The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

# Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

# Antecedentes: Tratamientos de FA

- Antiarritmicos (Amiodarona, Dofetilide):
  - Eficacia en control de Frecuencia
  - Sin influencia en función ventricular, descompensaciones por IC o sobrevivencia
- Ablación:
  - Eficacia de para revertir FA con y sin IC
  - Datos preliminaries de eficacia y mejoria de la función cardiaca:
    - 6-minute walking test,
    - LVEF,
    - quality of life
  - No evidencia solida (ECAs) sobre influencia en mortalidad o progresion de Fallo

# Metodologia: Diseño estudio CASTLE-AF

- Estudio multicentrico, abierto, randomizado
- Pacientes con FA (paroxistica o persistente) y Fallo cardiaco: NYHA class II, III, or IV and LVEF <= 35%
- Comparación:
  - Ablación versus Control Frecuencia o Ritmo: (aleatorizacion 1:1)
- Todos los pacientes tenian un desfibrilador (DAI) o resincronizacion (CRT-D) con capacidades de telemetria, para valorar la recurrencia de arritmia.
- Valorar morbimortalidad

# Metodologia: Tecnica ablacion por cateter

- Descartado trombo orejuela con ETE
- Aislamiento de las todas las venas pulmonares
- Hemodinamistas expertos con al menos 50 procedimientos efectuados
- Sesiones a discrecion
- Anticoagulación postprocedimiento al menos 6 meses.

# Metodologia: Seguimiento y Analisis

- Monitorización domiciliaria ritmo con equipo Biotronic
- Seguimiento regular 3, 6, 12, 24,36, 48, and 60 meses tras tratamiento
- Si recurrencia FA: repetición de Ablación
- Variable principal:
  - compuesto Muerte o ingreso por IC
- Variables secunarias:
  - Muerte por cualquier causa
  - Muerte causa cardiovascular
  - ACV
  - Hospitalizacion por IC
  - Hospitalización por causa cardiovascular
  - Hospitalizacion por cualquier causa
- Analisis por intención de tratar

# Reclutamiento

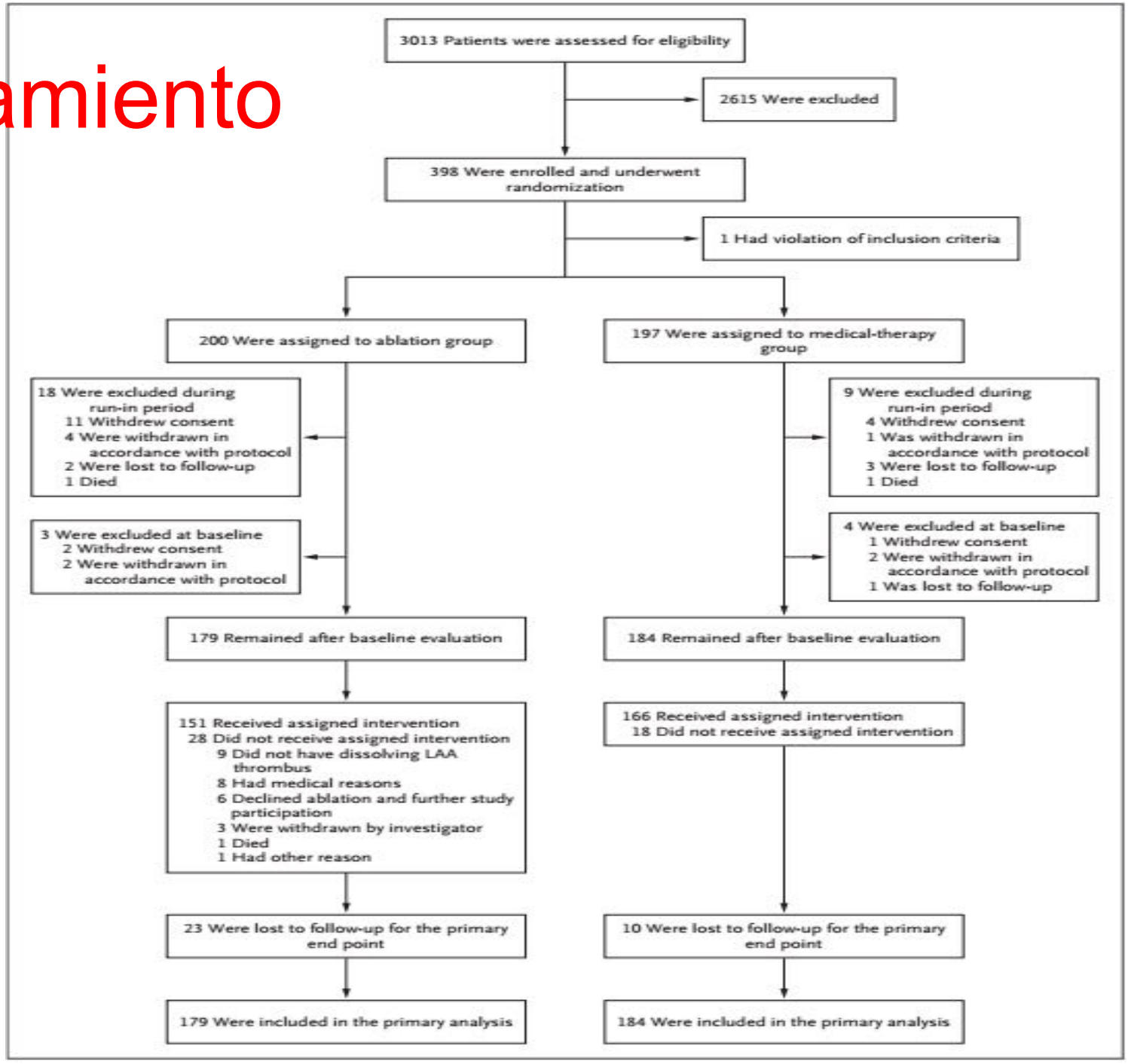


**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Treatment Type | |
|---|---|---|
| | Ablation (N = 179) | Medical Therapy (N = 184) |
| Age — yr | | |
| Median | 64 | 64 |
| Range | 56–71 | 56–73.5 |
| Male sex — no. (%) | 156 (87) | 155 (84) |
| Body-mass index† | | |
| Median | 29.0 | 29.1 |
| Range | 25.9–32.2 | 25.9–32.3 |
| New York Heart Association class — no./total no. (%) | | |
| I | 20/174 (11) | 19/179 (11) |
| II | 101/174 (58) | 109/179 (61) |
| III | 50/174 (29) | 49/179 (27) |
| IV | 3/174 (2) | 2/179 (1) |
| Cause of heart failure — no. (%)‡ | | |
| Ischemic | 72 (40) | 96 (52) |
| Nonischemic | 107 (60) | 88 (48) |
| Type of atrial fibrillation — no. (%) | | |
| Paroxysmal | 54 (30) | 64 (35) |
| Persistent | 125 (70) | 120 (65) |
| Long-standing persistent (duration >1 year) | 51 (28) | 55 (30) |
| Left atrial diameter | | |
| Total no. of patients evaluated | 162 | 172 |
| Median — mm | 48.0 | 49.5 |
| Interquartile range — mm | 45.0–54.0 | 5.0–55.0 |
| Left ventricular ejection fraction | | |
| Total no. of patients evaluated | 164 | 172 |
| Median — % | 32.5 | 31.5 |
| Interquartile range — % | 25.0–38.0 | 27.0–37.0 |
| CRT-D implanted — no. (%)§ | 48 (27) | 52 (28) |
| ICD implanted — no. (%)§ | 131 (73) | 132 (72) |
| Dual-chamber | 128 (72) | 123 (67) |
| Single-lead device with "floating" atrial sensing dipole | 3 (2) | 9 (5) |
| Indication for ICD implantation — no. (%) | | |
| Primary prevention | 160 (89) | 163 (89) |
| Secondary prevention | 19 (11) | 21 (11) |
| History of amiodarone use — no./total no. (%)¶ | | |
| Failure | 78/175 (45) | 82/176 (47) |
| Unacceptable side effects | 21/175 (12) | 24/176 (14) |
| Nonuse | 76/175 (43) | 70/176 (40) |

