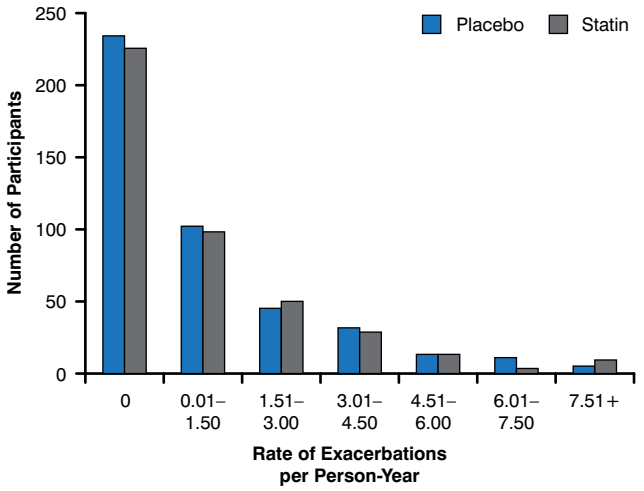
difference found in the severity of COPD exacerbations with simvastatin compared with placebo, with similar rates of mild, moderate, severe, and very severe exacerbations. No difference in the mean exacerbation rates was found with simvastatin compared with placebo for any prespecified subgroups, including smoking status, study center, gender, and race.

Figure 1. Mean Number of Exacerbations Per Person-Year



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There was no difference between simvastatin and placebo for the secondary endpoints of change in spirometric measures of lung function and quality of life, as assessed by the St. George's Respiratory Questionnaire. The rates of nonfatal serious adverse events (SAEs) were similar (0.63 and 0.62 per participant-year with simvastatin and placebo, respectively), but the overall number of SAEs was limited.

Simvastatin was associated with improvements in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C). Baseline lipid levels were similar in study participants. LDL-C was decreased by 33.2 mg/dL with simvastatin and 6.6 mg/dL with placebo, and HDL-C was increased by 2.5 mg/dL and decreased by 0.5 mg/dL, respectively.

Study limitations included not using C-reactive protein level as an inclusion criterion and restriction of the patient population to those with moderate or severe COPD.

The STATCOPE trial did not demonstrate a therapeutic benefit, from a respiratory perspective, of statins in patients with moderate to severe COPD, stated Dr. Criner.

Nintedanib Is Safe and Effective in Patients With IPF: Results of the INPULSIS Trials

Written by Brian Hoyle

Nintedanib, a tyrosine kinase inhibitor that targets fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor, was shown to lessen the decline in lung function and decrease acute exacerbations in patients with idiopathic pulmonary fibrosis (IPF) in the Phase 2 TOMORROW study [Richeldi L et al. *N Engl J Med* 2011]. Luca Richedli, MD, PhD, University of Southampton, Southampton, United Kingdom, presented the primary results for two 52-week Phase 3 randomized, placebo-controlled trials (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients [INPULSIS] I and II) [Richeldi L et al. *N Engl J Med* 2014].

In the INPULSIS trials, conducted at 205 sites in 24 countries globally, patients with IPF were randomly assigned in a 3:2 ratio to nintedanib 150 mg twice daily or placebo for 52 weeks. Key inclusion criteria were age ≥40 years, diagnosis of IPF within 5 years of randomization, chest high-resolution computed tomography (HRCT) performed within 12 months of screening, HRCT pattern and (if available) surgical lung biopsy pattern consistent with diagnosis of IPF as assessed centrally by 1 expert radiologist and 1 expert pathologist, forced vital capacity (FVC) ≥50% of predicted value, and carbon monoxide diffusing capacity 30% to 79% of predicted value. Key exclusion criteria included a ratio of forced expiratory volume in 1 second to FVC < 0.7 (prebronchodilator); treatment with N-acetylcysteine or prednisone >15 mg/day or equivalent within 2 weeks of screening; treatment with pirfenidone, azathioprine, cyclophosphamide, cyclosporine A, or any investigational drug within 8 weeks of screening; requirement for fibrinolysis, full-dose therapeutic anticoagulation, or high-dose antiplatelet therapy; and likelihood of undergoing lung transplantation during the study. The primary end point was the annual rate of decline in FVC. Key secondary end points were time to the first acute exacerbation and change in St. George's Respiratory Questionnaire total score over the 52 weeks.

Patient disposition is shown in Table 1. In total, 1066 patients were randomly assigned, with 25.2% and 17.6% medication discontinuation rates for nintedanib and placebo in INPULSIS-1 and 23.7% and 20.1% discontinuation rates, respectively, in INPULSIS-2 (Table 1).

