

# **OFEV<sup>®</sup> (nintedanib) Capsules for Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)**

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U.S. Food & Drug Administration  
Arthritis Advisory Committee

July 25, 2019



# Introduction

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# Nintedanib Is Effective in Pulmonary Fibrosis

- ▶ Nintedanib
  - Small-molecule tyrosine kinase inhibitor
  - Blocks numerous pro-fibrotic pathways implicated in pulmonary fibrosis
  - Established safety and efficacy in idiopathic pulmonary fibrosis (IPF)
  - Approved in >70 countries
- ▶ Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) is another fibrosing interstitial lung disease (ILD) that shares similar clinical and pathologic features with IPF

# Clinical Development of Nintedanib in Pulmonary Fibrosis

## Fibrosing Interstitial Lung Diseases

**Idiopathic Pulmonary  
Fibrosis (IPF)**

**INPULSIS**  
Approved

**Systemic Sclerosis-  
assoc. Interstitial Lung  
Disease (SSc-ILD)**

**SENSCIS**  
Under review

**Progressive Fibrosing  
ILDs**

**INBUILD**  
Ongoing

# Nintedanib in Idiopathic Pulmonary Fibrosis (IPF)

- ▶ Efficacy<sup>a</sup>
  - Replicate Phase 3, 52-week trials (INPULSIS-1 and INPULSIS-2)
  - Primary endpoint: Annual rate of decline in Forced Vital Capacity (FVC)
  - Nintedanib reduced the annual rate of decline in FVC by 49% vs placebo, consistent with slowing disease progression in patients with IPF
- ▶ Safety
  - >1500 individual patients exposed to nintedanib in IPF clinical trials
  - Long-term exposure in clinical trials up to 68 months
    - Median (range): 44.7 months (11.9-68.3 months)
  - Post-marketing exposure >80,000 patient-years

# Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)

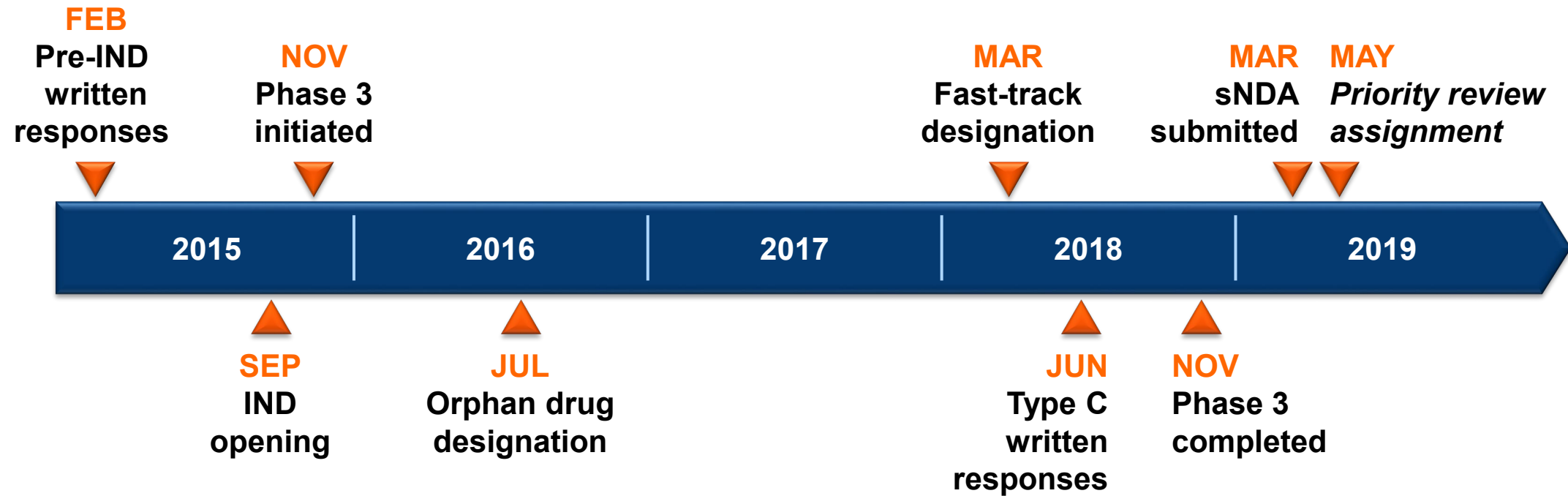
- ▶ Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by progressive fibrosis that has a high disease burden and high rate of mortality
- ▶ Interstitial lung disease (ILD) is a common manifestation and the leading cause of death in SSc
- ▶ Pulmonary fibrosis is progressive, and associated loss in lung function is irreversible
- ▶ Short-term changes in FVC as a surrogate for progression of pulmonary fibrosis may predict mortality in SSc-ILD

## Nintedanib in SSc-ILD

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- ▶ SENSICIS
  - Replicates design of IPF pivotal trials
  - Trial population reflected patients seen in clinical practice
    - Limited and diffuse cutaneous SSc
    - Background mycophenolate allowed
    - Wide range of pulmonary function
- ▶ 94% of eligible patients entered open-label extension (SENSICIS-ON)

# SSc-ILD Regulatory Milestones





## sNDA: Proposed Indication and Dosing

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- ▶ Proposed new indication

*Treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD)*

- ▶ Dosing and dose regimen same as approved for IPF

- 2 dosage strengths containing 100 mg or 150 mg

- Intended dosing will be 150 mg twice daily with an option to reduce dose to 100 mg twice daily to manage adverse events

## What You Will Hear Today

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- ▶ SENSCIS is the first placebo-controlled phase 3 study in SSc-ILD that reached the primary endpoint of slowing FVC decline
- ▶ Results of SENSCIS are consistent with what we can expect from IPF with regard to the relative FVC benefit
- ▶ Safety comparable to experience from IPF
- ▶ Nintedanib adds an antifibrotic treatment option with the target of slowing down loss of lung function in SSc-ILD
- ▶ Nintedanib has a positive benefit/risk profile

# Presenters

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**Disease Background/Unmet Need**

James R. Seibold, MD  
Scleroderma Research Consultants LLC

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**Clinical Development Rationale**

Susanne Stowasser, MD  
Boehringer Ingelheim

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**Efficacy**

Emmanuelle Clerisme-Beaty, MD  
Boehringer Ingelheim

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**Safety**

Veronika M. Kohlbrenner, MD  
Boehringer Ingelheim

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**Benefit Risk**

Kay Tetzlaff, MD  
Boehringer Ingelheim

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**Clinical Perspective**

Kevin K. Brown, MD  
National Jewish Health

## Advisors

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**Shervin Assassi, MD, MS**

University of Texas, Houston

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**Kevin Carroll, PhD**

KJC Statistics Ltd.

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**Toby Maher, MD, PhD**

Imperial College London

# **Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) Background and Unmet Medical Need**

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James R. Seibold, MD

Scleroderma Research Consultants

# Epidemiology and Demographics of Systemic Sclerosis in United States

- ▶ Annual US incidence: 20 to 24 per million<sup>a,b</sup>
- ▶ US prevalence: 276 to 300 per million<sup>a,b</sup>
  - Estimated 70,000 to 100,000 US patients<sup>a</sup>
  - Orphan disease
- ▶ ILD occurs in majority of patients<sup>d</sup>
- ▶ Female/male ratio: ~4:1<sup>b,c</sup>
- ▶ Peak onset ages: 40 to 50 years<sup>b,c</sup>
- ▶ More severe in African Americans<sup>e</sup>



<sup>a</sup> United States: Mayes MD, et al. *Arthritis Rheum.* 2003;48:2246-2255.

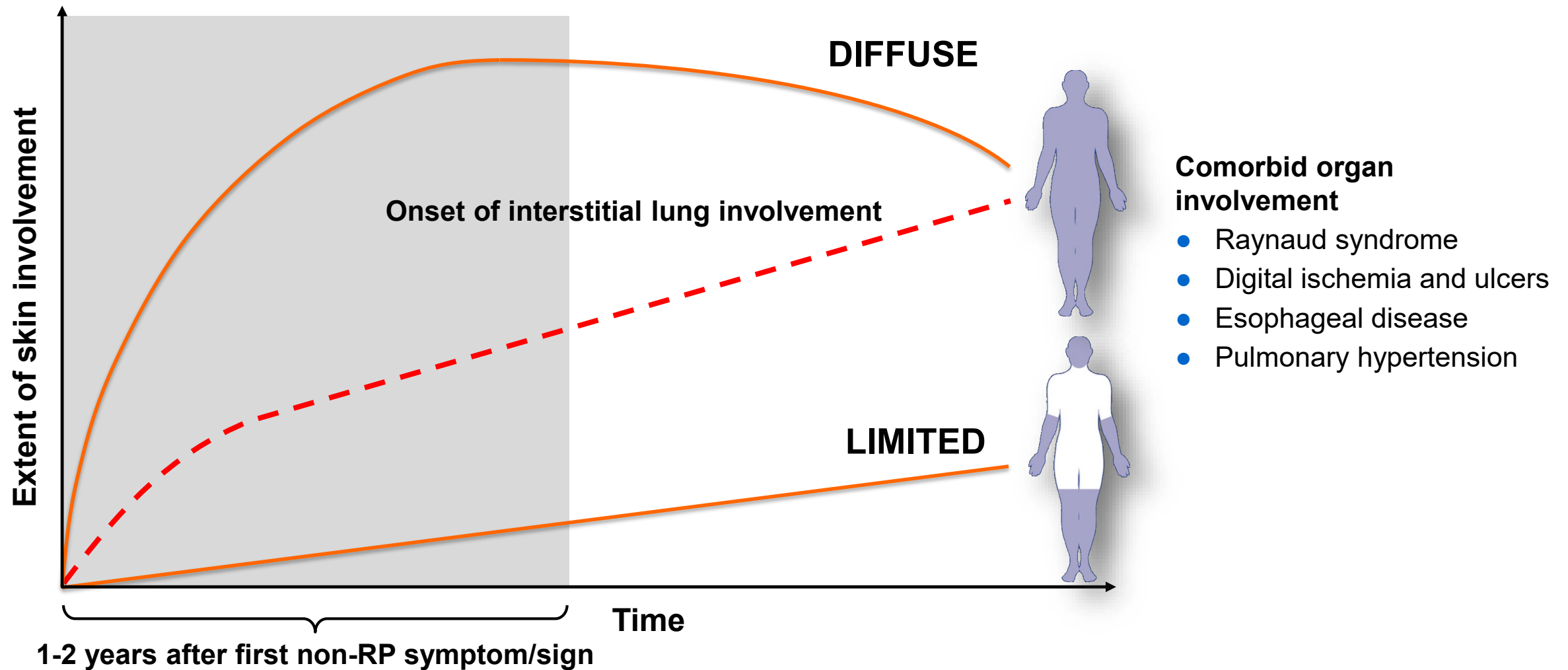
<sup>b</sup> Barnes and Mayes. *Curr Opin Rheumatol.* 2012;24:165-170.

<sup>c</sup> North America: Bergamasco A, et al. *Clin Epidemiol.* 2019;11:257-273.

<sup>d</sup> Solomon JJ, et al. *Eur Respir Rev.* 2013;22:6-19.

<sup>e</sup> Gelber AC, et al. *Medicine.* 2013;92:191-205.

# Progression of Skin and Lung Involvement in Diffuse and Limited Systemic Sclerosis



# The Human Impact of Scleroderma

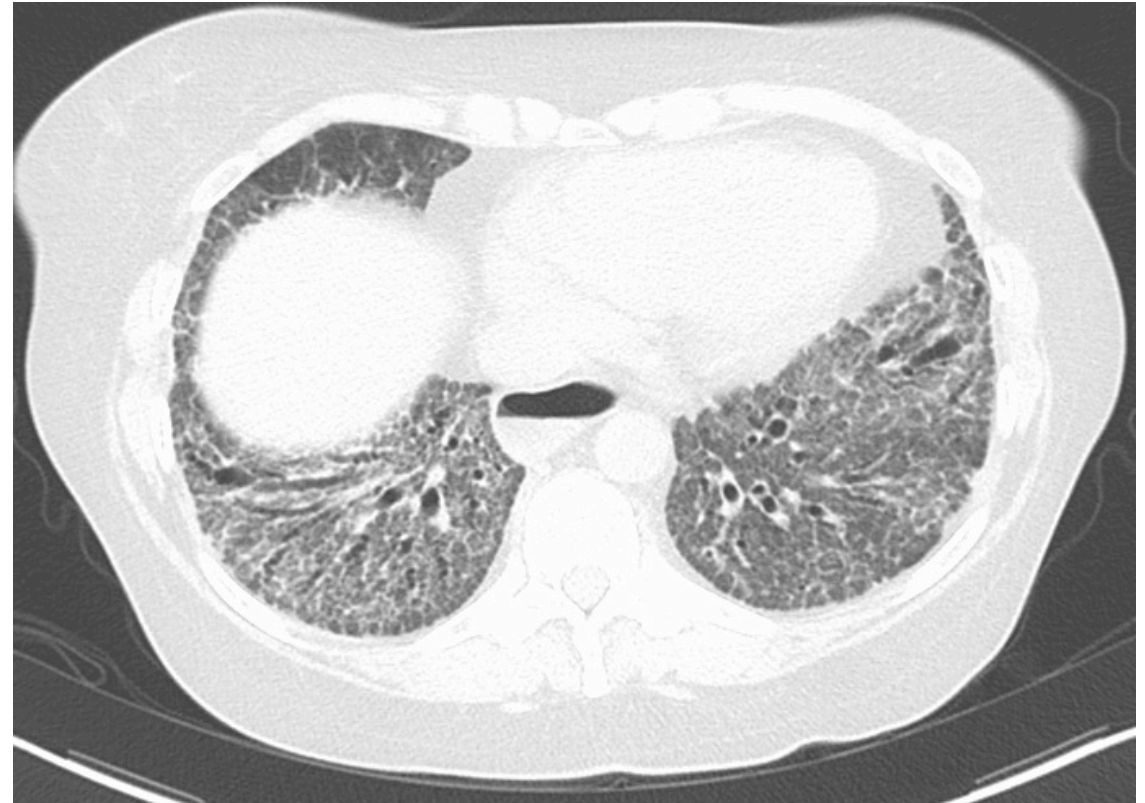
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- ▶ Onset in “prime of life”
- ▶ Women as family anchor for children and aging parents
- ▶ Impact of life-changing illness on career and social activities
- ▶ Uncertainty of future clinical course and outcome
- ▶ High symptom burden coupled with high risk of mortality
- ▶ Only approved therapies are for pulmonary arterial hypertension (PAH)



# Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)

- ▶ ILD is present in the majority of SSc patients
- ▶ Fibrotic NSIP is the most common HRCT pattern
- ▶ Clinically progressive in ~1/3 cases
- ▶ Onset is early and decline is continual
- ▶ Median survival 5 to 8 years after diagnosis

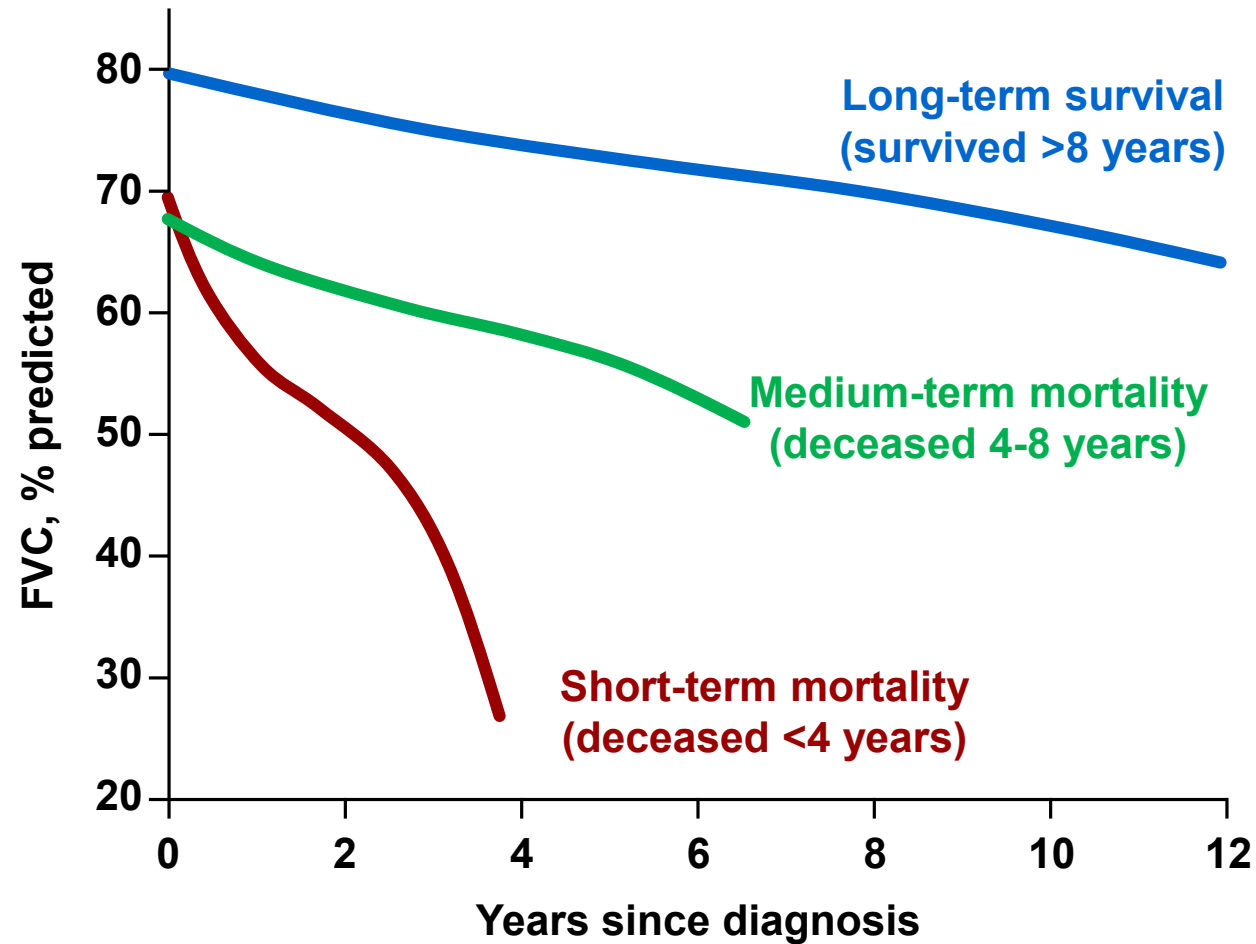


# Putative Risk Factors for ILD Progression

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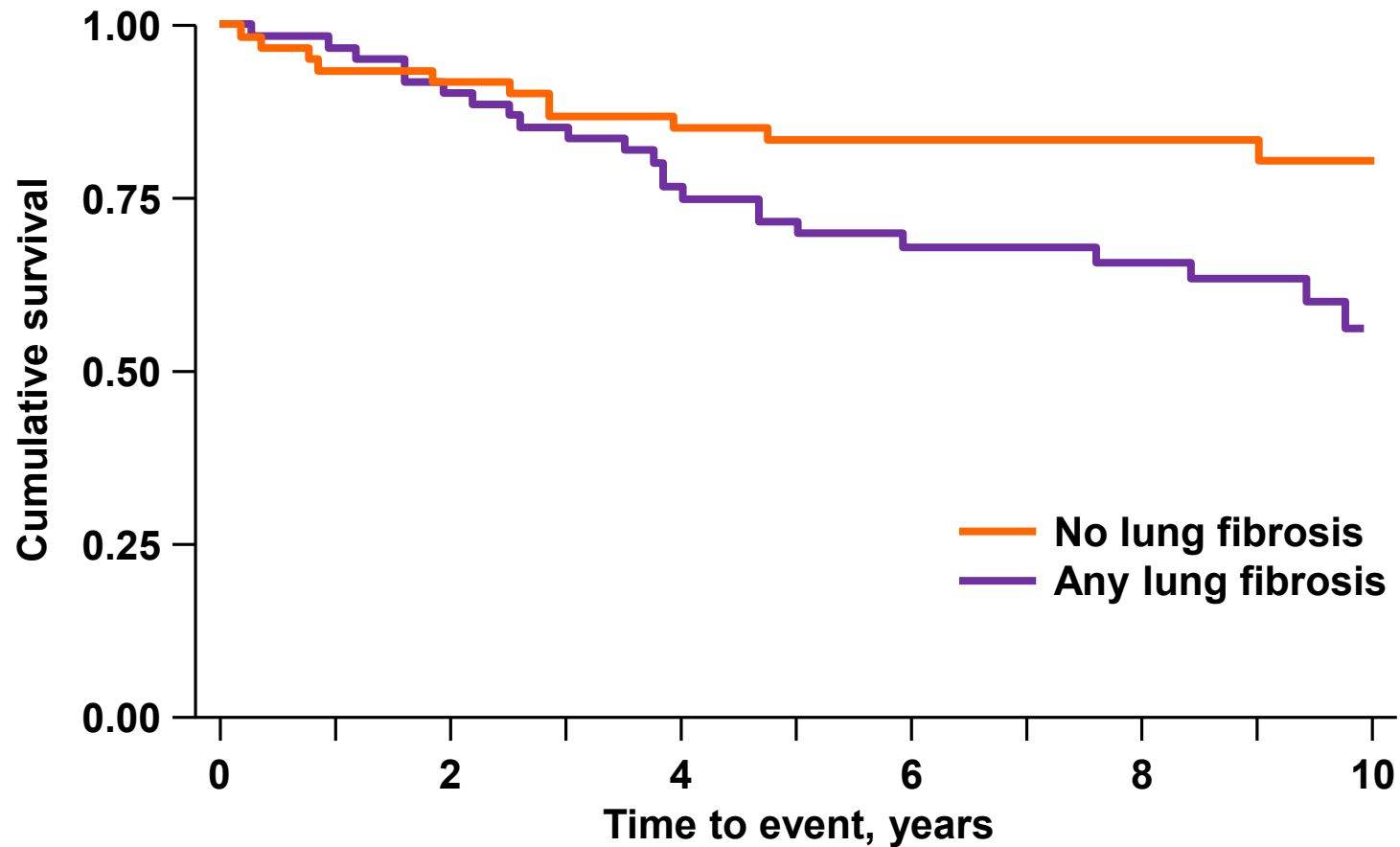
- ▶ Classification (diffuse vs limited)
- ▶ Disease duration <5 yr
- ▶ HRCT extent >20%
- ▶ FVC <70% predicted
- ▶ Presence of antitopoisomerase I antibody (ATA)