Edad media 64, clase II y III (87%), Isquemico/No isquémico 40/52%. FA persistente 70%/65% FEVI 32% Resincronizacion 27/28%/DAI 73/72%

# Resultados: comportamiento Ritmo

Ritmo sinusal, segun telemetrias acumuladas, a 60 meses

Ablacion: 63,1%  Tto medico: 21,7% (P<0.001)

Recurrencia de FA en grupo Ablacion , a 60 meses:

75 of 151 patients) 50,0%

(promedio de 1,3+-0,5 procedimientos de ablación)

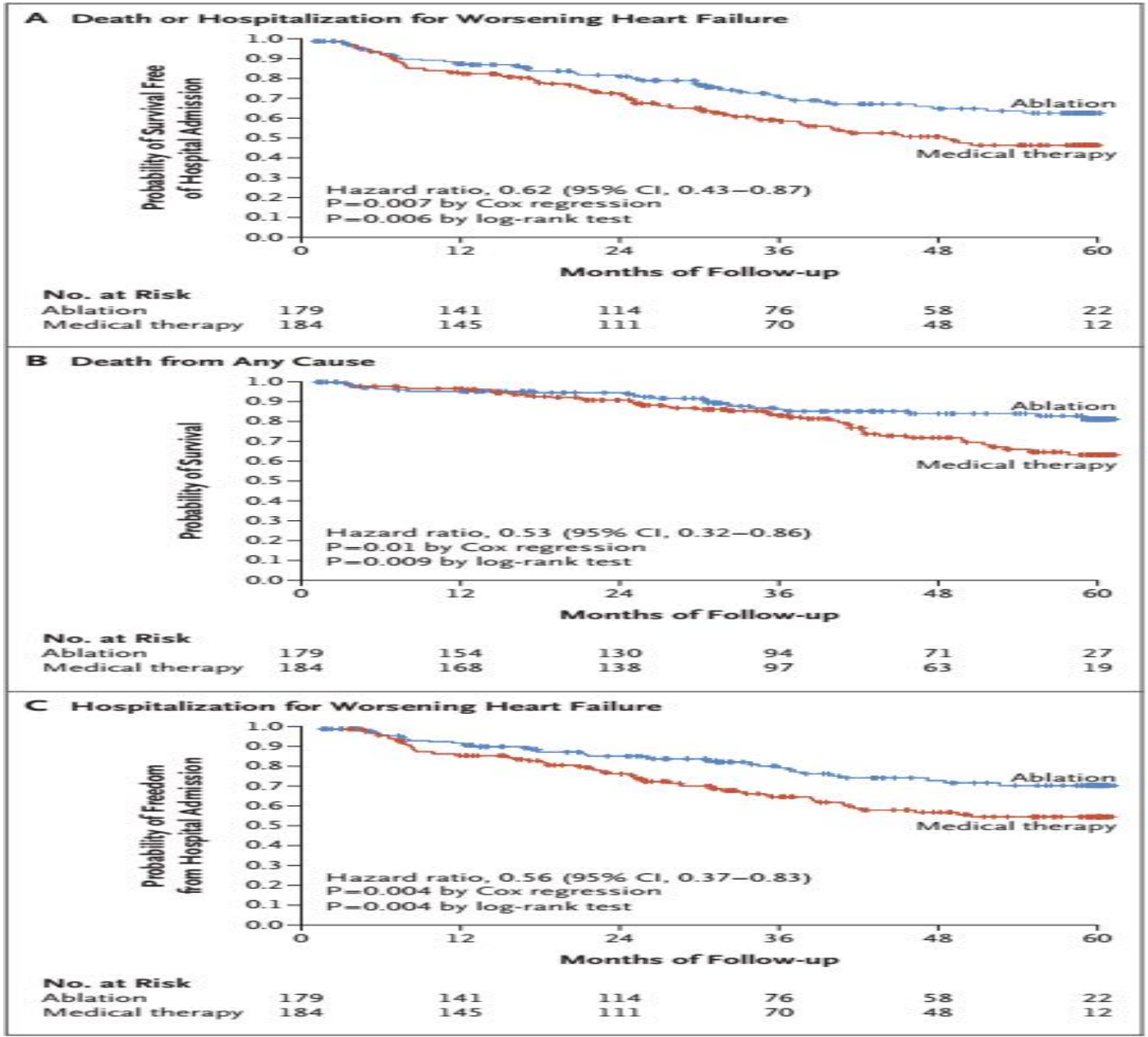
FA permanente 10,1%
Fa paroxistica 7,3%

# Resultados a 60 meses

**Table 2. Primary and Secondary Clinical End Points.***

| End Point | Ablation (N=179) | Medical Therapy (N=184) | Hazard Ratio (95% CI) | P Value | |
|---|---|---|---|---|---|
| | | | | Cox Regression | Log-Rank Test |
| | *number (percent)* | | | | |
| Primary† | 51 (28.5) | 82 (44.6) | 0.62 (0.43–0.87) | 0.007 | 0.006 |
| Secondary | | | | | |
| Death from any cause | 24 (13.4) | 46 (25.0) | 0.53 (0.32–0.86) | 0.01 | 0.009 |
| Heart-failure hospitalization | 37 (20.7) | 66 (35.9) | 0.56 (0.37–0.83) | 0.004 | 0.004 |
| Cardiovascular death | 20 (11.2) | 41 (22.3) | 0.49 (0.29–0.84) | 0.009 | 0.008 |
| Cardiovascular hospitalization | 64 (35.8) | 89 (48.4) | 0.72 (0.52–0.99) | 0.04 | 0.04 |
| Hospitalization for any cause | 114 (63.7) | 122 (66.3) | 0.99 (0.77–1.28) | 0.96 | 0.96 |
| Cerebrovascular accident | 5 (2.8) | 11 (6.0) | 0.46 (0.16–1.33) | 0.15 | 0.14 |

# Resultados a 60 meses



# Otras variables secundarias a 60 meses

## FEVI

FEVI:

Ablación 43,3%

Tto medico 37,1%

FEVI >=35%:

Ablación 68.0%

Tto medico 50.0%

Incremento en FEVI a 60 meses

Ablacion 8.0% (IR, 2.2 to 19.1)

Tto medico 0.2% (IR:-3.0 to 16.1)

(P=0.005).

# Complicaciones Ablacion

- Pericardial effusion: 3 pacientes (1 pericardiocentesis).
- Hemoragia severa con necesidad de transfusión: 3 pacientes
- Pseudoaneurysm femoral: 1 paciente
- Estenosis venas pulmonares, asintomática: 1 paciente

## CONCLUSIONS

Catheter ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening heart failure than was medical therapy. (Funded by Biotronik; CASTLE-AF ClinicalTrials.gov number, NCT00643188.)

## Fortalezas

- Poder discriminativo con variables objetivas y clínicamente relevantes
- Alta adherencia al tratamiento médico
- Monitorizacion continua
- Seguimiento prolongado

## Debilidades

- Muestra pequeña
- Selección de pacientes
- Ausencia de randomizacion
- Pericia hemodinamistas
- Centros de referencia

En la actualidad, es razonable ser mas agresivo en ofrecer Ablacion para FA en pacientes que también tienen ICC

# Recommendation for Catheter Ablation in HF

| COR | LOE | Recommendation |
|---|---|---|
| IIb | B-R | 1. **AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF.**<br>**NEW**: New evidence, including data on improved mortality rate, have been published for AF catheter ablation compared with medical therapy in patients with HF. |

ORIGINAL ARTICLE

# Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

## BACKGROUND

Preclinical data have suggested that nintedanib, an intracellular inhibitor of tyrosine kinases, inhibits processes involved in the progression of lung fibrosis. Although the efficacy of nintedanib has been shown in idiopathic pulmonary fibrosis, its efficacy across a broad range of fibrosing lung diseases is unknown.

