FDA Arthritis Advisory Committee Meeting
FDA Opening Remarks

NDA 205832s12: Nintedanib for the treatment of patients with systemic sclerosis interstitial lung disease

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US Food and Drug Administration
July 25, 2019

Overview

- **Product:** Nintedanib (Ofev®)
- **Applicant:** Boehringer Ingelheim (BI)
- **Mechanism of action**: Inhibitor of tyrosine kinases
- **Approved indication**: Treatment of idiopathic pulmonary fibrosis (IPF)
- **Proposed indication:** Treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD)

Systemic Sclerosis (SSc)

- Rare, multisystem connective tissue disease
  - Affects ~100,000 people in the United States
  - Microvascular damage and fibrosis of the skin and internal organs
  - Primary causes of SSc-related death
    - Pulmonary fibrosis, pulmonary arterial hypertension, heart failure, cardiac arrhythmia
  - Interstitial lung disease in 55 to 65%, median survival 5 to 8 years
- Therapies
  - None FDA-approved
  - Based on expert-derived guidelines
  - Toxicities associated with standard of care treatments
- Need for additional therapies

Proposed Usage

- **Indication and Usage**
  - "Treatment of systemic sclerosis-associated interstitial lung disease."
- **Dosage and Administration**
  - "Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food.
  - Recommended dosage in patients with mild hepatic impairment (Child Pugh A): 100 mg twice daily approximately 12 hours apart taken with food.
  - Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions."

Overview of Nintedanib Safety

- **Warnings/Precautions**
  - Hepatic impairment
  - Elevated liver enzymes and drug-induced liver injury
  - Gastrointestinal (GI) disorders
  - Embryo-fetal toxicity
  - Arterial thromboembolic events
  - Bleeding events
  - GI perforation

Clinical Program

Study No.	Description	Subjects	Design	Treatment	Key Endpoints at Week 52
1199.214	Phase 3 efficacy and safety	576 patients with SSc-ILD	52 wk, R, DB, PC, PG	Nintedanib 150 mg BID PBO	- FVC (mL) - mRSS - SGRQ

R=randomized; DB=double blind, PC=placebo controlled, PG=parallel group, BID=twice daily, FVC=forced vial capacity, mRSS=modified Rodnan skin score, SSc-ILD=systemic sclerosis associated interstitial lung disease, SGRQ=St. George Respiratory Questionnaire

FVC as Efficacy Outcome

- Forced Vital Capacity (FVC)
  - Restrictive lung diseases, such as IPF and SSc-ILD
- FVC used in IPF programs for nintedanib and pirfenidone
  - Reduced the decline in FVC over 52 weeks
  - Supported by other clinically meaningful endpoints, e.g. exacerbations
  - Baseline FVC and decline in FVC >10% correlates with mortality[†]
- FVC as a primary efficacy variable in SSc-ILD program
  - IPF and SSc-ILD both chronic progressive fibrosing diseases
  - Less information about meaningful treatment effect and correlation with other meaningful endpoints

[†] Ann Am Thorac Soc Vol 14(9): 1395-1402

Relevant Regulatory History

- Approved for treatment of IPF on October 15, 2014
- Pre-IND meeting February 2015
  - Include all-cause mortality as an endpoint
  - Include secondary endpoints that measure how patients feel and function
  - Whether single study adequate depends on persuasiveness of treatment effect
- Orphan designation granted July 6, 2016
- Fast track designation granted March 7, 2018
- Priority review

Orphan Drug

- Orphan drug is a drug intended for use in a rare disease or condition
  - Affects less than 200,000 persons in the U.S., or
  - No reasonable expectation costs of research and development can be recovered by sales in the U.S. (21CFR316.21)
- Evidentiary standards for efficacy and safety are the same
- Additional considerations
  - Amount of data required
  - Feasibility

Quantity of Evidence Necessary to Support Effectiveness

- *FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (1998)*
  - *……Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness……*
  - *……In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use……*

- Review considerations for a single-study
  - SSc-ILD is a rare disease
  - Commonalities in the pathological pathways involved in fibrogenesis in IPF and SSc-ILD
  - IPF trials with nintedanib were similar in design

Efficacy Considerations

- Decrease in adjusted FVC decline in nintedanib group (*treatment difference: 41 mL/year*)
- Clinically important secondary endpoints not supportive of efficacy
- Less robust treatment effect in pre-specified subgroup analyses:
  - Patients from US and Canada (*10 mL/year*)
  - Patients on mycophenolate at baseline (*27 mL/year*)

Safety Considerations

- In general, the safety profile of nintedanib in SSc-ILD appears consistent with the known safety profile of nintedanib in IPF
- Nintedanib was associated with gastrointestinal and hepatic adverse events
  - AEs and SAEs of pneumonia
  - Overall infections were similar between treatment groups

Benefit-Risk Considerations

Benefits

- Decrease in adjusted annual FVC decline
  - Not supported by secondary endpoints
- Relative slowing of rate of FVC decline similar between SSc-ILD and IPF programs
  - In IPF, FVC supported by decrease in exacerbations, improvement in SGRQ, positive trends in mortality

Risks

- Labeled risks:
  - Hepatic impairment
  - Elevated liver enzymes/drug-induced liver injury
  - Gastrointestinal disorders
  - Arterial thromboembolic events
  - Bleeding events
  - Gastrointestinal perforation
- Pneumonia

Discussion Points and Voting Questions

1. **DISCUSSION:** Discuss the efficacy of nintedanib for treatment of patients with systemic sclerosis interstitial lung disease (SSc-ILD)
   a. Discuss the clinical meaningfulness of the changes in FVC with nintedanib treatment in the population studied

2. **DISCUSSION:** Discuss the FVC data from the following subgroups and the implications for use of nintedanib in patients in the US
   a. US and Canada subgroup compared to the overall study population
   b. Patients on background mycophenolate vs. no background mycophenolate treatment

Discussion Points and Voting Questions

3. **VOTE:** Do the data provide substantial evidence of the efficacy of nintedanib for the treatment of SSc-ILD?
   a. If no, what further data are needed?

Discussion Points and Voting Questions

4. **VOTE:** Is the safety profile of nintedanib adequate to support approval of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

Discussion Points and Voting Questions

5. **VOTE:** Is the benefit-risk profile adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease?

   a. If no, what further data are needed?


