Table 2. (Continued)

ENT		Granulomatous changes on direct laryngoscopy (12-5-1) Consistent imaging studies (e.g. sinonasal erosion, mucoperiosteal thickening, positive PET scan) (6-8-4)	chronic sinusitis (0-1-17)	Nasal crusting, epistaxis, or anosmia associated with chronic sinus congestion (1-9-8)
Calcium-VitD	hypercalcemia plus all of the following: a) a normal serum PTH level; b) a normal or increased 1,25-OH dyhydroxy vitamin D level; c) a low 25-OH vitamin D level (17-2-0) hypercalciuria plus all of the following: a) a normal serum PTH level; b) a normal or increased 1,25-OH dyhydroxy vitamin D level; c) a low 25-OH vitamin D level (16-3-0)	nephrolithiasis plus all of the following: a) a normal serum PTH level; b) a normal or increased 1,25-diOH vitamin D level; c) a low 25-OH vitamin D level (12-7-0) hypercalciuria without serum PTH and 25 and 1,25 vitamin D levels (3-11-5) nephrolithiasis with calcium stones, without serum PTH and 25 and 1,25 vitamin D levels (4-11-4)	Nephrolithiasis, no stone anlaysis (1-3-15)	
Bone-Joint	Typical radiographic features (trabecular pattern, osteolysis, cysts/punched out lesions) (16-3-0)	Dactylitis (10-6-2) Nodular tenosynovitis (4-9-4) Positive PET, MRI, or gallium-67 bone imaging (8-9-1)	Arthralgias (0-5-14)	Non-specific arthritis (1-6-12)
Bone Marrow	PET displaying diffuse uptake (13-4-2)			leukopenia (2-8-8) anemia (1-5-13) thrombocytopenia (1-5-13)
Muscle		Positive imaging (MRI, Gallium-67) (13-7-0) Palpable muscle masses (3-11-6)	Myalgias (0-6-14)	Elevated serum muscle enzymes (5-8-7)
Extra-Thoracic Lymph Node		Multiple enlarged palpable cervical or epitrochelar lymph nodes without B symptoms (5-13-1) Enlarged lymph nodes identified by imaging in at least 2 peripheral or visceral lymph node stations without B symptoms (5-14-1)		Multiple enlarged palpable peripheral or visceral lymph nodes with B symptoms (1-10-9) Multiple palpable enlarged peripheral or visceral lymph nodes at sites other than cervical and epitrochlear (2-10-7)
Kidney		Treatment-responsive renal failure with no other risk factors. (9-9-1) Treatment-responsive renal failure in patient with diabetes and/or hypertension. (0-12-5)	Renal failure with other potential risk factors (0-4-15)	CT evidence of abnormal renal enhancement. (0-12-7)

Continued

Table 2. (Continued)

Nervous System	Clinical syndrome consistent with granulomatous inflammation of the meninges, brain, ventricular (CSF) system, cranial nerves, pituitary gland, spinal cord, cerebral vasculature or nerve roots -plus- An abnormal MRI characteristic of neurosarcoidosis, defined as exhibiting abnormal enhancement following the administration of gadolinium or a cerebrospinal fluid exam demonstrating inflammation (17-3-0)	Isolated facial palsy, negative MRI (6-8-5) Clinical syndrome consistent with granulomatous inflammation of the meninges, brain, ventricular (CSF) system, cranial nerves, pituitary gland, spinal cord, cerebral vasculature, nerve roots but without characteristic MRI or CSF findings (4-11-4)	Seizures, negative MRI (0-3-15) Cognitive decline, negative MRI (0-1-17)	Peripheral neuropathy involving large fibers (including axonal and demyelinating polyneuropathies and multiple mononeuropathies) (4-9-6) Cranial nerve palsies other than VII, negative MRI (4-7-8) Pleocytosis in the CSF (1-7-10) Low CSF glucose (0-6-12)
Cardiac		Treatment responsive CM or AVNB (12-7-1) Reduced LVEF in the absence of other clinical risk factors (2-13-4) Spontaneous or inducible sustained VT with no other risk factor (6-12-1) Mobitz type II or 3rd degree heart block (11-6-2) Patchy uptake on dedicated cardiac PET (10-8-1) Delayed enhancement on CMR (12-5-1) Positive gallium uptake (8-11-0) Defect on perfusion scintigraphy or SPECT scan (4-11-3) T2 prolongation on CMR (2-11-5)	Reduced LVEF in the presence of other risk factors (e.g., HTN, DM) (0-1-17) Atrial dysrhythmias (0-4-15)	Frequent ectopy (>5% QRS) (0-6-13) Bundle branch block (2-8-9) Impaired RV function with a normal PVR (0-8-10) Fragmented QRS or pathologic Q waves in ≥2 anatomically contiguous leads (0-7-10) At least one abnormal SAECG domain (0-6-10) Interstitial fibrosis or monocyte infiltration (4-8-7)
Other Organs		Positive imaging (3-8-3)		

*: *at least 70% agreement by the experts*

**: *for all clinical conditions, a) biopsy of that organ demonstrating granulomatous inflammation of no alternate cause implies highly probable involvement, b) another organ has demonstrated granulomatous inflammation of no alternate cause, c) alternative causes for the clinical manifestation have been reasonable excluded; CXR: chest radiograph; PFT: pulmonary function tests; Chest CT: chest computed tomography scan; TBNA: transbronchial needle aspiration (of a mediastinal lymph node); PET: positron emission tomography scan; Gallium-67: Gallium-67 nuclear scan; BAL: bronchoalveolar lavage; 3X: three times; PTH: serum parathyroid hormone; ENT: ear, nose, throat; Vit D: vitamin D; OH: hydroxy; di-OH: di-hydroxy; MRI: magnetic resonance imaging; B symptoms: fever, weight loss, or night sweats; CSF: cerebral spinal fluid; CM: cardiomyopathy; AVNB: atrioventricular nodal block; LVEF: left ventricular ejection fraction; HTN: systemic hypertension; DM: diabetes mellitus; VT: ventricular tachycardia; RV: right ventricular; SAECG: signal-averaged electrocardiogram; CMR: cardiovascular magnetic resonance imaging*

others who have expertise in the various organ manifestations of sarcoidosis. Unlike the original ACCESS organ assessment instrument, an organized process including a blinded vote was used to reach a consensus of the experts. In addition, the category of "definite" organ involvement in the ACCESS instrument was changed to "highly probable" because even histologic evidence of granulomatous inflammation is not definitive for the diagnosis of sarcoidosis.

This instrument should be viewed as a tool to assign probability to specific clinical findings as representing organ involvement with sarcoidosis. Many believe that because sarcoidosis is a multisystem disease, the diagnosis requires the presence of granulomatous inflammation in at least two organs.[1,4] It is unclear if this requirement is universally agreed upon. Regardless, this instrument assigns a probability for an additional organ having sarcoidosis based on clin-

ical criteria if another organ has demonstrated granulomatous inflammation of unknown cause previously. For clinicians who require that two organs demonstrate granulomatous inflammation of unknown cause for sarcoidosis to be diagnosed, this instrument would allow the diagnosis of sarcoidosis to be established in many cases without the need to biopsy a second organ.

This instrument is not designed to be used to assess activity or severity of sarcoidosis. Furthermore, this instrument is not a suggested algorithm to detect specific sarcoidosis organ involvement. In most cases, sarcoidosis organ involvement that does not cause significant symptoms does not require therapy.[5] Therefore, there is little reason in most cases to pursue a diagnosis of sarcoidosis in every possible organ that may be involved with the disease. Organ involvement may be occult without causing any clinical manifestations, and we are not advocating using this instrument to determine if organ involvement is clinically significant. In addition, the instrument is not designed to determine the need for treatment. It may be appropriate to treat clinical findings meeting only possible involvement criteria if the clinician determines that this is warranted.

