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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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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.
Methods: The INPULSIS™ trials are replicate Phase III, randomized, double-blind, studies

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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 as originally planned. In addition, vital status at week 52 was to be collected for all patients who prematurely

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