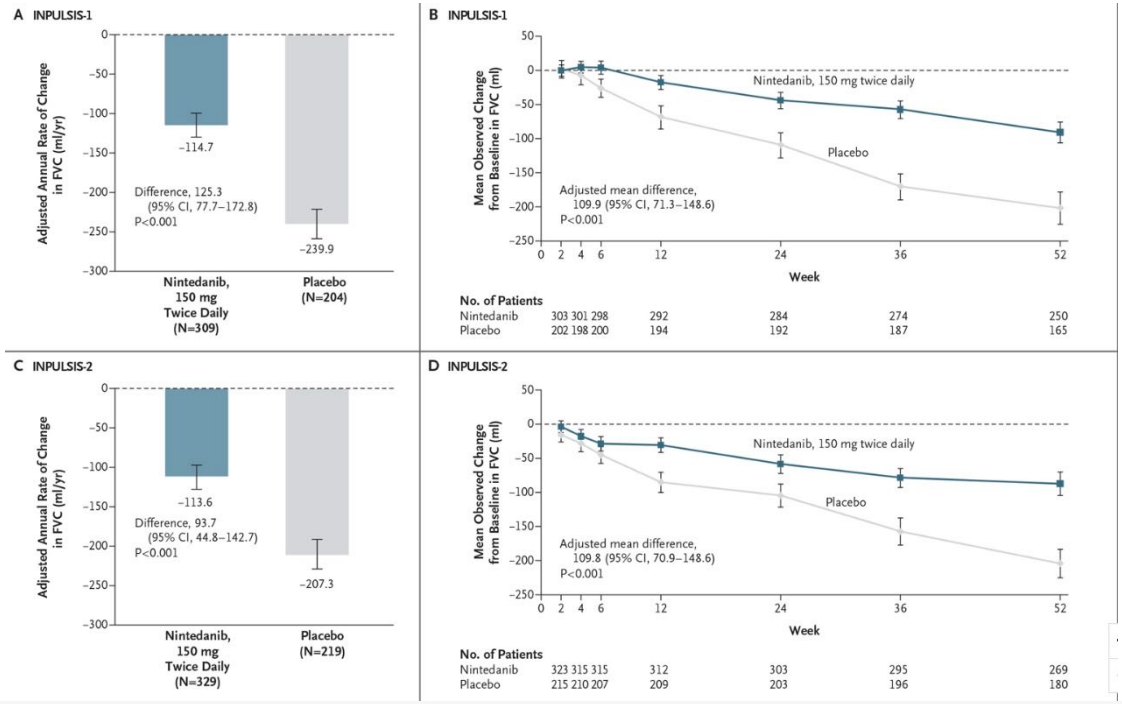



**Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.**

N Engl J Med 2014; 370:2071-2082
DOI: 10.1056/NEJMoa1402584

# METHODS

## TRIAL DESIGN AND OVERSIGHT

The INBUILD trial was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 153 sites in 15 countries.[3] The trial was carried out in compliance with the protocol (avail-

had already been studied, specific efforts were made to enroll patients with a progressive fibrotic phenotype other than IPF. Enrolled patients had

were analyzed by the sponsor, Boehringer Ingelheim. The authors assume responsibility for the

# METODS

Criterios

- Enfermedad progresiva en 24 meses previos
- CVF >45% valor teórico
- DLCO 30-80% teórico
- Descenso relativo  CVF 10%
- Descenso relativo CVF 5-10 y síntomas respiratorios
- Empeoramiento síntomas
- Aumento fibrosis en TACAR

N=600 and 400 UIP for power 90% between group difference of 100 ml/year

**Table S2: Clinical ILD diagnoses (grouped) in the overall population**

| | Nintedanib (n=332) | Placebo (n=331) |
|---|---|---|
| Hypersensitivity pneumonitis | 84 (25.3) | 89 (26.9) |
| Autoimmune ILDs | 82 (24.7) | 88 (26.6) |
| Rheumatoid arthritis-associated ILD | 42 (12.7) | 47 (14.2) |
| Systemic sclerosis-associated ILD | 23 (6.9) | 16 (4.8) |
| Mixed connective tissue disease-associated ILD | 7 (2.1) | 12 (3.6) |
| Other autoimmune ILDs | 10 (3.0) | 13 (3.9) |
| Idiopathic non-specific interstitial pneumonia | 64 (19.3) | 61 (18.4) |
| Unclassifiable idiopathic interstitial pneumonia | 64 (19.3) | 50 (15.1) |
| Other ILDs* | 38 (11.4) | 43 (13.0) |

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

trial population so that two thirds of the patients had a UIP-like fibrotic pattern (as identified ac-