This instrument may give guidance as to whether a clinical diagnosis of sarcoidosis organ involvement can be made without performing a biopsy to demonstrate granulomatous inflammation. Taking these individual clinical scenarios in isolation without regard to other clinical findings, we would propose that highly probable or at least probable involvement suggests that scenario is adequate for a clinical diagnosis of organ involvement. We acknowledge that the presence of a scenario voted as possible involvement may be adequate for a clinical diagnosis of sarcoidosis if additional other clinical findings are present.

There are several limitations of this instrument. First, the likelihood of each clinical finding described in the instrument is assigned a probability of representing sarcoidosis involvement of an organ based on the assumption that all other alternative causes for that clinical finding have been "reasonably excluded." This instrument provides no metric for this process, so that the method of excluding alternative diagnoses is arbitrary. At a minimum, attempts should be made to exclude mycobacterial infection, fungal infection, and malignancy. We acknowledge that if a very rigorous process is made to exclude alternative causes for the clinical findings discussed, that the likelihood of sarcoidosis could potentially be "upgraded." Second, there is no evidence that this instrument identifies sarcoidosis phenotypes that relate to specific genotypes or other specific mechanisms of disease. Other instruments have demonstrated evidence of such associations, albeit weakly.[6] It is possible that this instrument might function similarly, but that remains conjectural at this time. Third, the organ manifestations of sarcoidosis in our instrument are not comprehensive. Therefore, several manifestations were not appraised by the experts and, therefore, are unclassified. In addition, this instrument did not evaluate "para-sarcoidosis syndromes" that are often of major concern to sarcoidosis patients. These are conditions found frequently in sarcoidosis patients but are not directly attributable to granulomatous organ involvement and include small fiber neuropathy,[7-9] fatigue,[10-13] depression[13-15] and constitutional symptoms such as fever, weight loss, and malaise.[16] Finally, similar to our comments concerning the need for a biopsy in the preceding paragraph, each of the clinical manifestations that we assessed in this instrument does not always occur in isolation. It is possible that if a patient has evidence of multiple manifestations, each of which we regard as "probable" sarcoidosis, this may raise the probability of sarcoidosis to "highly probable." However, such an analysis is too complex to be examined presently.

We acknowledge that our position that highly probable or probable organ involvement is adequate for a clinical diagnosis of sarcoidosis involvement in an organ is arbitrary. Some may prefer to be more rigorous and require that organ involvement be highly probable for sarcoidosis organ involvement to be assumed without performing a confirmatory biopsy. For these reasons, Table 1 supplies the votes of all the experts for each clinical condition and designates the clinical conditions where a consensus was reached that they were highly probable.

In summary, we have presented an instrument that we consider useful in assessing the probability of organ involvement with sarcoidosis. Although we believe that this instrument will be useful for the clinician and clinical researcher involved with sarcoidosis patients, we suspect that it will require further modification over time as additional diagnostic tests are developed and new medical evidence is generated.

Appendix 1: Organ Groups for initial establishment of clinical scenarios for future voting

Lung
Lead: Robert Baughman. Members: Norman Soskel, Athol Wells, Elliott Crouser, Laura Koth, Marjolein Drent, Paola Rittoli, Daniel Culver, Milton Rossman, Ulrich Costabel, Lisa Maier, Dominique Valeyre, Hide Shigemitsu, Nadera Sweiss, Dominique Israel-Biet, Manuel Riberto Neto, Dheeraj Gupta, Eva Carmona; Patterson, Karen, Andrew P. Matragrano

Skin
Lead: Misha Rosenbach. Members: Marc Judson, Gloria Westney, Debasis Sahoo

Eye
Lead: Robert Baughman. Members: Elyse Lower, Adam Morgenthau

Liver
Lead: Adam Morgenthau. Members: Marjolein Drent, Gloria Westney, Lisa Maier; Nadera Sweiss

Calcium
Lead: Marc Judson. Members: Lisa Maier, Laura Koth, Hide Shigemitsu; Nadera Sweiss

Neuro
Lead: Jeffery Gelfand. Members: Marjolein Drent, Barney Stern, Jinny Tavee, Elske Hoitsma, Hide Shigemitsu, Kenkichi Nozaki, Fleur Cohen Aubart

Kidney
Lead: Elliott Crouser. Members: Milton Rossman, Daniel Culver; Nadera Sweiss

Heart
Lead: Daniel Culver. Members: Elliott Crouser, Nabeel Hamzeh, Milton Rossman, Ulrich Costabel, Vasanth Vedantham, Lisa Maier, Adam Morgenthau, Catherine Chapelon, David Bernie, Debabrata Bandyopadhyay

Peripheral Lymph Node
Lead: Lower. Member: Marc Judson

Bone Marrow
Lead: Adam Morgenthau. Members: Elyse Lower

Spleen
Lead: Elyse Lower. Members: Gloria Westney, Adam Morgenthau

Bone/Joint
Lead: Nadera Sweiss. Members: Laura Koth, Debasis Sahoo, Andrew Gross ; Arthur Yee

ENT
Lead: Marc Judson. Members: Gloria Westney, Lisa Maier

Parotid/Salivary Glands
Lead: Robert Baughman. Member: Debasis Sahoo

Muscle
Lead: Dominique Valeyre. Members: Marjolein Drent, Nadera Sweiss, Arthur Yee

Other organs
Lead: Marc Judson. Member: Robert Baughman

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Erratum corrige

In the issue 4-2013 of Sarcoidosis Vasculitis and Diffuse lung Diseases in the article "Role of Propionibacterium acnes in sarcoisosis: a meta-analysis "by Y. Zhou, Y. Hu, H. Li, The correct Corresponding Autor is: Huiping Li, MD E.mail: liw2013@126.com

Respiratory Medicine (2014) 108, 1023–1030

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Design of the INPULSIS™ trials: Two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis

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Received 1 March 2014; accepted 16 April 2014
Available online 29 April 2014

KEYWORDS
Clinical trial;
Phase III;
Drug therapy;

Summary
Background: Nintedanib is in clinical development as a treatment for idiopathic pulmonary fibrosis (IPF). Data from the Phase II TOMORROW study suggested that nintedanib 150 mg twice daily had clinical benefits with an acceptable safety profile.

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http://dx.doi.org/10.1016/j.rmed.2014.04.011

Protein kinase inhibitor; Protein tyrosine kinases

Methods: The INPULSIS™ trials are replicate Phase III, randomized, double-blind, studies comparing the efficacy and safety of nintedanib 150 mg twice daily with placebo in patients with IPF. Eligible patients were aged ≥40 years with a diagnosis of IPF within 5 years before randomization who had undergone a chest high-resolution computed tomography (HRCT) scan within 1-year before screening, and who had a forced vital capacity (FVC) of ≥50% predicted and a diffusing capacity for carbon monoxide of 30–79% predicted. Participants were randomized 3:2 to receive nintedanib or placebo for 52 weeks. The primary endpoint is the annual rate of decline in FVC. The key secondary endpoints are change from baseline in the total score on the St. George's Respiratory Questionnaire (a measure of health-related quality of life) over 52 weeks and time to first acute exacerbation.

Results: Enrolment of 1066 patients in 24 countries was completed in September 2012. Results will be reported in the first half of 2014.

