on health-related quality of life was observed in these studies. No heterogeneity was detected in the relative effect of nintedanib versus placebo on reducing the rate of FVC decline across diagnostic subgroups (19-22). Here, we present further analyses of the efficacy and

safety of nintedanib in subjects with progressive autoimmune disease-related ILDs in the INBUILD trial.

PATIENTS AND METHODS

INBUILD trial design

The INBUILD trial (NCT02999178) was a randomized, double-blind, placebo-controlled trial conducted in 15 countries (21). The trial was conducted in accordance with the protocol, the principles of the Declaration of Helsinki, and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and was approved by local authorities. Written informed consent was obtained from all subjects before study entry.

The design of the INBUILD trial has been described and the trial protocol and statistical analysis plan are publicly available (21). Briefly, eligible subjects had an ILD other than IPF, diagnosed by the investigator according to their usual practice, with reticular abnormality with traction bronchiectasis (with or without honeycombing) of >10% extent on HRCT, FVC ≥45% predicted and diffusing capacity of the lungs for carbon monoxide (DLco) ≥30%–<80% predicted. Subjects met ≥1 of the following criteria for ILD progression within the 24 months before screening, despite management deemed appropriate in clinical practice: relative decline in FVC ≥10% predicted; relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms; relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT; worsened respiratory symptoms and increased extent of fibrosis on HRCT. Subjects taking stable doses of approved medications to treat RA or connective tissue disease (CTD) could participate, but the protocol excluded those

taking azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids >20 mg/day. Investigators were asked not to consider patients with autoimmune disease that was managed using these therapies for participation in the trial. Patients who were taking one of these therapies to treat their ILD, and whose ILD was progressing, could participate if the restricted therapy was discontinued. Washout periods for therapies used to treat ILD are described in the supplementary appendix. Initiation of these medications was allowed after 6 months of the trial in cases of deterioration of ILD or autoimmune disease.

The investigator documented an ILD diagnosis on the case report form (CRF) based on the following options: idiopathic non-specific interstitial pneumonia, unclassifiable IIP, hypersensitivity pneumonitis, RA-ILD, MCTD-ILD, SSc-ILD, exposure-related ILD, sarcoidosis, other fibrosing ILD. These diagnoses were not centrally reviewed. Where the box for “other fibrosing ILD” was ticked, the investigator specified the diagnosis in a text box.

Subjects were randomized to receive nintedanib 150 mg bid or placebo, stratified by fibrotic pattern on HRCT (usual interstitial pneumonia [UIP]-like fibrotic pattern or other fibrotic pattern [described in Flaherty 2019]) based on central review. The trial consisted of two parts: Part A, which comprised 52 weeks of treatment, and Part B, a variable period beyond week 52 during which subjects continued to receive blinded treatment until all subjects had completed the trial. Subjects who discontinued treatment were asked to attend all visits as planned, including an end-of-treatment visit and a follow-up visit 4 weeks later. The second (final) database lock took place after all subjects had completed the follow-up visit or had entered the open-label extension study, INBUILD-ON (NCT03820726).

Outcomes

Here we report analyses in the subgroup of subjects with autoimmune disease-related ILDs (RA-ILD, SSc-ILD, MCTD-ILD, plus subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the CRF). We assessed the rate of decline in FVC (mL/year) over 52 weeks; the absolute change from baseline in FVC (mL) at week 52; the absolute change from baseline in FVC % predicted at week 52; the proportions of subjects with absolute declines or increases in FVC >0% to ≤5%, >5% to ≤10%, >10% to ≤15% and >15% predicted at week 52; and the change from baseline in the King's Brief ILD (K-BILD) questionnaire total score at week 52. The K-BILD questionnaire consists of 15 items in three domains (breathlessness and activities, psychological factors, chest symptoms); higher scores represent better health status (23). We report the time to absolute and relative declines from baseline in FVC ≥5% and ≥10% predicted, time to first acute exacerbation (defined in Flaherty 2019) of ILD or death, time to progression of ILD (absolute decline from baseline in FVC ≥10% predicted) or death, and time to death using data over the whole trial (*i.e.,* up to second database lock).

We conducted subgroup analyses of the rate of decline in FVC (mL/year) over 52 weeks in subgroups by fibrotic pattern on HRCT (UIP-like fibrotic pattern, other fibrotic patterns), by ILD diagnoses (RA-ILD, MCTD-ILD, SSc-ILD, other autoimmune disease-related ILDs), and by use versus non-use of DMARDs and/or glucocorticoids (any dose) at baseline.

Adverse events reported over 52 weeks (irrespective of causality) and coded using preferred terms in the Medical Dictionary for Regulatory Activities are presented

descriptively in all subjects with autoimmune disease-related ILDs and in subgroups by use of DMARDs and/or glucocorticoids at baseline. DMARDs were defined based on WHO standardized drug groupings.

Statistical analyses

Analyses were based on data from subjects who received ≥1 dose of trial drug. The annual rate of decline in FVC (mL/year) was analyzed in all subjects with autoimmune disease-related ILDs using a random coefficient regression model (with random slopes and intercepts) including baseline FVC (mL), HRCT pattern (UIP-like fibrotic pattern or other fibrotic patterns) and treatment, and treatment-by-time and baseline-by-time interactions. Subgroup analyses used the same model but with interaction terms for baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction. In subgroup analyses, the interaction *P*-value was an indicator of the potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups (*i.e.*, a *P*-value >0.05 indicated that there was no evidence that the treatment effect differed across the subgroups). Statistical analyses of other endpoints are described in the Supplementary Files. Analyses were not adjusted for multiplicity.