# Pace of FVC Decline and Early Mortality in SSc-ILD



# The Presence of ILD Is Associated With Mortality

## Nationwide Norwegian SSc Cohort

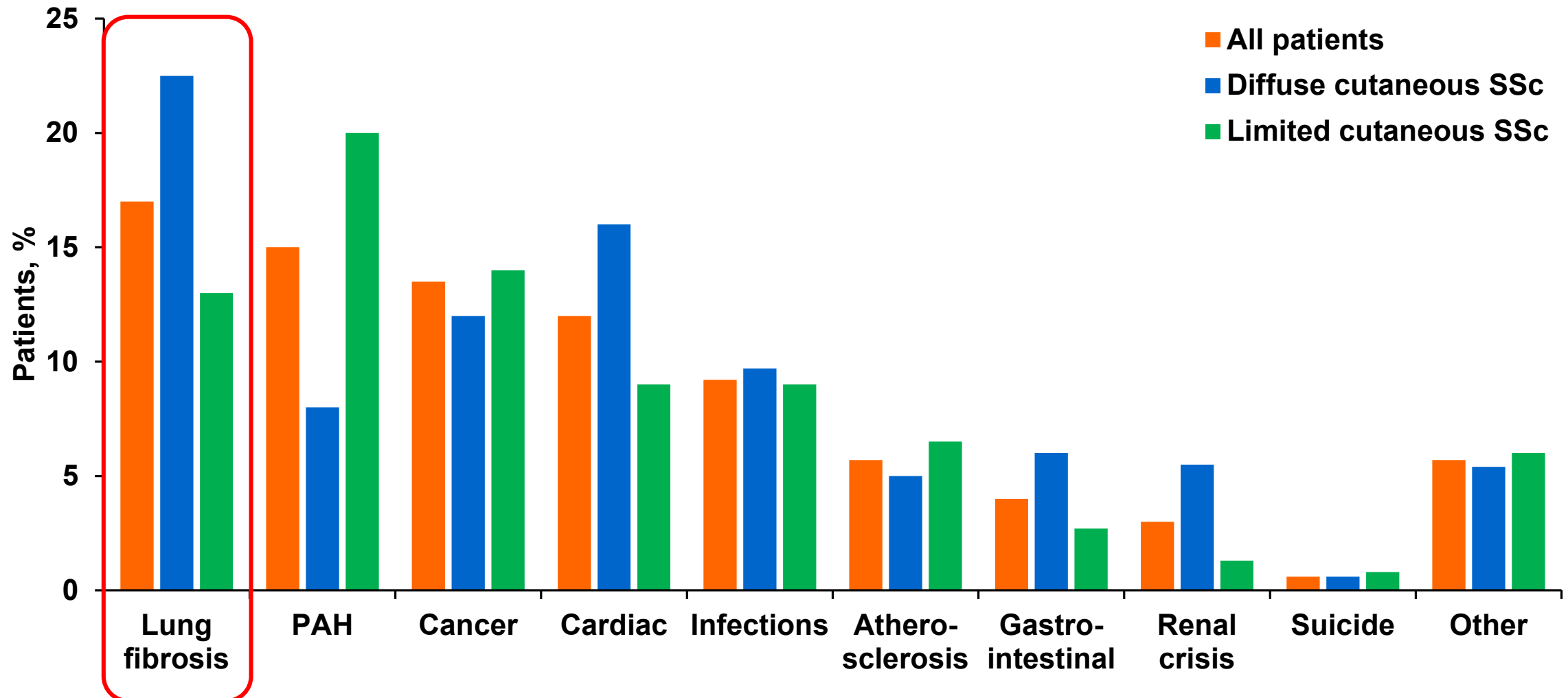


At risk, n

No lung fibrosis	61	55	50	45	35	20
Any lung fibrosis	61	55	45	36	29	14

# Causes of Death in Patients With SSc

## EUSTAR Cohort (N=11,193)



PAH=pulmonary arterial hypertension.

Reprinted from Elhai M, et al. *Ann Rheum Dis*. 2017;76:1897-1905.

# A Current View of SSc Pathogenesis: Key Cellular and Molecular Targets

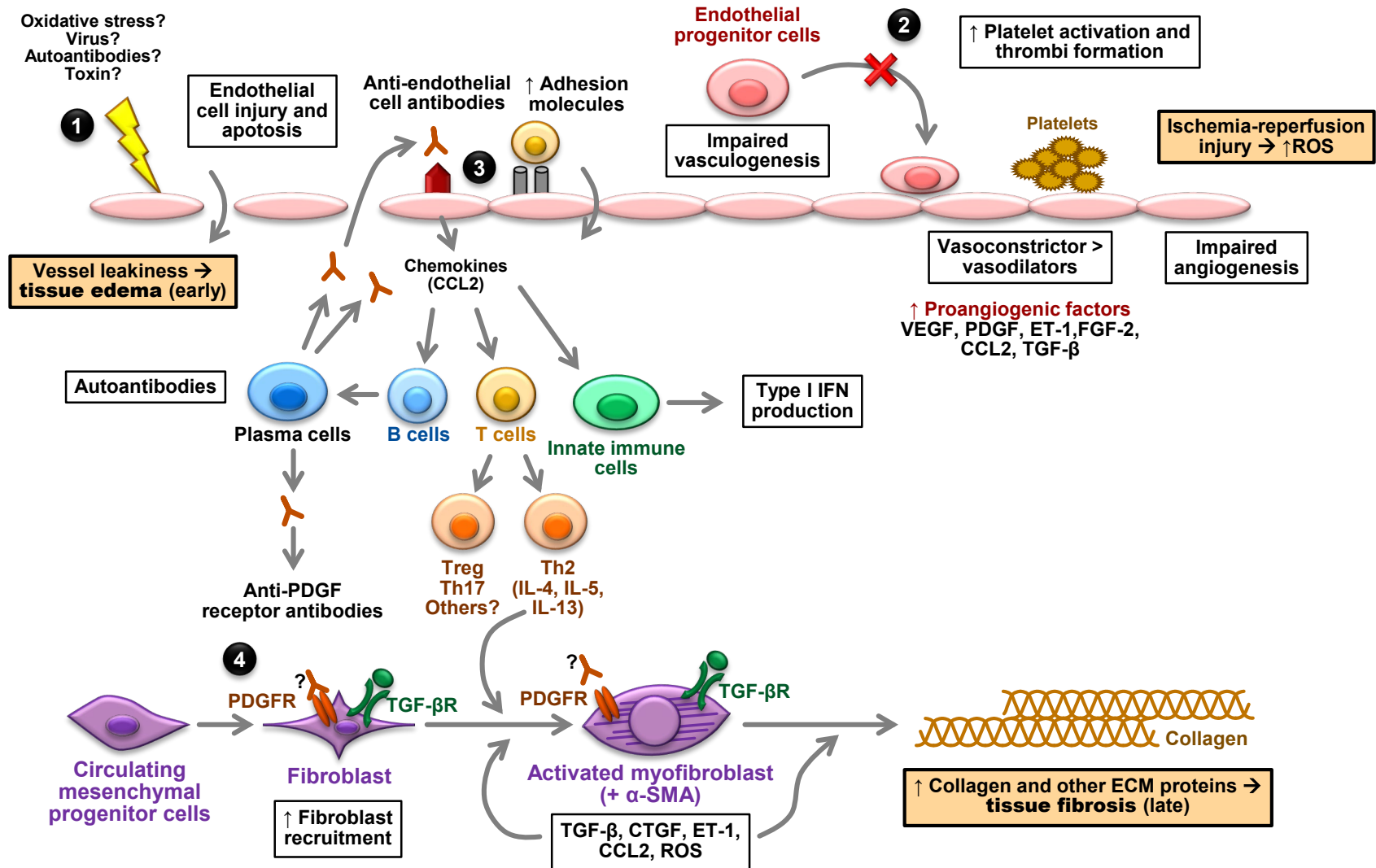
## Vascular injury

- Damage
- Defective repair (vasculogenesis)

## Immunity

- Adaptive immunity
- Autoantibodies
- Innate immunity

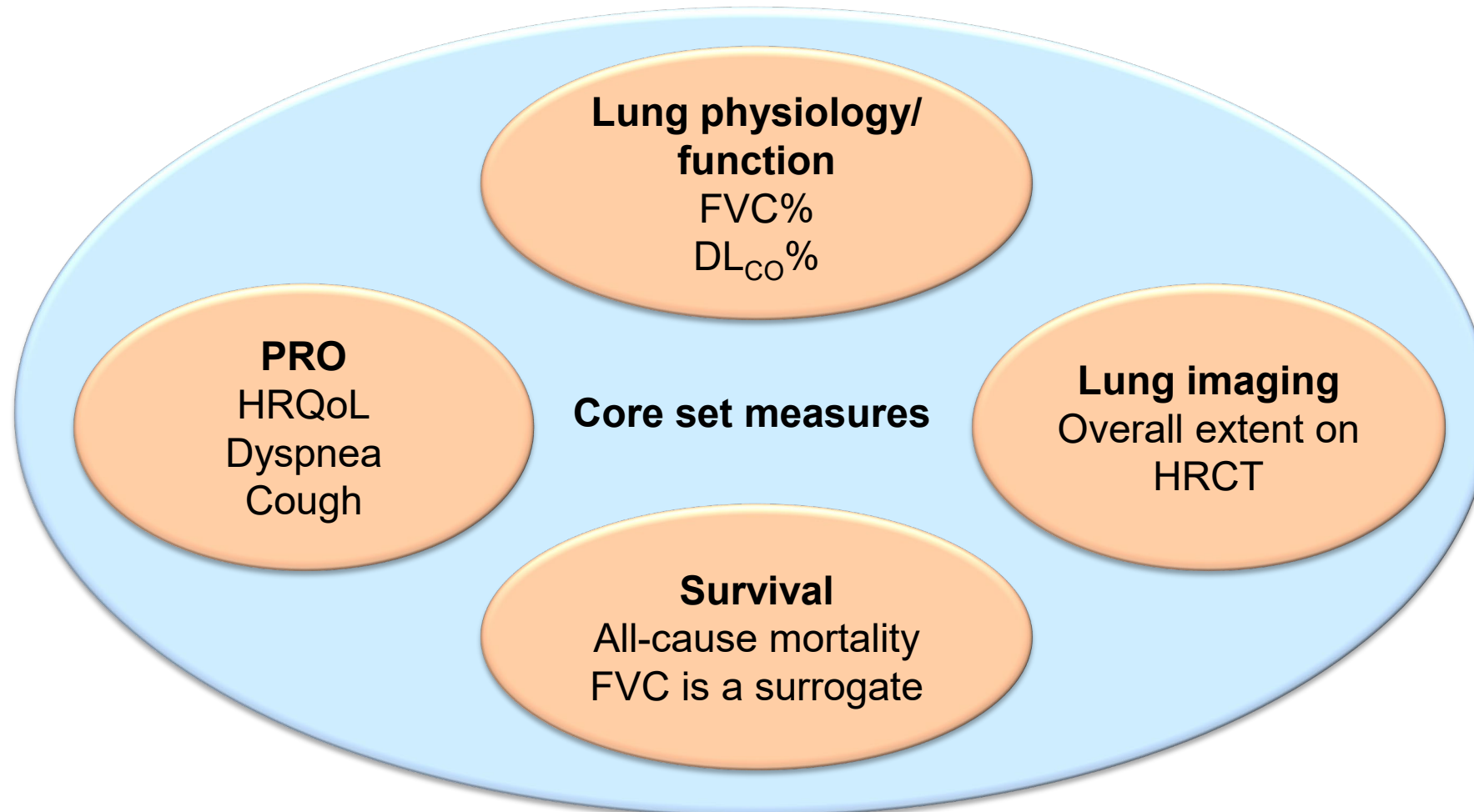
## Fibrosis



# IPF and SSc-ILD Share Pathophysiologic Features but Differ Clinically

	<b>IPF</b>	<b>SSc-ILD</b>
Demographics	Males >70 yr	Females 45-55 yr
Pathology	UIP	NSIP >> UIP
Acute exacerbations	++++	+
Progressivity	Variable	Variable
Pace of decline in FVC	++++	++
Median survival	3-5 yr	5-8 yr

# OMERACT Criteria for Outcome Assessment in CTD-ILD





## Forced Vital Capacity

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- ▶ Amount of air forcibly exhaled after maximum inhalation
- ▶ Reproducible, real time quality assurance via flow-volume loop
- ▶ Measure of lung elasticity
- ▶ Frequently expressed as % predicted to adjust for age, gender, ethnicity, and height
- ▶ Healthy individuals lose ~25 mL per year after age 25-30

# Assessing Dyspnea in SSc

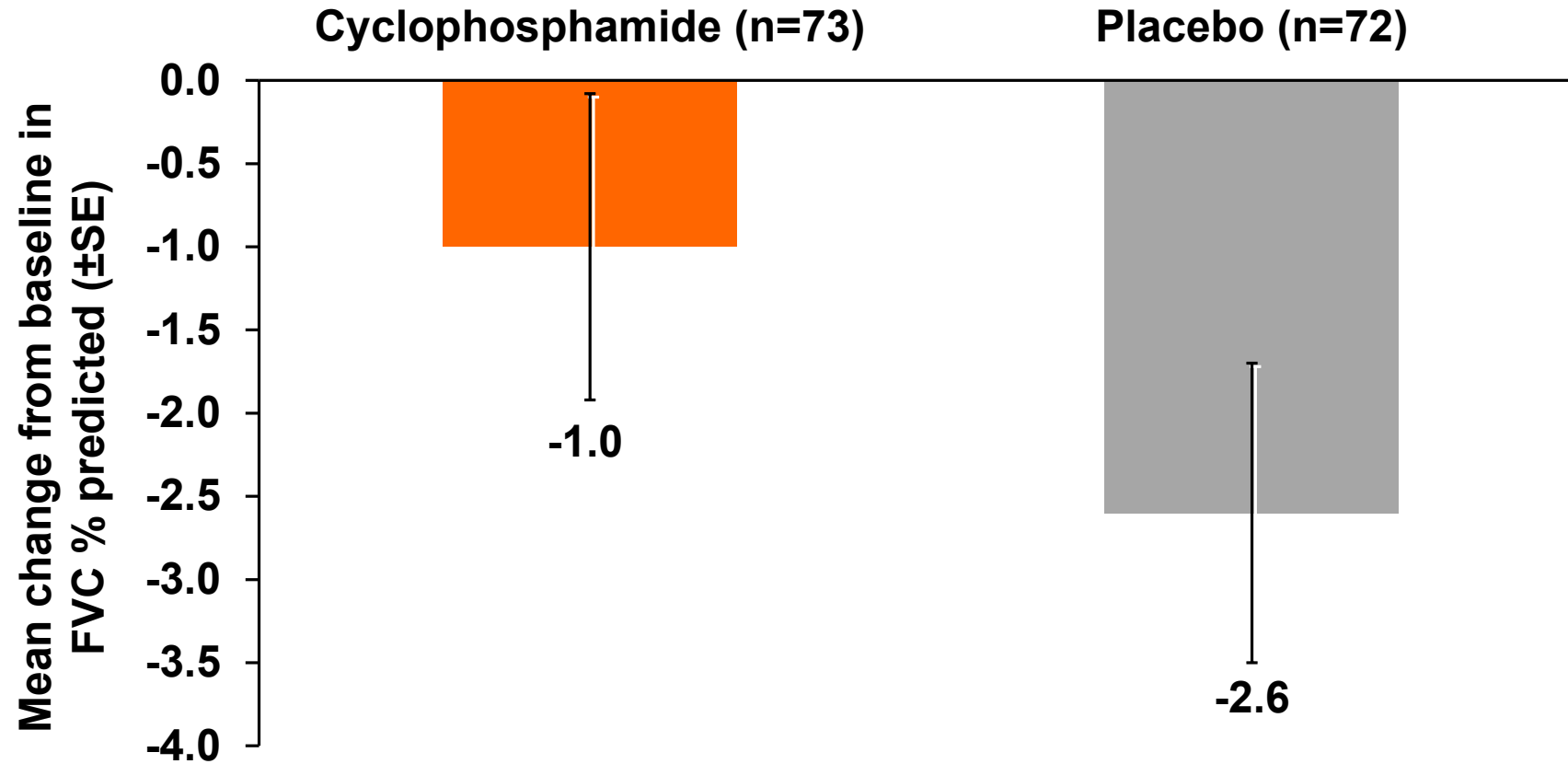
- ▶ Factors affecting dyspnea
  - Musculoskeletal involvement
  - Skeletal muscle perfusion
  - Fatigue/chronic catabolic disorder
  - Left ventricular diastolic disease
  - Pulmonary vascular involvement
  - Sedentary/deconditioned
- ▶ Dyspnea PRO for SSc-ILD are lacking

## Current Management of SSc-ILD

- ▶ No approved therapies
- ▶ Prevention or slowing of worsening is therapeutic goal
- ▶ Regeneration of alveolar tissue not biologically plausible
- ▶ Immunosuppressive therapies used in clinical practice
  - Oral cyclophosphamide (1-2 mg/kg/day)
  - IV cyclophosphamide (750 mg/m<sup>2</sup> BSA monthly × 6)
  - Oral mycophenolate mofetil (1500 mg bid)
  - IV or SC rituximab

# Change From Baseline in FVC % Predicted at Month 12<sup>CD-16</sup> (Primary Endpoint)

## Scleroderma Lung Study I



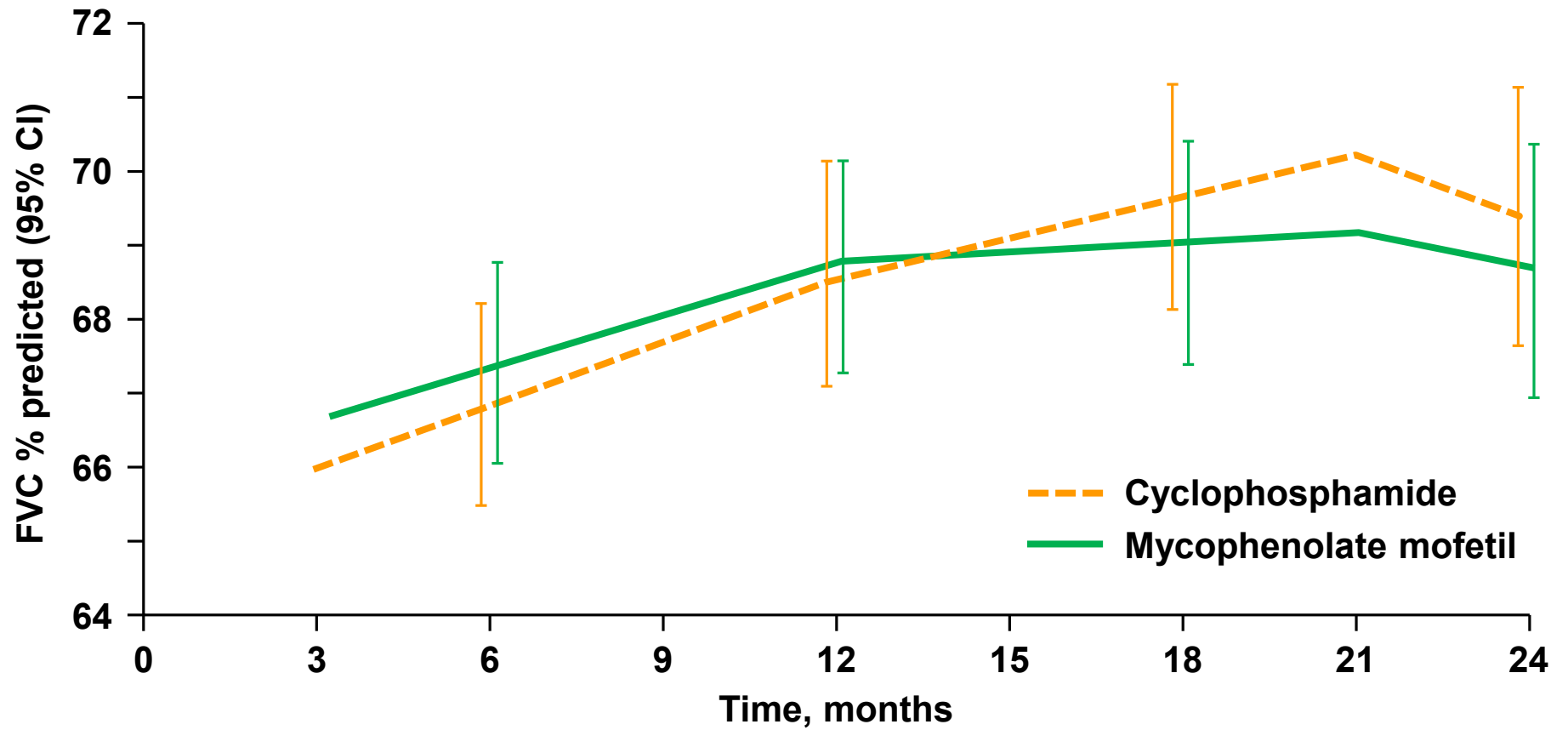
SE=standard error

p<0.05 for cyclophosphamide vs placebo.