Conclusion: The INPULSIS™ trials will determine the efficacy of nintedanib in patients with IPF, including its impact on disease progression as defined by decline in FVC, acute exacerbations and health-related quality of life. In addition, they will characterise the adverse event profile of nintedanib in this patient population.

Trial registration: Registered at ClinicalTrials.gov (identifiers: NCT01335464 and NCT01335477).

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia [1]. An accurate diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease, the presence of a specific radiological pattern of usual interstitial pneumonia (UIP) determined by high-resolution computed tomography (HRCT), or specific combinations of HRCT and histopathologic patterns in patients who have undergone surgical lung biopsy [1]. IPF is considered a rare disease [2]. In a retrospective cohort study conducted in the United States using data from a large healthcare claims database spanning a 5-year period, the prevalence of IPF was estimated to be 14 to 43 cases per 100,000, and the annual incidence to be 6.8 to 16.3 per 100,000, depending on how cases were defined [3]. Similarly, in the United Kingdom, the annual incidence of IPF was estimated to be 7.4 per 100,000 based on primary care data from 2000 to 2008 [4]. IPF is ultimately a fatal disease, with a reported median survival time of approximately 3 years from diagnosis [5]. In addition, the symptoms of IPF impact negatively on patients' physical function and emotional well-being, as well as their health-related quality of life (HRQoL) [6,7].

An improved understanding of the pathogenic mechanisms underlying IPF over the last decade has resulted in several agents being evaluated in clinical trials [8] and in pirfenidone being approved for the treatment of a subgroup of patients with IPF in several countries. Results of four large randomized, double-blind, placebo-controlled Phase III trials investigating the efficacy and safety of treatments for IPF are awaited this year: the PANTHER-IPF trial of N-acetylcysteine (NAC) (NCT00650091), the ASCEND trial of pirfenidone (NCT01366209), and the INPULSIS™ trials of nintedanib (NCT01335464 and NCT01335477).

Nintedanib (formerly known as BIBF 1120) is a potent tyrosine kinase inhibitor targeting intracellular receptors of fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) [9]. Activation of these receptor kinases has been implicated in multiple pathways in the pathogenesis of IPF [10,11]. *In vitro* studies and animal models suggest that nintedanib has anti-fibrotic and anti-inflammatory effects that may attenuate the progression of fibrosis [12,13]. Results from the Phase II TOMORROW trial suggested that 12 months' treatment with nintedanib 150 mg twice daily results in a reduced rate of decline in forced vital capacity (FVC), fewer acute exacerbations and preservation of HRQoL, measured using the St. George's Respiratory Questionnaire (SGRQ) [14]. The purpose of this manuscript is to describe the design of the INPULSIS™ studies, two replicate Phase III trials that further investigate the efficacy and safety of nintedanib 150 mg twice daily compared with placebo in patients with IPF.

Methods

Trial design

Both the INPULSIS™ trials are multinational, randomized, double-blind, parallel-group studies comparing the efficacy and safety of nintedanib 150 mg twice daily with placebo in patients with IPF. The INPULSIS™ trials were initiated in May 2011 and enrolment (n = 1066) was completed in September 2012. Patients were recruited in 24 countries in the Americas, Europe, Asia and Australia. Following a screening period, eligible patients were randomized 3:2 (using an interactive phone/web response system) to receive nintedanib or placebo for 52 weeks (Fig. 1). Each study concluded with a 4-week follow-up period after completion of the 52-week treatment period. A 3:2 ratio was chosen to aid enrolment. In order to reduce the amount of missing data, patients who discontinued trial drug, for any reason, prior to completing the 52 weeks' treatment were asked to attend all visits and undergo all examinations

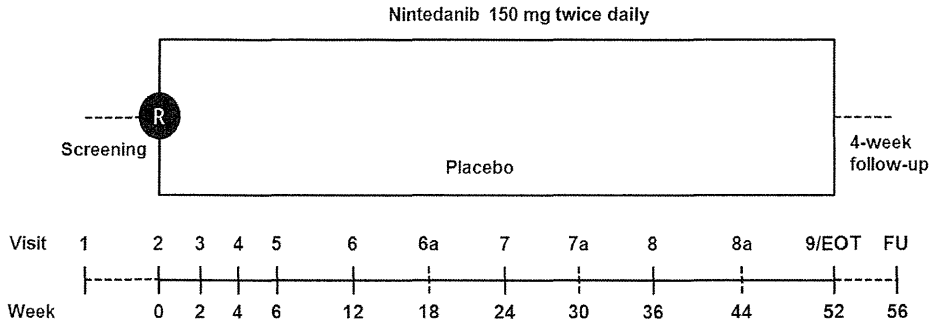

Figure 1 INPULSIS™ trial design. R, randomization (3:2 ratio for nintedanib:placebo); EOT, end of treatment; FU, follow-up. FVC was measured at all visits except visits 6a, 7a and 8a, which were for blood sampling for laboratory tests only.

as originally planned. In addition, vital status at week 52 was to be collected for all patients who prematurely discontinued but did not agree to attend all visits until week 52.

For each trial, the sample size was calculated to provide 90% power to detect a difference of 100 mL/year between the treatment groups in the rate of FVC decline. Based on the Phase II TOMORROW trial data, the common standard deviation for change from baseline in FVC was assumed to be 300 mL. Assuming data from 2% of patients would be non-evaluable, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib 150 mg twice daily group if using a 2 group *t*-test at a 1-sided 2.5% level. Since the primary analysis is a random coefficient regression model, including adjustment for several variables and taking into account information across time rather than at a single time-point, it is expected that the power will be greater than the 90% calculated for the *t*-test.

As in the Phase II TOMORROW trial, dose interruption and/or reduction of the dose from 150 mg twice daily to 100 mg twice daily was allowed for the management of adverse events. After an adverse event had resolved, the dose could be reinstituted at 150 mg twice daily. The investigators were provided with guidelines on the management of diarrhoea, a known side-effect related to treatment with tyrosine kinase inhibitors [15,16]. Guidelines on the management of liver enzyme elevations were also provided to the investigators. Patients who completed the 52-week treatment period and the 4-week follow-up period in the INPULSIS™ trials were invited to participate in an open-label extension trial (NCT01619085).

Trial organisation and oversight

The INPULSIS™ trials were guided by an advisory committee consisting of clinical experts in IPF and representatives of the sponsor, Boehringer Ingelheim. An independent Data Monitoring Committee (DMC) regularly reviewed the data, in particular serious adverse events, adverse events leading to discontinuation of study drug, and laboratory parameters, and made recommendations to the sponsor about the continuation of the trials. An Adjudication Committee reviewed medical documentation for all deaths to evaluate the primary cause of death in a blinded manner. This committee also adjudicated all events reported by the investigators as meeting the criteria for an acute exacerbation of IPF as defined in the protocol, classifying them as a confirmed acute exacerbation, suspected acute exacerbation, or not an acute exacerbation.

Both trials were conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and were approved by local authorities. The clinical trial protocol was approved by an Independent Ethics Committee and/or Institutional Review Board at all the participating centres. All patients provided written informed consent prior to study entry.

Patients

To be eligible to participate in the INPULSIS™ trials, patients had to be ≥40 years of age with a diagnosis of IPF established within 5 years before randomization, to have undergone chest HRCT within 12 months before screening, and to have an FVC ≥50% of predicted value [17] and a carbon monoxide diffusion capacity (DL_{CO}) of 30–79% of predicted value [18]. The diagnosis of IPF was established based on the central review of chest HRCT scans from all patients by an expert radiologist (DMH) according to protocol-specified criteria (Table 1). Surgical lung biopsy specimens were also centrally evaluated if available by an expert pathologist (AGN).