RESULTS

Subjects

Of 663 subjects in the INBUILD trial (Supplementary Figure 1), 170 (25.6%) had autoimmune disease-related ILDs, of whom 89 had RA-ILD, 39 had SSc-ILD, 19 had MCTD-ILD and 23 had other autoimmune disease-related ILDs. In subjects with

other autoimmune disease-related ILDs, the diagnoses reported on the CRF were Sjogren's disease-related ILD (n=7), interstitial pneumonia with autoimmune features (n=5), undifferentiated CTD-ILD (n=3), ILD associated with lupus (n=2), and anti-neutrophil cytoplasmic antibody-associated ILD, microscopic polyangiitis-associated ILD, polymyositis-related ILD, anti-synthetase syndrome, CTD-related organising pneumonia, and CTD-ILD (1 subject each). Among 158 subjects with available data, the autoimmune disease diagnosis was confirmed by a rheumatologist in 144 subjects (91.1%).

The baseline characteristics of the subgroup with autoimmune disease-related ILDs are shown in Table 1. Mean (SD) age was 64.3 (10.6) years, 52.9% of subjects were female and 67.6% were White; mean (SD) time since diagnosis of ILD was 4.2 (4.1) years. Baseline characteristics of the subgroups by ILD diagnoses are shown in Supplementary Table 1. Based on customized drug groupings, 77.1% of subjects were taking ≥1 immunomodulatory therapy (any dose). Glucocorticoids were taken by 67.6% of subjects, non-biological DMARDs by 35.9% and biological DMARDs by 11.8% (Supplementary Table 2). There were some differences between the groups of patients who were and were not taking DMARDs and/or glucocorticoids at baseline (Supplementary Table 3). The majority of the patients taking DMARDs and/or glucocorticoids at baseline had RA-ILD.

Exposure

Mean (SD) exposure over 52 weeks was 10.1 (4.0) months in the nintedanib group and 11.1 (3.1) months in the placebo group. Mean (SD) exposure over the whole trial was 15.4 (7.4) months and 16.9 (6.1) months in these groups, respectively.

FVC endpoints

Among subjects with autoimmune disease-related ILDs, the adjusted annual rate of decline in FVC over 52 weeks was -75.9 mL/year in the nintedanib group versus -178.6 mL/year in the placebo group (difference 102.7 mL/year [95% CI 23.2, 182.2]; nominal *P*=0.0117). No heterogeneity was detected in the effect of nintedanib versus placebo across the subgroups by ILD diagnosis (*P*=0.91) (Figure 1, Supplementary Figure 2). In subjects with RA-ILD, who comprised 89 of the 170 subjects with autoimmune disease-related ILDs, the adjusted annual rate of decline in FVC over 52 weeks was -79.0 mL/year in the nintedanib group versus -196.9 mL/year in the placebo group (difference 117.9 mL/year [95% CI 5.2, 230.7]; nominal *P*=0.041).

In subjects with a UIP-like fibrotic pattern on HRCT (n=127), the adjusted annual rate of decline in FVC over 52 weeks was -58.6 mL/year in the nintedanib group versus -182.8 mL/year in the placebo group (difference 124.2 mL/year [95% CI 31.1, 217.4]). In subjects with other fibrotic patterns on HRCT (n=43), the rates of FVC decline in these groups were -126.4 mL/year versus -168.1 mL/year, respectively (difference 41.7 mL/year [95% CI -112.2, 195.5]). The effect of nintedanib versus placebo was numerically greater in subjects with a UIP-like fibrotic pattern on HRCT than in those with other fibrotic patterns, but the exploratory interaction *P*-value did not indicate heterogeneity in the treatment effect between these subgroups (*P*=0.37) (Figure 2). Exploratory interaction *P*-values did not indicate heterogeneity in the effect of nintedanib versus placebo on the annual rate of decline in FVC across subgroups by use of DMARDs and/or glucocorticoids at baseline (Figure 3, Supplementary Figure 3). Mean (SE) absolute changes from baseline in FVC at week 52 were -92.7 (29.1) mL in the nintedanib group and -185.7 (27.3) mL in the placebo group (difference

93.0 [95% CI 14.1, 172.0]). Mean (SE) absolute changes from baseline in FVC % predicted at week 52 were -2.7 (0.9) in the nintedanib group and -6.0 (0.8) in the placebo group (difference 3.3 [95% CI 0.9, 5.6]). The proportion of subjects with absolute declines or increases in FVC >0% to ≤5%, >5% to ≤10%, >10% to ≤15% and >15% predicted at week 52 are shown in Supplementary Figure 4. Over the whole trial, the proportions of subjects with absolute and relative declines in FVC ≥5% predicted or ≥10% predicted were lower in the nintedanib group than in the placebo group (Table 2).

K-BILD questionnaire total score

Adjusted mean absolute changes from baseline in K-BILD total score at week 52 in the nintedanib and placebo groups, respectively, were 2.10 and 1.72 (difference 0.38 [95% CI -2.71, 3.48]; nominal *P*=0.81).