Tashkin DP, et al. *N Engl J Med.* 2006;354:2655-2666.

# FVC % Predicted Over 24 Months

## Scleroderma Lung Study II

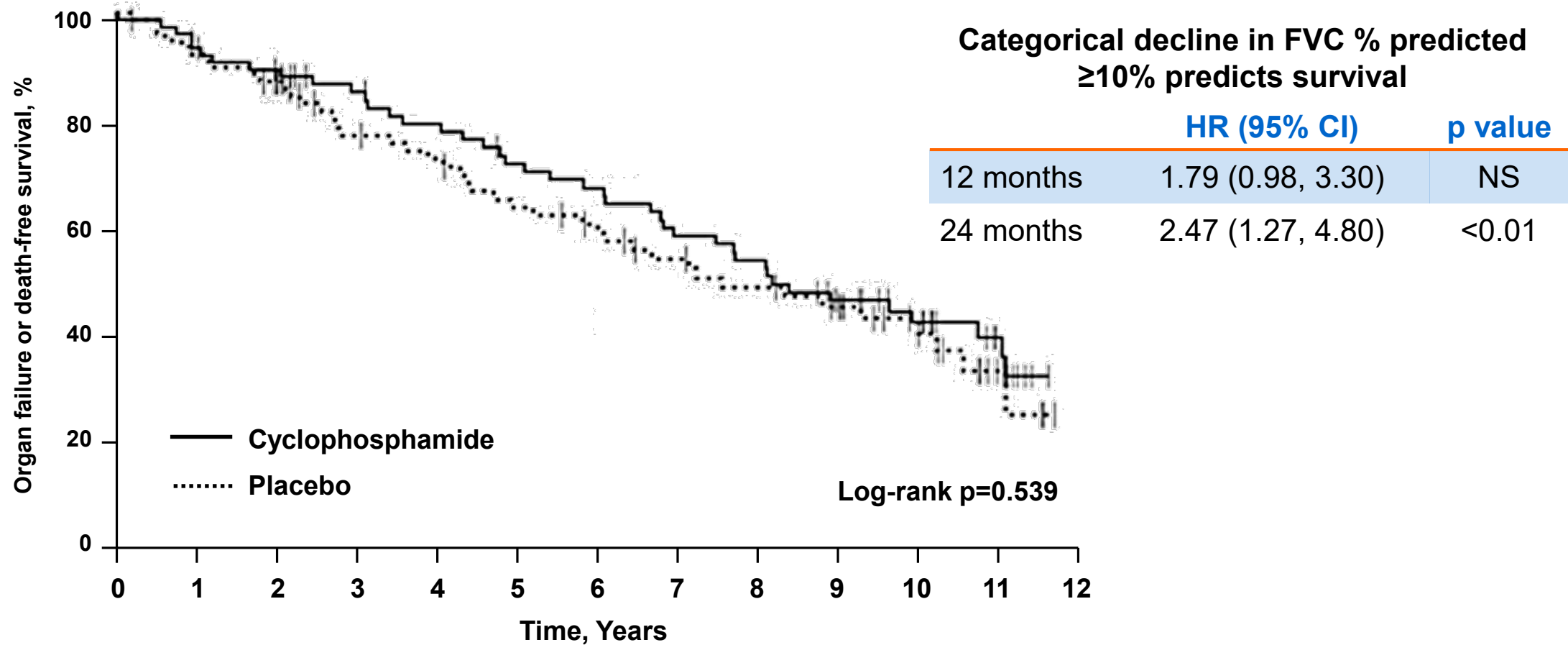


Patients, n	0	3	6	9	12	15	18	21	24
Cyclophosphamide	72	62	56	51	51	44	46	40	51
Mycophenolate mofetil	69	64	60	54	59	51	49	47	53

CI=confidence interval.  
 Reprinted from Tashkin DP, et al. *Lancet Respir Med.* 2017;4:708-719, with permission from Elsevier.

# Time to Death or Organ Failure From Randomization

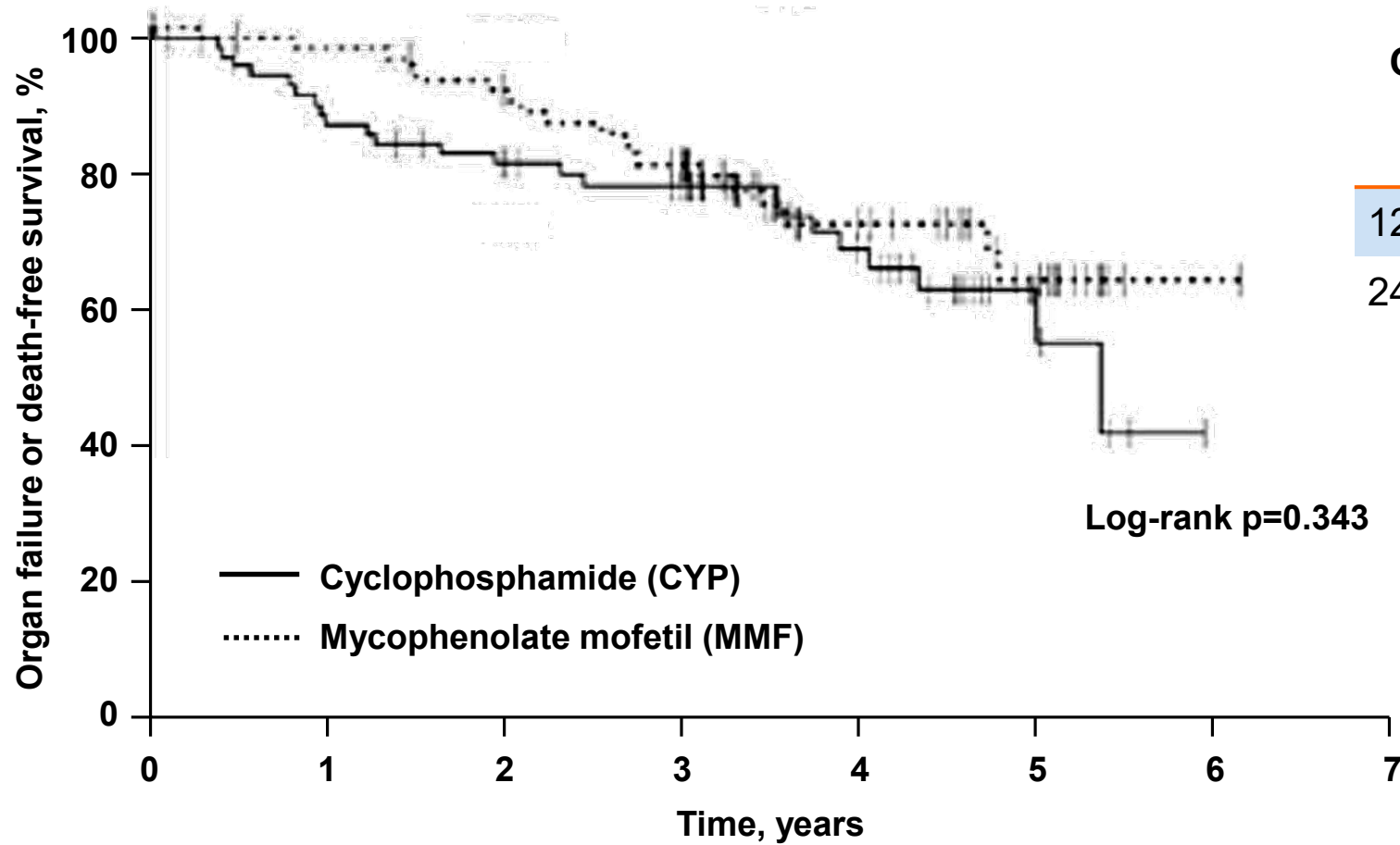
## Scleroderma Lung Study I



Cyclophosphamide	79	71	66	59	54	48	45	39	36	27	21	11	0
Placebo	79	73	67	53	49	42	37	32	28	24	15	5	0

# Time to Death or Organ Failure From Randomization

## Scleroderma Lung Study II



Categorical decline in FVC % predicted  $\geq 10\%$  predicts survival

	HR (95% CI)	p value
12 months	8.22 (2.91, 23.22)	<0.0001
24 months	4.02 (1.15, 14.02)	<0.05

	0	1	2	3	4	5	6	7
CYP	73	60	53	47	27	8	0	
MMF	69	64	58	49	26	16	1	0

## SSc-ILD Current Status

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- ▶ High disease burden
- ▶ Lung fibrosis is leading cause of death
- ▶ Prevention or slowing of worsening is the therapeutic goal
- ▶ No approved therapies
- ▶ Unapproved immunosuppressive therapies may provide short-term benefit in selected subsets
- ▶ Effective antifibrotic therapy is lacking



# Clinical Development Rationale for SSc-ILD

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Susanne Stowasser, MD

Associate Head Medicine, Therapeutic Area Respiratory Diseases  
Boehringer Ingelheim

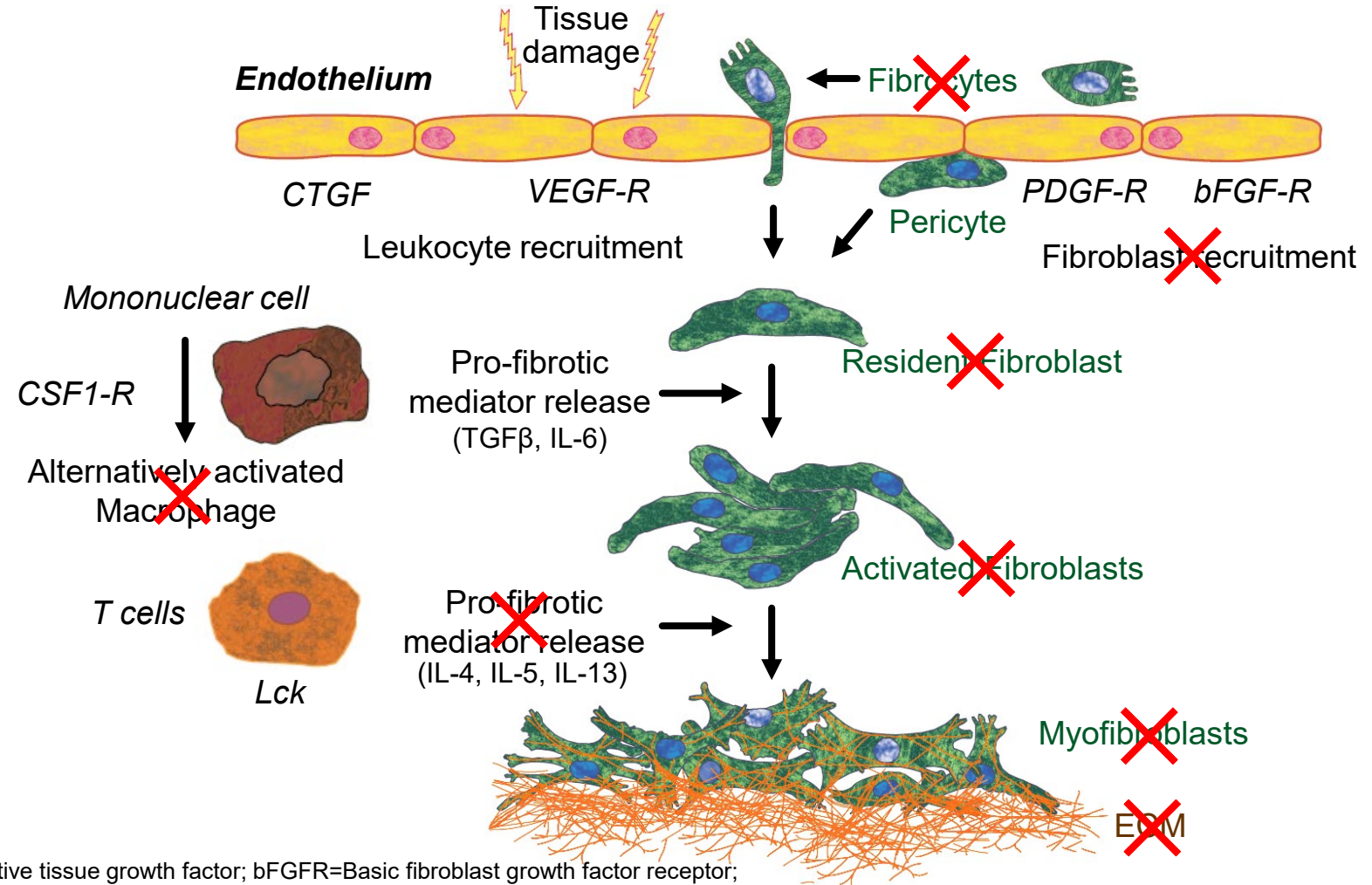
# Rationale for Clinical Development of Nintedanib in SSc-ILD

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- ▶ High unmet need in SSc-ILD
- ▶ Established benefit in IPF
- ▶ Similar pathogenesis across fibrosing ILDs with final common pathways of lung fibrosis
- ▶ Demonstrated anti-fibrotic activity in different *in vitro* models with human fibroblasts and animal models

# Nintedanib Attenuates Signaling Pathways Implicated in Fibrosis

- ▶ **Nintedanib** is a small-molecule **tyrosine kinase inhibitor** with a **distinct inhibitory spectrum**



CSF1R=Colony-stimulating factor 1 receptor; CTGF=Connective tissue growth factor; bFGFR=Basic fibroblast growth factor receptor; IL-4, -5, -6, -13= Interleukin; Lck=Lymphocyte-specific protein tyrosine kinase; PDGFR=Platelet derived growth factor receptor; TGFβ=Transforming growth factor beta; VEGFR=Vascular endothelial growth factor receptor.  
Reprinted from Wollin L, et al. *Journal of Scleroderma and Related Disorders*. 2019. [e-pub ahead of print]

# Clinical Development of Nintedanib in Fibrosing Interstitial Lung Diseases

## Fibrosing Interstitial Lung Diseases

**Idiopathic Pulmonary  
Fibrosis (IPF)**

**INPULSIS**  
Approved

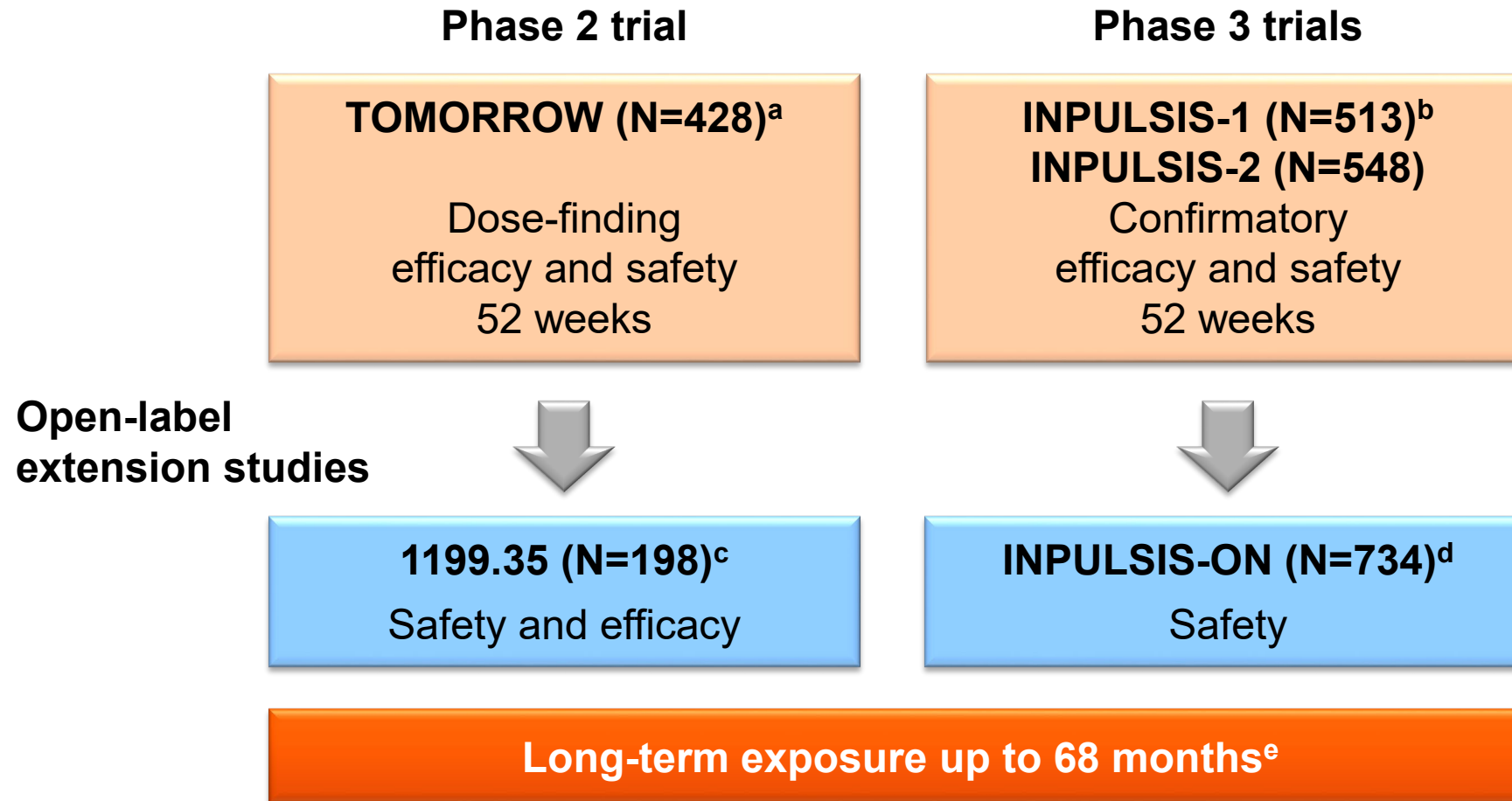
**Systemic Sclerosis-  
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**SENSCIS**  
Under review

**Progressive Fibrosing  
ILDs**

**INBUILD**  
Ongoing

# The Nintedanib Program in IPF Is the Foundation for Development in SSc-ILD



<sup>a</sup> Richeldi L, et al. *N Engl J Med*. 2011;365(12):1079-1087; <sup>b</sup> Richeldi L, et al. *N Engl J Med*. 2014;370(22):2071-2082;

<sup>c</sup> Richeldi L, et al. *Thorax*. 2018;73:581-583; <sup>d</sup> Crestani B, et al. *Lancet Resp Med*. 2019;7(1):60-68;

<sup>e</sup> For patients treated with nintedanib in INPULSIS and INPULSIS-ON.