Table 1 Diagnostic criteria for IPF based on chest HRCT if surgical lung biopsy was not available. To qualify for a diagnosis of IPF if a surgical lung biopsy was not available, the criteria A and B and C; or criteria A and C; or criteria B and C had to be met.

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Patients with abnormal laboratory parameters (liver transaminases or bilirubin above 1.5-fold upper limit of normal), cardiac disease (i.e. myocardial infarction within 6 months or unstable angina within 1 month of randomization), or who, in the opinion of the investigator, were likely to receive a lung transplant during the study were not permitted to enter the trial. Patients who were taking full-dose anticoagulant therapy or high-dose antiplatelet therapy at screening, or had received treatment with NAC or prednisone >15 mg/day or equivalent within 2 weeks of screening, or pirfenidone, azathioprine, cyclophosphamide, cyclosporine A or any investigational drug within 8 weeks of screening, were excluded. Concomitant therapy with prednisone ≤15 mg/day or equivalent was permitted if the dose had been stable for ≥8 weeks prior to screening. Patients who experienced deterioration, as judged by the investigator, were permitted to receive concomitant treatment with azathioprine, cyclophosphamide, cyclosporine A, NAC, or prednisone >15 mg/day or equivalent at the discretion of the investigator 6 months or more after starting to receive study medication. In cases of acute exacerbation, any treatments could be freely initiated or increased as deemed appropriate by the investigator. However, pirfenidone and any investigational treatments for IPF were not allowed throughout the trial.

Outcome measures

The primary endpoint for the INPULSIS™ trials is the annual rate of decline in FVC (mL/year), calculated from measurements obtained over the 52 weeks of treatment (Fig. 2). Spirometry testing was conducted according to ATS/ERS criteria, including daily calibration of the spirometer, regular calibration of the calibration pump and FVC tests conducted in triplicate, with the highest result selected [19]. All spirometry was performed on sponsor-provided machines and ongoing feedback and training were provided.

The key secondary endpoints are change from baseline in SGRQ total score over 52 weeks and time to first acute exacerbation. Acute exacerbations were defined as events meeting all of the following criteria: unexplained worsening or development of dyspnoea within 30 days, new diffuse pulmonary infiltrates on chest X-ray and/or HRCT, or parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit. Causes of the acute worsening, including infection, left heart failure, pulmonary embolism or any identifiable cause of acute lung injury were to be excluded as per routine clinical practice and microbiological studies. Investigator-reported exacerbations were adjudicated by the Adjudication Committee. Other secondary endpoints include absolute changes from baseline in FVC (mL and % predicted); proportion of FVC responders (patients who did not have an absolute decline in FVC % predicted of >5% or >10%); risk of an acute exacerbation; change from baseline in SpO_2 (oxygen saturation) at rest; change from baseline in DL_{CO} at rest (measured in accordance with ATS/ERS guidelines [20]); all-cause, respiratory, and 'on-treatment' time to death. Composite endpoints of time to death or lung transplant, and time to death or lung transplant or meeting arbitrary pre-defined criteria for lung transplant (FVC <45% predicted *or* DL_{CO} <30% predicted *or* SpO_2 <88% at rest) were also included in order to capture a range of outcomes indicating an unfavourable clinical course.

Further patient-reported outcomes (PROs) investigated in the INPULSIS™ trials are the change from baseline to week 52 in the score on the three SGRQ domains (impact, symptoms, activity) [21], SGRQ-I [22], University of California San Diego Shortness of Breath Questionnaire [UCSD-SOBQ] [23], EuroQol 5-dimensional quality of life questionnaire [EQ5D], Cough and Sputum Assessment Questionnaire cough domains [CASA-Q(CD)] [24]; the proportion of 4-point responders on SGRQ total score; and the proportion of responders on Patient's Global Impression of Change (PGI-C). Safety assessment will include reporting of

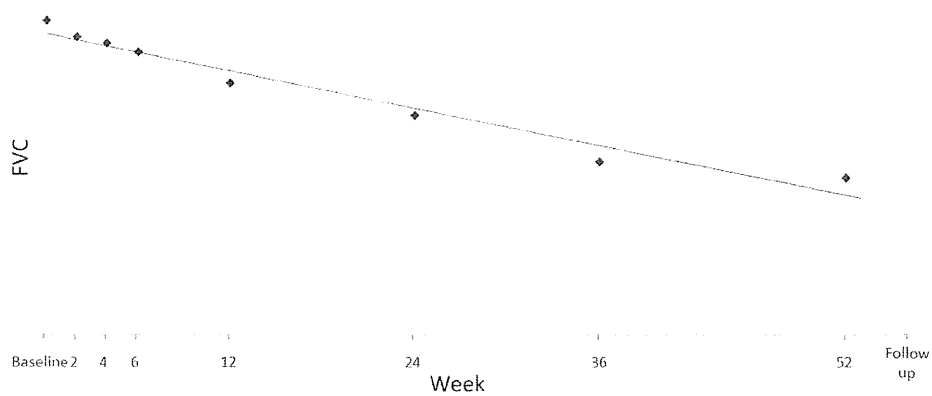

Figure 2 Methodology for calculating slope of FVC decline. The primary endpoint will be analysed using a random coefficient regression (random slopes and intercepts) model, including gender, age and height as covariates. Visits are planned at 2, 4, 6, 12, 24, 36 and 52 weeks after randomization. All available FVC values except the value from the follow-up visit will be used in this analysis except for patients who prematurely discontinue trial medication, in which case the value from the follow-up visit will also be used.

adverse events; assessment of vital signs, physical examination and weight; clinical laboratory tests (haematology, clinical chemistry and urinalysis).

Statistical analysis

Efficacy and safety analyses will be conducted on patients who were randomized to treatment (nintedanib or placebo) and received ≥1 dose of study medication. The annual rate of decline in FVC will be primarily analysed using a random coefficient regression (random slopes and intercepts) model including gender, age and height as covariates. All available FVC values from baseline to week 52 will be used in the primary model, including FVC measurements from the follow-up visit for patients who prematurely discontinued trial medication and did not complete study visits until week 52. A linear model was chosen as in this patient population, FVC is expected to decline linearly over time. However, a number of alternative and sensitivity analyses have been pre-specified in the statistical analysis plan, such as change from baseline to week 52 in FVC and other functional forms for the rate of decline (quadratic and exponential) to assess the robustness of the linear model. Model assumptions also include a normal distribution for the intercepts and slopes with an arbitrary covariance matrix. An unstructured variance-covariance structure will be used to model within-patient measurements. The variance-covariance matrix, modeled to estimate the inter-individual variability, will be considered to have a Variance-Components structure. The Roger-Kenward approximation will be used to estimate denominators degrees of freedom.

Change from baseline in SGRQ total score over 52 weeks will be primarily analysed using mixed model repeated measures (MMRM) with treatment and visit as fixed effects, baseline SGRQ total score as a covariate, and treatment-by-visit and baseline-by-visit as interaction terms. The patient effect will be assumed to be random and compound symmetry covariance structure will be assumed for within-patient variation.

Kaplan–Meier estimates will be derived for the probability of a first acute exacerbation over time, and time to first acute exacerbation will be primarily analysed using the log rank test. The hazard ratios and their confidence intervals will be computed using a Cox proportional hazards model adjusted for gender, age and height. These covariates were chosen in order to be consistent with the analyses performed in the Phase II TOMORROW trial [14] and are the same covariates as included in the primary endpoint model. The key secondary endpoint uses data on acute exacerbations as reported by the site investigators, in keeping with the Phase II methodology. Events adjudicated as confirmed or suspected acute exacerbations by the Adjudication Committee will be assessed in a sensitivity analysis of data pooled from both INPULSIS™ trials.