Acute exacerbations, progression of ILD and death

Over the whole trial, acute exacerbation of ILD or death occurred in 10 patients (12.2%) in the nintedanib group and 18 (20.5%) in the placebo group (HR 0.58 [95% CI 0.27, 1.27]; nominal *P*=0.17) (Table 2; Supplementary Figure 5). Acute exacerbations of ILD were reported in 4 patients (4.9%) in the nintedanib group and 8 patients (9.1%) in the placebo group. The proportions of subjects with progression of ILD or death were 40.2% in the nintedanib group and 53.4% in the placebo group (HR 0.72 [95% CI 0.46, 1.13]; nominal *P*=0.15) (Table 2). Deaths occurred in 9.8% of subjects in the nintedanib group and 12.5% in the placebo group (HR 0.80 [95% CI 0.32, 1.98]; nominal *P*=0.62) (Table 2; Supplementary Figure 5).

Safety and tolerability

Over 52 weeks, the most frequent adverse event was diarrhea, reported in 63.4% and of 27.3% of subjects treated with nintedanib and placebo, respectively. Nausea, vomiting, decreased appetite, constipation, abdominal pain and weight decrease were also more frequently reported in the nintedanib group than in the placebo group (Table 3). Adverse events led to permanent discontinuation of trial drug in 17.1% of subjects in the nintedanib group and 10.2% of those who received placebo. The most frequent adverse events leading to permanent discontinuation of nintedanib was diarrhea (Table 3).

Increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were more common in subjects treated with nintedanib than placebo (Table 3). Based on laboratory tests, elevations in ALT and/or AST to ≥3 times the upper limit of the normal range were observed in 12 subjects (14.6%) in the nintedanib group and 1 subject (1.1%) in the placebo group. Liver enzyme levels normalized or showed a trend towards normalization after dose adjustment or discontinuation (or spontaneously). No subjects met criteria for Hy's law.

Adverse events among subjects taking versus not taking DMARDs and/or glucocorticoids at baseline are presented in Supplementary Table 4.

DISCUSSION

These analyses of data from the INBUILD trial support the clinical observation that there is a group of patients with autoimmune disease-related ILDs who develop a progressive fibrosing phenotype with a natural history similar to IPF. In the INBUILD

trial, such patients were identified using inclusion criteria based on worsening fibrosis on HRCT, lung function decline and worsening symptoms, which are similar to the criteria used in clinical practice to identify patients with progressive ILD. Compared with placebo, nintedanib reduced the rate of decline in FVC over 52 weeks in patients with progressive fibrosing autoimmune ILDs by 58%, a similar relative reduction to that observed in the overall population of the INBUILD trial (57%) (21), subjects with SSc-ILD in the SENSCIS trial (44%) (20) and subjects with IPF in the INPULSIS trials (49%) (19). The INBUILD trial was not designed or powered to study patients with individual diseases. However, in subgroup analyses, no heterogeneity was detected in the effect of nintedanib versus placebo among patients with RA-ILD, SSc-ILD, MCTD-ILD, or other fibrosing autoimmune ILDs.

Previous studies suggested that in patients with autoimmune-related ILDs, a UIP-like fibrotic pattern on HRCT is associated with faster decline in lung function than other fibrotic patterns (5, 24-26), although this has not been demonstrated in patients with SSc-ILD. In the overall population of the INBUILD trial, patients with a UIP-like fibrotic pattern on HRCT showed a greater rate of decline in FVC over 52 weeks than patients with other fibrotic patterns on HRCT (8, 21). In patients with progressive autoimmune disease-related ILDs, the rate of decline in FVC over 52 weeks in the placebo group was similar between subjects with a UIP-like pattern and with other fibrotic patterns on HRCT. Although numerical differences were observed, based on statistical testing, no heterogeneity was detected in the effect of nintedanib versus placebo across subgroups by fibrotic pattern on HRCT, either in the overall population (21) or in patients with progressive autoimmune disease-related ILDs. These subgroup analyses should be interpreted with caution given that the INBUILD trial was not powered for these analyses.

Patients who were taking low-dose glucocorticoids or DMARDs to treat their autoimmune disease were allowed to participate in the INBUILD trial. Among patients with autoimmune disease-related ILDs, glucocorticoids (mostly prednisone or prednisolone <20 mg/day) were taken at baseline by 68%, non-biological DMARDs by 36%, and biological DMARDs by 12% of patients. Over half of the overall trial population were taking glucocorticoids at baseline. Previous analyses of data from the overall trial population showed that the effect of nintedanib on reducing the rate of decline in FVC, and its adverse event profile, were consistent between subgroups by use of glucocorticoids at baseline and between patients who did and did not take immunomodulatory medications at baseline or over 52 weeks of the trial (27).

Acute exacerbations in patients with fibrosing autoimmune-related ILDs are rare events but are associated with high mortality (28-30). While the INBUILD trial was not powered to show an effect of nintedanib on this endpoint, over the whole trial, nintedanib was associated with a numerically reduced risk of the composite of acute exacerbation of ILD or death (HR 0.58). In the overall trial population, the HR for this endpoint was 0.67 and statistical significance was reached (p=0.04) (31). Further research is needed into the effect of nintedanib on acute exacerbations of autoimmune-related ILDs.

The adverse events associated with nintedanib in subjects with autoimmune ILDs in the INBUILD trial were consistent with those observed in the overall trial population (21, 31) and in subjects with SSc-ILD (20, 32) and IPF (19, 31). Gastrointestinal adverse events, particularly diarrhea, were the most common adverse events. Elevations in liver enzymes were more common in subjects treated with nintedanib than placebo.