# Key Commonalities Across IPF and SSc-ILD Phase 3 Studies

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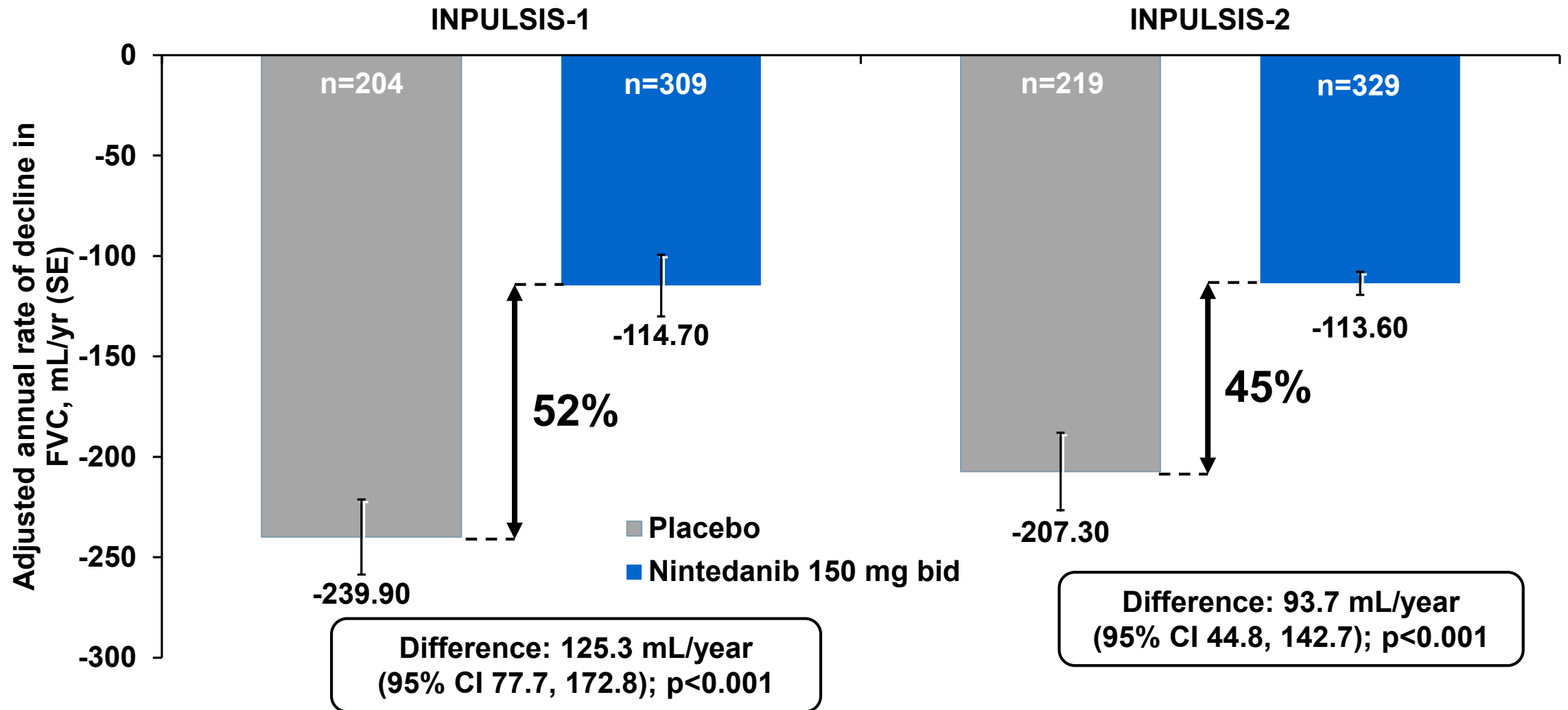
- ▶ Dosing regimen
  - Nintedanib 150 mg bid
  - Dose reduction or treatment interruption to manage AEs
- ▶ Treatment period: 52 weeks to assess benefit-risk
- ▶ Primary endpoint: annual rate of decline in FVC

## Rationale for FVC as Primary Endpoint in SSc-ILD

- ▶ FVC reflects the underlying pathophysiology of the scarring process
- ▶ In IPF, FVC is accepted surrogate for clinically meaningful benefit<sup>a</sup>
- ▶ In SSc-ILD, FVC decline is associated with mortality<sup>b,c,d,e</sup>
- ▶ FVC is the primary outcome in SSc trials that assess ILD progression<sup>f</sup>
- ▶ OMERACT CTD-ILD working group proposes FVC as the preferred outcome measure in trials of 1-year duration<sup>g,h</sup>

# Annual Rate of Decline in FVC (Primary Endpoint)

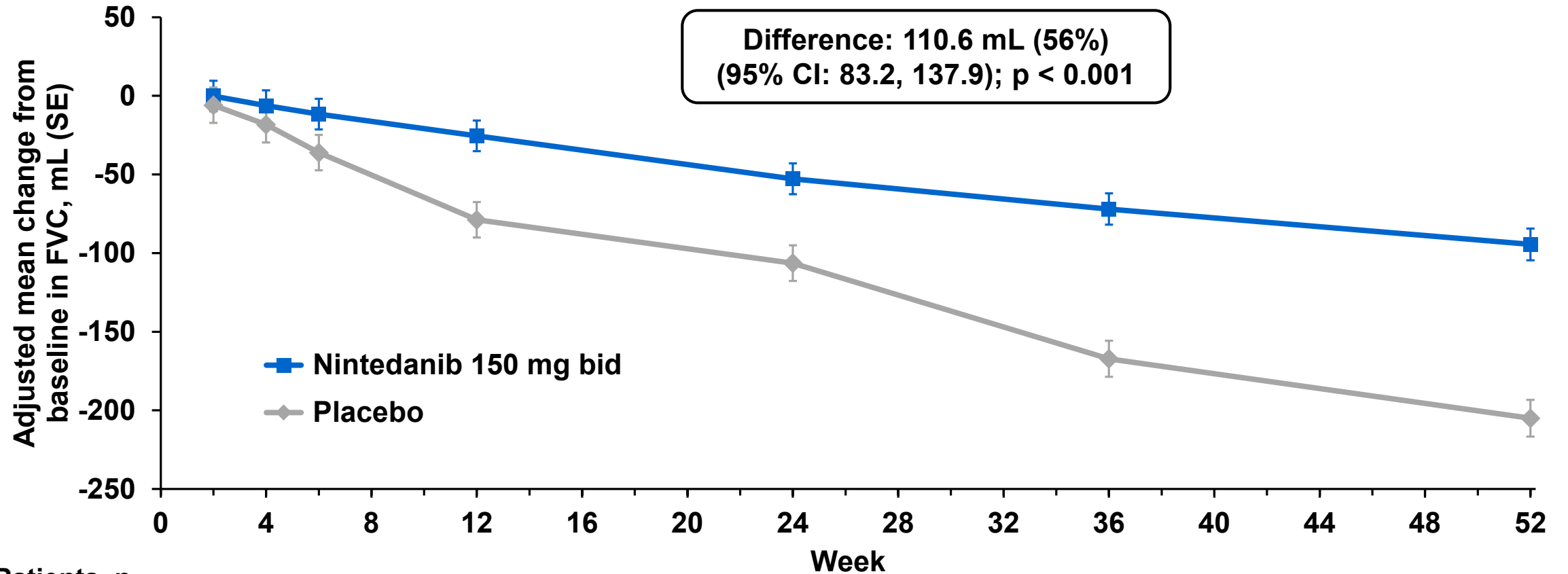
## INPULSIS Studies in IPF





# Adjusted Change From Baseline in FVC

## INPULSIS Studies in IPF (Pooled)



**Patients, n**

<b>Nintedanib</b>	<b>626</b>	<b>616</b>	<b>613</b>	<b>604</b>	<b>587</b>	<b>569</b>	<b>519</b>
<b>Placebo</b>	<b>417</b>	<b>408</b>	<b>407</b>	<b>403</b>	<b>395</b>	<b>383</b>	<b>345</b>

<sup>a</sup> Adjusted mean difference vs placebo at Week 52.

Reprinted from Supplement to Richeldi L, et al. *N Engl J Med*. 2014;370(22):2071-2082.

# Building on the IPF Experience

## SENSCIS Phase 3 Study in SSc-ILD

- ▶ Nintedanib addresses the same underlying pathophysiology in IPF and SSc-ILD
- ▶ SENSCIS is the largest randomized placebo-controlled trial in SSc-ILD
  - Includes a broad patient population generalizable to clinical practice
- ▶ Same dosing regimen with dose reduction/interruption to manage AEs
- ▶ Same primary endpoint: annual rate of decline in FVC over 52 weeks

# Efficacy of Nintedanib for SSc-ILD

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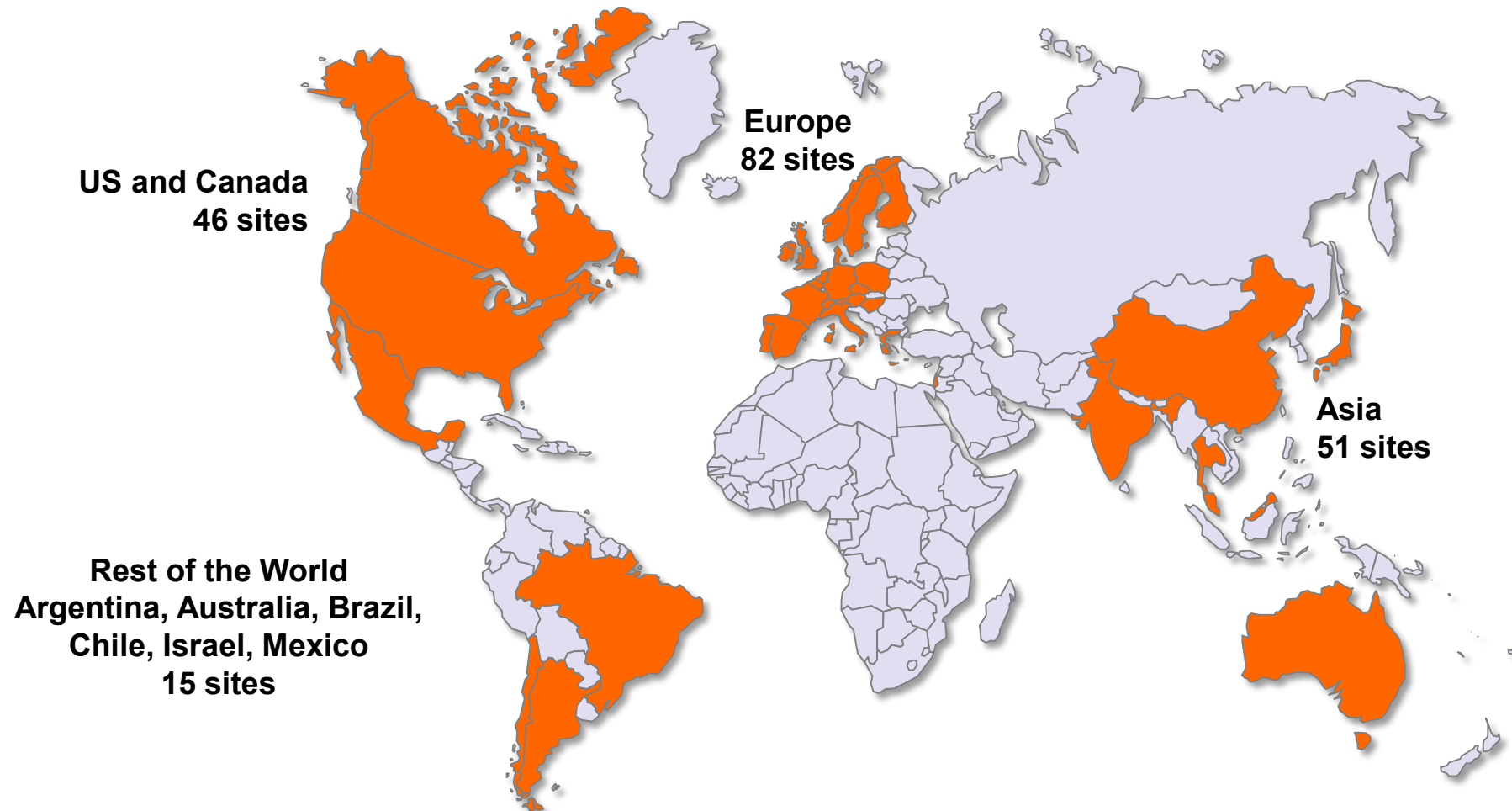
Emmanuelle Clerisme-Beaty, MD

Senior Clinical Program Leader

Boehringer Ingelheim

# Participating Countries (194 Sites)

## SENSCIS



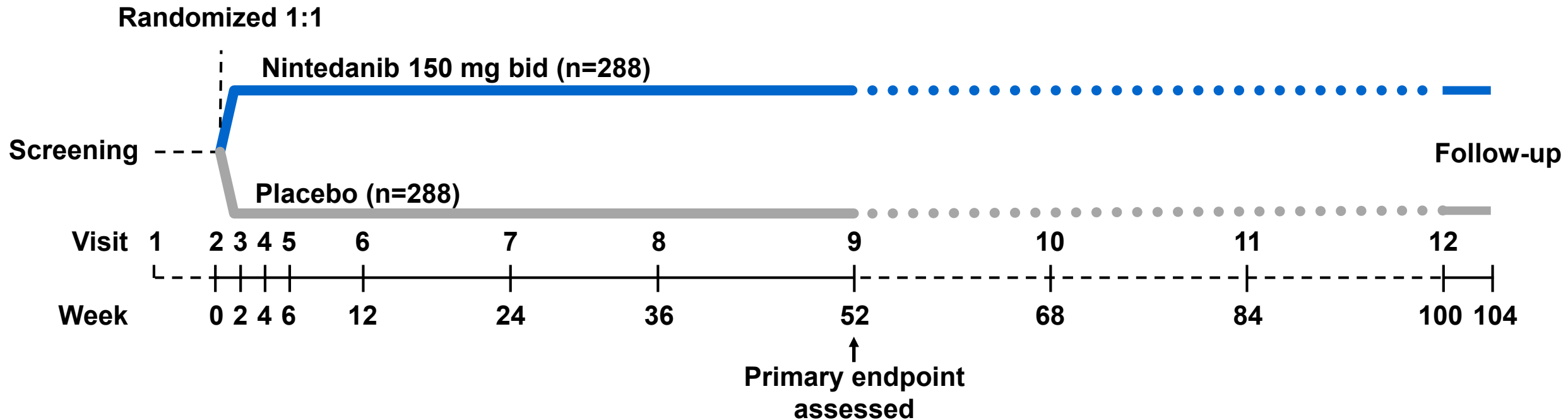
Europe: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom.

Asia: China, India, Japan, Malaysia, Thailand.

Rest of the world: Argentina, Australia, Brazil, Chile, Israel, Mexico.

# Trial Design

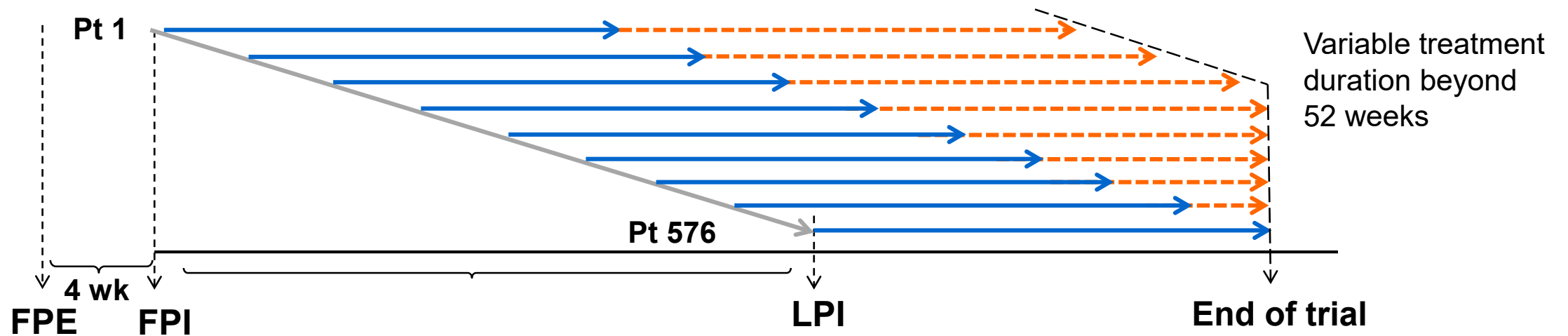
## SENSCIS



- ▶ Stratification by anti-topoisomerase antibody (ATA) status (positive or negative)
- ▶ Primary assessment over 52 weeks
- ▶ Patients remained on blinded treatment up to 100 weeks or until the last patient had reached Week 52

# Treatment Duration Beyond 52 Weeks Varied

## SENSCIS



- 52-week treatment period for primary endpoint
- - - - -> Treatment period beyond 52 weeks but  $\leq 100$  weeks

- ▶ 146 patients (73 per arm) were able to complete 100-week treatment period

# Key Inclusion Criteria

## SENSCIS

- ▶ Age  $\geq 18$  years
- ▶ SSc (based on 2013 ACR/EULAR criteria<sup>a</sup>) with disease onset (first non-Raynaud symptom)  $< 7$  years from screening
- ▶ ILD based on chest HRCT performed within 12 months of screening with  $\geq 10\%$  extent of fibrosis of the lungs (confirmed by central reviewer)
- ▶ FVC  $\geq 40\%$  predicted
- ▶ DL<sub>CO</sub> 30% to 89% predicted

# Key Exclusion Criteria

## SENSCIS

- ▶ ALT or AST or bilirubin  $>1.5 \times \text{ULN}$
- ▶ Bleeding risk (eg, requiring full-dose therapeutic anticoagulation or high-dose antiplatelet therapy)
- ▶ Myocardial infarction or unstable angina within 6 months of screening
- ▶ History of thrombotic event within 12 months of screening
- ▶ More than 3 digital ulcers or history of severe digital necrosis requiring hospitalization
- ▶ Significant pulmonary hypertension<sup>a</sup>
- ▶ History of scleroderma renal crisis
- ▶  $\text{FEV}_1/\text{FVC} < 70\%$

ALT=alanine transaminase; AST=aspartate transaminase;  $\text{FEV}_1$ =forced expiratory volume in 1 second; ULN=upper limit of normal.

<sup>a</sup> Defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization showing a cardiac index  $\leq 2 \text{ L/min/m}^2$ , or pulmonary hypertension requiring parenteral therapy with epoprostenol/treprostinil.