Rates of study completion were similar, at 84.1% for nintedanib and 85.3% for placebo in INPULSUS-1 and 82.7% and 81.7%, respectively, in INPULSIS-2.

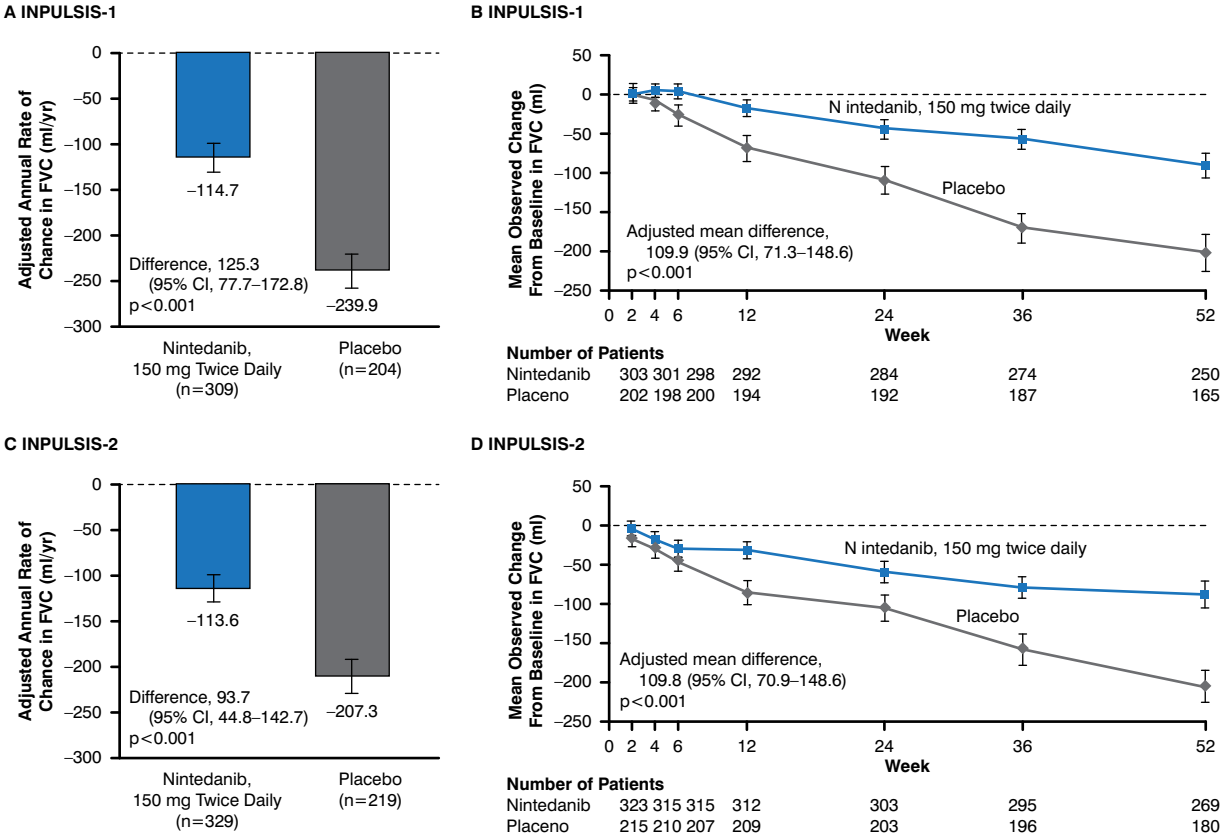
Table 1. Patient Disposition in the INPULSIS Trials*

Variable	INPULSIS-1		INPULSIS-2	
	Nintedanib 150 mg Twice Daily	Placebo	Nintedanib 150 mg Twice Daily	Placebo
Screened patients, Number	718		794	
Screen failure rate, %	28		31	
Randomized patients, Number	309	206	331	220
Treated patients, Number	309	204	329	219
Prematurely discontinued trial medication, Number (%)	78 (25.2)	36 (17.6)	78 (23.7)	44 (20.1)
Prematurely discontinued because of adverse event, Number (%)	65 (21.0)	24 (11.8)	62 (18.8)	35 (16.0)
Completed planned observation time, Number (%)	260 (84.1)	174 (85.3)	272 (82.7)	179 (81.7)

INPULSIS=Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients.

*On November 21, 2014, the data in the Screened patients and Screen failure rate rows were moved from appearing under the INPULSIS-1 Nintedanib 150 mg Twice Daily and Placebo columns to being centered under the INPULSIS-1 and INPULSIS-2 columns, respectively.