Consistent with observations in the overall trial population (21), there was no meaningful change in health-related quality of life assessed using the K-BILD questionnaire in patients with autoimmune disease-related ILDs in either treatment group. This likely reflects the challenges of measuring changes in health-related quality of life in patients with autoimmune diseases over relatively short time-frames, and the weak association observed between small changes in FVC and changes in quality of life in patients with ILD and moderately impaired FVC at baseline (19, 20, 34).

Strengths of our analyses include the large cohort of patients with autoimmune disease-related ILDs (n=170), the identification of ILD progression based on criteria that may be used in clinical practice, the randomized placebo-controlled trial design, and the robust collection of FVC measurements and data on adverse events throughout the trial. Limitations of our analyses include that the INBUILD trial was not designed or powered to show a benefit of nintedanib in the subgroup of patients with autoimmune disease-related ILDs and the trial protocol excluded patients taking some commonly used immunomodulatory medications. Data were not collected on the medications that patients took prior to being enrolled in the INBUILD trial. The trial was not designed or powered to enable analyses based on individual clinical diagnoses or use of background therapies. In interpreting the subgroup analyses, it is important not to over-interpret the point estimates and confidence intervals for individual subgroups, but rather to look at the interaction *P*-value that assessed whether there was evidence of heterogeneity across subgroups.

In conclusion, data from the INBUILD trial suggest that nintedanib slows the rate of decline in FVC in patients with progressive fibrosing ILDs, including autoimmune disease-related ILDs, with adverse events that can be tolerated by most patients.

Rheumatologists need to be aware of risk factors for ILD, incorporate judicious assessment strategies that can aid in identifying patients with ILD, monitor for progression of ILD, and formulate an appropriate treatment plan for patients with ILD in co-operation with colleagues in pulmonology and other relevant providers.

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AUTHOR CONTRIBUTIONS

KRF, RSH, SSt, JRS and PFD were involved in the conceptualization or design of the study. AJ was involved in data analysis. All authors were involved in interpretation of the data and the writing and critical review of the manuscript and all approved the final version.

ROLE OF THE STUDY SPONSOR

The sponsor participated in the study design, data collection, statistical analyses, data interpretation, and the writing of the report. The corresponding author had full access to all the data presented in this manuscript and had final responsibility for the decision to submit for publication. Data are available upon reasonable request (see Supplementary Files).

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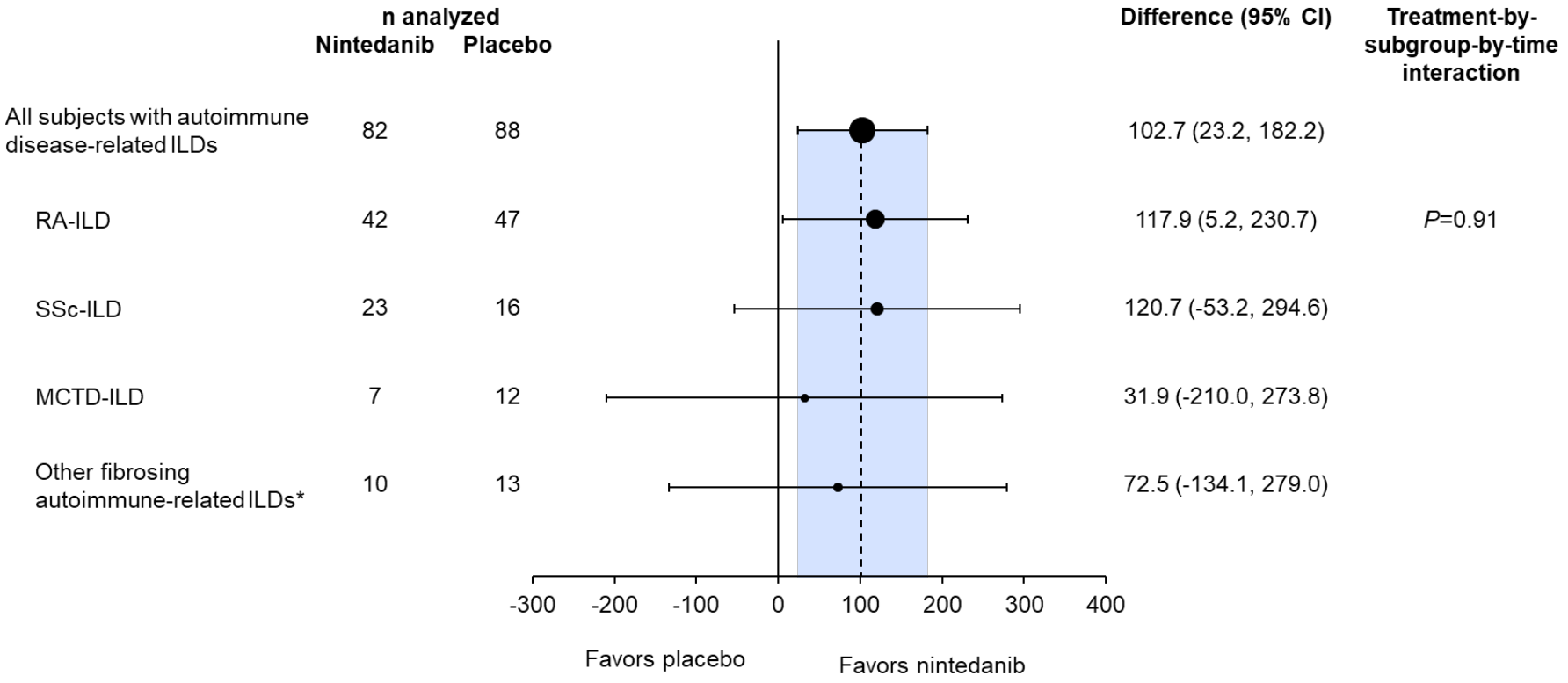
Figure 1. Rate of decline in FVC (mL/year) over 52 weeks in subjects with autoimmune disease-related ILDs treated with nintedanib versus placebo in the INBUILD trial. FVC, forced vital capacity; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SSc, systemic sclerosis.



*Subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form.

Figure 2. Rate of decline in FVC (mL/year) over 52 weeks in subjects with autoimmune disease-related ILDs treated with nintedanib versus placebo in the INBUILD trial by fibrotic pattern on HRCT. FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; UIP, usual interstitial pneumonia.

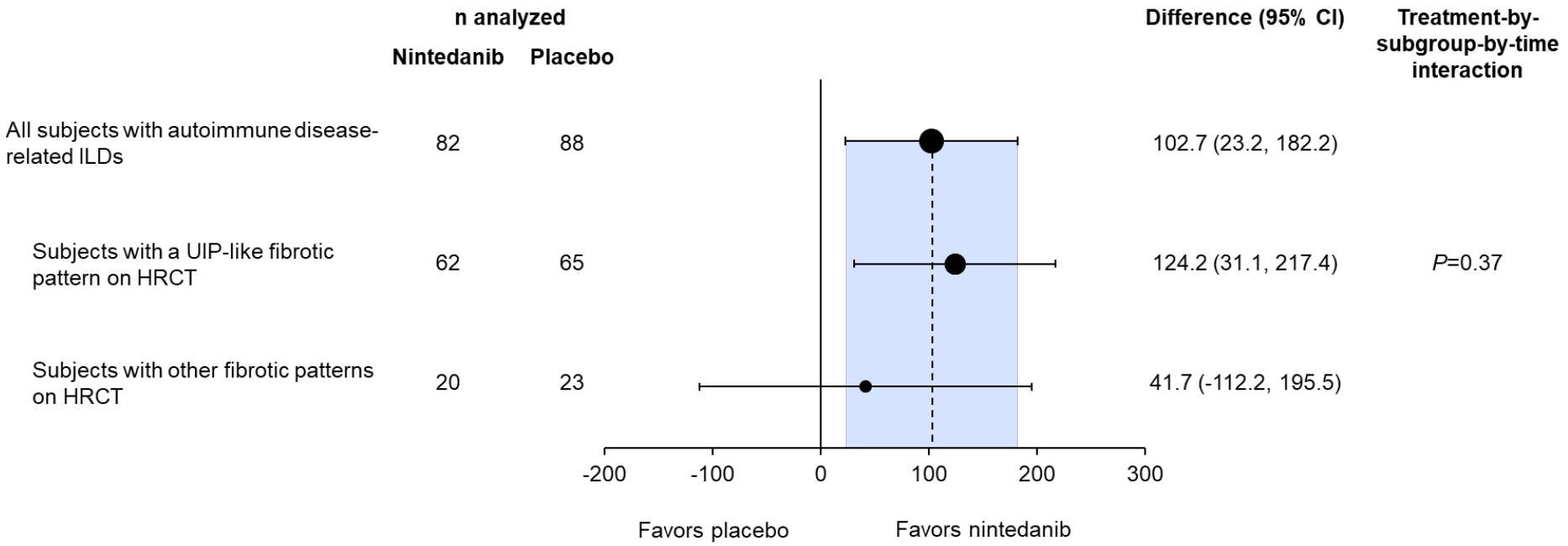
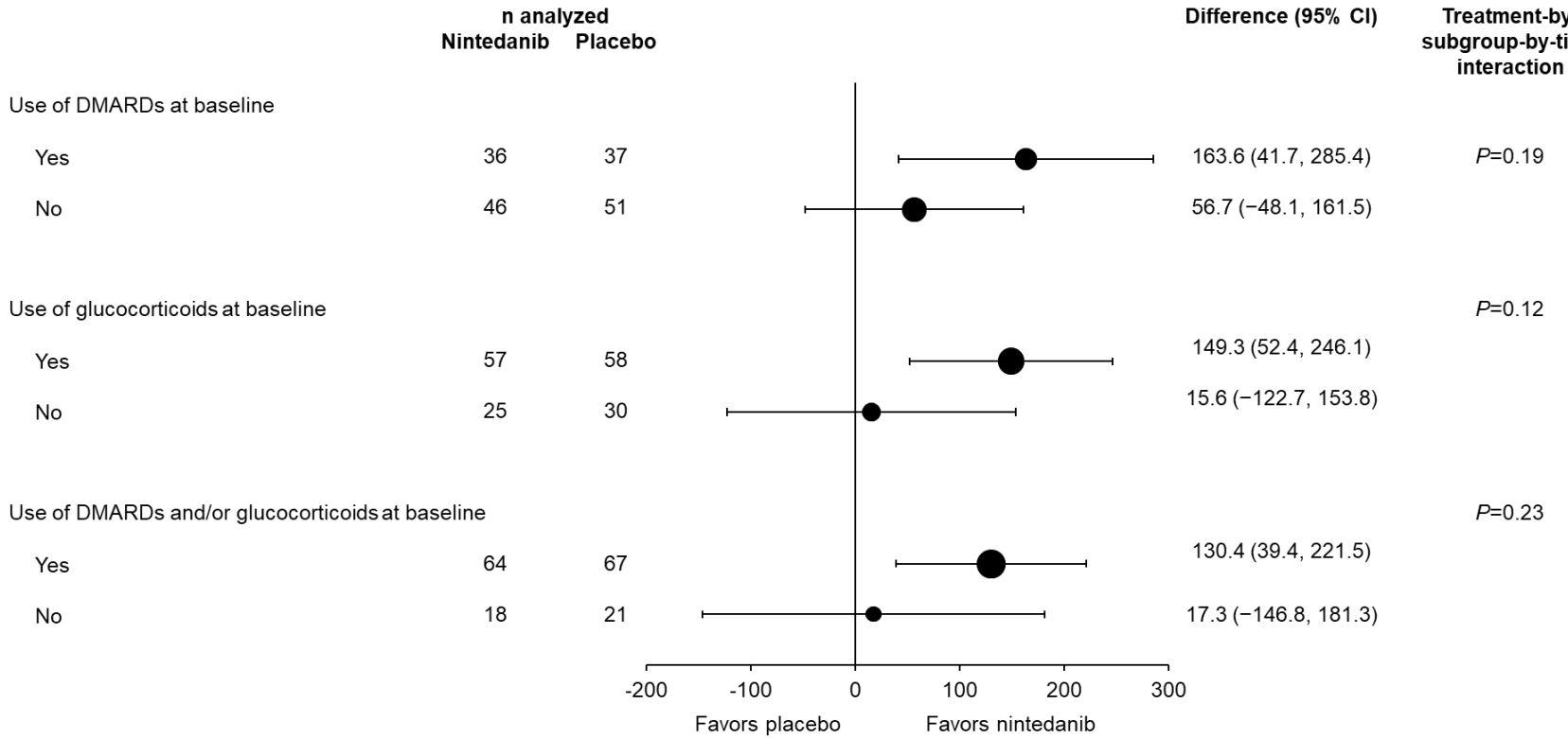