## Main Concomitant Medications at Baseline

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- ▶ Permitted
  - Prednisone ( $\leq 10$  mg/day or equivalent)
  - Stable therapy with mycophenolate or methotrexate for  $\geq 6$  months prior to randomization
- ▶ Excluded
  - Cyclophosphamide
  - Azathioprine
  - Rituximab
  - Cyclosporine A

# Primary and Key Secondary Endpoints

## SENSCIS

- ▶ Primary endpoint
  - Annual rate of decline in FVC (mL/year) assessed over 52 weeks
- ▶ Key secondary endpoints
  - Absolute change from baseline in mRSS at Week 52
  - Absolute change from baseline in SGRQ total score at Week 52

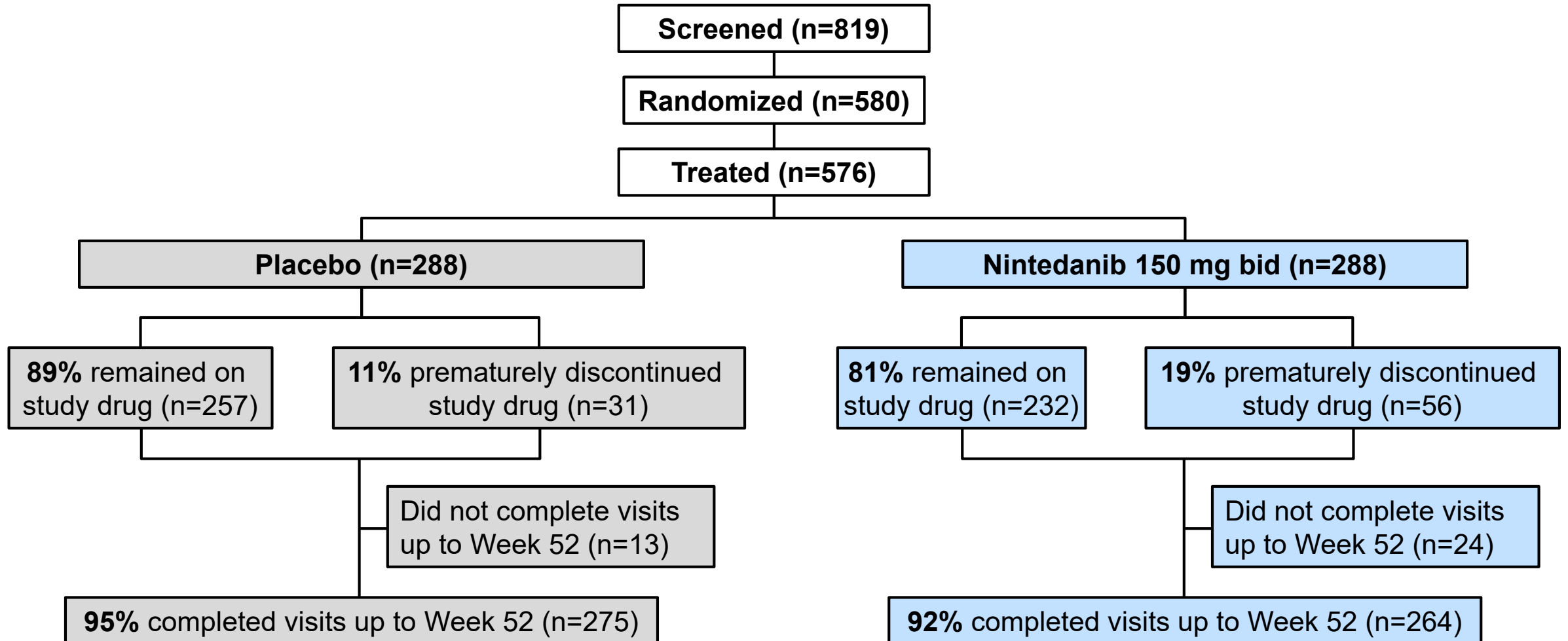
# Analysis of Primary Endpoint

## SENSCIS

- ▶ Hierarchical testing procedure used to protect type I error rate
- ▶ Primary endpoint
  - On all measurements taken within first 52 weeks, including those from patients who discontinued study drug or who did not have an FVC measurement at Week 52
  - Slope of FVC decline (mL/year) calculated for every patient and the average compared between treatment groups
  - A random coefficient regression model used with ATA status, age, height, sex, and baseline FVC (mL) as covariates

# Disposition of Patients Over 52 Weeks

## SENSCIS



## Handling of Missing FVC Measurements at Week 52

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- ▶ Prespecified analyses
  - 78 of 576 treated patients did not provide FVC measurement at Week-52 time window (up to 373 days)
    - 28 of those 78 patients had values just after the window (median 9 days)
- ▶ Revised analyses include data from these 28 patients
  - 50 of 576 patients had a missing 52-week FVC value

# Baseline Demographics

## SENSCIS

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Mean age, years (SD)	53.4 (12.6)	54.6 (11.8)
Female, n (%)	212 (73.6)	221 (76.7)
Mean weight, kg (SD)	70.0 (16.4)	69.4 (15.4)
Mean body mass index, kg/m <sup>2</sup> (SD)	25.8 (5.1)	25.9 (4.8)
Race, n (%) <sup>a</sup>		
White	186 (64.6)	201 (69.8)
Asian	81 (28.1)	62 (21.5)
Black/African American	16 (5.6)	20 (6.9)
American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander	3 (1.0)	2 (0.7)

SD=standard deviation.

<sup>a</sup> Data from patients who selected one race. Four patients ticked two boxes.

# Baseline Disease Characteristics

## SENSCIS

	Placebo n=288	Nintedanib n=288
Type of SSc, n (%)		
Diffuse cutaneous	146 (50.7)	153 (53.1)
Limited cutaneous	142 (49.3)	135 (46.9)
mRSS, mean (SD)	10.9 (8.8)	11.3 (9.2)
Years since onset of first non-Raynaud symptom, median (minimum, maximum)	3.5 (0.4, 7.2)	3.4 (0.3, 7.1)
Anti-topoisomerase antibody positive, n (%)	177 (61.5)	173 (60.1)
Taking mycophenolate, n (%)	140 (48.6)	139 (48.3)
Taking corticosteroids, n (%)	135 (46.9)	152 (52.8)
Taking methotrexate, n (%)	15 (5.2)	23 (8.0)

# Baseline Pulmonary Characteristics

## SENSCIS

	Placebo n=288	Nintedanib n=288
Mean extent of fibrotic ILD on HRCT, (SD) <sup>a</sup>	35.2 (20.7)	36.8 (21.8)
HRCT features, n (%)		
Reticulation	272 (94.4)	266 (92.4)
Ground glass opacities	246 (85.4)	241 (83.7)
Honeycombing	45 (15.6)	44 (15.3)
Mean FVC, mL (SD)	2541 (816)	2459 (736)
Mean FVC, % predicted (SD)	72.7 (16.6)	72.4 (16.8)
Mean DL <sub>co</sub> , % predicted (SD) <sup>b</sup>	53.2 (15.1)	52.9 (15.1)
Mean SpO <sub>2</sub> , % (SD)	97.5 (2.5)	97.6 (1.9)

SpO<sub>2</sub>=peripheral capillary oxygen saturation.

<sup>a</sup> Qualitative assessment by central review by expert radiologist.

<sup>b</sup> Corrected for hemoglobin.

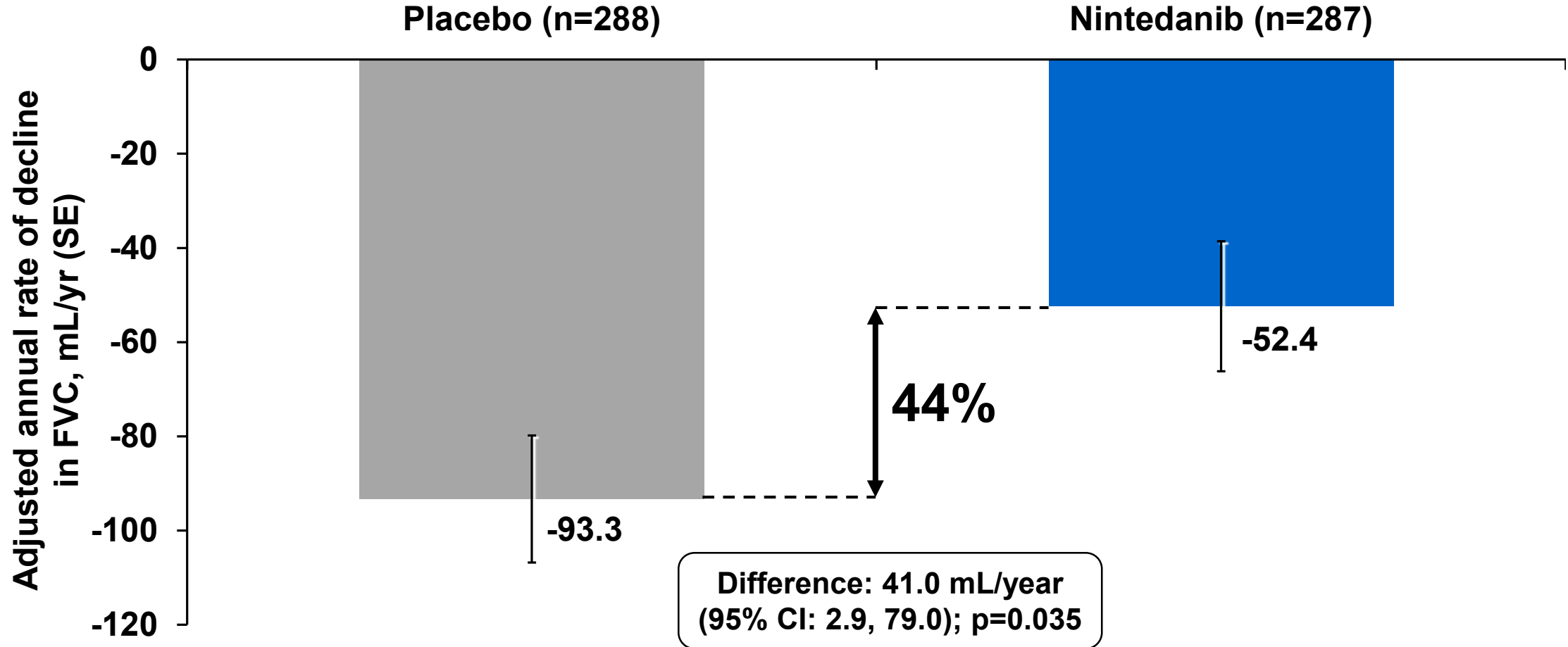


# Study Results

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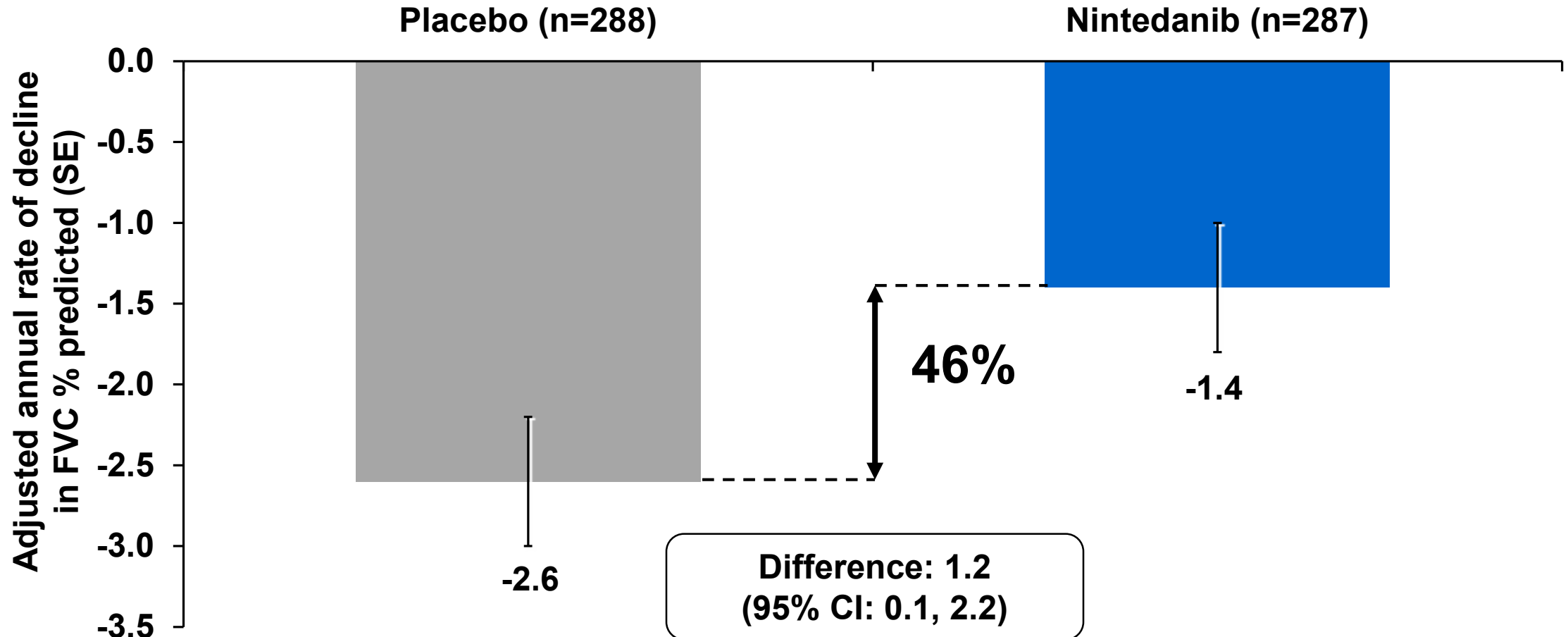
# Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

SENSCIS



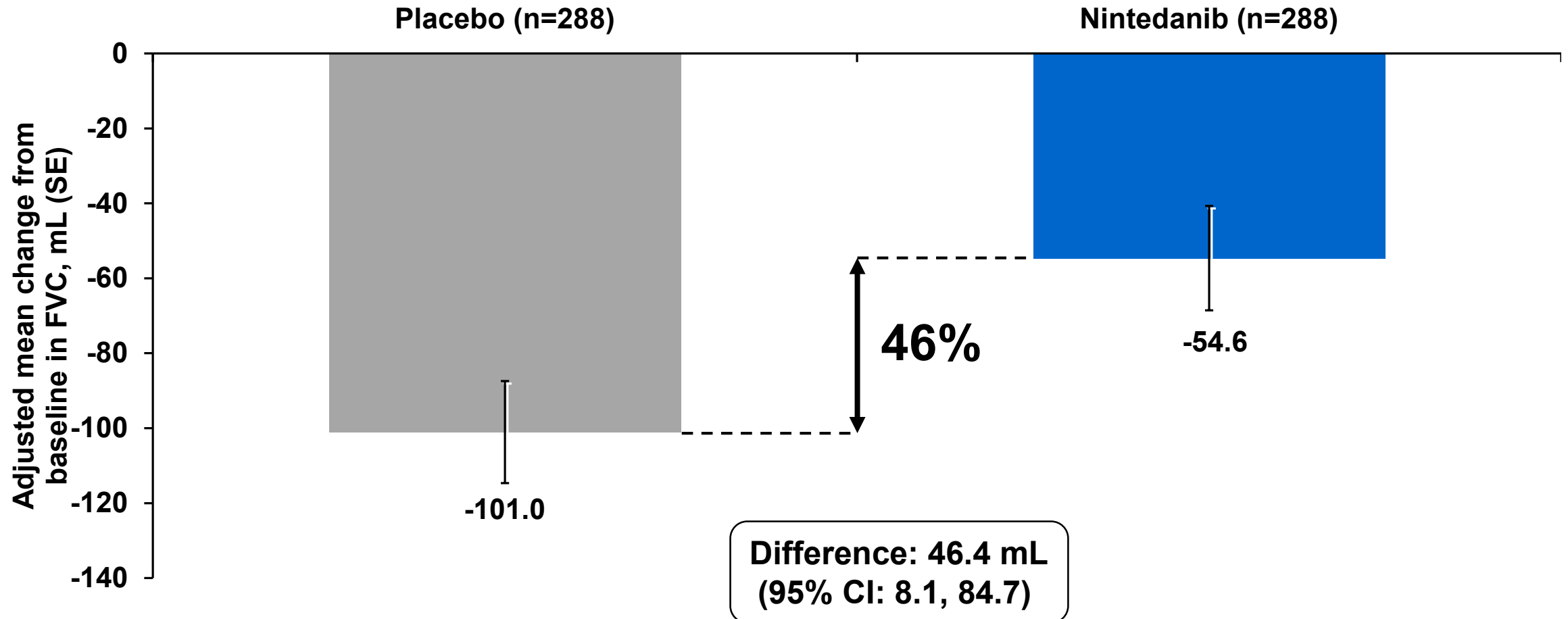
# Rate of Decline in FVC % Predicted Over 52 Weeks

## SENSCIS



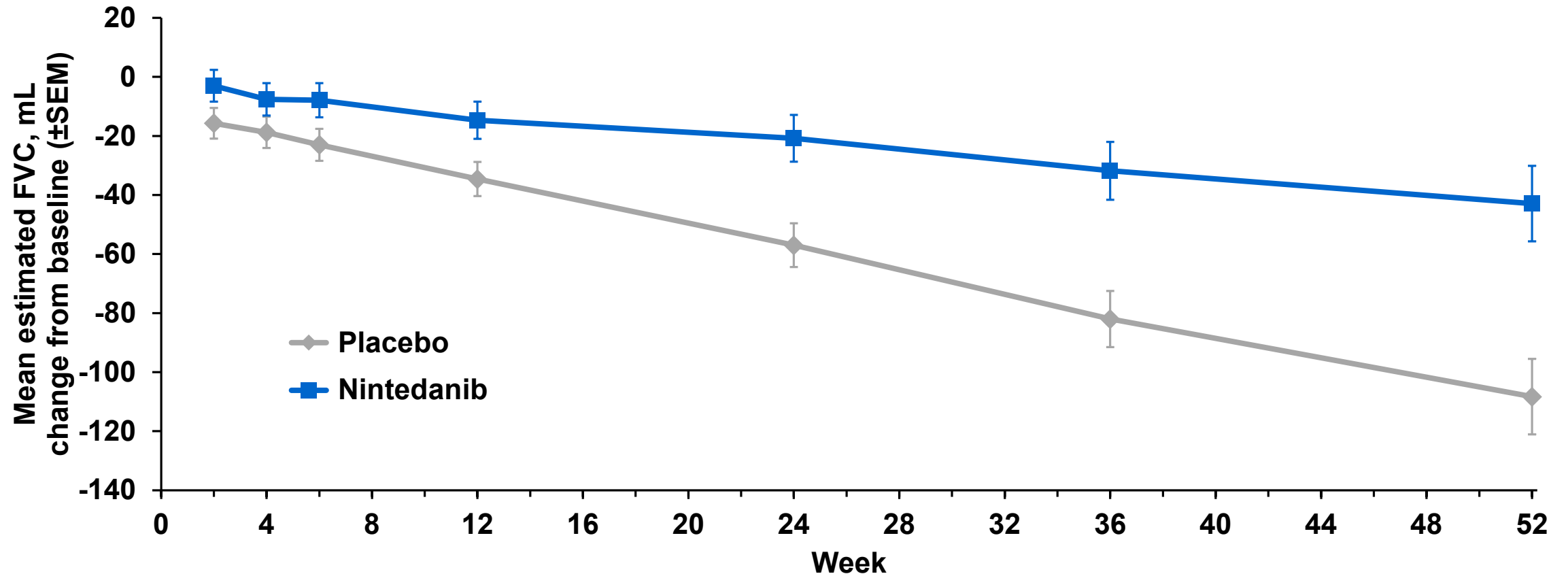
# Absolute Change From Baseline in FVC (mL) at Week 52

## SENSCIS



# Change From Baseline in FVC (mL) Over 52 Weeks

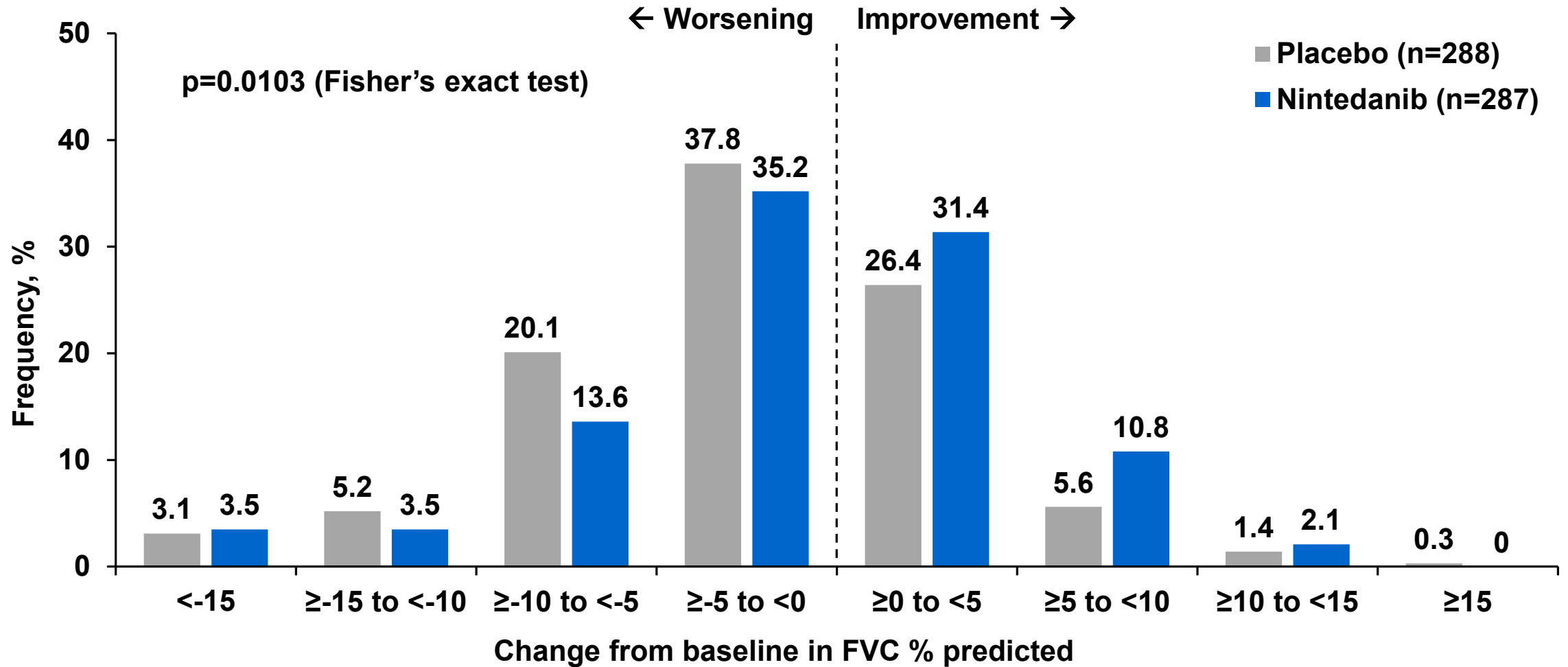
## SENSCIS



Patients, n

Placebo	288	283	281	280	283	280	268	257
Nintedanib	288	283	281	273	278	265	262	241