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FDA Arthritis Advisory Committee Meeting
FDA Overview of Clinical Program

NDA 205832s12: Nintedanib for the treatment of patients with systemic sclerosis interstitial lung disease

Nadia Habal, MD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
US Food and Drug Administration
July 25, 2019

FDA Presentation Outline

- Overview of Clinical Program
  - *Nadia Habal, MD, Medical Officer*
- Statistical Review of Efficacy
  - *Yu Wang, PhD, Statistical Reviewer*
- Clinical Review of Safety and Benefit-Risk Assessment
  - *Nadia Habal, MD, Medical Officer*

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SSc-ILD Overview and Therapies

- Systemic Sclerosis is a serious disease with considerable morbidity and mortality
  - Cardiac and **pulmonary** complications
- No FDA-approved therapies
- Treatment based on expert guidelines
  - Cyclophosphamide
  - Mycophenolate

IPF vs SSc-ILD

		IPF	SSc-ILD
Similarities	**Chronic, Progressive, Fibrotic**		
Differences	***Demographics***	Older Men	Middle-aged Women
	Histopathology	Usual interstitial pneumonitis	Non-specific interstitial pneumonitis
	Findings on High Resolution Computed Tomography	Traction bronchiectasis with peripheral basilar predominant opacities and honeycombing	Peripheral ground glass opacities
	Exacerbations	Yes	No
	Prognosis/ Mortality	More rapidly declining/ 2 to 5 years	5 to 8 years

Clinical Development in SSc-ILD

Study	Description	Subjects	Design	Treatment	Duration	Key Endpoints
1199.214	Phase 3 Efficacy and Safety	576 patients with SSc-ILD	R, DB, PC, PG	• Nintedanib 150 mg BID • Placebo	52 weeks	• FVC (mL) • mRSS • SGRQ

Abbreviations: R: randomized; DB: double blind; PC: placebo controlled; PG: parallel group; BID: twice daily; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; mRSS: modified Rodnan skin score; SSc-ILD: systemic sclerosis associated interstitial lung disease

1199.214: Study Design

Dose Reduction	Dose Interruption	Dose Discontinuation	Rescue
• Adverse events (AE) • Liver enzyme elevations	• AE considered drug related: 4 weeks • Not drug related: 8 weeks	• If AE persisted at 100 mg BID dose • If severe AE on 150 mg BID dose • If repeat liver enzymes ≥3 times upper limit of normal	• Absolute decline in FVC % predicted >10% • Change in mRSS >25% or >5 points • Deterioration in other organ systems or clinical parameters

Efficacy Endpoints

- Primary
  - Rate of decline in Forced Vital Capacity in mL over 52 weeks
- Key Secondary at Week 52
  - Change in modified Rodnan Skin Score
  - Change in St. George's Respiratory Questionnaire

Efficacy Endpoints

- Secondary
  - Time to death
- Secondary pulmonary endpoints
  - Annual rate of decline in % predicted FVC
  - FVC in mL
  - Absolute change in DL_{CO} % predicted
  - FACIT dyspnea scale
- Secondary SSc and physical function endpoints
  - Relative % change in mRSS
  - HAQ-DI total score
  - CRISS index score
  - Digital ulcer net burden

Abbreviations: DL_{CO}: diffusing capacity of lung for carbon monoxide; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire Disability Index; CRISS: composite response index in systemic sclerosis

Demographics

		Placebo N=288	Nintedanib N=288
Gender	Female	74%	77%
Race	Asian	28%	22%
	Black or African American	6%	7%
	White	65%	70%
Age	Median age in years	54	57
Region	Asia	25%	21%
	Canada and United States	25%	24%
	Europe	44%	49%

Baseline Disease Characteristics

	Placebo N=288	Nintedanib N=288
Anti-topoisomerase antibodies	62%	60%
Mean time since first onset of non-Raynaud symptoms	3.5 years	3.5 years
Diffuse cutaneous SSc	51%	53%
FVC % predicted	73%	72%
DL_{CO} % predicted	53%	53%
Pulmonary hypertension at screening	8%	7%
Mean mRSS	10.9	11.3
Prior digital ulcers	35%	42%
Mycophenolate use	49%	48%

Disposition

	Placebo N=288 n (%)	Nintedanib N=288 n (%)
Treated set	288	288
Completed study	275 (95)	264 (92)
Early study withdrawal	13 (5)	24 (8)
Early treatment discontinuation	31 (11)	56 (19)
Dose reduction	13 (5)	117 (41)
Treatment interruption	33 (11)	109 (38)

FDA Arthritis Advisory Committee Meeting
FDA Statistical Review of Efficacy

NDA 205832s12: Nintedanib for the treatment of patients with systemic sclerosis interstitial lung disease

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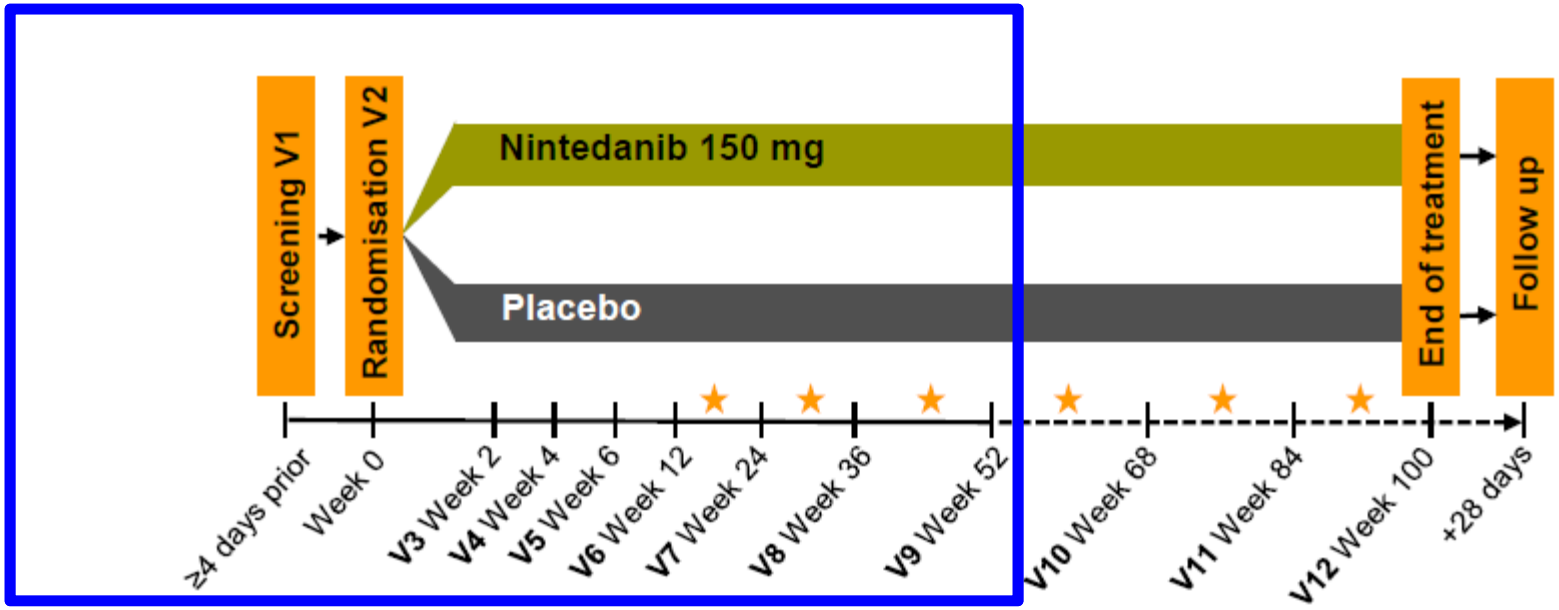
US Food and Drug Administration
July 25, 2019