A hierarchical procedure will be used to demonstrate the superiority of nintedanib over placebo for the primary and key secondary endpoints. The consecutive steps of the hierarchy will only be considered if the previous step is significant at the 1-sided 2.5% level and the results are in favour of nintedanib. Two hierarchies of endpoints, with a different order of the key secondary endpoints for submissions to US and EU/rest of world regulatory authorities, will be tested. For the US submission, time to first acute exacerbation is the first key secondary endpoint; for the EU/rest of world submissions, change from baseline in SGRQ total score over 52 weeks is the first key secondary endpoint. No hierarchy will be used for the other secondary endpoints.

Absolute and relative changes from baseline in FVC over 52 weeks will be analysed using MMRM, with treatment and visit as fixed effects and baseline value, gender, age and height as covariates, and treatment-by-visit and baseline-by-visit as interaction terms. Changes in other respiratory parameters will be analysed in the same way as change in FVC. Changes in other PROs will be analysed in the same way as change in SGRQ total score.

For the survival analyses, a log rank test will be used to compare treatment groups and a Cox model adjusted for gender, age and height will be used to determine hazard ratios. These covariates were chosen in order to be consistent with the analyses performed in the Phase II TOMORROW trial [14] and are the same covariates as included in the primary endpoint model. Since the number of deaths is expected to be low, the protocol specified that survival analyses will additionally be performed on the pooled data from both INPULSIS™ trials. Safety analyses will be descriptive.

Sensitivity analyses will be performed to assess the robustness of the results of the primary and key secondary endpoints. Model assumptions will be checked and sensitivity to data handling, including missing data handling, will be assessed. In order to improve the precision of the treatment effect estimates for the efficacy endpoints and to increase the size of the safety database, a pooled analysis of the two trials was pre-specified as an additional supportive analysis.

Discussion

Rationale for dose selection

The dose of nintedanib used in the INPULSIS™ trials was selected based on findings from the 12-month Phase II TOMORROW study [14]. In the TOMORROW trial, the annual rate of decline in FVC in the nintedanib 150 mg twice daily group was −0.06 L (95% CI, −0.14 to 0.02) compared with −0.19 L (95% CI, −0.26 to −0.12) in the placebo group: a difference of 0.13 L (95% CI, 0.03–0.24). In addition, treatment with nintedanib 150 mg twice daily was associated with preservation of HRQoL (mean change in SGRQ total score of −0.66 [95% CI, −4.02 to 2.71] versus 5.46 [95% CI, 2.06, 8.86] with placebo: a difference of −6.12 [95% CI, −10.57 to −1.67]) and a reduction in the risk of acute exacerbations (risk ratio compared with placebo: 0.16 [95% CI, 0.03 to 0.70]).

Rationale for endpoints

The most robust primary endpoint for Phase III clinical trials in IPF is all-cause mortality [25]. However, the mortality rate of patients enrolled in the TOMORROW trial was low,

and it was assessed that it was not feasible to use mortality as the primary endpoint in the INPULSIS™ trials. Based on the 1-year survival rates observed in the TOMORROW study (89.2% of patients in the placebo group and 91.7% of patients in the nintedanib 150 mg twice daily group) it was calculated that a 1-year trial would require the inclusion of a total of approximately 6000 patients to provide 90% power to detect a difference between groups with a 2-sided *p*-value of 5%.

In the absence of an alternative explanation, a decrease in FVC in patients with IPF is consistent with progressive disease [1] and has been shown to be associated with reduced survival time in patients with IPF [26–32]. Change in FVC over 1 year has been used as a primary endpoint for Phase III clinical trials in patients with IPF [25,33]. The annual rate of decline in FVC – the primary endpoint in the INPULSIS™ trials – uses all the FVC values collected during the trial. This was considered to be a more robust methodology than using only the FVC value from baseline and 52 weeks because it enables calculation of the rate of decline even in patients without a week 52 value.

Several PROs for the assessment of the symptoms of IPF and the broader construct of HRQoL have been included as secondary endpoints in the INPULSIS™ trials. The SGRQ, chosen as a key secondary endpoint in the INPULSIS™ trials, has demonstrated acceptable psychometric characteristics in patients with IPF, including construct validity, reliability, and ability to detect change over time [22,34–36]. The two PROs used to assess dyspnoea, the UCSD-SOBQ and CASA-Q (CD), have been shown to have content validity in patients with IPF [37], with the UCSD-SOBQ also shown to detect change over time [36,38].

In the INPULSIS™ trials, acute exacerbations reported by the investigators will be assessed as a key secondary endpoint, as was done in the Phase II TOMORROW trial, in which a clinically relevant efficacy signal on acute exacerbations was observed. Furthermore, recent data suggest that suspected acute exacerbations (events that the investigator thinks are acute exacerbations but that cannot be adjudicated as acute exacerbations due to missing data or criteria) are clinically indistinguishable from confirmed acute exacerbations defined according to the consensus diagnostic criteria [39] and that both are clinically meaningful events [40]. Investigator-identified acute exacerbations were felt to best capture both definite and suspected acute exacerbations.

Conclusions

The INPULSIS™ trials will investigate the efficacy of nintedanib in patients with IPF, including its impact on disease progression as defined by decline in FVC, acute exacerbations and HRQoL. In addition, the data collected will characterise the adverse event profile of nintedanib in this patient population. The INPULSIS™ trials will report results in the first half of 2014. Together with the results of the other large ongoing randomized placebo-controlled trials in IPF, the INPULSIS™ trials will add significantly to scientific understanding of the natural history of IPF and will have potential implications for disease management.

Conflicts of interest

The INPULSIS™ trials were funded by Boehringer Ingelheim.

Luca Richeldi has received grants for research and fees for lectures, advisory boards meetings, and steering committee meetings from InterMune, Boehringer Ingelheim, Roche, Takeda, Shionogi, Biogen Idec, Sanofi-Aventis, MedImmune and ImmuneWorks.

Kevin R. Flaherty has received consulting fees from Boehringer Ingelheim, FibroGen, Genentech, Gilead, Ikaria, ImmuneWorks, MedImmune, Novartis, Roche, Takeda, Vertex and Veracyte; fees for lectures from Boehringer Ingelheim, Forest and GlaxoSmithKline; fees for participation in review activities and travel reimbursement from Boehringer Ingelheim; employment fees from the Pulmonary Fibrosis Foundation; royalties from NACE and payments for the development of educational presentations from Excel, France Foundation and NACE. His institute has received research grants from Bristol-Myers Squibb, ImmuneWorks and InterMune.

Vincent Cottin has received grants for research, and fees for lectures, advisory board meetings, and steering committee meetings from InterMune, Boehringer Ingelheim, Gilead and Roche.

Yoshikazu Inoue has received fees for lectures, advisory board meetings, steering committee meetings, or safety boards from Boehringer Ingelheim, Shionogi, Bayer, Novartis Pharmaceuticals, Nobel Pharma, Teijin Pharma, Chugai Pharmaceutical, Takeda, Genzyme Japan and Eisai.

Martin Kolb has received consulting fees from Boehringer Ingelheim, InterMune and GlaxoSmithKline for activities related to IPF and his institution has received research grants from Boehringer Ingelheim, InterMune and GlaxoSmithKline.