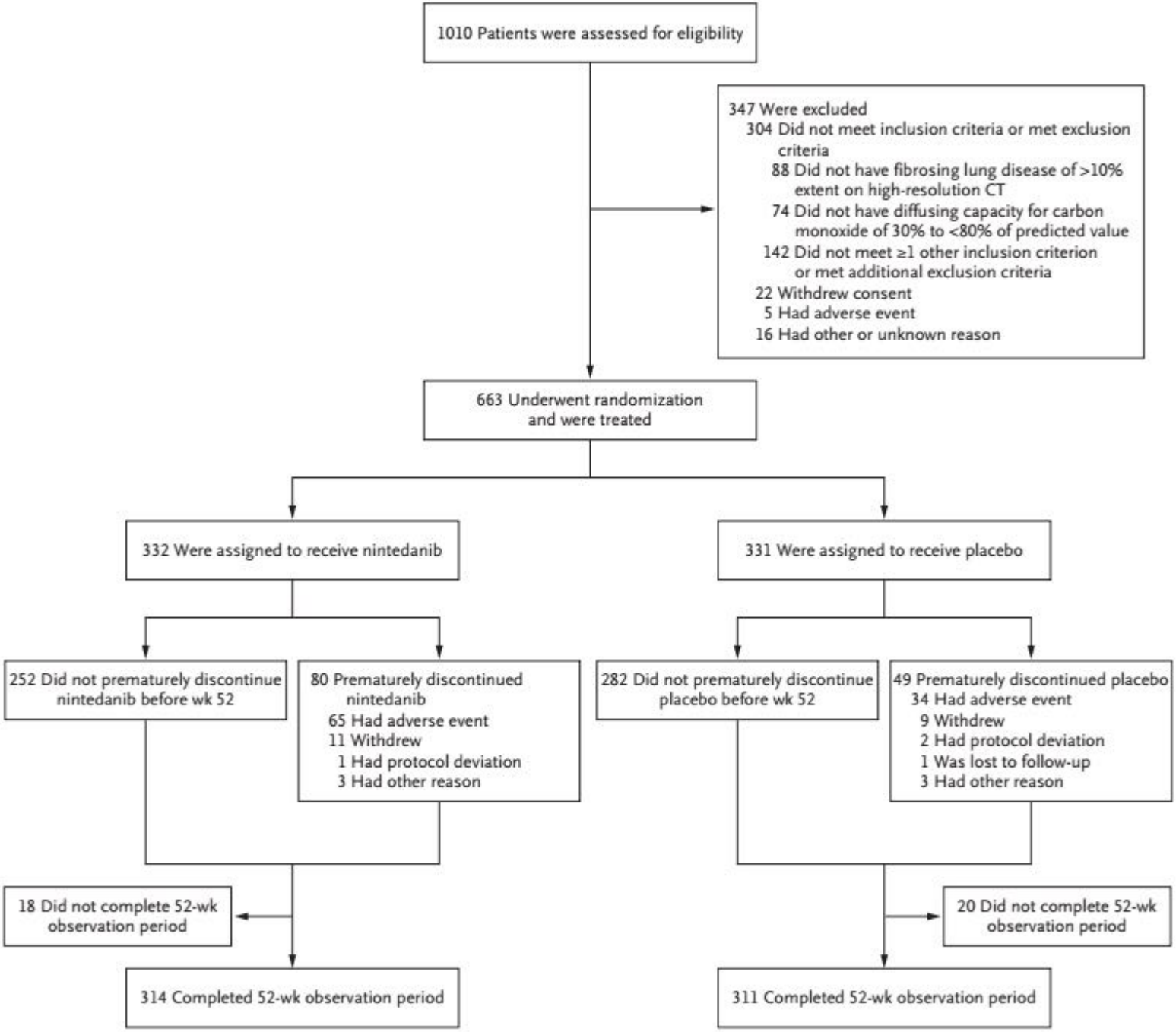

1010 Patients were assessed for eligibility
347 Were excluded
304 Did not meet inclusion criteria or met exclusion criteria
88 Did not have fibrosing lung disease of >10% extent on high-resolution CT
74 Did not have diffusing capacity for carbon monoxide of 30% to <80% of predicted value
142 Did not meet ≥1 other inclusion criterion or met additional exclusion criteria
22 Withdrew consent
5 Had adverse event
16 Had other or unknown reason
663 Underwent randomization and were treated
332 Were assigned to receive nintedanib
331 Were assigned to receive placebo
252 Did not prematurely discontinue nintedanib before wk 52
80 Prematurely discontinued nintedanib
65 Had adverse event
11 Withdrew
1 Had protocol deviation
3 Had other reason
282 Did not prematurely discontinue placebo before wk 52
49 Prematurely discontinued placebo
34 Had adverse event
9 Withdrew
2 Had protocol deviation
1 Was lost to follow-up
3 Had other reason
18 Did not complete 52-wk observation period
20 Did not complete 52-wk observation period
314 Completed 52-wk observation period
311 Completed 52-wk observation period

**Table 1. Characteristics of the Overall Population at Baseline.***

| Characteristic | Nintedanib (N=332) | Placebo (N=331) |
|---|---|---|
| Male sex — no. (%) | 179 (53.9) | 177 (53.5) |
| Age — yr | 65.2±9.7 | 66.3±9.8 |
| Former or current smoker — no. (%) | 169 (50.9) | 169 (51.1) |
| UIP-like fibrotic pattern on high-resolution CT — no. (%) | 206 (62.0) | 206 (62.2) |
| Criteria for disease progression in previous 24 mo — no. (%) | | |
| Relative decline in FVC of ≥10% of predicted value | 160 (48.2) | 172 (52.0) |
| Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT | 110 (33.1) | 97 (29.3) |
| Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT | 62 (18.7) | 61 (18.4) |
| FVC | | |
| Mean value — ml | 2340±740 | 2321±728 |
| Percent of predicted value | 68.7±16.0 | 69.3±15.2 |
| Diffusing capacity for carbon monoxide† | | |
| Mean value — mmol/min/kPa | 3.5±1.2 | 3.7±1.3 |
| Percent of predicted value | 44.4±11.9 | 47.9±15.0 |
| Total score on K-BILD questionnaire‡ | 52.5±11.0 | 52.3±9.8 |

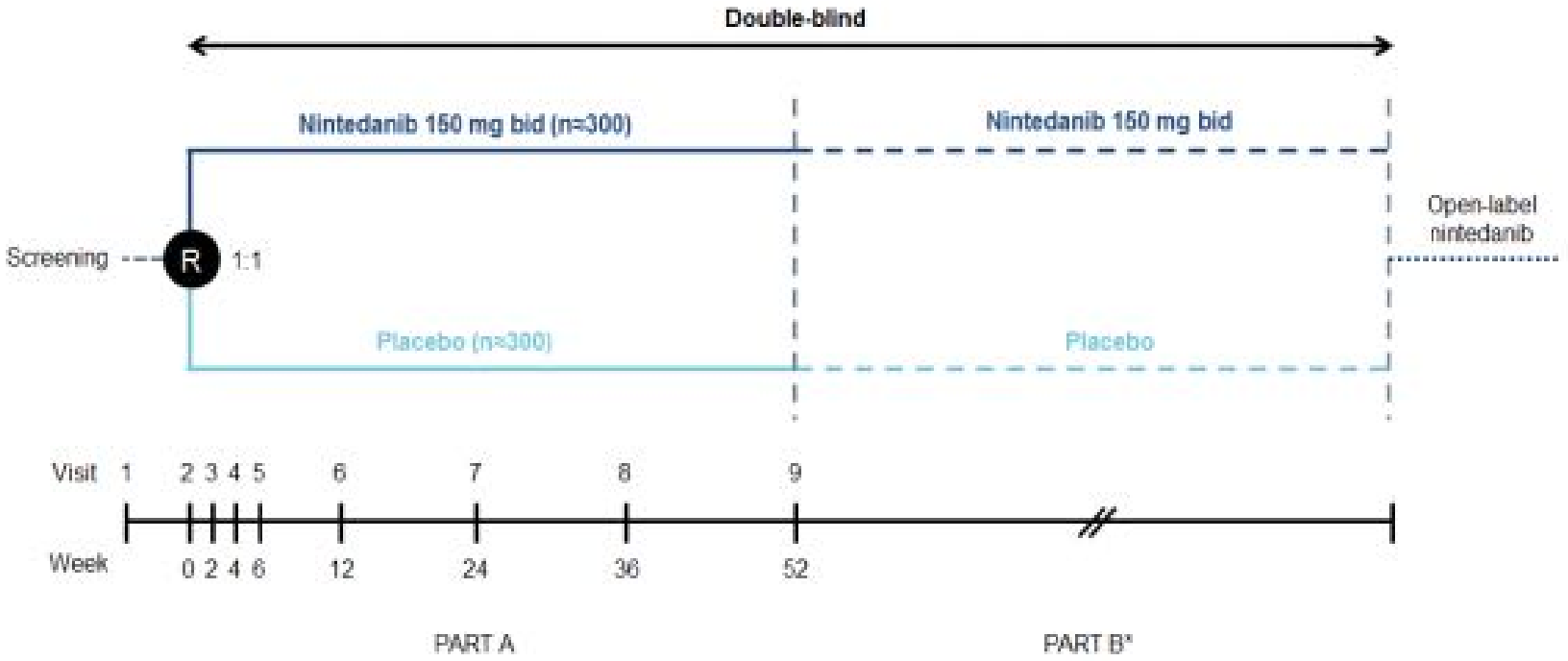
Edad 65 años, 53% varones, UIP 62%, FVC 69%, DLCO 45%

| | Patients with a UIP-like fibrotic pattern on HRCT | | Patients with other fibrotic patterns on HRCT | |
|---|---|---|---|---|
| | Nintedanib (n=206) | Placebo (n=206) | Nintedanib (n=126) | Placebo (n=125) |
| Male – no. (%) | 120 (58.3) | 127 (61.7) | 59 (46.8) | 50 (40.0) |
| Age – yr | 67.5±8.1 | 68.5±8.7 | 61.6±10.9 | 62.6±10.4 |
| Former or current smoker – no. (%) | 118 (57.3) | 118 (57.3) | 51 (40.5) | 51 (40.8) |
| Criteria for ILD progression in 24 months before screening (grouped) – no. (%) | | | | |
| Relative decline in FVC ≥10% predicted | 100 (48.5) | 98 (47.6) | 60 (47.6) | 74 (59.2) |
| Relative decline in FVC ≥5–<10% predicted combined with worsening of respiratory symptoms and/or increased extent of fibrotic changes on HRCT | 76 (36.9) | 68 (33.0) | 34 (27.0) | 29 (23.2) |
| Worsened respiratory symptoms and increased extent of fibrotic changes on HRCT only | 30 (14.6) | 39 (18.9) | 32 (25.4) | 22 (17.6) |
| Clinical ILD diagnosis (grouped) – no. (%) | | | | |
| Hypersensitivity pneumonitis | 44 (21.4) | 46 (22.3) | 40 (31.7) | 43 (34.4) |
| Autoimmune ILDs | 62 (30.1) | 65 (31.6) | 20 (15.9) | 23 (18.4) |
| Rheumatoid arthritis-associated ILD | 36 (17.5) | 41 (19.9) | 6 (4.8) | 6 (4.8) |

# METODS

Patients were randomly assigned in a 1:1 ratio to receive oral nintedanib (at a dose of 150 mg twice daily) or placebo with the use of interac-

**Figure S1A: Overall trial design**




R, randomization.
*Visits to occur every 16 weeks until end of treatment.