Figure 3. Rate of decline in FVC (mL/year) over 52 weeks in subjects with autoimmune disease-related ILDs treated with nintedanib versus placebo in the INBUILD trial in subgroups by use of DMARDs and/or glucocorticoids at baseline. DMARDs, disease-modifying anti-rheumatic drugs; FVC, forced vital capacity; ILD, interstitial lung disease.



DMARDs and glucocorticoids were coded according to WHO Drug Dictionary version 19.MAR. DMARDs and glucocorticoids were based on standardised drug groupings. DMARDs included baricitinib and excluded denosumab. Glucocorticoids were restricted to oral, IV, IV bolus, IV drip or intramuscular administration.

Table 1. Baseline characteristics of subjects with autoimmune disease-related interstitial lung diseases in the INBUILD trial

	Nintedanib (n=82)	**Placebo (n=88)**
Female, n (%)	47 (57.3)	43 (48.9)
Age, years, mean (SD)	63.3 (10.0)	65.1 (11.1)
Body mass index, kg/m^2, mean (SD)	26.7 (5.2)	28.0 (4.9)
Current or former smoker, n (%)	40 (48.8)	45 (51.1)
Race, n (%)		
White	53 (64.6)	62 (70.5)
Asian	25 (30.5)	25 (28.4)
Black/African-American	3 (3.7)	1 (1.1)
American Indian/Alaska Native/Native Hawaiian/other Pacific Islander	1 (1.2)	0
Criteria for ILD progression within 24 months before screening		
Relative decline in FVC ≥10% predicted	43 (52.4)	42 (47.7)

Relative decline in FVC ≥5–<10% predicted plus worsened respiratory symptoms and/or increased extent of fibrosis on HRCT	26 (31.7)	31 (35.2)
Worsened respiratory symptoms and increased extent of fibrosis on HRCT only	13 (15.9)	15 (17.0)
ILD diagnosis		
Rheumatoid arthritis-associated ILD	42 (51.2)	47 (53.4)
Systemic sclerosis-associated ILD	23 (28.0)	16 (18.2)
MCTD-associated ILD	7 (8.5)	12 (13.6)
Other autoimmune ILDs*	10 (12.2)	13 (14.8)
Years since diagnosis of ILD based on imaging, mean (SD)	4.6 (4.4)	4.0 (3.9)
UIP-like fibrotic pattern on HRCT, n (%)†	62 (75.6)	65 (73.9)
FVC, mL, mean (SD)	2291 (722)	2366 (680)
FVC, % predicted, mean (SD)	69.6 (15.1)	72.1 (14.6)
DLco, % predicted, mean (SD)‡	44.9 (13.4)	50.8 (16.0)
K-BILD questionnaire total score§, mean (SD)	51.3 (10.8)	52.6 (9.7)

*Subjects with an autoimmune disease noted in the “Other fibrosing ILDs” category of the case report form. †Two subjects with a non-determined HRCT pattern were randomized and counted as having other fibrotic patterns. ‡Corrected for hemoglobin. §Scores range from 0 to 100, with higher scores representing better health status.