Hiroyuki Taniguchi has received consultancy fees from Boehringer Ingelheim for steering committee meetings and advisory board meetings and from Olympus Corporation and AstraZeneca for advisory board meetings. He has received fees for lectures from Shionogi, Boehringer Ingelheim, Asahi Kasei Pharma Corp, Bayer, Chugai, GlaxoSmithKline, Ono Pharmaceutical Co, Teijin Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Fukuda Denshi Co, Terumo Corp, Taiho Pharmaceutical Co, Kyorin Pharmaceutical Co, Meiji Seika Pharma Co, Philips Respironics, Pfizer, Abbott, Nippon Shinyaku Co, Eisai and Merck Sharp & Dohme.

David M. Hansell has received fees for consultancy and evaluating CT scans from Boehringer Ingelheim, InterMune and AstraZeneca.

Andrew G. Nicholson has no competing interests.

Ganesh Raghu has received travel reimbursements from Boehringer Ingelheim to attend scientific advisory board meetings.

Florence Le Maulf and Susanne Stowasser are employees of Boehringer Ingelheim.

Harold R. Collard has received consultancy fees (paid to his institution) from Biogen, FibroGen, Gilead, InterMune, Promedior, Pfizer, Bayer and Stromedix; grants from Boehringer Ingelheim, Genentech and the NIH/NHLBI; royalties (paid to his institution) from UpToDate; and payments for the development of educational presentations (paid to his institution) from Medscape.

Authors' contributions

All authors contributed to the study design and/or discussions regarding how the data from these trials would be analysed and interpreted. All authors contributed to the development of the manuscript. All authors have approved the final manuscript.

Acknowledgements

We thank the following employees of Boehringer Ingelheim for their contributions: Dr Rozsa Schlenker-Herceg for scientific advice and Mannaïg Girard for statistical advice. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Wendy Morris and Julie Fleming of Fleishman-Hillard Group, Ltd, London, UK, during the preparation of this manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

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*A complete list of investigators in the INPULSIS trials is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 18, 2014, at NEJM.org.

N Engl J Med 2014;370:2071-82.
DOI: 10.1056/NEJMoa1402584

IDIOPATHIC PULMONARY FIBROSIS IS A FATAL lung disease characterized by worsening dyspnea and progressive loss of lung function.[1] A decline in forced vital capacity (FVC) is consistent with disease progression and is predictive of reduced survival time.[1-6]

Idiopathic pulmonary fibrosis is believed to arise from an aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts.[7] The activation of cell-signaling pathways through tyrosine kinases such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) has been implicated in the pathogenesis of the disease.[8-10]

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases, including the VEGF, FGF, and PDGF receptors.[11] The results of an earlier trial (To Improve Pulmonary Fibrosis with BIBF 1120 [TOMORROW]), a randomized, double-blind, placebo-controlled, phase 2 dose-finding study involving 432 patients with idiopathic pulmonary fibrosis, suggested that 12 months of treatment with 150 mg of nintedanib twice daily was associated with a reduced decline in FVC, fewer acute exacerbations, and the preservation of health-related quality of life.[12] We conducted two replicate phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of treatment with 150 mg of nintedanib twice daily in patients with idiopathic pulmonary fibrosis.

METHODS

STUDY DESIGN AND OVERSIGHT

The INPULSIS studies were randomized, double-blind, placebo-controlled, parallel-group trials performed at 205 sites in 24 countries in the Americas, Europe, Asia, and Australia. An independent data monitoring committee regularly reviewed the data, particularly serious adverse events, adverse events leading to discontinuation of the study drug, and the results of laboratory analyses, and made recommendations concerning the continuation of the trials. An adjudication committee that was independent of the investigators and whose members were unaware of the group assignments reviewed medical documentation to adjudicate the primary cause of all deaths. The committee also adjudicated all adverse events reported by site investigators as acute exacerbations, in order to determine whether the events met the criteria for an acute exacerbation of idiopathic pulmonary fibrosis as defined in the protocol, available with the full text of this article at NEJM.org. The members of these committees are listed in Section B in the Supplementary Appendix, also available at NEJM.org.

Both trials were conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and were approved by local authorities. The clinical protocol was approved by an independent ethics committee or institutional review board at each participating center. All patients provided written informed consent before study entry.

All the authors were involved in the design of the study and had access to the data, which were analyzed by the study sponsor, Boehringer Ingelheim. All the authors vouch for the accuracy and completeness of the data analyses and the fidelity of each study to the protocol. The protocol and statistical analysis plans are available at NEJM.org. The manuscript was drafted by the first, second, and last authors and revised by all the authors. Medical writing assistance, paid for by Boehringer Ingelheim, was provided by the Fleishman-Hillard Group.

PATIENTS

Patients were eligible to participate in the two trials if they were 40 years of age or older and had received a diagnosis of idiopathic pulmonary fibrosis within the previous 5 years. Additional eligibility criteria were an FVC that was 50% or more of the predicted value, a diffusion capacity of the lung for carbon monoxide (DLCO) that was 30 to 79% of the predicted value, and high-resolution computed tomography (HRCT) of the chest performed within the previous 12 months. HRCT images (for all patients) and lung-biopsy specimens (if available) were reviewed centrally by a single radiologist and a single pathologist to verify eligibility according to the protocol. Eligibility criteria with regard to findings on HRCT and surgical lung biopsy are shown in Table S1 and Table S2, respectively, in the Supplementary Appendix.

Concomitant therapy with up to 15 mg of prednisone per day, or the equivalent, was permitted if the dose had been stable for 8 or more

weeks before screening; patients receiving other therapies for idiopathic pulmonary fibrosis, including high-dose prednisone, azathioprine, *N*-acetylcysteine, and any investigational treatments for idiopathic pulmonary fibrosis, were excluded. After 6 months of study treatment, patients whose condition had deteriorated could receive azathioprine, cyclophosphamide, cyclosporine, *N*-acetylcysteine, or more than 15 mg of prednisone per day, or the equivalent, at the discretion of the investigator. In cases of acute exacerbation reported by an investigator at any time during the trial, any treatments could be initiated or doses increased as deemed appropriate by the investigator. Other key exclusion criteria are listed in Section C in the Supplementary Appendix.

STUDY PROTOCOL

After a screening period, eligible patients were randomly assigned in a 3:2 ratio to receive 150 mg of nintedanib twice daily or placebo for 52 weeks. An interactive telephone and Web-based response system was used to perform randomization. Patients, investigators, and the study sponsor were unaware of the study-group assignments throughout the study. Completion of the 52-week treatment period was followed by a follow-up visit 4 weeks later. Spirometric tests were conducted at baseline; at 2, 4, 6, 12, 24, 36, and 52 weeks; and at the follow-up visit. Spirometric testing was conducted in accordance with criteria published by the American Thoracic Society and the European Respiratory Society.[13] All spirometric measurements were performed on machines provided by the sponsor, and the results were centrally reviewed, with training and ongoing feedback provided for the site investigators.

Dose interruption or reduction of the dose from 150 mg twice daily to 100 mg twice daily was allowed for the management of adverse events. After an adverse event had resolved, the dose could be reinstituted at 150 mg twice daily. The site investigators were provided with recommendations for the management of diarrhea and elevated levels of liver enzymes. To minimize the amount of missing data, patients who discontinued the study drug prematurely were asked to attend all scheduled visits and to undergo all examinations as originally planned. For patients who discontinued the drug prematurely but did not agree to attend all visits, data on vital status were collected at week 52.