Outline

- Study Design and Statistical Analysis Plan
- Disposition of Patients
- Key Efficacy Results
  - Primary endpoint: annual rate of decline in FVC in mL
  - Key secondary endpoints: absolute change from baseline in mRSS and SGRQ
  - Other secondary endpoint: time to death
- Efficacy Review Summary

STUDY DESIGN AND STATISTICAL ANALYSIS PLAN

Study Design



Efficacy Endpoints and Analysis Methods

Category	Endpoint	Primary Analysis Model
Primary	FVC (mL): annual rate of decline over 52 weeks	A restricted maximum likelihood (REML)-based approach using a random coefficient regression model
Key Secondary	mRSS: change from baseline at week 52	A REML based Mixed Model Repeated Measures (MMRM) analysis
	SGRQ: change from baseline at week 52	
Other Secondary	Change from baseline endpoints: DL_{CO} % predicted, CRISS index score, Digital ulcer net burden, HAQ-DI (disability index) score, FACIT dyspnea score	
	FVC % predicted: annual rate of decline	A random coefficient regression model
	Death: time to death over the whole trial	A Cox proportional hazards model
Exploratory	FVC (mL): relative decline >10% FVC (% predicted): absolute decline >5%	Cochran-Mantel-Haenszel (CMH) model

Primary Estimand and Sensitivity Analyses

- Primary estimand: de facto or treatment policy
  - Intercurrent event handling: primary analysis based on both on-treatment and, where available, off-treatment data
- Sensitivity analyses to missing-at-random (MAR) assumption
  - Pre-planned: Pattern Mixture Modeling (PMM) approaches
  - Information Request: Tipping Point Analysis

Efficacy Analysis Population

- Treated set (TS): all randomized patients who received at least one dose of trial medication

Sequential Testing Procedure for Type I Error Control

Category	Endpoint	Significance
Primary	FVC: annual rate of decline over 52 weeks	2-sided p-value <0.05 ⬇
Key Secondary	mRSS: change from baseline at week 52	2-sided p-value <0.05 ⬇
	SGRQ: change from baseline at week 52	2-sided p-value <0.05

DISPOSITION OF PATIENTS OVER 52 WEEKS

Disposition of Patients over 52 Weeks

(Trial Medication Discontinuation Status at Week 52)

	Placebo N=288 n (%)	Nintedanib N=288 n (%)	Total N=576 n (%)
Prematurely Discontinued from **Trial Medication** before 52 Weeks			
Continued	257 (89)	232 (81)	489 (85)
Discontinued	31 (11)	56 (19)	87 (15)
Reasons for Discontinuing **Trial Medication**			
Adverse Event	21 (7)	40 (14)	61 (11)
Patient refusal to continue taking trial medication	7 (2)	9 (3)	16 (3)
Non-compliant with protocol	1 (<1)	1 (<1)	2 (<1)
Other	2 (<1)	6 (2)	8 (1)

Disposition of Patients over 52 Weeks

(Primary Efficacy Follow-up Status at Week 52)

	Placebo N=288 n (%)	Nintedanib N=288 n (%)	Total N=576 n (%)	Missing/Complete Pattern
With FVC Data at 52 Weeks	257 (89)	241 (83)	498 (86)	
Trial drug until 52 weeks	245 (85)	217 (75)	462 (80)	1: Complete follow-up
Trial drug prematurely discontinued	12 (4)	24 (8)	36 (6)	2: Retrieved drop-out
No FVC Data at 52 weeks	31 (11)	47 (17)	78 (14)	
Alive at 52 weeks	25 (9)	36 (13)	61 (11)	3: Incomplete but alive
Died before 52 weeks	6 (2)	11 (4)	17 (3)	4: Incomplete and dead

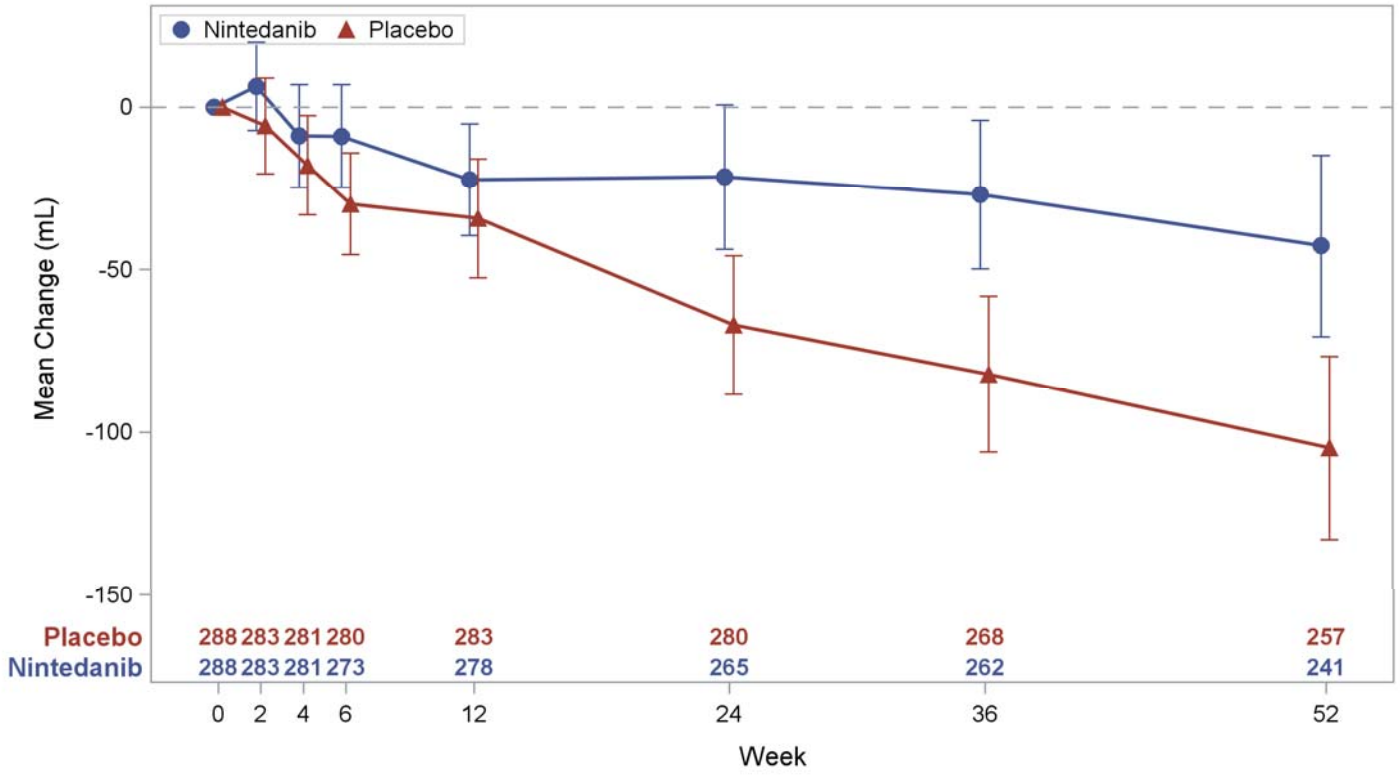
PRIMARY EFFICACY ENDPOINT RESULTS:

PRIMARY, SENSITIVITY, AND SUPPORTIVE ANALYSES

Primary Endpoint: Rate of decline in FVC (mL/yr) over 52 weeks (Primary Analysis, Treated Set)

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	288	287
Adjusted Rate of Decline, mL/Year (SE)	-93 (14)	-52 (14)
Nintedanib vs. Placebo		
Difference (SE)		41 (19)
95% CI		3, 79
p-value		0.035

Observed Visit-wise Mean (95% CI) Change from Baseline in FVC in mL over 52 Weeks



Effect in FVC:
Sensitivity Analyses and Supportive Analyses

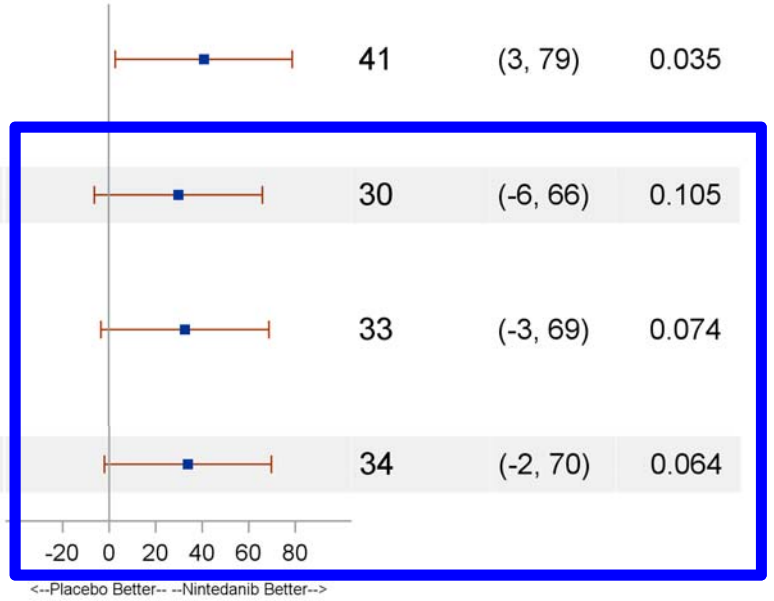
- Sensitivity analyses for robustness to MAR assumptions
  - PMM approaches
  - Tipping point analysis
- Supportive Analyses
  - FVC: Rate of decline in FVC in % predicted
  - FVC: Categorical (responder) analysis approaches

Primary Endpoint Sensitivity Analysis 1: Pattern Mixture Model Approaches

Imputation Scenarios	Imputation Rule for Patients with Week 52 FVC Data Missing	
	Alive at Week 52 (Pattern 3)	Dead at Week 52 (Pattern 4)
PMM1	Based on estimated rates of decline in the retrieved dropouts (Pattern 2), by Treatment Arm	Based on estimated rate of decline in the worse half of retrieved dropouts (Pattern 2), in Placebo
PMM2	Based on estimated rate of decline in the retrieved dropouts (Pattern 2), in Placebo	*Same as above*
PMM3	Based on estimated rate of decline in patients with week 52 FVC (Pattern 1 and 2), in Placebo	Based on estimated rate of decline in the worse half of in patients with week 52 FVC (Pattern 1 and 2), in Placebo

Primary Endpoint Sensitivity Analysis 1:
Pattern Mixture Approaches

Subgroup	No. of Patients (%)	Mean Difference (95% CI)	Annual Rate of Decline		
			Mean Difference	95% CI	p-Value
Primary Analysis	575 (100)		41	(3, 79)	0.035
PMM1: Retrieved Dropout, by Arm	576 (100)		30	(-6, 66)	0.105
PMM2: Retrieved Dropout, Control	576 (100)		33	(-3, 69)	0.074
PMM3: Pattern 1 and 2, Control	576 (100)		34	(-2, 70)	0.064



Primary Endpoint Sensitivity Analysis 2:

Tipping Point Analysis

p-values		Shift in Placebo (Change in mL/Year)						
		-60	-45	-30	-15	0	15	30
Shift in Nintedanib (Change in mL/Year)	-60	0.048	0.052	0.056	0.060	0.065	0.070	0.075
	-45	0.042	0.046	0.049	0.053	0.057	0.061	0.066
	-30	0.037	0.040	0.043	0.046	0.0498	0.054	0.058
	-15	0.032	0.035	0.037	0.040	0.044	0.047	0.051
	0	0.028	0.030	0.032	0.035	0.038	0.041	0.044
	15	0.024	0.026	0.028	0.030	0.033	0.036	0.039
	30	0.020	0.022	0.024	0.026	0.029	0.031	0.034

Secondary Endpoint:

Rate of decline in FVC in % Predicted over 52 weeks (Treated Set)