Figure 1. Primary Efficacy End Point



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The primary end point was met in both trials, with significantly less decline of FVC in patients receiving nintedanib versus placebo (–114.7 vs –239.9 mL/year in INPULSIS-1 [p<0.001]; –113.6 vs –207.3 mL/year in INPULSIS-2 [p<0.0011]; Figure 1). Significance was maintained when the data were pooled (–113.6 vs –207.3 mL/year, p<0.0001). The trial arms were not significantly different in the time to first exacerbation

Table 2. Adverse Events[a]

Category	INPULSIS-1		INPULSIS-2	
	Nintedanib 150 mg Twice Daily (n=309)	Placebo	Nintedanib 150 mg Twice Daily (n=329)	Placebo
Any adverse events	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Severe adverse events	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to drug discontinuation	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)

INPULSIS=Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients.

[a]Data are expressed as number (percentage).

for INPULSIS-1 alone (HR, 1.15; 95% CI, 0.54–2.42; p=0.67) or when the 2 trials were pooled (HR, 0.64; 95% CI, 0.39–1.05; p=0.08) but were significantly different in INPULSIS-2 (HR, 0.38; 95% CI, 0.19–0.77; p=0.005). A similar pattern was found for the respiratory questionnaire scores. Mortality was not significantly different between the treatment and placebo arms in the pooled data (5.5% for nintedanib and 7.8% for placebo; HR, 0.70; 95% CI, 0.43–1.12; p=0.14).

Adverse event data are summarized in Table 2. The most frequent adverse events included diarrhea, nausea, cough, and bronchitis and were generally considered mild to moderate in severity. The rates of serious adverse events were similar between arms. However, it was noted that a higher proportion of patients in the nintedanib groups had elevated liver enzymes (4.9%–5.2% vs 0.5%–0.9%) and myocardial infarctions (1.5%–1.6% vs 0.5%) compared with placebo.

Prof. Richeldi concluded that the INPULSIS-1 and INPULSIS-2 trials established the efficacy of nintedanib for minimizing the decline in lung function in patients with IPF and was generally well tolerated.

ASPIRE Study: Results at Early Termination of LVR Study

Written by Mary Mosley

A study of a nonsurgical lung volume reduction (LVR) approach using an emphysematous lung sealant (ELS) demonstrated that >50% of treated patients experienced minimal, clinically important differences in health status and respiratory measures compared with patients treated only with optimal medical therapy. However, the rate of serious adverse events (SAEs) was higher in patients who responded to ELS treatment. The Study of the AeriSeal System for Hyperinflation Reduction in Emphysema [ASPIRE; NCT01449292; Washko GR et al. *Am J Respir Crit Care Med* 2014] was terminated early for financial reasons. George Washko, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data on the 90 patients who completed the 3- and the 6-month follow-up.

The multicenter, multinational, randomized, controlled trial used ELS, a synthetic polymer that targets the alveolar compartment of the lung to block the distal airways and collateral ventilation, to achieve nonresectional inflation in patients with hyperinflation. The goal was to achieve the clinical and physiologic benefit of LVR without the morbidity and mortality associated with surgery. In ASPIRE, 2 subsegments each in the right and upper left lobes were treated endoscopically with ELS, and patients were hospitalized overnight for observation.

The study patients had upper lobe–predominant emphysema, with forced expiratory volume in 1 second (FEV_1) <50%, total lung capacity >100%, and a diffusing capacity of the lungs for carbon monoxide of 20% to 60%. In total, 95 patients were randomized to optimal medical therapy plus ELS (ELS treated; n=61) or optimal medical therapy alone (control; n=34). Their mean age was 65 years, most were men (~60%), and they had smoking histories of >20 pack-years. Patients with a_1 antitrypsin deficiency, a genetic risk factor for emphysema, and those who had prior LVR were excluded.

The primary outcome was change in FEV_1 at 12 months from baseline. Data were available at 3 months for 34 ELS-treated and 23 control patients and at 6 months for 21 ELS-treated and 13 control patients. The changes in FEV_1 in the ELS-treated patients were +11% and +19% at 3 and 6 months, compared with –2% and +1% in the control patients, respectively. The change in health status as measured by the St. George's Respiratory Questionnaire, a secondary end point, was –11 and –12 at 3 and 6 months in the ELS-treated patients and –4 and –3, respectively, in the control patients. The change in the Modified Medical Research Council dyspnea scale was small: –1 at 3 and