END POINTS

The primary end point for both INPULSIS trials was the annual rate of decline in FVC (measured in milliliters per year). Key secondary end points were the time to the first acute exacerbation (as reported by a site investigator) and the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ), both assessed over the 52-week treatment period. The SGRQ is a self-administered questionnaire that is used to assess health-related quality of life. It comprises three domains (symptoms, activity, and impact). The total score and the score for each domain range from 0 to 100, with higher scores indicating worse health-related quality of life.[14,15] A minimally important difference in the score has not been established for patients with idiopathic pulmonary fibrosis; in patients with chronic obstructive pulmonary disease, this difference is 4 points.[16] Patients completed the SGRQ at baseline and at 6, 12, 24, and 52 weeks. Acute exacerbations were defined as events meeting all of the following criteria: unexplained worsening or development of dyspnea within the previous 30 days; new diffuse pulmonary infiltrates visualized on chest radiography, HRCT, or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit; and exclusion of any known causes of acute worsening, including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, in accordance with routine clinical practice and microbiologic studies. All acute exacerbations reported by the site investigators were categorized by the adjudication committee, whose members were unaware of the study-group assignments, as confirmed or suspected or were not considered to be an acute exacerbation according to prespecified criteria.[17]

Other prespecified secondary end points included the absolute change from baseline in FVC (in milliliters and as a percentage of the predicted value) over the 52-week treatment period, the proportion of patients with an FVC response (defined as the proportion of patients in whom the percentage of predicted FVC did not decline by more than 5 percentage points or by more than 10 percentage points at week 52), the risk of an acute exacerbation, the change from baseline in SGRQ domain scores over the 52-week treatment period, death from any cause, death

from a respiratory cause, and death that occurred between randomization and 28 days after the last dose of the study drug. All mortality end points were measured as the time to death. Safety was assessed by means of clinical and laboratory evaluation at study visits and the recording of adverse events.

STATISTICAL ANALYSIS

Efficacy and safety analyses were conducted for patients who were randomly assigned to a study group and received at least one dose of the study medication. The primary end point was analyzed with the use of a random coefficient regression model (with random slopes and intercepts) that included sex, age, and height as covariates. The treatment effect was determined by using estimated slopes for each study group (on the basis of the time-by-treatment interaction term from the mixed model). All available FVC values from baseline to week 52 were used in the primary model, including FVC measurements at the follow-up visit for patients who discontinued the study medication prematurely and did not complete the study visits through week 52. The statistical model used for the primary analysis allowed for missing data, assuming that they were missing at random; missing data were not imputed for the primary analysis, but data collected after discontinuation of the study drug were used in the primary analysis. Significance tests were two-sided, with an alpha value of 0.05.

The superiority of nintedanib over placebo with respect to the primary and key secondary end points was tested with the use of a hierarchical procedure to account for multiple comparisons (see Section D in the Supplementary Appendix). Sensitivity analyses were performed to assess the robustness of the results for the primary and key secondary end points. Multiple imputation sensitivity analyses were performed to assess the effect of missing data and provide estimates of the treatment effect under different assumptions about missing data (Fig. S2 in the Supplementary Appendix). For the time to the first acute exacerbation, a sensitivity analysis based on the occurrence of confirmed or suspected acute exacerbations (as determined by the adjudication committee) in pooled data from the two trials was prespecified.

The frequency and severity of adverse events were documented according to the *Medical Dictionary for Regulatory Activities*, version 16.1. Safety analyses were descriptive. For information on the statistical analysis of other end points, see Section D in the Supplementary Appendix.

For each trial, the sample size was calculated to provide 90% power to detect a between-group difference of 100 ml in the annual rate of FVC decline. On the basis of data from the phase 2 trial, the standard deviation for the change in FVC from baseline was assumed to be 300 ml in both groups. Assuming that it would not be possible to evaluate data for 2% of patients, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib group for a two-group t-test at a one-sided significance level of 2.5%. Since the primary analysis was based on a random coefficient regression model that included adjustment for several variables and took into account information across time, we expected that the power would be greater than the 90% calculated for the t-test.

RESULTS

PATIENTS

Between May 2011 and September 2012, a total of 1066 patients underwent randomization: 515 patients in INPULSIS-1 and 551 patients in INPULSIS-2 (Fig. S1 in the Supplementary Appendix). In INPULSIS-1, a total of 513 patients received at least one dose of the study medication (309 received nintedanib and 204 received placebo). A total of 78 patients (25.2%) in the nintedanib group and 36 patients (17.6%) in the placebo group discontinued the study medication prematurely. Of these patients, 31 (39.7%) in the nintedanib group and 11 (30.6%) in the placebo group completed visits up to week 52. The most frequent reason for premature discontinuation of the study medication was at least one adverse event (65 patients [21.0%] in the nintedanib group and 24 [11.8%] in the placebo group). In INPULSIS-2, a total of 548 patients received at least one dose of the study medication (329 received nintedanib and 219 received placebo). A total of 78 patients (23.7%) in the nintedanib group and 44 patients (20.1%) in the placebo group discontinued the study medication prematurely. Of these patients, 26 (33.3%) in the nintedanib group and 10 (22.7%) in the placebo group completed visits up to week 52. The most frequent reason for premature discontinu-

ation of the study medication was at least one adverse event (62 patients [18.8%] in the nintedanib group and 35 [16.0%] in the placebo group). The proportion of patients with missing FVC data at week 52 was approximately 15%; the proportion of patients with missing data did not differ significantly between the nintedanib and placebo groups (Fig. S2 in the Supplementary Appendix).

In each trial, the baseline characteristics of patients in the nintedanib and placebo groups were similar (Table 1, and Table S3 in the Supplementary Appendix). The mean duration of exposure to the study drug in the nintedanib and placebo groups was similar (approximately 45 weeks in each trial), but a higher proportion of patients in the nintedanib group than in the placebo group had dose reductions or interrup-

Table 1. **Baseline Characteristics of Patients in INPULSIS-1 and INPULSIS-2.***

Characteristic	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
Male sex — no. (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age — yr	66.9±8.4	66.9±8.2	66.4±7.9	67.1±7.5
Weight — kg	82.0±16.8	81.2±16.3	76.6±15.9	76.3±16.5
Body-mass index†	28.6±4.5	28.1±4.6	27.6±4.6	27.2±4.5
Smoking status — no. (%)				
Never smoked	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
Former smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)
Current smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)
Time since diagnosis of idiopathic pulmonary fibrosis — yr	1.7±1.4	1.6±1.4	1.6±1.3	1.6±1.3
Specimen from surgical lung biopsy available — no. (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Systemic corticosteroid therapy — no. (%)‡	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC				
Mean — ml	2757±735	2845±820	2673±776	2619±787
Median — ml	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC (%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
DLCO				
mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value§	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8
SpO_2 — %	95.9±2.0	95.9±1.9	95.8±2.6	95.7±2.1
Total SGRQ score¶	39.6±17.6	39.8±18.5	39.5±20.5	39.4±18.7

* Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SpO_2 oxygen saturation of peripheral blood.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Prednisone at a dose of no more than 15 mg per day or the equivalent was permitted if the dose had been stable for at least 8 weeks before screening.

§ The percentage of the predicted value for the diffusion capacity of the lung for carbon monoxide (DLCO) was calculated with the use of the equation described by the European Community for Steel and Coal in Cotes et al.[18] In INPULSIS-2, data were available for 218 patients in the placebo group.

¶ In INPULSIS-1, the total score on the St. George's Respiratory Questionnaire (SGRQ) was available for 298 patients in the nintedanib group and 202 patients in the placebo group; in INPULSIS-2, the total SGRQ score was available for 326 patients in the nintedanib group and 217 patients in the placebo group. The total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life.