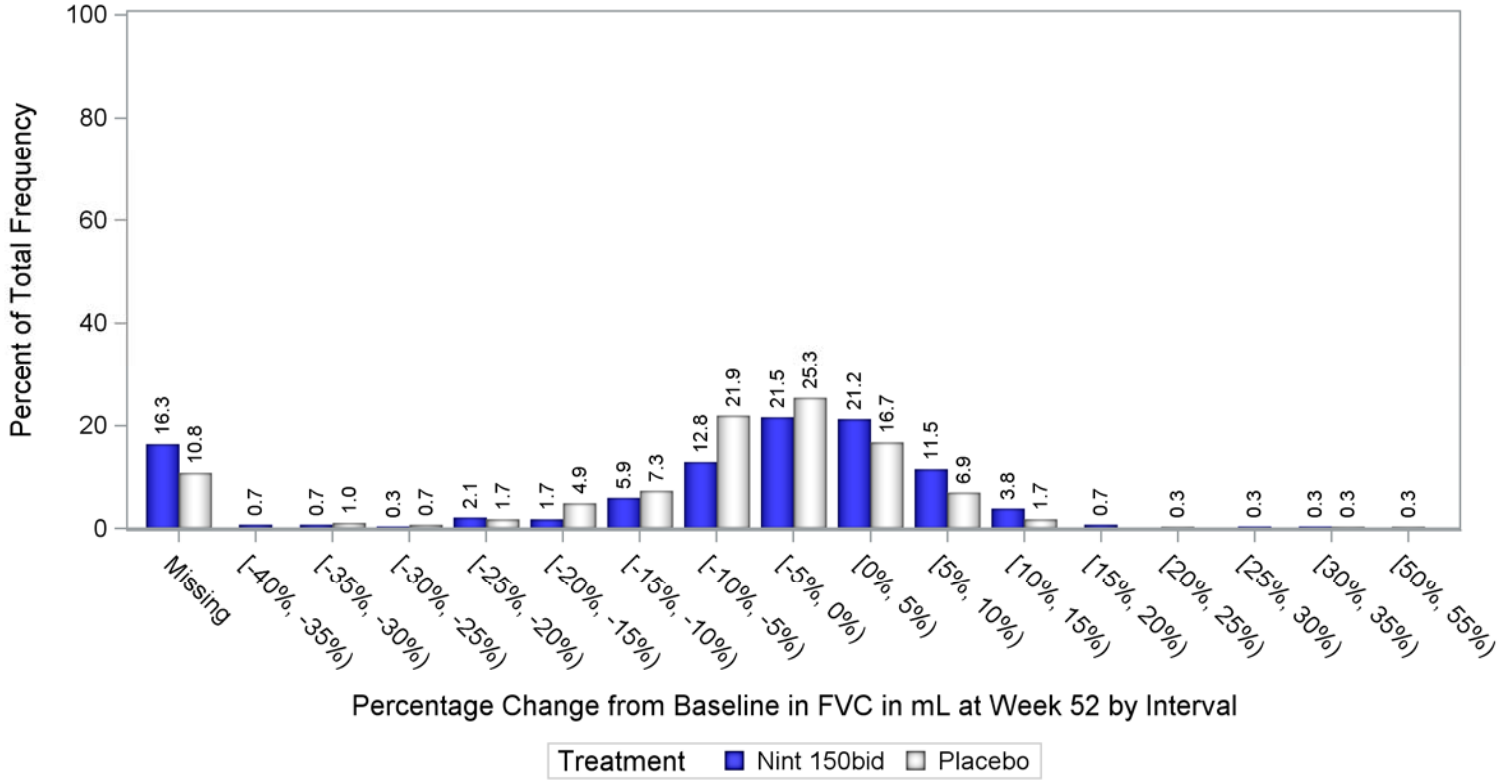
	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	288	287
Adjusted Annual Rate of Decline, %/year (SE)	-2.6 (0.38)	-1.4 (0.4)
Nintedanib vs. Placebo		
Difference (SE)		1.2 (0.5)
95% CI		(0.1, 2.2)
p-value		0.033

FVC: Proportions of Responders Analysis Results

		Placebo (N=288)	Nintedanib (N=288)	Comparison vs. Placebo	
		n (%)	n (%)	Odds Ratio	Nominal p-value
Responder definition using relative decline from baseline in FVC in mL at Week 52					
Relative decline	≤5%	149 (52)	171 (59)	1.4 (0.98, 1.9)	0.07
	≤10%	212 (74)	208 (72)	0.9 (0.6, 1.3)	0.70
	≤15%	233 (81)	225 (78)	0.8 (0.6, 1.3)	0.41
Responder definition using absolute decline from baseline in FVC in % predicted at Week 52					
Absolute decline	≤5%	186 (65)	196 (68)	1.2 (0.8, 1.6)	0.39
	≤10%	236 (82)	227 (79)	0.8 (0.5, 1.2)	0.35
	≤15%	249 (87)	233 (81)	0.7 (0.4, 1.04)	0.07

