FVC decline $\geq 10\%$ pred in INPULSIS had higher mortality in INPULSIS-ON than patients with FVC decline $< 10\%$ pred.

Conclusion Independent of FVC decline in the first year, most patients had FVC decline $< 10\%$ pred with continued nintedanib for a second year. FVC decline $\geq 10\%$ pred over 1 year did not predict subsequent FVC decline, but was associated with higher mortality.

Please refer to page A261 for declarations of interest in relation to abstract M29.

Abstract M29 Table 1

Absolute decline in FVC from baseline to week 52 of INPULSIS in patients treated with nintedanib (first year of treatment)	Outcome in the first year of INPULSIS-ON (second year of treatment)*	n (%)
<10% predicted (n=383)	Absolute decline in FVC<10% predicted [†]	301 (78.6)
	Absolute decline in FVC $\geq 10\%$ predicted	64 (16.7)
	Death	18 (4.7)
$\geq 10\%$ predicted (n=47)	Absolute decline in FVC<10% predicted [†]	31 (66.0)
	Absolute decline in FVC $\geq 10\%$ predicted	8 (17.0)
	Death	8 (17.0)

*Patients who discontinued INPULSIS-ON without having an absolute decline in FVC $\geq 10\%$ predicted or having died were counted in the category "absolute decline in FVC $< 10\%$ predicted". [†]Includes patients with an increase, no decline, or an absolute decline in FVC $> 0\%$ but $< 10\%$ predicted in the first year of INPULSIS-ON.

M30

EFFECT OF DOSE REDUCTIONS AND/OR INTERRUPTIONS ON THE EFFICACY OF NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF): SUBGROUP ANALYSIS OF THE INPULSIS TRIALS

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Introduction and Aim The efficacy and safety of nintedanib in patients with IPF were assessed in two replicate Phase III placebo-controlled INPULSIS trials. In both trials, nintedanib reduced disease progression by reducing decline in FVC. The recommended dose of nintedanib was 150 mg bid, but dose reductions to 100 mg bid and treatment interruptions were allowed for the management of adverse events. Following dose reduction, the dose could be re-escalated to 150 mg bid. We assessed whether dose reductions and/or treatment interruptions influenced the effect of nintedanib on reducing FVC decline.

Methods We assessed change from baseline in FVC (mL) at week 52 in subgroups of patients by their last dose (150 mg bid or 100 mg bid) and whether they had experienced a dose reduction and/or treatment interruption using pooled data from both INPULSIS trials. Patients who prematurely

discontinued trial medication but had an FVC value at week 52 were included in the analysis. Analyses were descriptive and based on observed cases.

Results A total of 864 patients were included in the analysis (519 treated with nintedanib, 345 with placebo). Most (75%) patients did not have a dose reduction or treatment interruption. Mean (SD) changes from baseline in FVC at week 52 in subgroups by dose are shown in the Table. In patients who took nintedanib 150 mg bid as their last dose, absolute mean changes from baseline in FVC at week 52 were -118 mL and -90 mL in patients who did and did not have any prior dose reduction and/or treatment interruption, respectively. In patients who took nintedanib 100 mg bid as their last dose, mean change from baseline in FVC at week 52 was -74 mL. These changes were consistent with the decline in FVC observed in the whole nintedanib group (-89 mL).

Conclusion Pooled data from the INPULSIS trials show that decline in FVC was similar in patients treated with nintedanib irrespective of whether they had dose reductions and/or treatment interruptions. These Results suggest that the dosing regimen used in the INPULSIS trials was effective at reducing disease progression in patients with IPF.

Please refer to page A261 for declarations of interest in relation to abstract M30.