For each patient, the trial consisted of two parts: Part A, which was conducted during the first 52 weeks, and Part B, which was a variable treatment period beyond week 52 during which

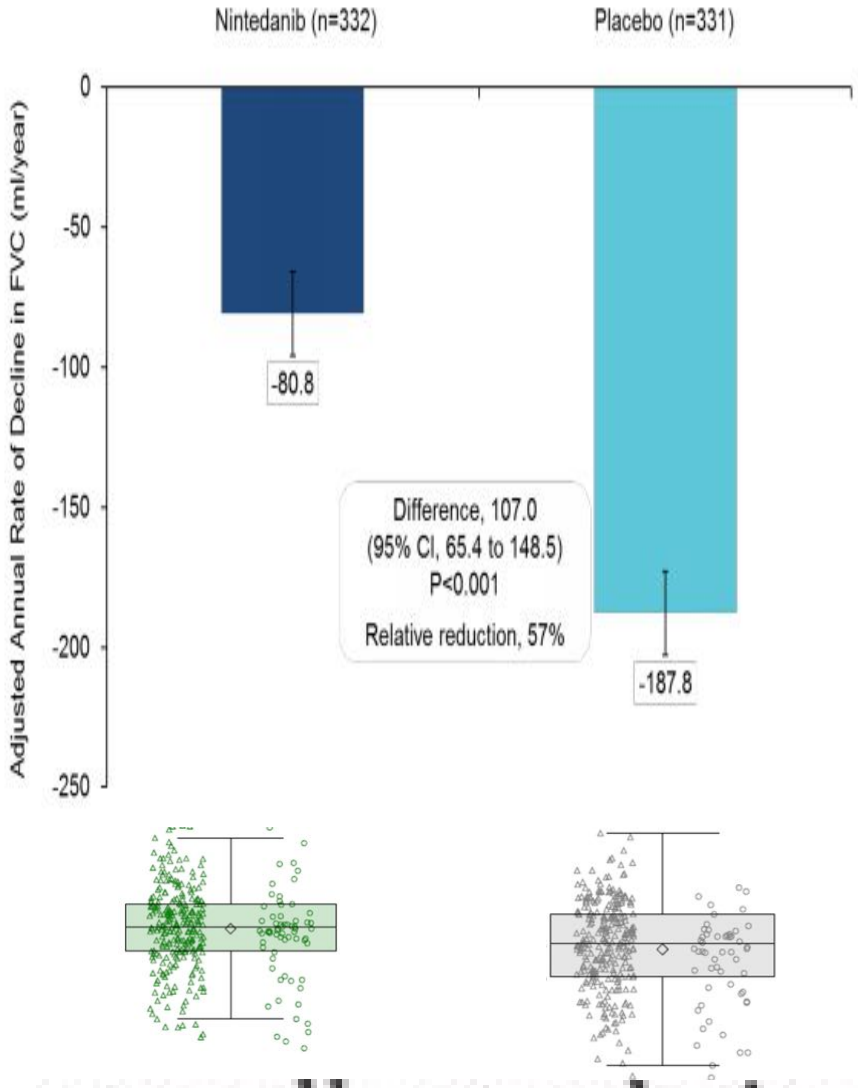
# END POINTS

Primary end point: annual decline FVC

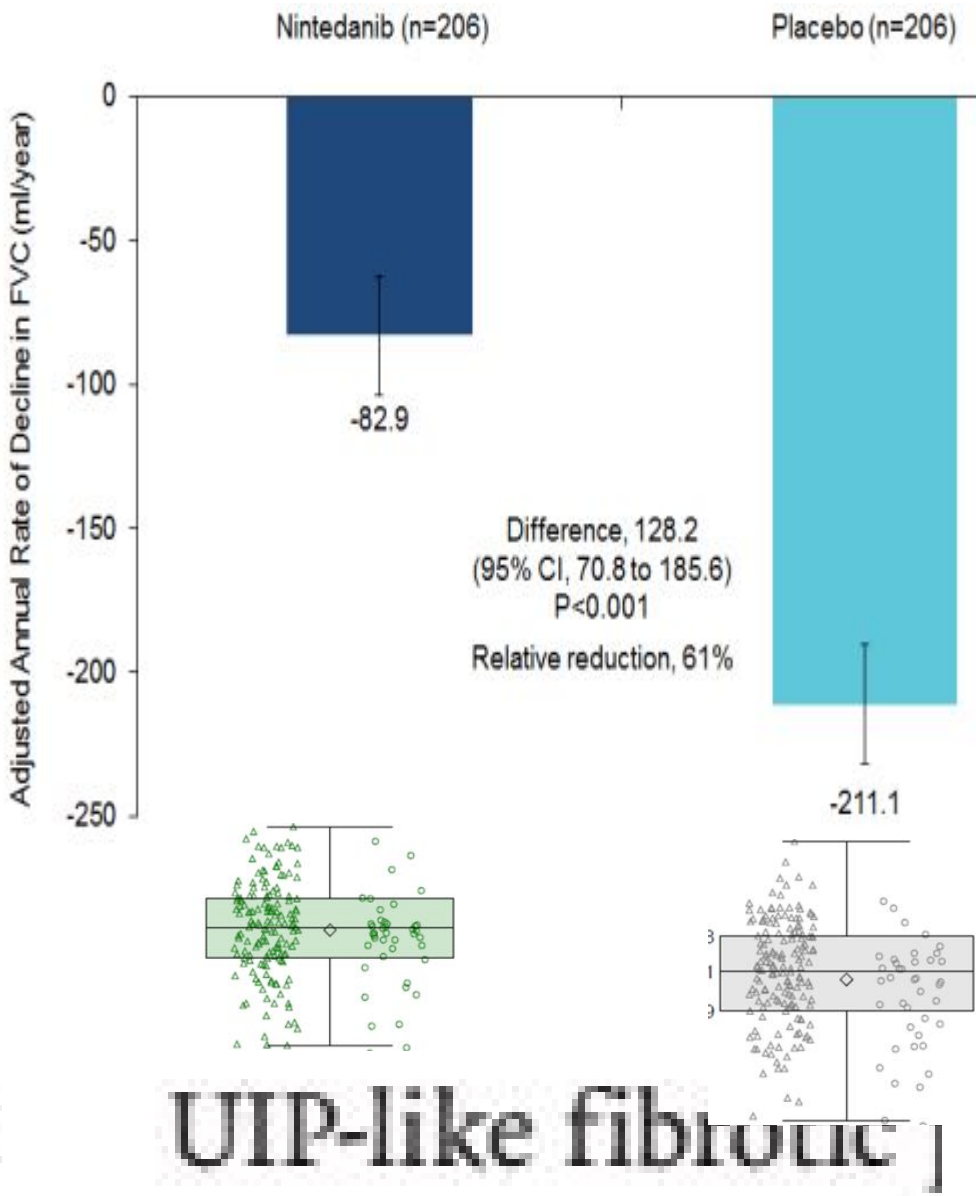
Secondary end point: K-BILD* symptomatic questionnaire at week 52 (0-100 points. 4-8 points represent meaningful change)