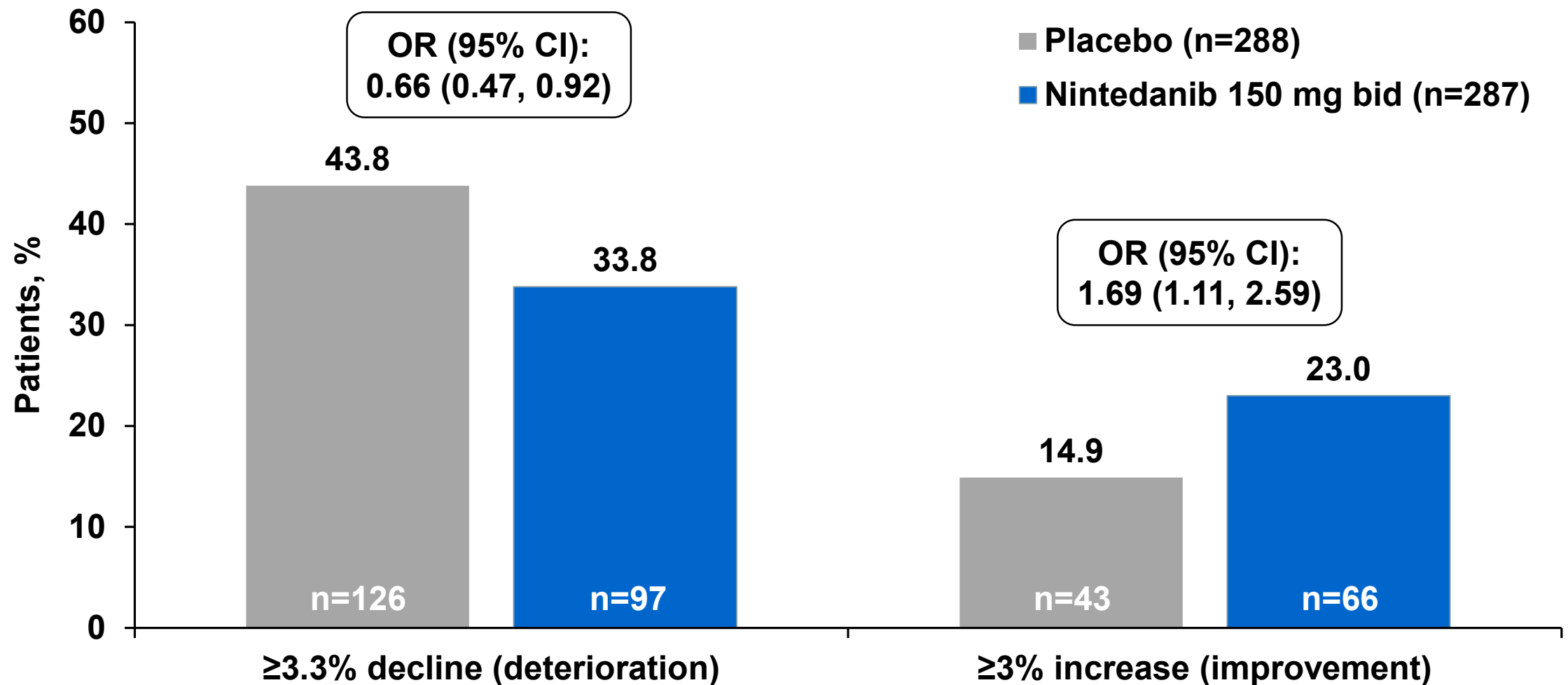
# Categorical Analysis— Change in FVC % Predicted at 52 Weeks<sup>a</sup>



<sup>a</sup> Worst observation carried forward.

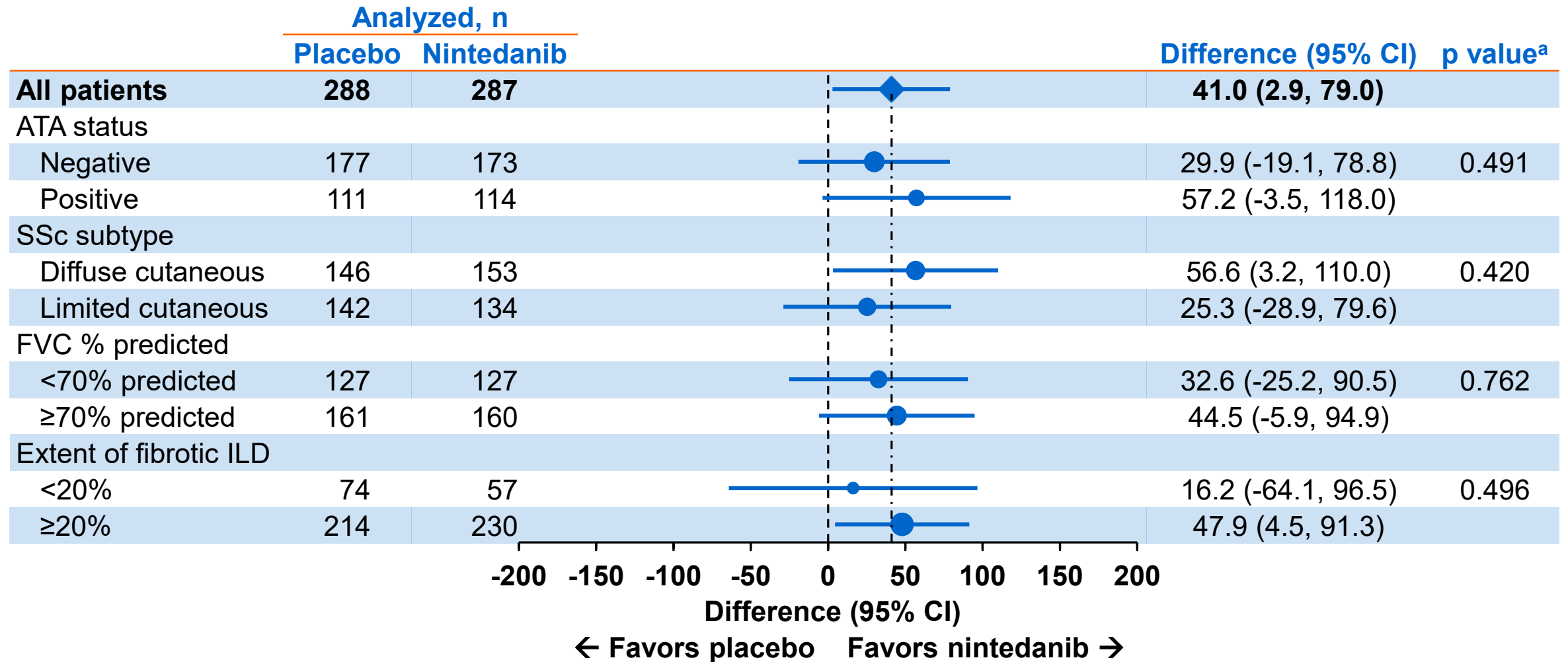
# Additional Responder Analysis

## Change From Baseline in FVC % Predicted at 52 Weeks<sup>a</sup>



# Subgroup Analyses of Primary Endpoint 1/2

## SENSCIS Treated Set

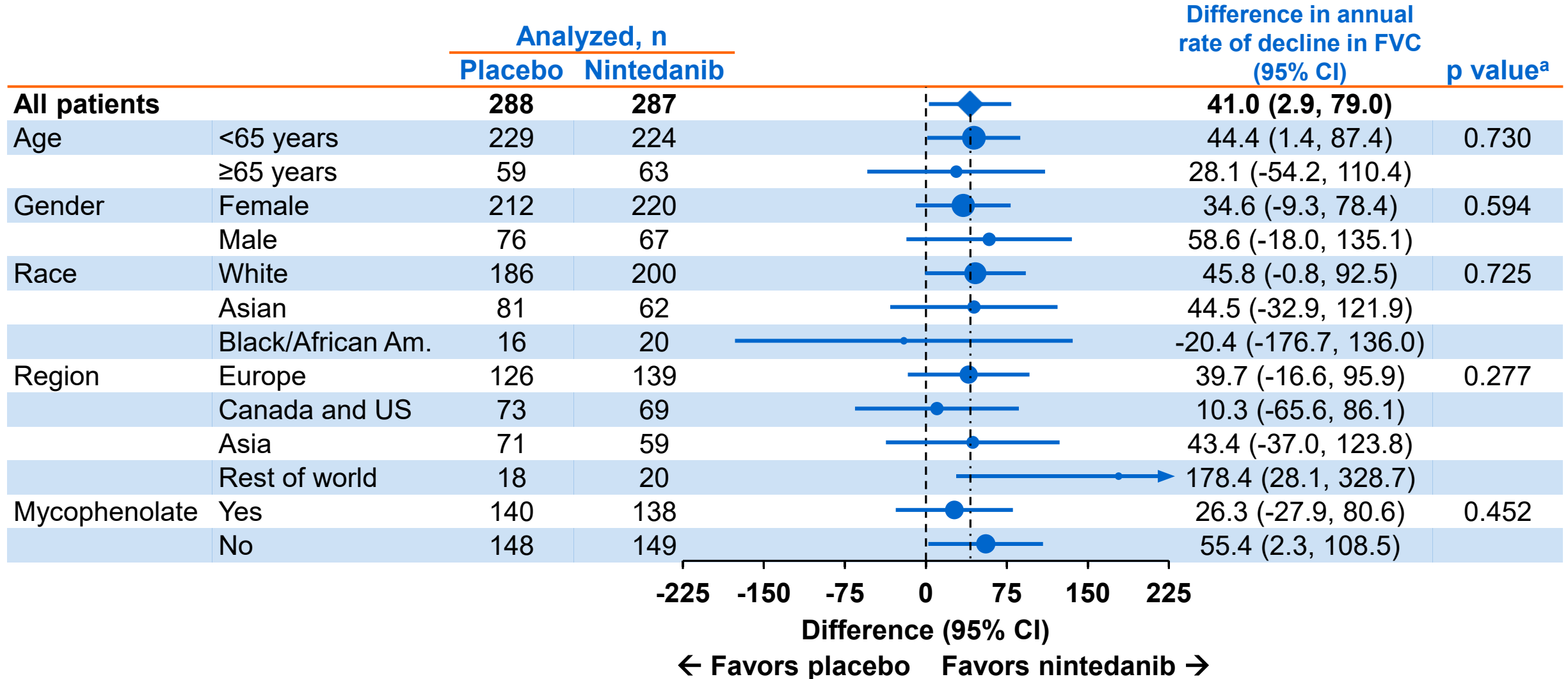


<sup>a</sup> Treatment-by-time-by-subgroup interaction.



# Subgroup Analyses of Primary Endpoint 2/2

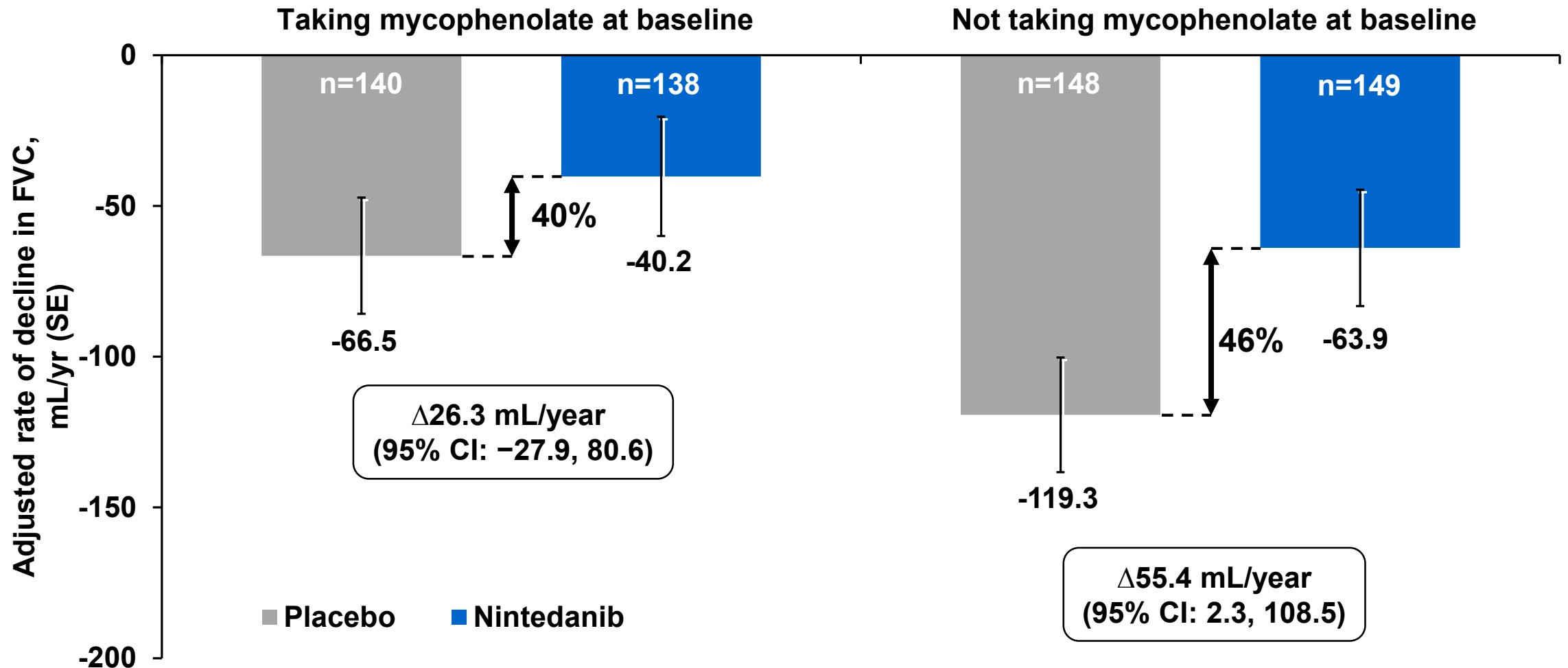
## SENSCIS



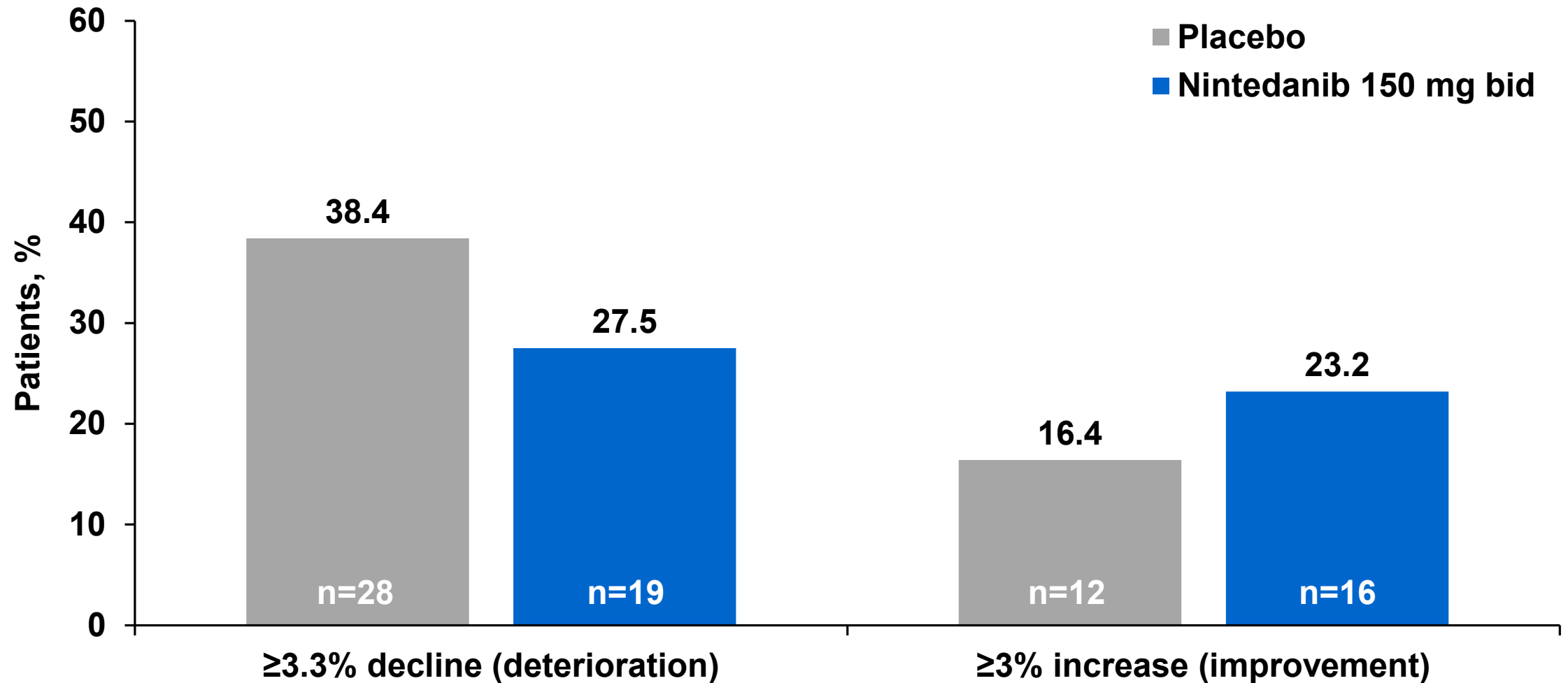
<sup>a</sup> Treatment-by-time-by-subgroup interaction.