Abstract M30 Table 1 Change from baseline in FVC (mL) at week 52 by dose subgroups in INPULSIS

	Nintedanib		Placebo	
	N	Mean (SD)	N	Mean (SD)
All patients	519	-89 (264)	345	-203 (293)
Patients who did not have a dose reduction or treatment interruption	340	-90 (265)	309	-200 (292)
Patients who took 150 mg bid as last dose and had ≥ 1 dose reduction and/or treatment interruption	56	-118 (251)	31	-203 (273)
Patients who took 100 mg bid as last dose after ≥ 1 dose reduction and/or treatment interruption	123	-74 (269)	5	-391 (422)

M31

SAFETY OF COMBINED PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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Background Safety data on combined pirfenidone and nintedanib use are limited.

Methods A single-arm, open-label study (NCT02598193) assessed safety and tolerability of 24 weeks' pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day) in patients with idiopathic pulmonary fibrosis (IPF) with forced vital capacity (FVC) $\geq 50\%$ and diffusing capacity of the lung for carbon monoxide (DLco) $\geq 30\%$. Before initiating nintedanib, patients had received pirfenidone for ≥ 16 weeks and tolerated a stable dose

Abstract M31 Table 1 Summary of safety profile at the pre-specified interim analysis

N=63	Patients with at least one TEAE ^a n (%)	Patients with at least one TEAE related ^b to pirfenidone only n (%)	Patients with at least one TEAE related ^b to nintedanib only n (%)	Patients with at least one TEAE related ^b to both pirfenidone and nintedanib n (%)
All treatment-related TEAEs (total of 330 events)				
≥1 TEAE	50 (79.4)	11 (17.5)	47 (74.6)	14 (22.2)
≥1 serious TEAE	2 (3.2)	0	2 (3.2)	0
Common treatment-related TEAEs (occurring in ≥10% of patients)				
Diarrhoea	30 (47.6)	2 (3.2)	26 (41.3)	3 (4.8)
Nausea	28 (44.4)	2 (3.2)	24 (38.1)	6 (9.5)
Vomiting	11 (17.5)	1 (1.6)	9 (14.3)	4 (6.3)
Fatigue	9 (14.3)	0	7 (11.1)	2 (3.2)
Decreased appetite	8 (12.7)	1 (1.6)	4 (6.3)	3 (4.8)
Serious treatment-related TEAEs				
Transient ischaemic attack	1 (1.6)	0	1 (1.6)	0
Deep vein thrombosis	1 (1.6)	0	1 (1.6)	0

^aEach of the patients could have experienced ≥1 treatment-related event, with the potential for different events to be related to different treatments; ^bdetermined by the investigator to be related to pirfenidone; ^cdetermined by the investigator to be related to nintedanib; ^ddetermined by the investigator to be related to both pirfenidone and nintedanib
TEAE, treatment-emergent adverse event

of ≥1602 mg/day pirfenidone for ≥28 days. Investigators recorded treatment-emergent adverse events (TEAEs), attributing them to pirfenidone, nintedanib, both or neither. Change from baseline FVC, DLco and King's Brief Interstitial Lung Disease (K-BILD) score were assessed at 24 weeks. The study is monitored by a data monitoring committee.

Results Eighty-nine patients were enrolled.

A pre-specified interim analysis was conducted once 63 patients (mean age 68.7 years, 85.7% male) completed (n=50) or discontinued (n=13) 24 weeks' combination treatment. Fifty patients had 330 treatment-related TEAEs (Table); 11 patients discontinued due to TEAEs. Two patients had serious treatment-related TEAEs (Table) but none led to death. Final Results for all 89 patients, including change from baseline FVC, DLco and K-BILD score, will be presented at BTS.

Conclusions Combined pirfenidone and nintedanib use for 24 weeks did not reveal a different safety profile to that expected for either treatment alone. Patients had tolerated a stable dose of pirfenidone before initiation of nintedanib, which may explain why investigators attributed more TEAEs to nintedanib than pirfenidone.