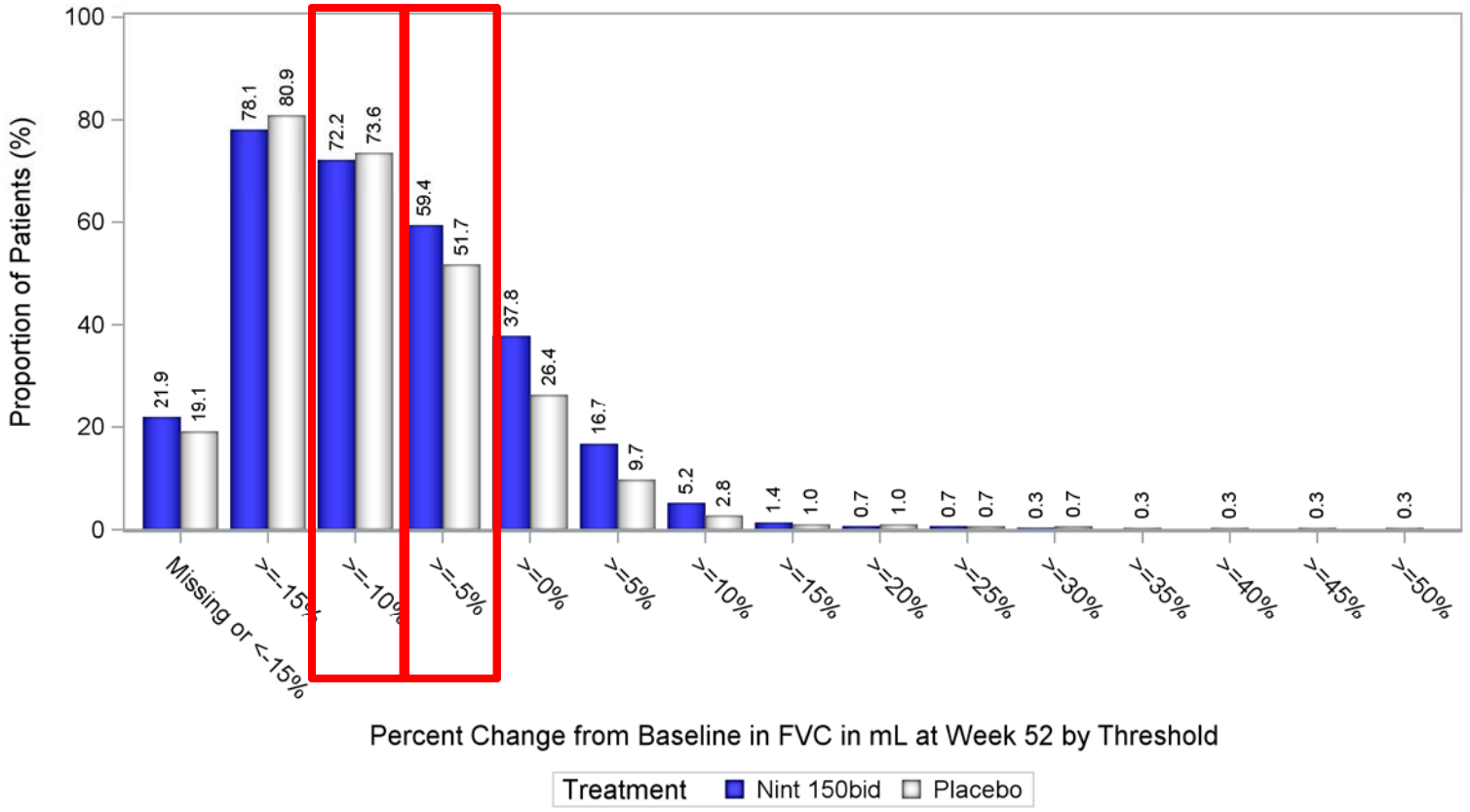
Relative Decline in FVC in mL:

Histogram of % Change from Baseline at Week 52



Relative Decline in FVC in mL:

Proportions of Responders Defined by a Series of Thresholds



SECONDARY EFFICACY ENDPOINT RESULTS

Key Secondary: mRSS

Absolute change from baseline in mRSS at Week 52

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	286	288
Baseline Mean mRSS Score (SD)	10.9 (8.8)	11.3 (9.2)
Adjusted Change from Baseline (SE)	-2.0 (0.3)	-2.2 (0.3)
Nintedanib vs. Placebo		
Difference (SE)		-0.2 (0.4)
95% CI		-0.9, 0.5
p-value		0.579

Key Secondary: SGRQ Total Score

Absolute change from baseline in SGRQ at Week 52

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	283	282
Baseline Mean SGRQ Total Score (SD)	39.4 (20.9)	40.7 (20.2)
Adjusted Change from Baseline (SE)	-0.9 (0.9)	0.8 (0.9)
Nintedanib vs. Placebo		
Difference (SE)		1.7 (1.2)
95% CI		-0.7, 4.1

Secondary Endpoint:
Time to death over the whole trial

	Placebo (N=288)	Nintedanib (N=288)
Survival status at the end of study, n (%)		
Dead	9 (3.0)	10 (3.5)
Lost to follow-up (Vital status at the End of Study Unknown)	1 (<1)	5 (2)
Alive (Censored at the End of Study)	278 (97)	273 (95)
Cox Proportional Hazard Model Analysis		
Nintedanib vs. Placebo		
Hazard Ratio		1.2
95% CI		0.5, 2.9

SUBGROUP ANALYSES ON THE PRIMARY EFFICACY ENDPOINT

Primary Endpoint Subgroup Analyses by MMF Use at Baseline, by Region and by Region x MMF Use

Subgroup	No. of Patients (%)	Mean Difference (95% CI)	Annual Rate of Decline		
			Mean Difference	95% CI	p-Value
Overall	575 (100)		41	(3, 79)	
MMF use at baseline					0.452
N	297 (52)		56	(0, 111)	
Y	278 (48)		27	(-26, 79)	
Region					0.350
Other than US and Canada	433 (75)		52	(8, 95)	
US and Canada	142 (25)		10	(-69, 89)	
Region and MMF Use					0.600
Other, MMF	164 (29)		32	(-35, 99)	
Other, No MMF	269 (47)		64	(7, 122)	
US & Canada, MMF	114 (20)		17	(-68, 101)	
US & Canada, No MMF	28 (5)		-24	(-242, 194)	

The p-value for Region and MMF Use is from the test statistic for testing the interaction between the treatment and a cross-classification of Region x Baseline Mycophenlate Use

Abbreviations

Other: Other country than US and Canada

EFFICACY REVIEW SUMMARY

Summary of Efficacy

Category	Endpoints	Statistical Significance	Effect Measure (95% CI)	Sensitivity Analysis Results
Primary	FVC: annual Rate (mL/yr)	p=0.035	Diff: 41 (3, 79)	Lack of Robustness
Key Secondary	mRSS: Δ at week 52	p=0.579	Diff: -0.2 (-0.9, 0.5)	
	SGRQ: Δ at week 52	P=0.171	Diff: 1.7 (-0.7, 4.1)	
Other secondary	FVC % predicted: annual rate	P=0.033	Diff: 1.2 (0.1, 2.2)	
	Time to death: HR	P=0.751	HR: 1.2 (0.5, 2.8)	
Exploratory	Relative decline <=10% in FVC in mL	P=0.704	OR: 0.9 (0.6, 1.3)	Note: Primary analyses were based on Non-responder imputation
	Absolute decline <=5% in FVCpp	P=0.386	OR: 1.2 (0.8, 1.6)	

Statistical Review Summary

The Primary Measure: FVC

- Primary analysis result: statistically significant
- PMM sensitivity analyses results: loss of significance
- Tipping Point analysis result: needs clinical interpretation
- Other measures of FVC:
  - FVC in % predicted: consistent with the primary analysis result
  - Responder analyses (decline by thresholds: ≤5%, ≤10%, or ≤15%): treatment effect not statistically significant
- Subgroup analyses: tests for interaction were not significant
  - smaller point estimate for US and Canada patients, and
  - smaller point estimate for MMF users at baseline

Other Efficacy Endpoints:

- Results from secondary endpoints were not supportive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FDA Clinical Review of Safety and Benefit-Risk Assessment

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Outline

- Safety
  - Safety Summary
  - Deaths
  - Serious Adverse Events (SAE)
  - Treatment Emergent Adverse Events (TEAE)
  - Labeled Adverse Events
  - Safety Conclusions
- Benefit/Risk Assessment