Not all subjects provided data for all variables. DLco, diffusion capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; K-BILD, King’s Brief Interstitial Lung Disease; MCTD, mixed connective tissue disease; UIP, usual interstitial pneumonia.

Table 2. Efficacy endpoints in subjects with autoimmune disease-related ILDs in the INBUILD trial

	Nintedanib (n=82)	**Placebo (n=88)**
Annual rate of decline in FVC (mL/year) over 52 weeks		
Rate of decline in FVC (mL/year) over 52 weeks, adjusted mean (SE)	-75.9 (29.3)	-178.6 (27.5)
Difference (95% CI)	102.7 (23.2, 182.2)	
Nominal *P*-value	0.012	
Changes in FVC (mL and % predicted) at week 52		
Absolute change from baseline in FVC (mL) at week 52, adjusted mean (SE)	-92.7 (29.1)	-185.7 (27.3)
Difference (95% CI)	93.0 (14.1, 172.0)	
Nominal *P*-value	0.021	
Absolute change from baseline in FVC % predicted at week 52, adjusted mean (SE)	-2.7 (0.9)	-6.0 (0.8)
Difference (95% CI)	3.3 (0.9, 5.6)	
Nominal *P*-value	0.0073	
Change in K-BILD questionnaire total score at week 52		

Absolute change from baseline in K-BILD questionnaire total score at week 52, adjusted mean (SE)	2.10 (1.14)	1.72 (1.08)
Difference (95% CI)	0.38 (-2.71, 3.48)	
Nominal *P*-value	0.81	
Time to event endpoints assessed over the whole trial		
Relative decline from baseline in FVC ≥5% predicted, n (%)	60 (73.2)	73 (83.0)
Hazard ratio (95% CI)	0.89 (0.63, 1.26)	
Nominal *P*-value	0.50	
Relative decline from baseline in FVC ≥10% predicted, n (%)	41 (50.0)	55 (62.5)
Hazard ratio (95% CI)	0.85 (0.57, 1.28)	
Nominal *P*-value	0.43	
Absolute decline from baseline in FVC ≥5% predicted, n (%)	52 (63.4)	69 (78.4)
Hazard ratio (95% CI)	0.78 (0.54, 1.12)	
Nominal *P*-value	0.17	
Absolute decline from baseline in FVC ≥10% predicted, n (%)	29 (35.4)	42 (47.7)
Hazard ratio (95% CI)	0.72 (0.45, 1.16)	
Nominal *P*-value	0.17	
Acute exacerbation of ILD or death, n (%)	10 (12.2)	18 (20.5)
Hazard ratio (95% CI)	0.58 (0.27, 1.27)	

Nominal *P*-value	0.17	
Progression of ILD* or death, n (%)	33 (40.2)	47 (53.4)
Hazard ratio (95% CI)	0.72 (0.46, 1.13)	
Nominal *P*-value	0.15	
Death, n (%)	8 (9.8)	11 (12.5)
Hazard ratio (95% CI)	0.80 (0.32, 1.98)	
Nominal *P*-value	0.62	

*Defined as absolute decline from baseline in FVC ≥10% predicted.

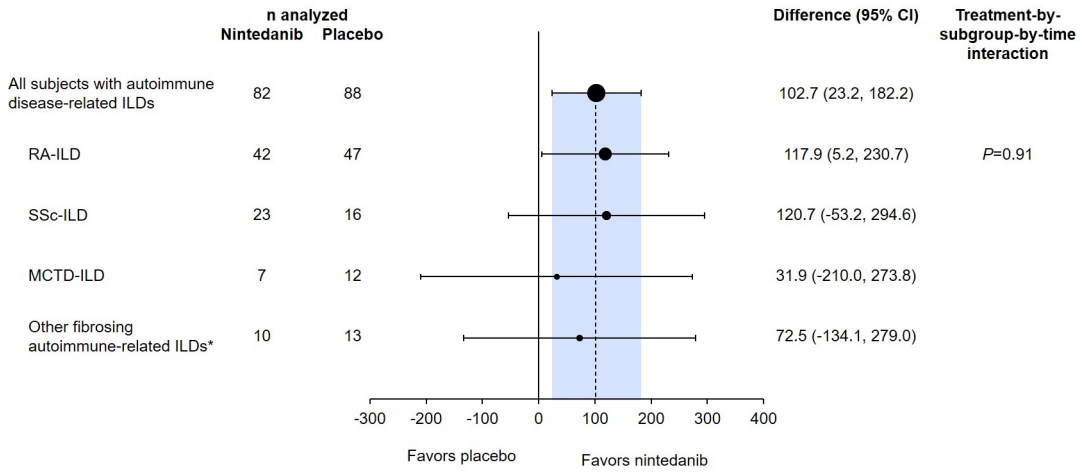
Not all subjects provided data for all variables. FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease.