Completed treatment at 52 weeks:
75,9% nintedanib group
85,9 placebo group

## RESULTS



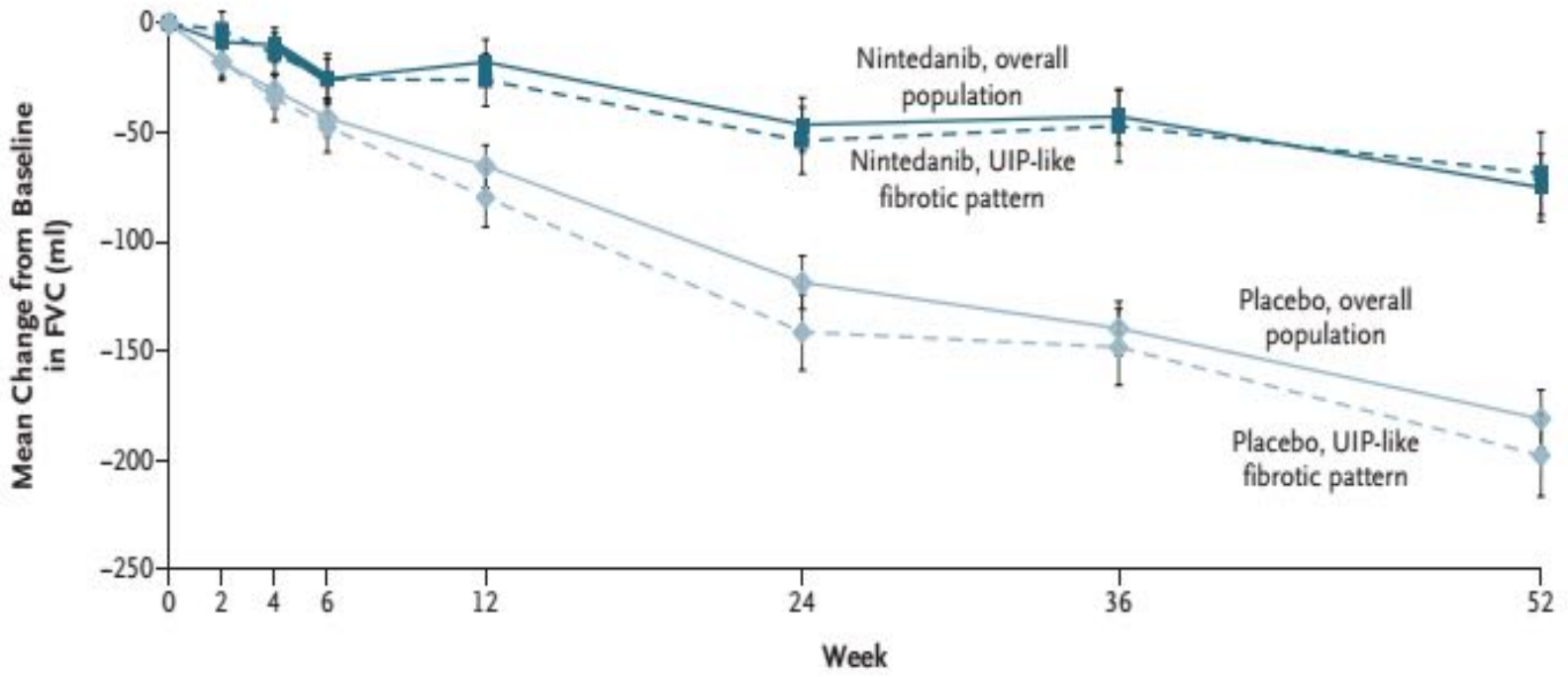

## PRIMARY AND OTHER FVC END POINTS




overall population,

UIP-like fibrotic

tures. The patients who received nintedanib had a slower progression of interstitial lung disease than those who received placebo, as shown by a

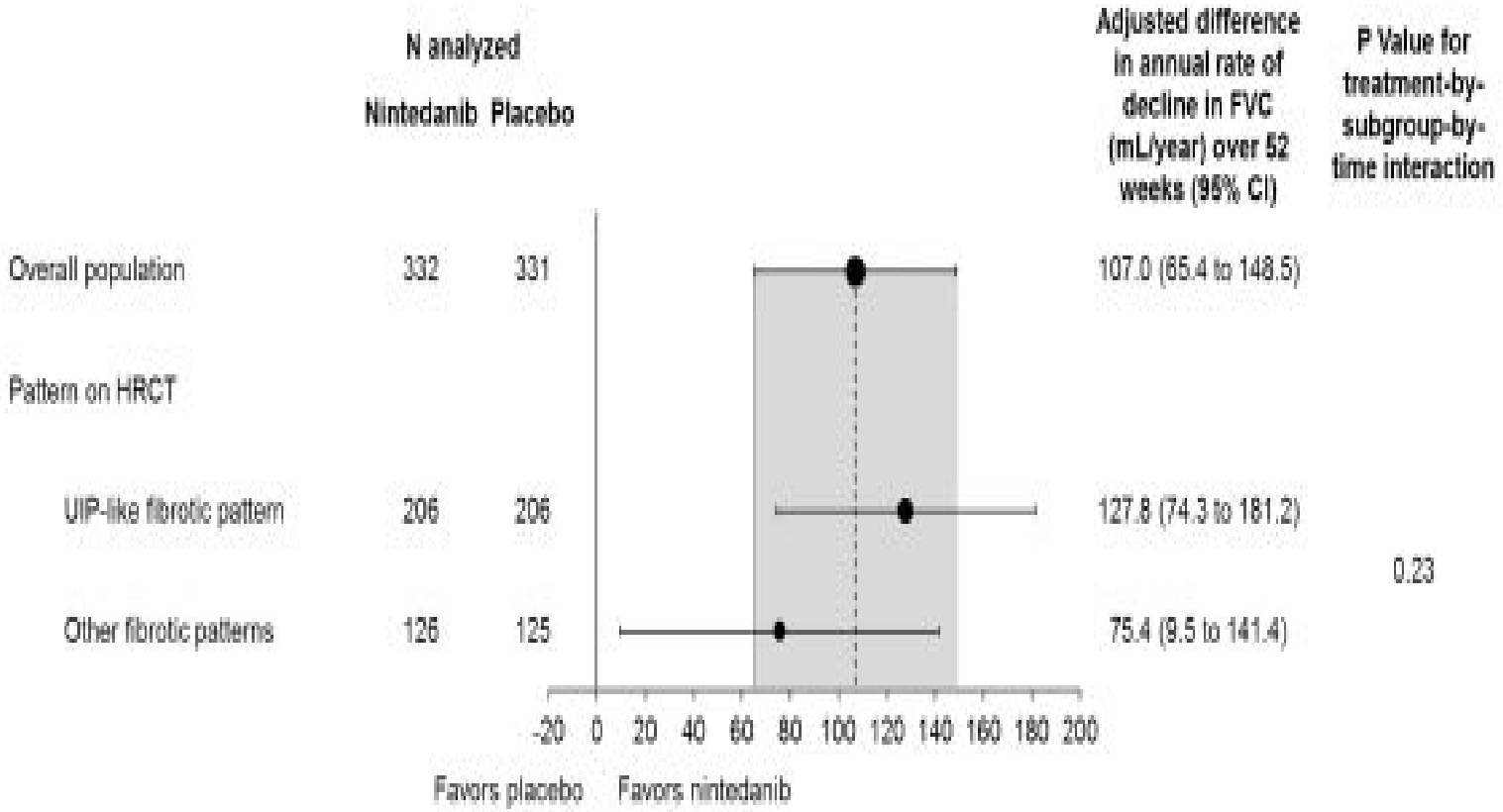



**No. of Patients**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Overall population | | | | | | | | |
| Nintedanib | 332 | 326 | 320 | 322 | 314 | 298 | 285 | 265 |
| Placebo | 331 | 325 | 326 | 325 | 320 | 311 | 296 | 274 |
| Patients with UIP-like fibrotic pattern | | | | | | | | |
| Nintedanib | 206 | 203 | 200 | 199 | 193 | 180 | 171 | 160 |
| Placebo | 206 | 202 | 202 | 201 | 197 | 190 | 176 | 162 |

**Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).**

# Figure S7. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in subgroups by HRCT pattern



RESULTS

MAIN SECONDARY END POINTS

overall population,

UIP-like fibrotic

score on the K-BILD

+0,55 nintedanib versus -0,79 placebo

+0,78 nintedanib versus -0,78 placebo

Died or acute exacerbation

7,85 nintedanib versus 9,75 placebo

8,3% nintedanib versus 12,1% placebo

Died

4,8% nintedanib versus 5,1% placebo

5,3% nintedanib versus 7,81% placebo

Figure S8: Kaplan-Meier estimate of time to first acute exacerbation of ILD or death in the overall population using data up to first database lock

