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

6 months in the ELS-treated and 0 at both time points in the control patients.

The rate of all SAEs was higher for the ELS-treated than for control patients, with 43% and 16%, respectively, requiring hospitalization, primarily for respiratory SAEs (39% of treatment and 15% of control patients). Two patients in the treatment group died (1 treatment related).

The individual patient data at 6 months showed that the improvement in FEV_1 ranged from a nearly 25% reduction to an approximately 120% increase in the ELS-treated patients. The median change in FEV_1 was approximately 19% and the mean change was approximately 28% in the ELS-treated patients, which is comparable with surgical LVR outcomes, stated Dr. Washko.

Consistent Targeted Dosing of BUD Benefits Asthma Patients Needing Long-term Oral Corticosteroids

Written by Mary Beth Neirengarten

In patients with severe asthma who depend on long-term oral corticosteroid therapy, additional treatment with consistent doses of budesonide (BUD) delivered by a novel inhalation system significantly improved lung function and control of asthma exacerbations.

Sebastian Canisius, MD, Vectura GmbH, Frankfurt, Germany, reported outcomes from the AKITA Inhaled Steroid Suspension for Inhalation in Subjects With Asthma [AICS; NCT01200108; Canisius S et al. *Am J Respir Crit Care* 2014]—a Phase 2/3, randomized, placebo-controlled trial featuring 4 arms and parallel groups. In it, researchers evaluated the efficacy of a novel computer-controlled, compressor-driven inhalation system (Akita; Activaero) that delivered consistent doses of BUD as add-on treatment in patients with severe asthma on long-term oral corticosteroids therapy.

In the study, adult patients (age, 18 to 65 years; Table 1) from 27 respiratory outpatient centers in Germany, Poland, and Ukraine were randomly assigned in a double-blind fashion to 1 of 4 treatment arms for 18 weeks:

1. AICS-BUD (1 mg): AKITA-inhaled corticosteroid+BUD (1 mg, twice a day [BID]; n=80)
2. AICS-BUD (0.5 mg): AKITA-inhaled corticosteroid+BUD (0.5 mg, BID; n=39)
3. AICS-placebo: AKITA-inhaled corticosteroid+placebo (BID; n=40)
4. CN-BUD: open-label treatment with BUD (1 mg, BID) administered with a conventional nebulizer (n=40)

The doses of long-term corticosteroid therapy were tapered until Week 14, and patients were followed to Week 20.

Table 1. Baseline Characteristics[a]

	AICS-BUD				
	1 mg (n=80)	0.5 mg (n=39)	Placebo (n=40)	CN-BUD (n=40)	Total (n=199)
Age, years	52.0 ± 8.8	51.6 ± 10.0	52.3 ± 9.2	49.7 ± 10.6	51.5 ± 9.5
Female	56 (70.0)	14 (64.1)	24 (60.0)	24 (60.0)	129 (64.8)
Duration of asthma, years	19.2 ± 12.1	21.2 ± 12.6	19.9 ± 11.7	18.4 ± 10.6	19.6 ± 11.8
MiniAQLQ, total score	3.6 ± 0.9	3.7 ± 1.0	3.7 ± 0.7	3.6 ± 1.0	2.6 ± 0.9
ACQ, total score	3.2 ± 0.8	3.2 ± 0.9	3.0 ± 0.7	3.1 ± 1.0	3.1 ± 0.80
Predicted FEF_{25-75}, %	59.0 ± 11.8	56.4 ± 9.5	57.0 ± 11.2	58.1 ± 12.3	57.9 ± 11.3
FEV_1, L/s	1.11 ± 0.56	1.00 ± 0.51	1.00 ± 0.51	1.11 ± 0.61	ND
OCS,[b] baseline dose, mg/day	10.0 ± 7.1	10.6 ± 9.0	10.4 ± 8.2	10.1 ± 6.2	10.2 ± 7.5
SABA, puffs/day[c]	4.6 ± 3.7	4.0 ± 3.6	4.3 ± 3.6	4.3 ± 3.1	4.4 ± 3.5
Ex-smokers[d]	7 (8.8)	4 (10.3)	3 (7.5)	9 (22.5)	23 (11.6)
Pack-years	5.3 ± 3.0	5.5 ± 2.6	8.0 ± 1.0	5.2 ± 3.1	5.3 ± 3.0

ACQ=Asthma Control Questionnaire; AICS-BUD= AKITA-inhaled corticosteroid; AQLQ=Asthma Quality of Life Questionnaire; BUD=budesonide; CN=conventional nebulizer; FEF_{25-75}=forced expiratory flow from 25% to 75% of vital capacity; FEV_1=forced expiratory volume in 1 second; ICS=inhaled corticosteroid; ND=not determined; OCS=oral corticosteroids; SABA=short-acting beta agonist.

[a]Values in mean ± SD or n (%).

[b]All patients were receiving OCS; prednisone was specified by the protocol for use during the study.

[c]n=75, 34, 37, 38, and 184 for 5 columns in the table.

[d]Study eligibility specified patients were nonsmokers or ex-smokers.