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M32

EFFECT OF PIRFENIDONE ON ALL-CAUSE MORTALITY (ACM) AND FORCED VITAL CAPACITY (FVC) IN IDIOPATHIC PULMONARY FIBROSIS (IPF) PATIENTS WITH LOW FVC AND/OR LOW DLCO: ANALYSIS OF POOLED DATA FROM ASCEND AND CAPACITY

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Introduction The pivotal trials of the two approved therapies in IPF, pirfenidone and nintedanib, assessed patients with protocol-defined mild to moderate disease. The effect of pirfenidone in patients with more severe lung function impairment warrants further investigation. Pooled Results from ASCEND and CAPACITY studies (NCT01366209, NCT00287729 and NCT00287716) showed a significant reduction at 12 months in the risk of ACM (hazard ratio [HR], 0.52; 95% CI, 0.31, 0.87)¹ and in decline of percent predicted FVC (%FVC; 14.8% vs. 26.3% patients with ≥10% decline in %FVC or death, $p < 0.0001$)² for patients treated with pirfenidone vs. placebo. We present pooled subgroup analyses from ASCEND and CAPACITY for patients with low baseline %FVC (<50%) and/or low percent predicted diffusing capacity for carbon monoxide (%DL_{CO} <35%) to further inform on treatment effect of pirfenidone in patients with more severe lung function impairment.

Methods ACM was compared using the log-rank test, and HR was estimated using Cox regression. The categorical change in %FVC was summarised with the percent of patients with a ≥10% absolute decline or death, and treatment comparison was performed using the rank ANCOVA method. Annual rate of FVC decline was estimated using the mixed-effects model.

Results 170 patients (90 pirfenidone, 80 placebo) had low %DL_{CO} (n=157) or %FVC (n=13) at baseline. Treatment with pirfenidone was associated with a 72% reduction in risk of ACM over 12 months vs. placebo (4 vs. 12 deaths; HR, 0.28; 95% CI, 0.09, 0.86; $p = 0.018$; Table). There was a 56% relative reduction in the proportion of patients with a ≥10% absolute decline in %FVC or death at 12 months vs. placebo (18.9% vs. 42.5%; $p = 0.0038$). The annual rates of FVC decline were 150 and 278 mL in the pirfenidone and placebo arms, respectively ($p = 0.003$).

Conclusions Treatment with pirfenidone resulted in clinically meaningful benefits for ACM and FVC decline in patients with baseline %FVC <50% and/or %DL_{CO} <35%. These data suggest that patients with more severe lung function impairment can also benefit from pirfenidone therapy.

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Abstract M32 Table 1 ACM and FVC outcomes at 12 months in patients with IPF with low FVC and/or low DLCO at baseline*

Endpoint at 12 Months	Patients With Low FVC and/or Low DL _{CO} (n=170)	All Patients (n=1247)
Pirfenidone vs placebo	0.28 (0.09–0.86)	0.52 (0.31–0.87)
ACM: HR (95% CI)		
Pirfenidone vs. placebo:	18.9% vs. 42.5%	14.8% vs.
≥10% absolute decline in %FVC or death	($p = 0.0038$)	26.3% ($p < 0.0001$)
Pirfenidone vs. placebo:	150 vs. 278	109 vs. 208
Annual rate of FVC decline, mL	($p = 0.003$)	($p < 0.0001$)

*All pirfenidone-treated patients included in these analyses were randomised to receive 2403 mg/day.

M33

LONG-TERM EFFICACY OF NINTEDANIB IS MAINTAINED IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF) IRRESPECTIVE OF DOSE: SUBGROUP ANALYSIS OF INPULSIS-ON

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Introduction and Aim In the INPULSIS trials, nintedanib reduced the annual rate of decline in FVC versus placebo in patients with IPF (−113.6 versus −223.5 mL/year). Patients completing the 52 week treatment period could receive open-label nintedanib in an extension trial (INPULSIS-ON). Patients receiving nintedanib or placebo 150 mg bid at the end of INPULSIS received nintedanib 150 mg bid in INPULSIS-ON; patients receiving nintedanib or placebo 100 mg bid at the end of INPULSIS received nintedanib 100 mg bid or 150 mg bid in INPULSIS-ON, based on patient/investigator discussions. Dose reduction from 150 mg bid to 100 mg bid was allowed to manage adverse events; re-escalation to 150 mg bid was permitted. Our objective was to assess whether dose influenced the effect of nintedanib on FVC decline in INPULSIS-ON.