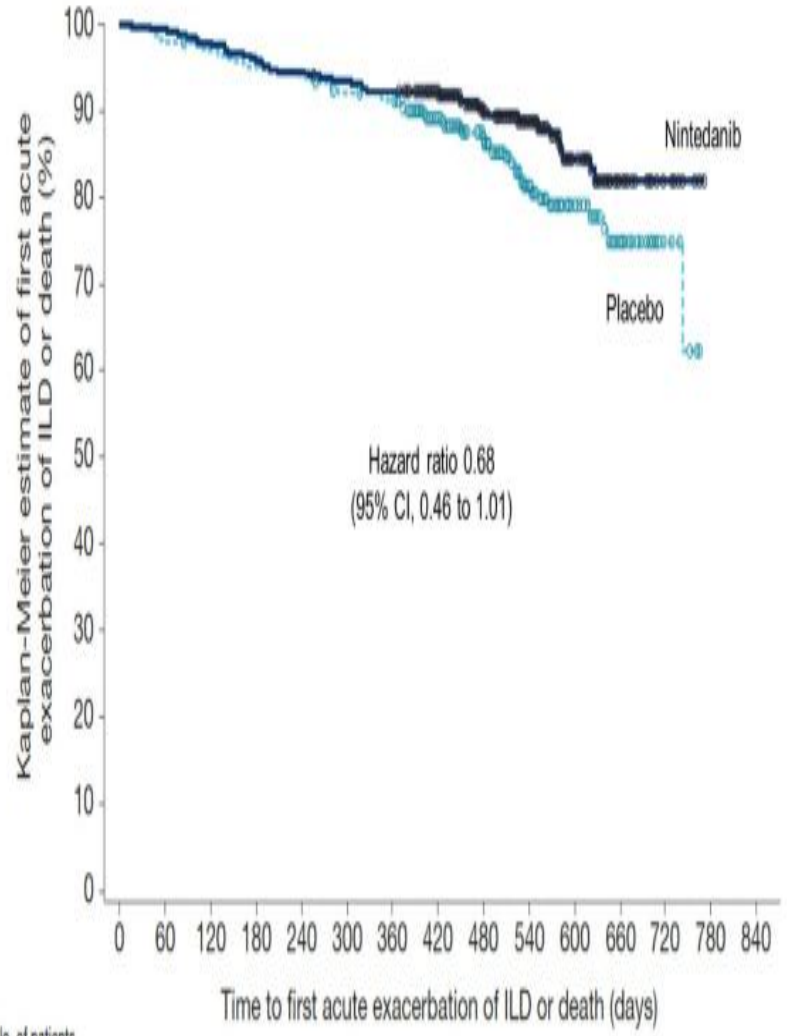



Figure S9: Kaplan-Meier estimate of time to first acute exacerbation of ILD or death in patients with a UIP-like fibrotic pattern on HRCT using data up to first database lock

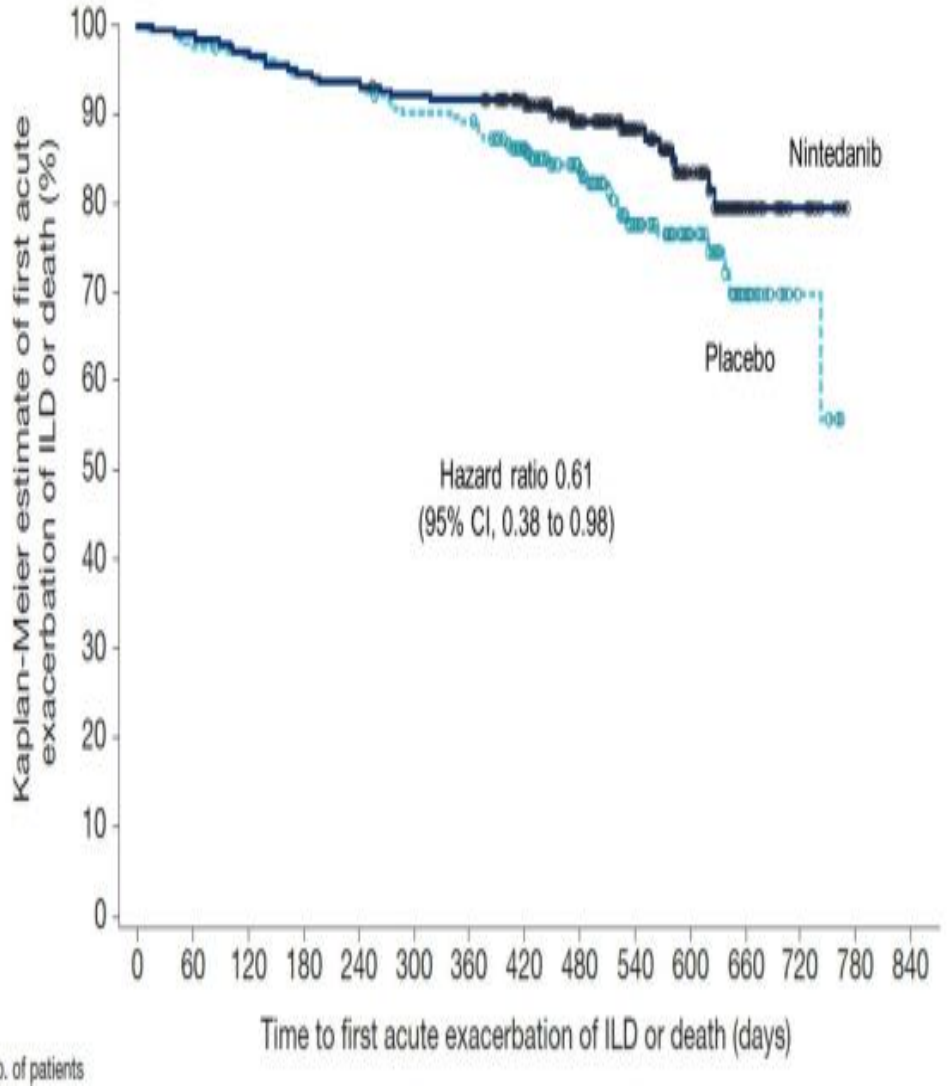


Figure S10: Kaplan-Meier estimate of time to death in the overall population using data up to first database lock