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Safety: Summary Over 52 Weeks

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Deaths *Over Whole Study*	9 (3)	10 (3)
-Treatment period	5 (2)	6 (2)
-Post-treatment period (≥29 days)	4 (1)	4 (1)
Serious Adverse Events	62 (22)	69 (24)
Severe Adverse Events	36 (13)	52 (18)
Adverse Events leading to drug discontinuation	25 (9)	46 (16)
Adverse Events leading to dose decrease	10 (3)	98 (34)
Any Adverse Event	276 (96)	283 (98)

AEs Leading to Death over Entire Study by Preferred Term (Treated Set)

Placebo (9)	Nintedanib (10)
Cardiac arrests (2)	Chest pain
Acute myocardial infarction	Arrythmia
Sudden death	Circulatory collapse
Septic shock	Acute lung injury
Pneumonia	Pneumonia
Dyspnea	Respiratory failure
Interstitial lung disease	Scleroderma renal crisis/thrombotic microangiopathy
Lung neoplasm malignant	Mesothelioma malignant
	Small cell lung cancer
	Lung adenocarcinoma

Safety: Serious Adverse Events

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Patients with ≥1 SAE	62 (21.5)	69 (24)
Interstitial lung disease	5 (1.7)	7 (2.4)
Pneumonia	1 (0.3)	8 (2.8)
Pulmonary hypertension	4 (1.4)	4 (1.4)
Dyspnea	5 (1.7)	3 (1.0)
Pulmonary fibrosis	4 (1.4)	3 (1.0)
Systemic sclerosis pulmonary	3 (1.0)	2 (0.7)
Acute kidney injury	1 (0.3)	3 (1.0)
Pulmonary arterial hypertension	0	3 (1.0)

Abbreviations: SAE=serious adverse event

Safety: Treatment Emergent AEs

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Patients with ≥1 TEAE	276 (96)	283 (98)
Diarrhea	91 (32)	218 (76)
Nausea	39 (14)	91 (32)
Vomiting	30 (10)	71 (25)
Abdominal pain	21 (7)	33 (12)
Weight decreased	12 (4)	34 (12)

- Over 52 weeks, 21% of patients in nintedanib group lost > 10% of their body weight at some point during the first 52 weeks of treatment vs 5% of placebo

Safety: Labeled Adverse Events

- Elevated liver enzymes and drug-induced liver injury
- Diarrhea, nausea, vomiting
- Arterial thromboembolic events
- Bleeding events
- Gastrointestinal perforation

Safety: Labeled Adverse Events

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Elevated liver enzymes	9 (3)	38 (13)
DILI	1 (0.3)	1 (0.3)
Diarrhea	91 (32)	218 (76)
Nausea	39 (14)	91 (32)
Vomiting	30 (10)	71 (25)
Bleeding	24 (8)	32 (11)
Arterial thromboembolic events	2 (0.7)	2 (0.7)
GI Perforation	1 (0.3)*	0

*GI perforation based on SMQ analysis, preferred term: anal abscess; DILI=drug-induced liver injury

Safety: Conclusions

- Safety generally consistent with known safety profile of nintedanib
- Deaths were balanced between treatment groups
- Other than pneumonia, the types and frequencies of SAEs were balanced by treatment group
- Most frequently reported TEAEs in the nintedanib group were consistent with those known for nintedanib

Outline

- Safety
  - Safety Summary
  - Deaths
  - Serious Adverse Events
  - Treatment Emergent Adverse Events
  - Labeled Adverse Events
  - Safety Conclusions
- Benefit/Risk Assessment

Benefit Assessment

- SSc-ILD is a rare and serious disease associated with high morbidity and mortality
- High unmet need for new therapies
- Decrease in adjusted annual FVC decline
- Relative slowing of rate of FVC decline similar between SSc-ILD and IPF programs

Risk Assessment

- **Labeled Warnings/ Precautions**
  - Hepatic impairment
  - Elevated liver enzymes and drug-induced liver injury
  - Gastrointestinal (GI) disorders
  - Embryo-fetal toxicity
  - Arterial thromboembolic events
  - Bleeding events
  - GI perforation
- **Pneumonia**

Benefit-Risk Assessment

- Annual rate of decline in FVC had a small effect of 41mL/year
  - Less robust treatment effect in subgroups on MMF and in the US/ Canada
  - Secondary efficacy endpoints were non-supportive
- Safety: USPI warnings and precautions
  - GI adverse events
- Unmet clinical need


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FDA Arthritis Advisory Committee Meeting
Charge to the Committee

NDA 205832s12: Nintedanib for the treatment of patients with systemic sclerosis interstitial lung disease

Rachel L. Glaser, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
US Food and Drug Administration
July 25, 2019

Efficacy Considerations

- Decrease in adjusted FVC decline in nintedanib group (*treatment difference: 41 mL/year*)
- Clinically important secondary endpoints not supportive of efficacy
- Less robust treatment effect in pre-specified subgroup analyses:
  - Patients from US and Canada (*10 mL/year*)
  - Patients on mycophenolate at baseline (*27 mL/year*)

Safety Considerations

- In general, the safety profile of nintedanib in SSc-ILD appears consistent with the known safety profile of nintedanib in IPF
- Nintedanib was associated with gastrointestinal and hepatic adverse events
  - AEs and SAEs of pneumonia
  - Overall infections were similar between treatment groups

Benefit-Risk Considerations

Benefits

- Decrease in adjusted annual FVC decline
  - Not supported by secondary endpoints
- Relative slowing of rate of FVC decline similar between SSc-ILD and IPF programs
  - In IPF, FVC supported by decrease in exacerbations, improvement in SGRQ, positive trends in mortality

Risks

- Labeled risks:
  - Hepatic impairment
  - Elevated liver enzymes/drug-induced liver injury
  - Gastrointestinal disorders
  - Arterial thromboembolic events
  - Bleeding events
  - Gastrointestinal perforation
- Pneumonia

Quantity of Evidence Necessary to Support Effectiveness

- *FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (1998)*
  - *……Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness……*
  - *……In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use……*

- Review considerations for a single-study
  - SSc-ILD is a rare disease
  - Commonalities in the pathological pathways involved in fibrogenesis in IPF and SSc-ILD
  - IPF trials with nintedanib were similar in design

Approval of an Application
21 CFR 314.105 (c)

- "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling."