Methods The annual rate of decline in FVC over 96 weeks in INPULSIS-ON was assessed in subgroups of patients by whether they were treated with nintedanib 150 mg bid only, 100 mg bid only, or both 150 mg bid and 100 mg bid. All available FVC measurements collected at time points between baseline and week 96 were used to calculate FVC decline. These analyses were descriptive and based on a data snapshot in October 2015.

Results A total of 734 patients received nintedanib in INPULSIS-ON: 436 patients (59.4%) received nintedanib 150 mg bid, 53 patients (7.2%) received nintedanib 100 mg bid, and 245 patients (33.4%) received both doses. The annual rates of decline in FVC over 96 weeks were −116.4 (8.9) mL/year, −79.0 (30.1) mL/year, and −126.2 (11.4) mL/year in patients treated with nintedanib 150 mg bid, 100 mg bid, or both doses, respectively, and were consistent with the annual rate of decline in FVC over 96 weeks in all patients treated with nintedanib (−117.8 [6.8] mL/year).

Conclusion Data from INPULSIS-ON demonstrated that the annual rate of decline in FVC was similar in patients treated with nintedanib 150 mg bid, 100 mg bid, or both doses. The long-term efficacy of nintedanib in reducing disease progression was maintained in patients with IPF who required dose adjustments to manage adverse events.

Please refer to page A262 for declarations of interest in relation to abstract M33.

M34

CARDIOVASCULAR SAFETY OF NINTEDANIB IN SUBGROUPS BY CARDIOVASCULAR RISK AT BASELINE IN THE TOMORROW AND INPULSIS TRIALS

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Introduction and Aim Nintedanib is a tyrosine kinase inhibitor, a drug class that may be associated with increased risk of arterial thromboembolic events. The efficacy and safety of 52 weeks' treatment with nintedanib versus placebo in patients with IPF were assessed in the TOMORROW and INPULSIS trials. Patients with myocardial infarction in the previous 6 months, unstable angina in the previous month, or stroke in the previous year were excluded. We assessed the effect of CV risk at baseline on the CV safety of nintedanib 150 mg bid.

Methods Incidence rates of major adverse CV events (MACE) in subgroups of patients with a history of atherosclerotic CV disease and/or ≥1 CV risk factor at baseline (higher CV risk), and patients with no history of atherosclerotic CV disease and no CV risk factors at baseline (lower CV risk), were analysed using pooled data from the TOMORROW and INPULSIS trials. CV risk factors were defined as hypertension, dyslipidaemia, BMI ≥30 kg/m², current/former smoking, and diabetes. MACE were based on fatal adverse events included in the system organ classes "cardiac disorders" and "vascular disorders" in MedDRA; events in the subordinate standardised MedDRA query (SMQ) "myocardial infarction"; stroke based on selected preferred terms from the subordinate SMQs "haemorrhagic cerebrovascular conditions" and "ischaemic cerebrovascular

Abstract M34 Figure 1

conditions”; and MedDRA preferred terms “sudden death”, “cardiac death” and “sudden cardiac death”.

Results At baseline, 1107 (89.9%) patients (656 nintedanib, 451 placebo) had higher CV risk and 124 (10.1%) patients (67 nintedanib, 57 placebo) had lower CV risk. In patients with higher CV risk, incidence rates (95% CI) of MACE were 3.88 (2.58, 5.84) and 3.49 (2.10, 5.79) per 100 patient-years in the nintedanib and placebo groups, respectively. In patients with lower CV risk, incidence rates (95% CI) of MACE were

4.78 (1.54, 14.82) and 5.37 (1.73, 16.65) per 100 patient-years in the nintedanib and placebo groups, respectively.

Conclusion In pooled data from the TOMORROW and INPULSIS trials, the incidence of MACE was similar between the nintedanib and placebo groups in patients with higher CV risk at baseline and in patients with lower CV risk at baseline.

Please refer to page A262 for declarations of interest in relation to abstract M34.