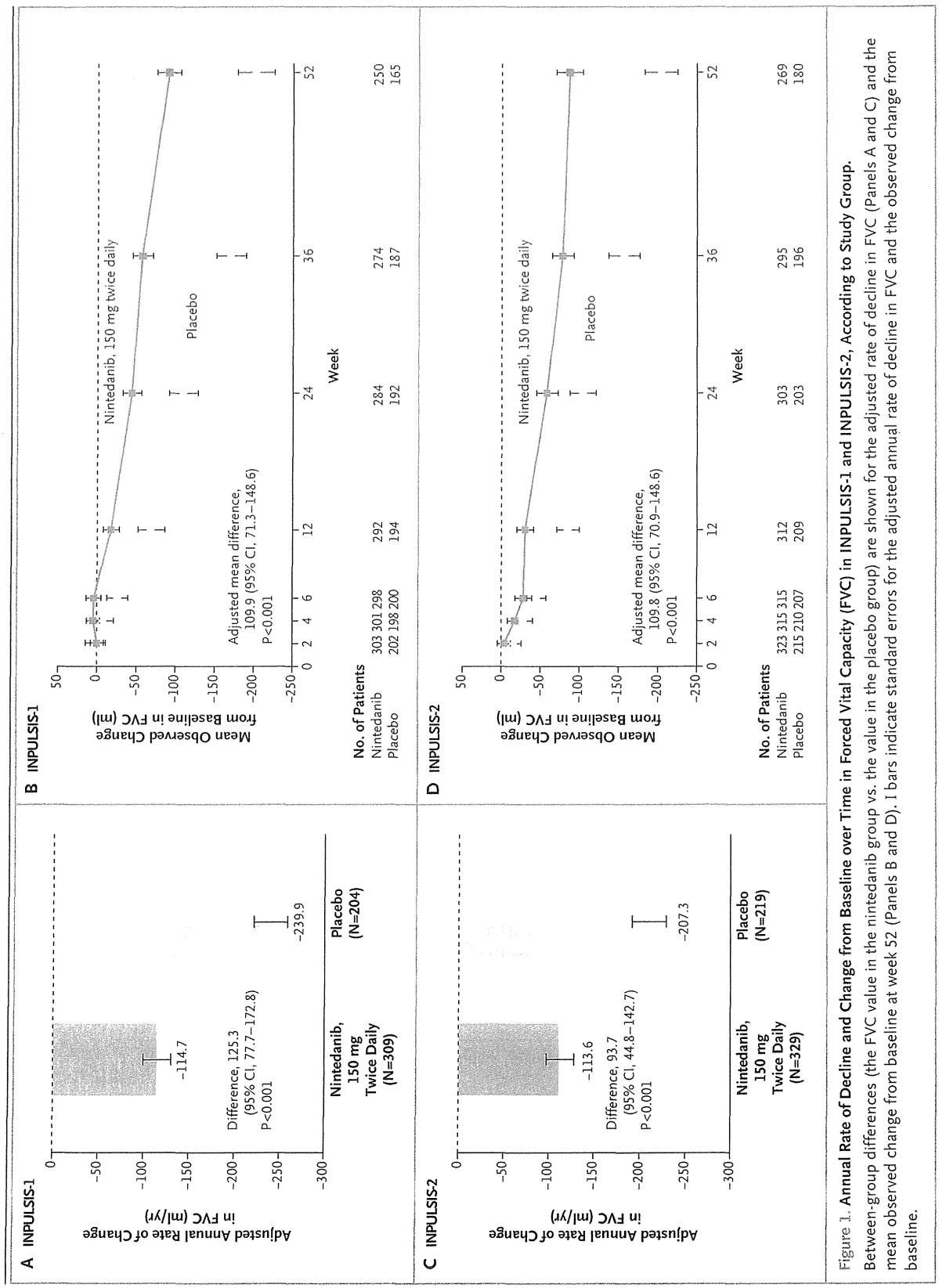

Figure 1. **Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.**
Between-group differences (the FVC value in the nintedanib group vs. the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rate of decline in FVC and the observed change from baseline.

tions (Table S4 in the Supplementary Appendix). The dose intensity — the amount of drug administered divided by the amount that would have been administered had the regimen of 150 mg twice daily been followed throughout the study or until permanent discontinuation of the study medication — was more than 90% in 75.9% of patients in the nintedanib groups.

LUNG FUNCTION

In both trials, the adjusted annual rate of change in FVC was significantly lower in the nintedanib group than in the placebo group. In INPULSIS-1, the rate was −114.7 ml per year in the nintedanib group as compared with −239.9 ml per year in the placebo group, representing a difference of 125.3 ml per year (95% confidence interval [CI], 77.7 to 172.8; P<0.001) (Fig. 1A). In INPULSIS-2, the rate was −113.6 ml per year in the nintedanib group as compared with −207.3 ml per year in the placebo group, representing a difference of 93.7 ml per year (95% CI, 44.8 to 142.7; P<0.001) (Fig. 1C). In both trials, the results of prespecified sensitivity analyses were consistent with the results of the primary analysis (Fig. S2 in the Supplementary Appendix). In particular, in the multiple imputation analyses, which were based on the conservative assumption that missing data were informative rather than random, the estimates of treatment effect and the corresponding confidence intervals were consistent with the results of the primary analysis in each study. This finding shows that the primary results are robust and were not influenced by alternative assumptions about missing data. In addition, the mean observed changes in FVC over time (unadjusted, nonimputed results) were consistent with the results of the primary analysis in both trials (Fig. 1B and 1D).

In each trial, a significantly greater proportion of patients in the nintedanib group than in the placebo group had a response in FVC when patients with a response were defined as those who did not have an absolute decline in the percentage of predicted FVC that was more than 5 percentage points at week 52 (Table 2). When patients with a response in FVC were defined as those who did not have an absolute decline in the percentage of predicted FVC that was more than 10 percentage points at week 52, a significantly greater proportion of patients in the nintedanib group than in the placebo group had a response

Table 2. **Secondary Lung-Function End Points at Week 52.**

End Point	INPULSIS-1				INPULSIS-2			
	Nintedanib (N=307)	Placebo (N=204)	Difference, Nintedanib vs. Placebo (95% CI)	P Value	Nintedanib (N=327)	Placebo (N=217)	Difference, Nintedanib vs. Placebo (95% CI)	P Value
Adjusted absolute mean change from baseline in FVC — ml	−95.1	−205.0	109.9 (71.3 to 148.6)	<0.001	−95.3	−205.0	109.8 (70.9 to 148.6)	<0.001
Adjusted absolute mean change from baseline in FVC — % of predicted value	−2.8	−6.0	3.2 (2.1 to 4.3)	<0.001	−3.1	−6.2	3.1 (1.9 to 4.3)	<0.001
FVC response at wk 52 — no. (%)*								
FVC decline ≤5 percentage points	163 (52.8)	78 (38.2)	1.85 (1.28 to 2.66)	0.001	175 (53.2)	86 (39.3)	1.79 (1.26 to 2.55)	0.001
FVC decline ≤10 percentage points	218 (70.6)	116 (56.9)	1.91 (1.32 to 2.79)	<0.001	229 (69.6)	140 (63.9)	1.29 (0.89 to 1.86)	0.18

* Between-group differences are expressed as odds ratios for FVC response. FVC decline denotes an absolute decline in the percentage of the predicted value. For the FVC response at week 52, there was a total of 309 participants in the nintedanib group in INPULSIS-1 and a total of 329 participants in the nintedanib group and 219 participants in the placebo group in INPULSIS-2.