Table 3. Adverse events in subjects with autoimmune disease-related ILDs in the INBUILD trial

	Nintedanib (n=82)	**Placebo (n=88)**
Any adverse event	79 (96.3)	79 (89.8)
Most frequent adverse events*		
Diarrhea	52 (63.4)	24 (27.3)
Nausea	22 (26.8)	10 (11.4)
Decreased appetite	15 (18.3)	1 (1.1)
Vomiting	14 (17.1)	6 (6.8)
Alanine aminotransferase increased	14 (17.1)	3 (3.4)
Bronchitis	13 (15.9)	13 (14.8)
Aspartate aminotransferase increased	11 (13.4)	4 (4.5)
Nasopharyngitis	10 (12.2)	13 (14.8)
Dyspnea	6 (7.3)	10 (11.4)
Constipation	10 (12.2)	5 (5.7)
Abdominal pain upper	10 (12.2)	2 (2.3)
Weight decreased	10 (12.2)	1 (1.1)
Urinary tract infection	9 (11.0)	2 (2.3)
Severe adverse event†	13 (15.9)	16 (18.2)
Serious adverse event‡	28 (34.1)	28 (31.8)
Fatal adverse event	3 (3.7)	4 (4.5)

Adverse event leading to treatment discontinuation	14 (17.1)	9 (10.2)
Most frequent adverse events leading to treatment discontinuation[§]		
Diarrhea	4 (4.9)	1 (1.1)
Alanine aminotransferase increased	3 (3.7)	0 (0.0)
Aspartate aminotransferase increased	2 (2.4)	0 (0.0)
Dyspnea	0 (0.0)	2 (2.3)

Data are n (%) of subjects with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake for subjects who discontinued trial drug before week 52). *Adverse events reported in >10% of subjects in either treatment group, coded using preferred terms in the Medical Dictionary for Regulatory Activities. [†]Adverse event that was incapacitating or that caused an inability to work or to perform usual activities. [‡]Adverse event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason. [§]Adverse events leading to treatment discontinuation reported in >2% of subjects in either treatment group.



*Subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form.

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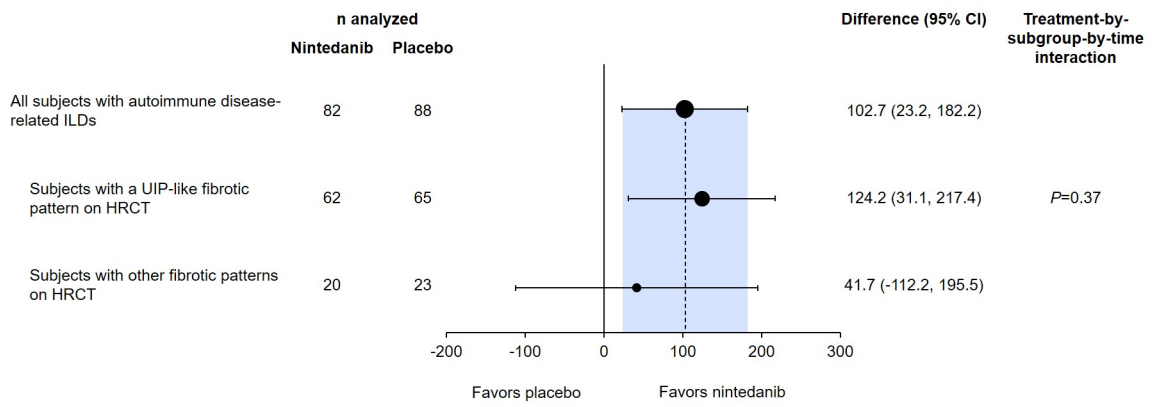

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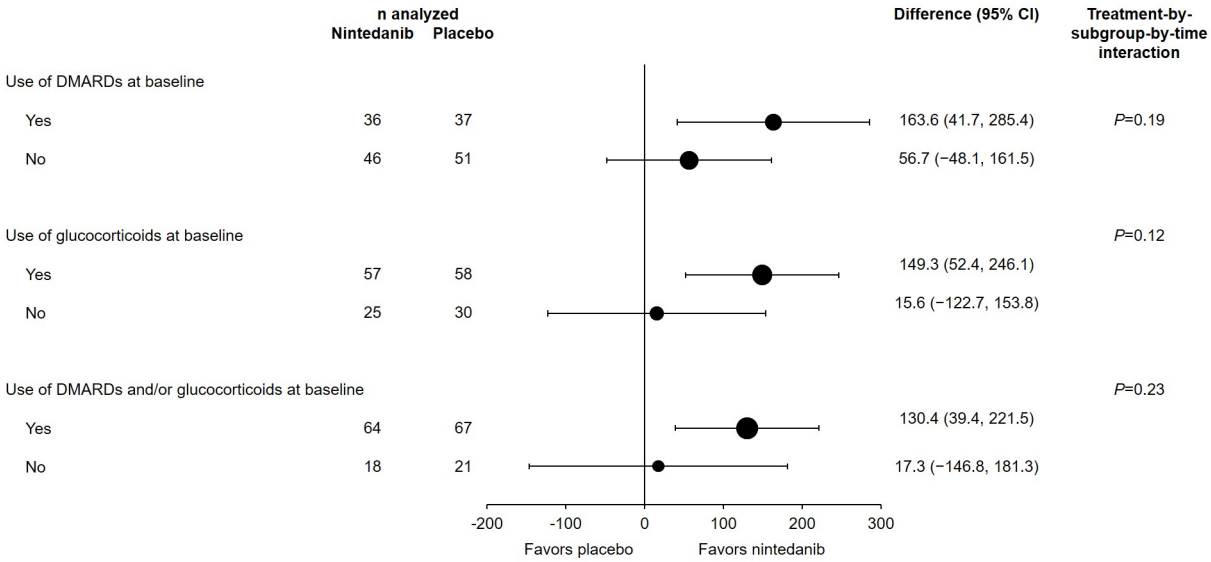

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