# Prespecified Subgroup Analyses of Primary Endpoint by Mycophenolate Use

## SENSCIS



# Responder Analysis for US/Canada



# Key Secondary Endpoints

---

# Key Secondary Endpoints

## SENSCIS

Secondary endpoint at Week 52	Placebo	Nintedanib	Adjusted mean difference (95% CI)	p value
<b>mRSS</b>	<b>n=286</b>	<b>n=288</b>		
Mean baseline (SD)	10.9 (8.8)	11.3 (9.2)		
Adjusted absolute mean change from baseline <sup>a</sup> (SE)	-1.96 (0.26)	-2.17 (0.27)	-0.21 (-0.94, 0.53)	0.579
<b>SGRQ</b>	<b>n=283</b>	<b>n=282</b>		
Mean baseline (SD)	39.4 (20.9)	40.7 (20.1)		
Adjusted absolute mean change from baseline (SE)	-0.88 (0.87)	0.81 (0.88)	1.69 (-0.73, 4.12)	0.171

- ▶ No treatment differences in mRSS or SGRQ between treatment groups

# Time to Death Over Whole Trial

## SENSCIS

	Placebo	Nintedanib
Analyzed, n	288	288
Patients with event, n (%)	9 (3.1)	10 (3.5)
Hazard ratio (95% CI)	1.16 (0.47, 2.84)	
p value	0.754	

- ▶ No treatment differences in mortality between treatment groups

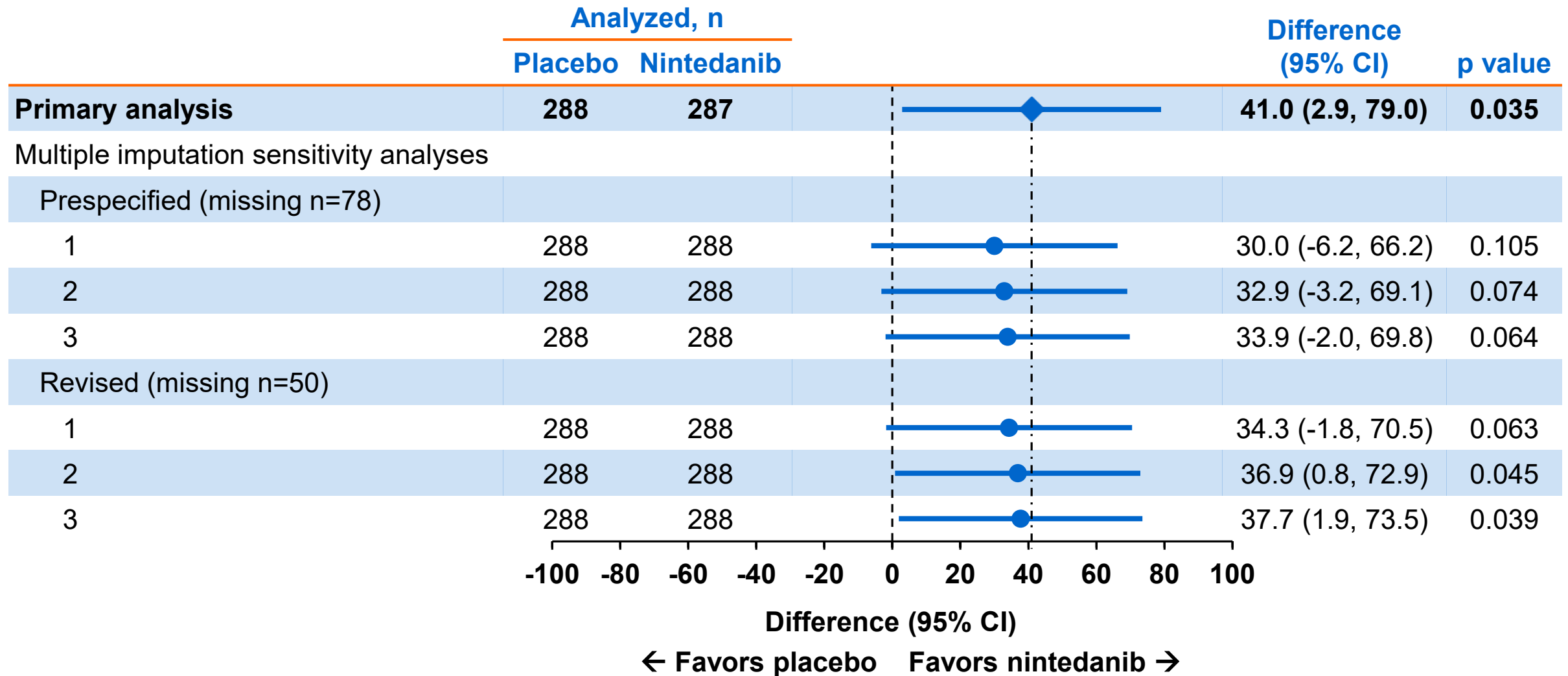
## Points of Interest

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- Sensitivity analysis of primary endpoint
- Tipping point analysis
- Available data over 100 weeks

# Annual Rate of Decline in FVC

## Prespecified and Revised Sensitivity Analyses





# Tipping Point Analysis

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- ▶ Post-hoc tipping point analysis
  - FVC missing from 78 patients at 52 weeks
  - Penalty in nintedanib group of 30 mL/year required to lose significance
- ▶ Revised tipping point analysis
  - All available data including 28 patients (FVC missing from 50 patients at 52 weeks)
  - Penalty of 120 mL/year required to lose significance
- ▶ Both analyses support robustness of primary findings

## Analysis of FVC Over the Entire Trial (up to 100 Weeks<sup>a</sup>)

- ▶ Analyses including FVC data collected beyond 52 weeks suggest treatment effect persist
- ▶ Using intent-to-treat approach, adjusted treatment difference at 100 weeks compared with placebo was 65.3 mL (95% CI: 6.6, 124.1)

<sup>a</sup> Including all off-treatment data of patients who prematurely discontinued.

## Summary of Efficacy Results

- ▶ Nintedanib reduced ILD progression in patients with SSc-ILD
  - 44% relative effect on annual rate of FVC decline in SENSICIS similar to that observed in the INPULSIS trials
  - Findings overall consistent across patient subgroups
  - Sensitivity analyses and tipping point analysis support robustness of findings
- ▶ No effect of nintedanib observed on mRSS or SGRQ (key secondary endpoints)
- ▶ Observed treatment effect is considered clinically meaningful in patients with SSc-ILD

# Safety of Nintedanib for SSc-ILD

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Veronika M. Kohlbrenner, MD  
Director, Global Pharmacovigilance  
Boehringer Ingelheim

## Safety Overview

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- ▶ Exposure in SENSCIS
- ▶ Summary of adverse events comparing SENSCIS and INPULSIS
- ▶ Safety topics of special interest in SENSCIS
- ▶ Conclusions

# Exposure

## SENSCIS

	<b>Placebo n=288</b>	<b>Nintedanib n=288</b>
Mean exposure through 52 weeks, mo (SD)	11.4 (2.4)	10.5 (3.4)
Mean exposure over entire trial, <sup>a</sup> mo (SD)	15.7 (5.7)	14.5 (6.7)
Categorical exposure over entire trial, %		
>6 months	93.4	85.8
>12 months	67.4	60.4
>18 months	37.8	36.8

<sup>a</sup> Entire trial represents up to 100 weeks.

# Summary of Adverse Events

## SENSCIS and INPULSIS – 52 Weeks

Adverse event	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Any AE	95.8	98.3	89.6	95.5
AE leading to discontinuation	8.7	16.0	13.0	19.3
SAE	21.5	24.0	30.0	30.4
AE resulting in death	1.4	1.7	7.3	5.8

# Most Common AEs >10%

## SENSCIS and INPULSIS – 52 Weeks

Preferred term	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Diarrhea	31.6	75.7	18.4	61.6
Nausea	13.5	31.6	6.6	24.5
Vomiting	10.4	24.7	2.6	11.6
Skin ulcer	17.4	18.4	0	0.2
Nasopharyngitis	17.0	12.5	16.1	13.6
Cough	18.1	11.8	13.5	13.3
Weight decrease	4.2	11.8	3.5	9.7
Abdominal pain	7.3	11.5	2.4	8.8
Upper respiratory tract infection	12.2	11.5	9.9	9.1
Fatigue	6.9	10.8	7.8	6.3
Decreased appetite	4.2	9.4	5.7	10.7
Dyspnea	8.7	7.3	11.3	7.7
Bronchitis	8.3	5.6	10.6	10.5



# Safety Topics of Special Interest

## SENSCIS and INPULSIS – 52 Weeks

Safety topics	Patients, %			
	SENSCIS		INPULSIS 1 and 2	
	Placebo n=288	Nintedanib n=288	Placebo n=423	Nintedanib n=638
Diarrhea	31.6	75.7	18.4	61.6
Hepatic events <sup>a</sup>	4.9	17.4	4.5	17.7
Bleeding events <sup>b</sup>	8.3	11.1	7.8	10.3
MACE <sup>c</sup>	1.7	1.4	2.6	3.6

<sup>a</sup> Combination of 4 hepatic disorder SMQ searches.

<sup>b</sup> SMQ of hemorrhage terms, excluding laboratory.

<sup>c</sup> MACE (as reported by investigator): Composite endpoint of any fatal or non-fatal events in SMQ “myocardial infarction” (broad), any fatal or non-fatal stroke, any fatal events in system organ classes “cardiac disorders” or “vascular disorders,” and the preferred terms “sudden death,” “cardiac death,” or “sudden cardiac death.”

MACE=major adverse cardiovascular events; SMQ = Standardized MedDRA queries.

# Diarrhea

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Diarrhea events		
AEs	91 (31.6)	218 (75.7)
Mild	61 (21.2)	108 (37.5)
Moderate	27 (9.4)	98 (34.0)
Severe	3 (1.0)	12 (4.2)
SAEs	2 (0.7)	2 (0.7)
Clinical consequence		
Dose reduction	2 (0.7)	57 (19.8)
Premature treatment discontinuation	1 (0.3)	20 (6.9)
Recovered	86/91 (94.5)	202/218 (92.7)

Mild: awareness of signs or symptoms, which are easily tolerated.

Moderate: enough discomfort to cause interference with usual activity.

Severe: incapacitating or causing inability to work or to perform usual activities.

# Hepatic Events

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Hepatic events <sup>a</sup>		
AEs	14 (4.9)	50 (17.4)
SAEs	1 (0.3)	3 (1.0)
Clinical consequence		
Dose reduction	2 (0.7)	11 (3.8)
Premature treatment discontinuation	1 (0.3)	6 (2.1)

- ▶ No cases of hepatic failure
- ▶ No liver-related death

<sup>a</sup> Combination of 4 hepatic disorder SMQ searches.

# Liver Enzymes and Bilirubin

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
ALT and/or AST $\geq 1.5 \times \text{ULN}$	11 (3.8)	52 (18.1)
ALT and/or AST $\geq 3 \times \text{ULN}$	2 (0.7)	14 (4.9)
ALT and/or AST $\geq 5 \times \text{ULN}$	1 (0.3)	3 (1.0)
ALT and/or AST $\geq 8 \times \text{ULN}$	1 (0.3)	0
Hy's Law lab constellation <sup>a</sup>	0	0

- ▶ Transaminase abnormalities resolved on dose reduction or discontinuation

<sup>a</sup> ALT and/or AST  $\geq 3 \times \text{ULN}$  and bilirubin  $\geq 2 \times \text{ULN}$ .  
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

# Bleeding Events

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Bleeding events <sup>a</sup>		
AEs	24 (8.3)	32 (11.1)
SAEs	2 (0.7)	4 (1.4)
Epistaxis	11 (3.8)	8 (2.8)
Skin contusion	3 (1.0)	7 (2.4)
Rectal hemorrhage	0	5 (1.7)
Hematochezia	1 (0.3)	2 (0.7)
Central nervous system bleeding	0	2 (0.7)

- ▶ All patients continued study medication uninterrupted

<sup>a</sup>SMQ of hemorrhage terms, excluding laboratory.

# Cardiovascular Events

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
MACE <sup>a</sup>	5 (1.7)	4 (1.4)
Myocardial infarction	3 (1.0)	2 (0.7)
Stroke	1 (0.3)	1 (0.3)
Fatal cardiovascular events	2 (0.7)	1 (0.3)
Adjudicated MACE	3 (1.0)	1 (0.3)
Other cardiovascular events		
Cardiac failure	1 (0.3)	1 (0.3)
Venous thromboembolism	3 (1.0)	4 (1.4)
Pulmonary embolism	1 (0.3)	0
Pulmonary arterial hypertension	4 (1.4)	7 (2.4)
Hypertension	4 (1.4)	11 (3.8)

<sup>a</sup> Major Adverse Cardiovascular Events (as reported by investigator): Composite endpoint of any fatal or non-fatal events in SMQ “myocardial infarction” (broad), any fatal or non-fatal stroke, any fatal events in system organ classes “cardiac disorders” or “vascular disorders,” and the preferred terms “sudden death,” “cardiac death,” or “sudden cardiac death.”

## Summary of Safety

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- ▶ Safety and tolerability profile of nintedanib in SSc-ILD is consistent with that observed in IPF
- ▶ No new safety findings in SENSCIS
- ▶ Common AEs associated with nintedanib were manageable with treatment strategies
- ▶ SENSCIS trial results demonstrate the safety of nintedanib in the treatment of patients with SSc-ILD

# Benefit/Risk of Nintedanib for SSc-ILD

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Kay Tetzlaff, MD

Medical Head, Therapeutic Area Respiratory Diseases  
Boehringer Ingelheim

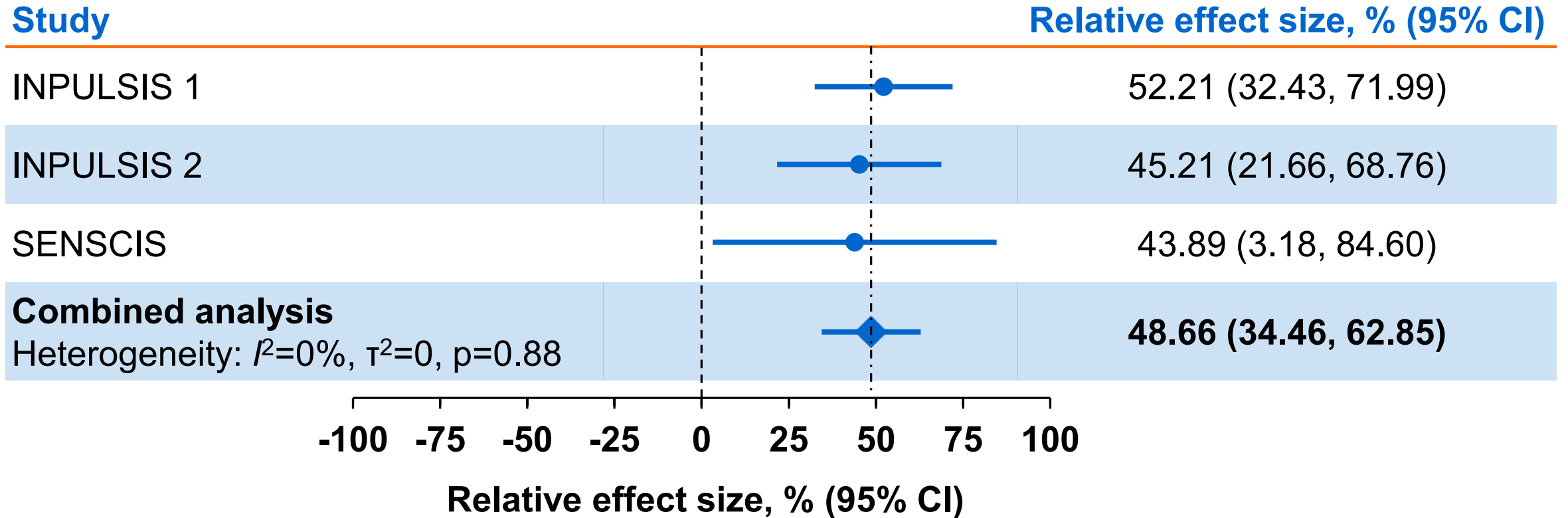


## Benefit/Risk of Nintedanib in SSc-ILD

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- ▶ ILD is a common manifestation of SSc and is associated with high mortality
- ▶ Progression of SSc-ILD is irreversible
- ▶ Nintedanib significantly reduced annual rate of decline in FVC by 44% relative to placebo in a population allowing generalization of results to clinical practice
- ▶ Relative treatment effect similar to that in IPF

# Consistency of Relative Treatment Effect Across Trials



## Benefit/Risk of Nintedanib in SSc-ILD

- ▶ Effects considered clinically meaningful, given the
  - Typical age of onset of SSc-ILD
  - Natural progression/gradual lung function decline accumulating over years
- ▶ Nintedanib was safe and well tolerated in the SSc-ILD population, and the safety profile was consistent with the experience of nintedanib in IPF

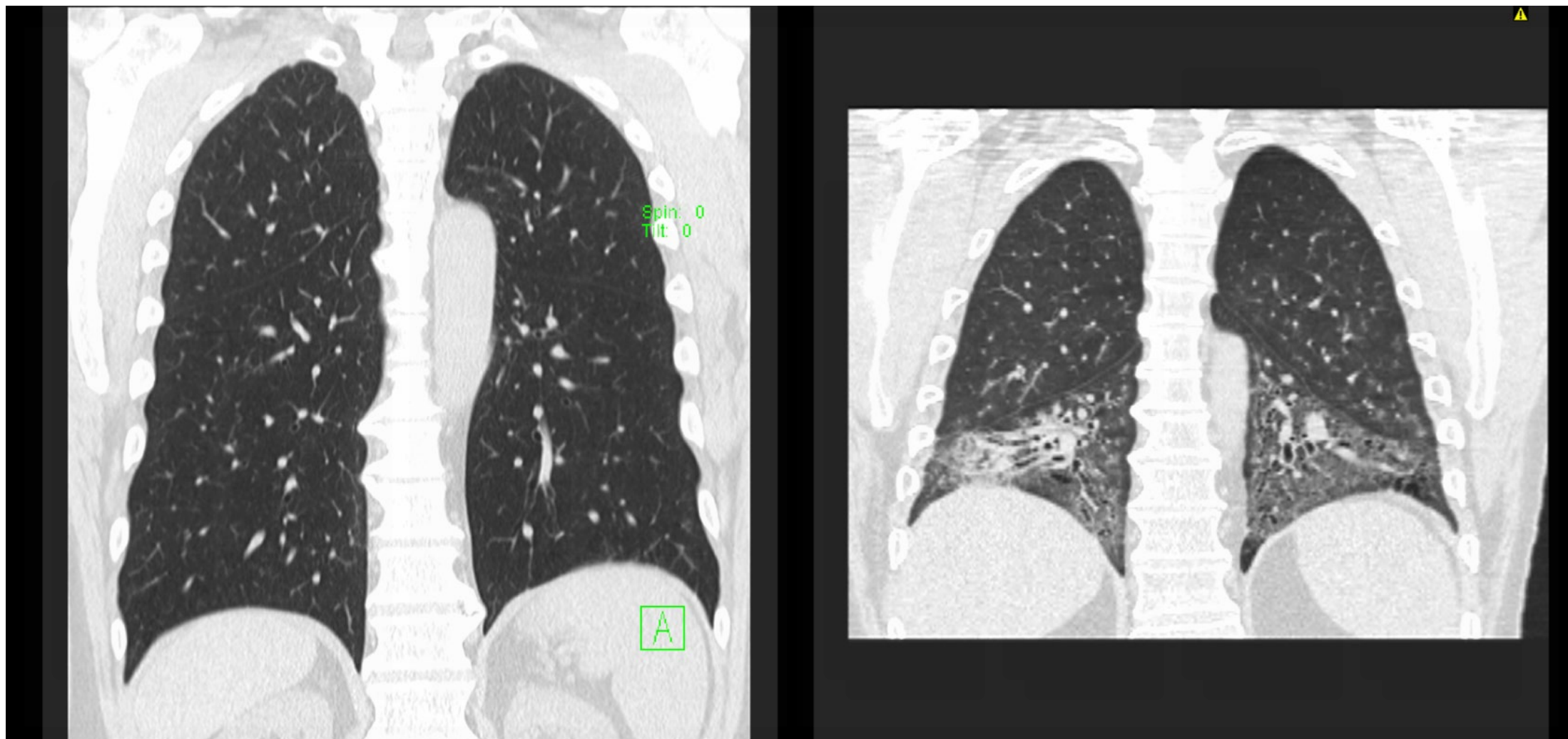
## Conclusion

The benefit-risk profile of nintedanib is positive for the treatment of patients with SSc-ILD