Efficacy Standard
21 CFR 314.125
Refusal to Approve an Application

- (b)(5) "…substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Safety Standard
21 CFR 314.125
Refusal to Approve an Application

- (b)(2) "…do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling"
- (b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."
- (b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Discussion Points and Voting Questions

1. **DISCUSSION:** Discuss the efficacy of nintedanib for treatment of patients with systemic sclerosis interstitial lung disease (SSc-ILD)
   a. Discuss the clinical meaningfulness of the changes in forced vital capacity (FVC) with nintedanib treatment in the population studied

2. **DISCUSSION:** Discuss the FVC data from the following subgroups and the implications for use of nintedanib in patients in the US:
   a. US and Canada subgroup compared to the overall study population
   b. Patients on background mycophenolate versus no background mycophenolate treatment

Discussion Points and Voting Questions

3. **VOTE:** Do the data provide substantial evidence of the efficacy of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

Discussion Points and Voting Questions

4. **VOTE:** Is the safety profile of nintedanib adequate to support approval of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
   a. If no, what further data are needed?

Discussion Points and Voting Questions

5. **VOTE:** Is the benefit-risk profile adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease?

   a. If no, what further data are needed?


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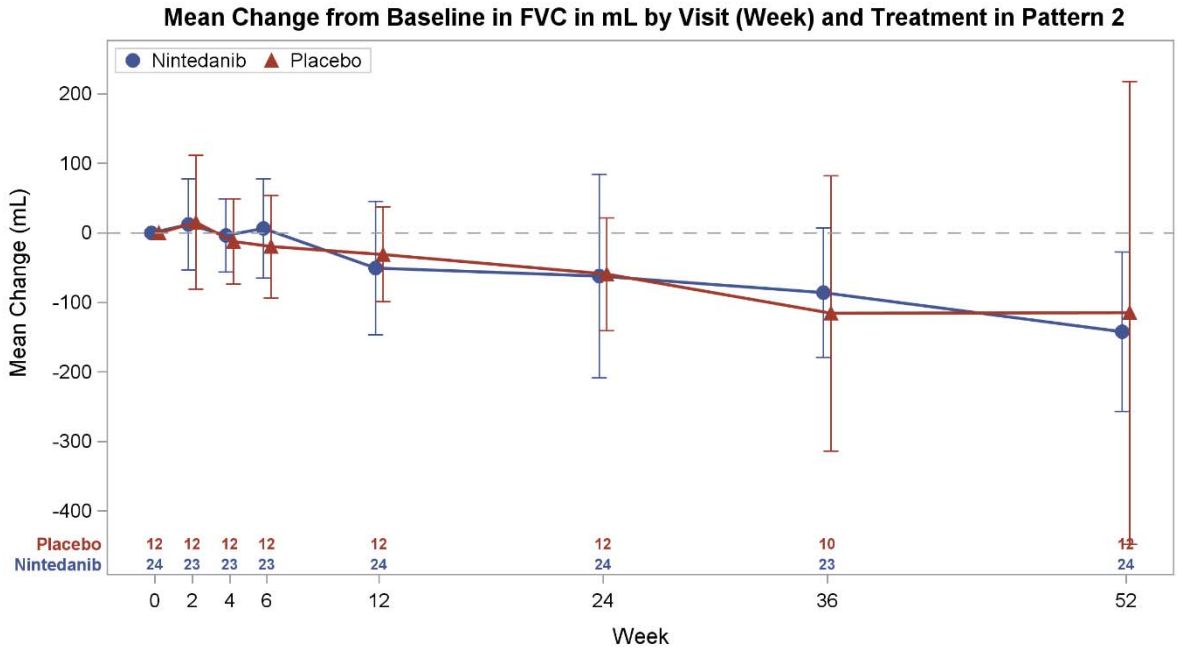
BACKUP SLIDES SHOWN

Observed Visit-wise Mean (95% CI) Change from Baseline in FVC in mL over 52 Weeks in Pattern 2



FVC (mL) at Week 52: Missing Data Pattern (Nintedanib)

TRT01P	Group	Week 2	Week 4	Week 6	Week 12	Week 24	Week 36	Week 52	Frequency	Percent	Observed Data ≥ 52 Week
Nint 150bid	1	X	X	X	X	X	X	X	221	76.74	
	2	X	X	X	X	X	X	.	20	6.94	
	3	X	X	X	X	X	.	X	1	0.35	
	4	X	X	X	X	X	.	.	4	1.39	
	5	X	X	X	X	.	X	X	2	0.69	
	6	X	X	X	X	.	X	.	1	0.35	
	7	X	X	X	X	.	.	.	11	3.82	
	8	X	X	X	.	X	X	X	1	0.35	
	9	X	X	X	.	X	.	X	1	0.35	
	10	X	X	X	.	.	.	.	2	0.69	
	11	X	X	.	X	X	X	X	8	2.78	
	12	X	X	.	X	X	X	.	2	0.69	
	13	X	X	.	.	.	.	.	3	1.04	
	14	X	.	X	X	X	X	X	3	1.04	
	15	X	.	X	X	.	.	.	1	0.35	
	16	X	.	X	.	.	.	.	1	0.35	
	17	X	.	.	.	.	.	.	1	0.35	
	18	.	X	X	X	X	X	X	4	1.39	
	19	O	O	O	O	O	O	O	1	0.35	
Patients missing Week 52 FVC data									N=47	16%	16/47

FVC (mL) at Week 52: Missing Data Pattern (Placebo)

TRT01P	Group	Week 2	Week 4	Week 6	Week 12	Week 24	Week 36	Week 52	Frequency	Percent	Observed Data ≥ 52 Week
Placebo	1	X	X	X	X	X	X	X	236	81.94	
	2	X	X	X	X	X	X	.	13	4.51	
	3	X	X	X	X	X	.	X	6	2.08	
	4	X	X	X	X	X	.	.	8	2.78	
	5	X	X	X	X	.	X	X	1	0.35	
	6	X	X	X	X	.	X	.	2	0.69	
	7	X	X	X	X	.	.	.	2	0.69	
	8	X	X	X	.	X	X	X	2	0.69	
	9	X	X	X	.	X	.	.	1	0.35	
	10	X	X	X	.	.	.	.	1	0.35	
	11	X	X	.	X	X	X	X	5	1.74	
	12	X	.	X	X	X	X	X	4	1.39	
	13	X	.	.	X	X	X	.	1	0.35	
	14	X	.	.	.	.	.	.	1	0.35	
	15	.	X	X	X	X	X	X	2	0.69	
	16	.	X	X	X	.	.	.	1	0.35	
	17	.	X	.	X	X	X	.	1	0.35	
	18	.	.	X	X	X	X	X	1	0.35	
Patients missing Week 52 FVC (mL) data									N=31	11%	12/31