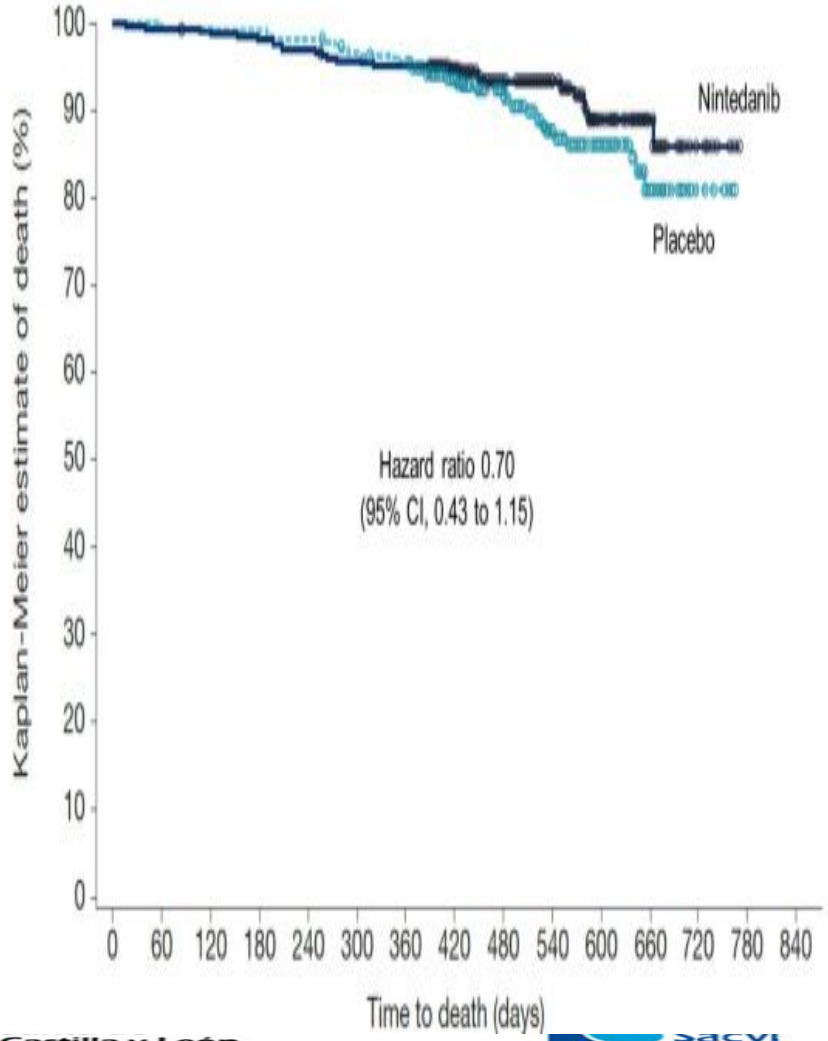
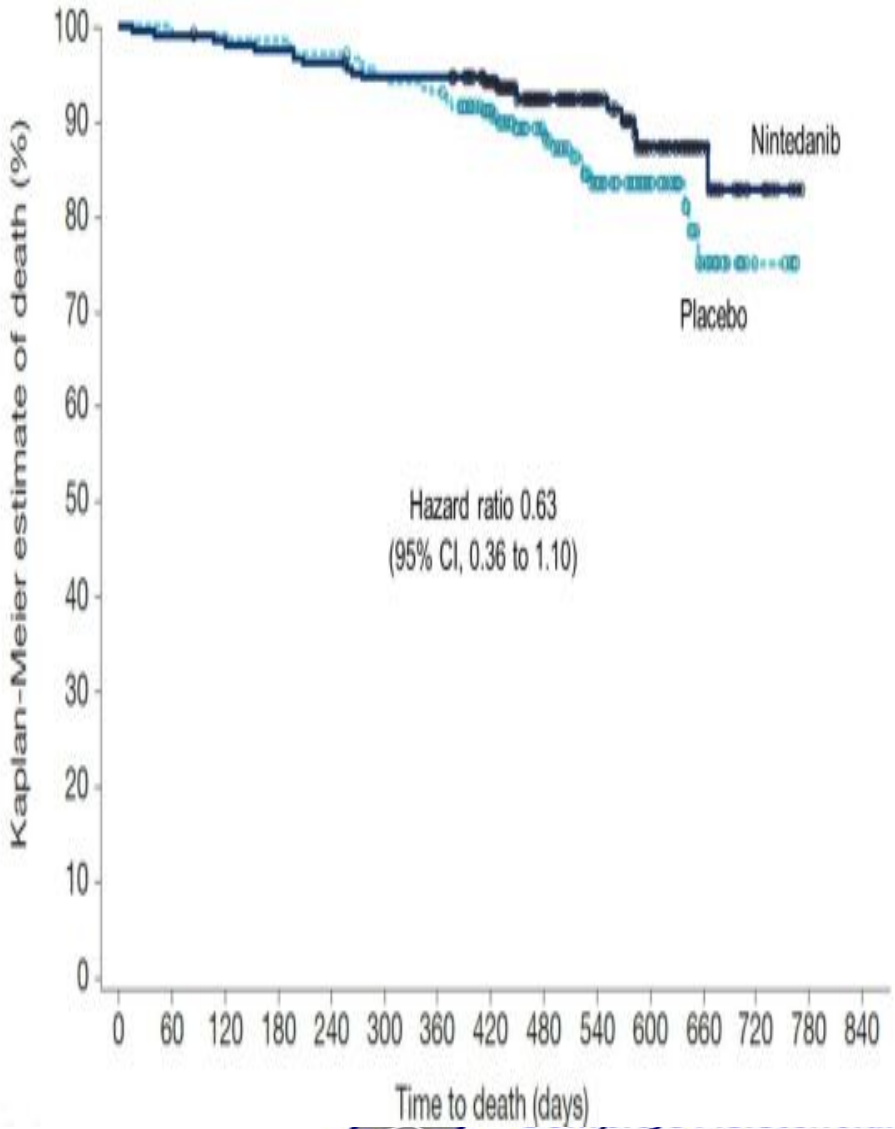



Figure S11: Kaplan-Meier estimate of time to death in patients with a UIP-like fibrotic pattern on HRCT using data up to first database lock



adverse events were similar

**Table 3. Adverse Events in the Overall Population.***

| Event | Nintedanib (N=332) | Placebo (N=331) |
|---|---|---|
| | *no. of patients (%)* | |
| Adverse event | | |
| Any | 317 (95.5) | 296 (89.4) |
| Any except for progression of interstitial lung disease† | 317 (95.5) | 295 (89.1) |
| Most frequent adverse events‡ | | |
| Diarrhea | 222 (66.9) | 79 (23.9) |
| Nausea | 96 (28.9) | 31 (9.4) |
| Bronchitis | 41 (12.3) | 47 (14.2) |
| Nasopharyngitis | 44 (13.3) | 40 (12.1) |
| Dyspnea | 36 (10.8) | 44 (13.3) |
| Vomiting | 61 (18.4) | 17 (5.1) |
| Cough | 33 (9.9) | 44 (13.3) |
| Decreased appetite | 48 (14.5) | 17 (5.1) |
| Headache | 35 (10.5) | 23 (6.9) |
| Alanine aminotransferase increased | 43 (13.0) | 12 (3.6) |
| Progression of interstitial lung disease† | 16 (4.8) | 39 (11.8) |
| Weight loss | 41 (12.3) | 11 (3.3) |
| Aspartate aminotransferase increased | 38 (11.4) | 12 (3.6) |
| Abdominal pain | 34 (10.2) | 8 (2.4) |
| Severe adverse event§ | 60 (18.1) | 73 (22.1) |
| Serious adverse event¶ | 107 (32.2) | 110 (33.2) |
| Fatal adverse event | | |
| Any | 11 (3.3) | 17 (5.1) |
| Any except for progression of interstitial lung disease† | 10 (3.0) | 14 (4.2) |
| Adverse event leading to treatment discontinuation | 65 (19.6) | 34 (10.3) |
| Adverse event leading to permanent dose reduction | 110 (33.1) | 14 (4.2) |

Hepatic adverse events were more common in patients treated with nintedanib than in those treated with placebo (Table 3). On the basis of

| | | |
|---|---|---|
| Alanine aminotransferase | | |
| ≥3 x upper limit of normal | 40 (12.0) | 5 (1.5) |
| ≥5 x upper limit of normal | 4 (1.2) | 1 (0.3) |
| ≥8 x upper limit of normal | 1 (0.3) | 0 (0.0) |
| Aspartate aminotransferase | | |
| ≥3 x upper limit of normal | 18 (5.4) | 5 (1.5) |
| ≥5 x upper limit of normal | 7 (2.1) | 1 (0.3) |
| ≥8 x upper limit of normal | 1 (0.3) | 1 (0.3) |
| Alanine aminotransferase and/or aspartate aminotransferase | | |
| ≥3 x upper limit of normal | 43 (13.0) | 6 (1.8) |
| ≥5 x upper limit of normal | 10 (3.0) | 1 (0.3) |
| ≥8 x upper limit of normal | 2 (0.6) | 1 (0.3) |
| Total bilirubin | | |
| ≥1.5 x upper limit of normal | 3 (0.9) | 5 (1.5) |
| ≥2 x upper limit of normal | 1 (0.3) | 1 (0.3) |
| Alkaline phosphatase | | |
| ≥1.5 x upper limit of normal | 17 (5.1) | 5 (1.5) |
| ≥2 x upper limit of normal | 8 (2.4) | 2 (0.6) |

# CONCLUSIONS

In conclusion, we found that patients who received nintedanib had a slower rate of progression of interstitial lung disease than those who received placebo, independent of the fibrotic pattern on high-resolution CT. This change in physiological outcomes was not accompanied by meaningful changes in measures of quality of life, although nintedanib was associated with a higher frequency of diarrhea, nausea, and vomiting.

vious observations.[15-18] These data support the hypothesis that progressive fibrosing interstitial lung diseases, regardless of clinical diagnosis, have a similar pathobiologic mechanism.