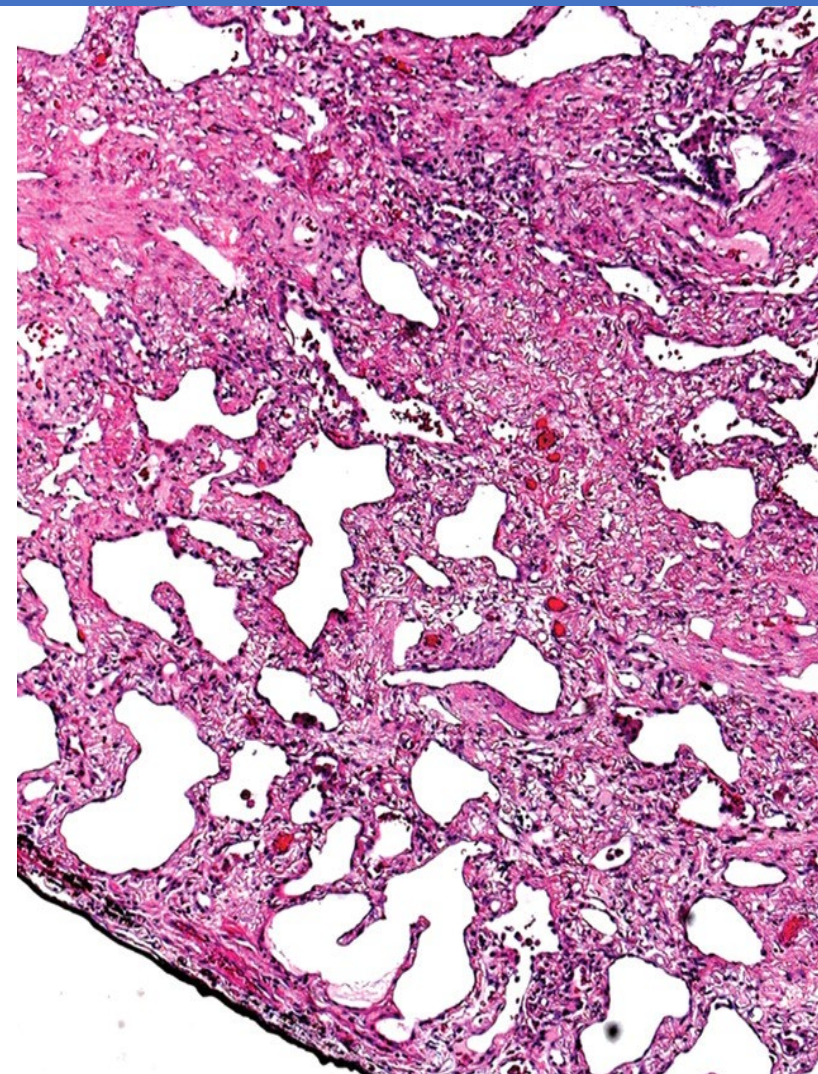
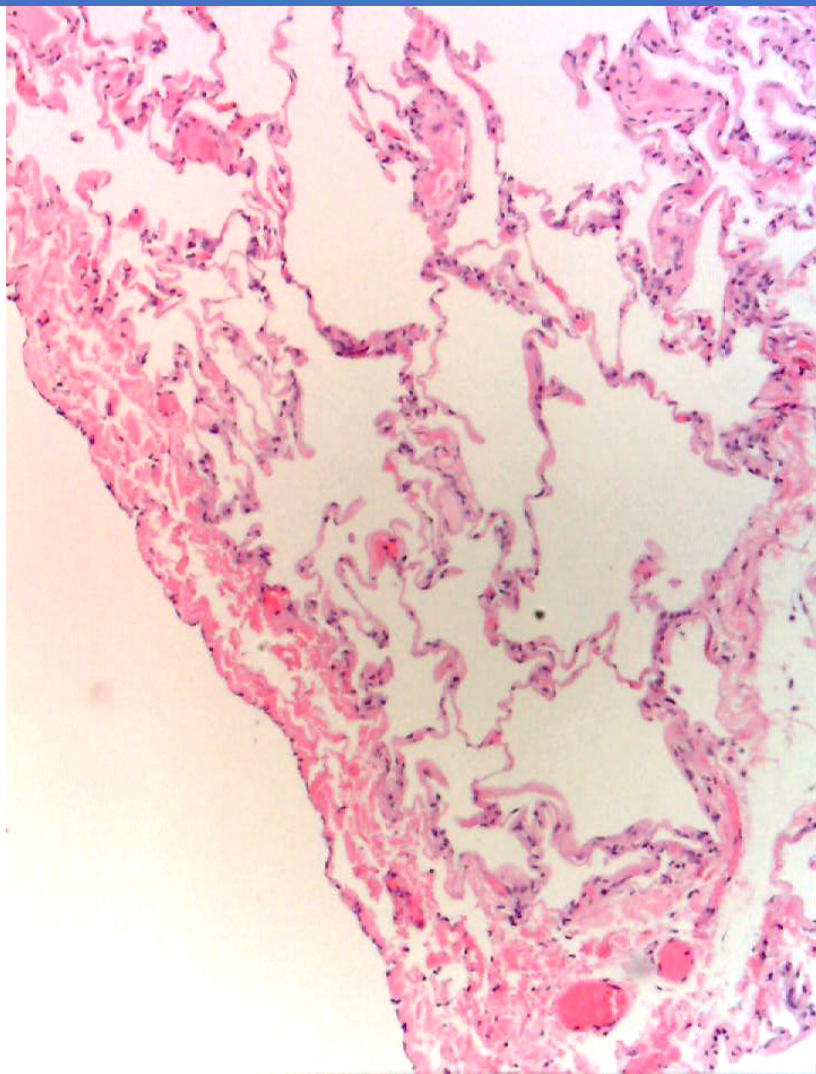
# Clinical Perspective

Kevin K. Brown, MD  
National Jewish Health

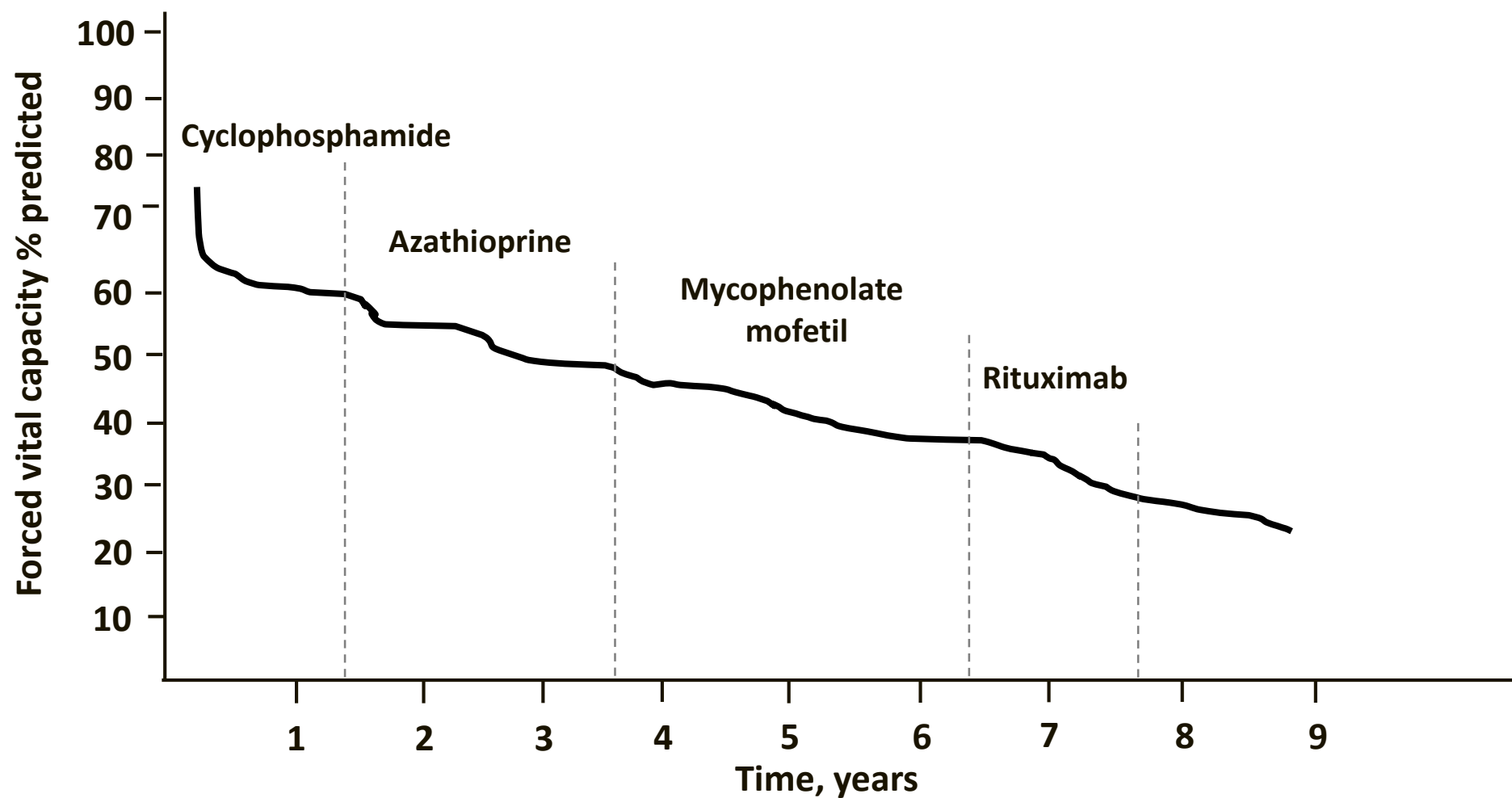
# SSc-ILD



# SSc-ILD

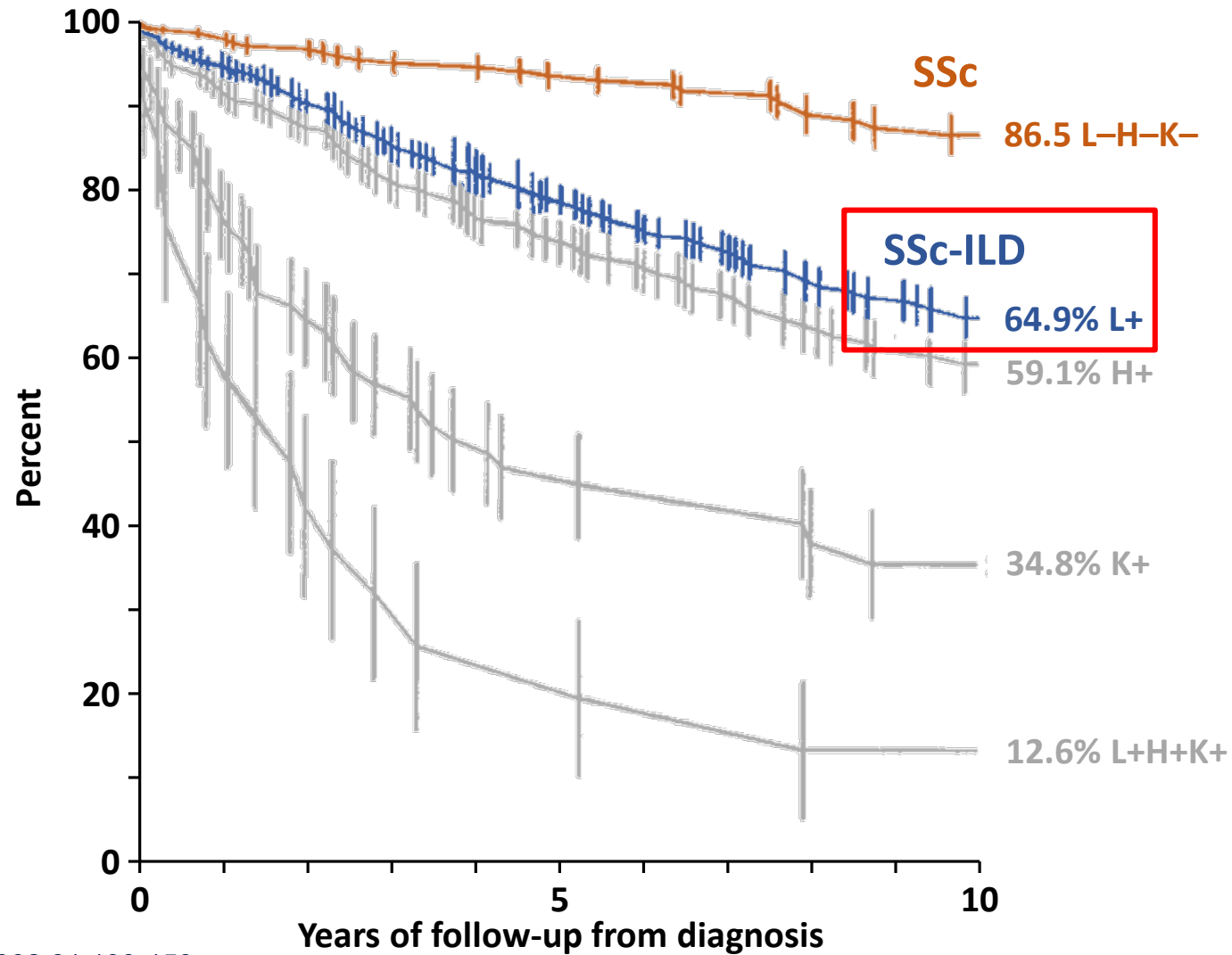


# One Individual's History of Lung Function Loss



# ILD Shortens Survival in Scleroderma

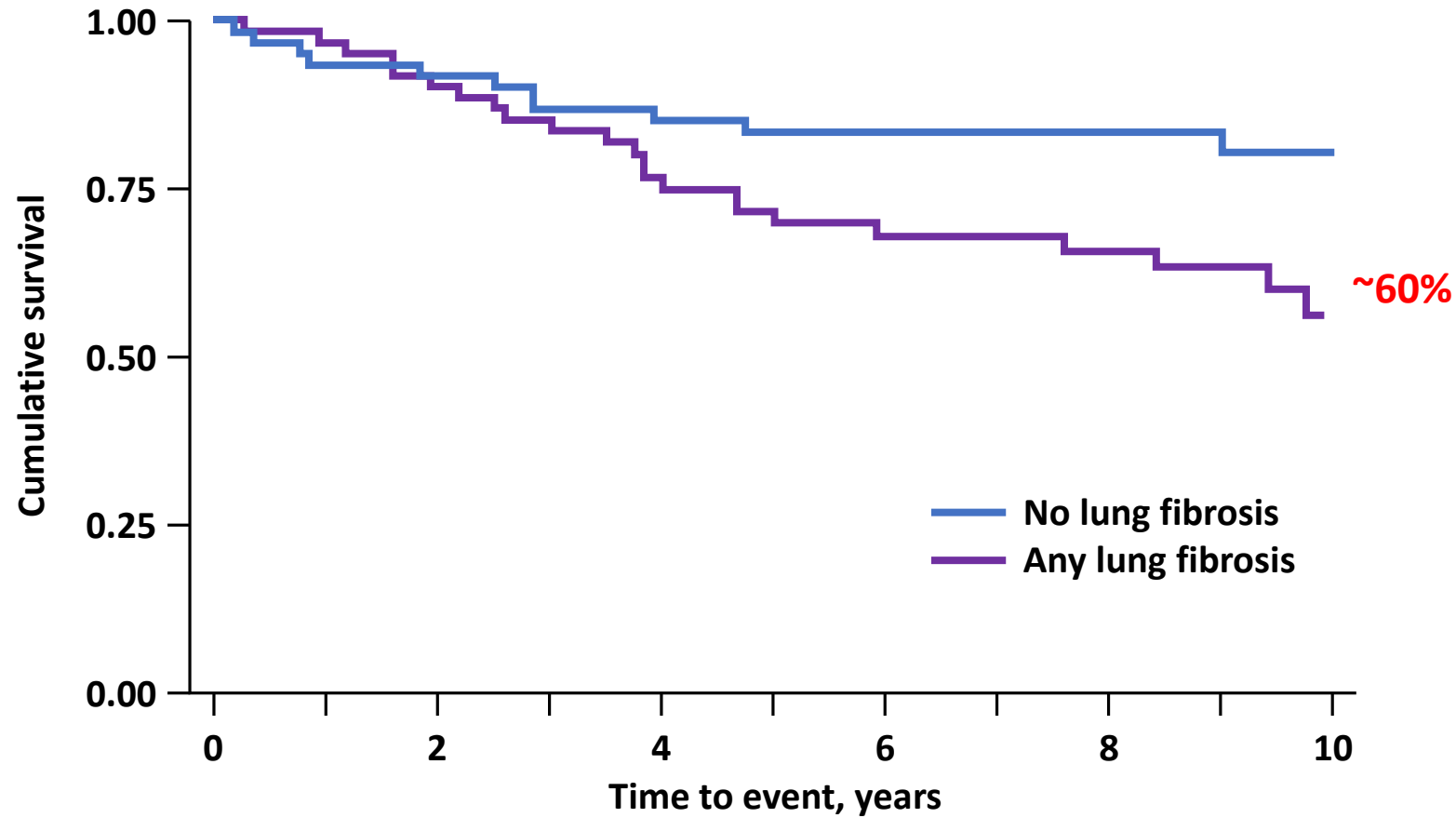
## Survival and SSc Organ Involvement





# The Presence of ILD Is Associated With Mortality

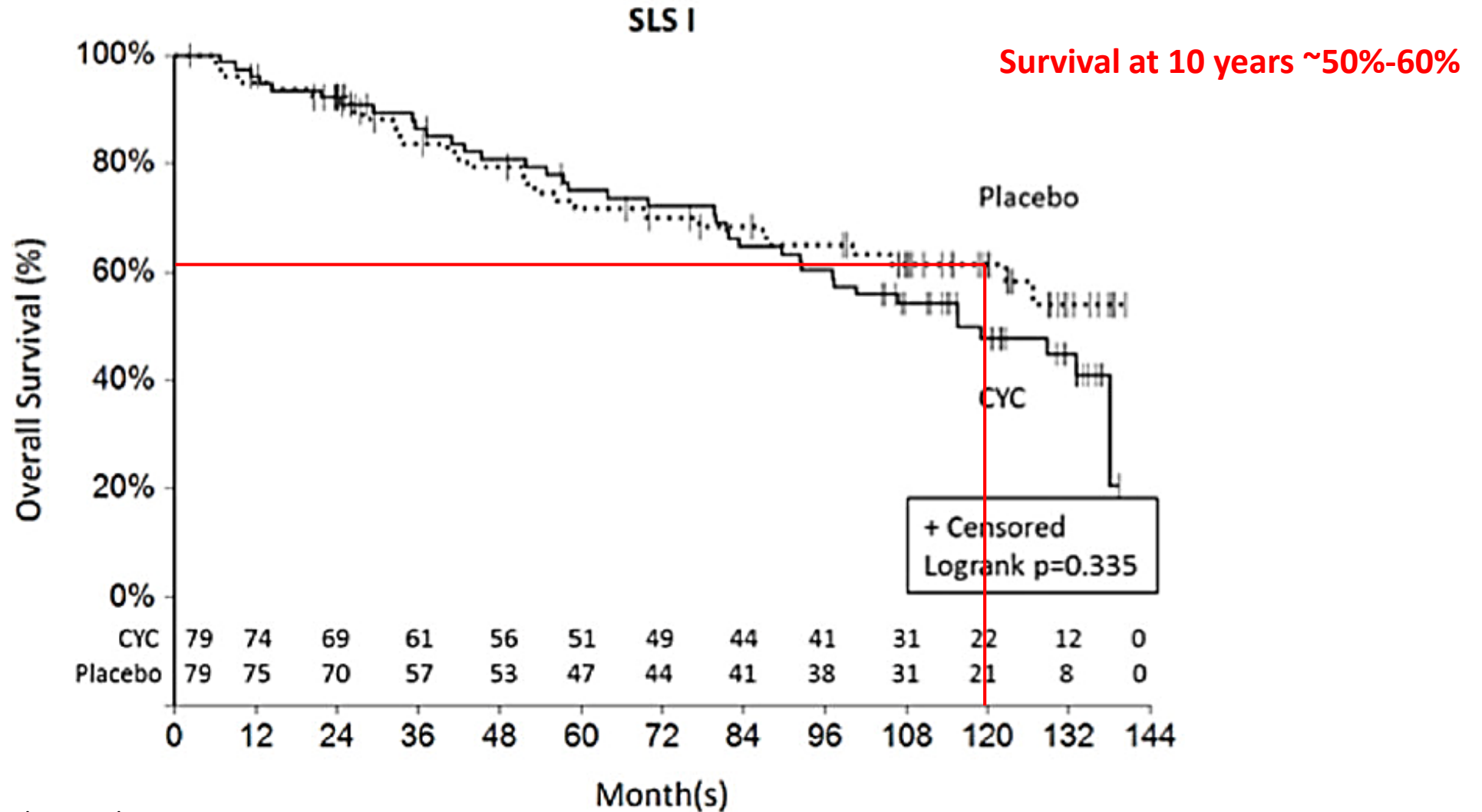
## Nationwide Norwegian SSc Cohort



At risk, n

No lung fibrosis	61	55	50	45	35	20
Any lung fibrosis	61	55	45	36	29	14

# Anti-inflammatory Therapy Has Not Altered Long-term Survival



# ATS 2019: Clinical Topics in Pulmonary Medicine

## When There Is No Right Answer: A Pro/Con Debate on Controversies in ILD

Assemblies on Clinical Problems, Behavioral Science and  
Health Services Research

**9:15 AM - 11:15 AM**

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**Chairing:** SM Bhorade, MD, Chicago, IL  
R Jablonski, MD, Chicago, IL

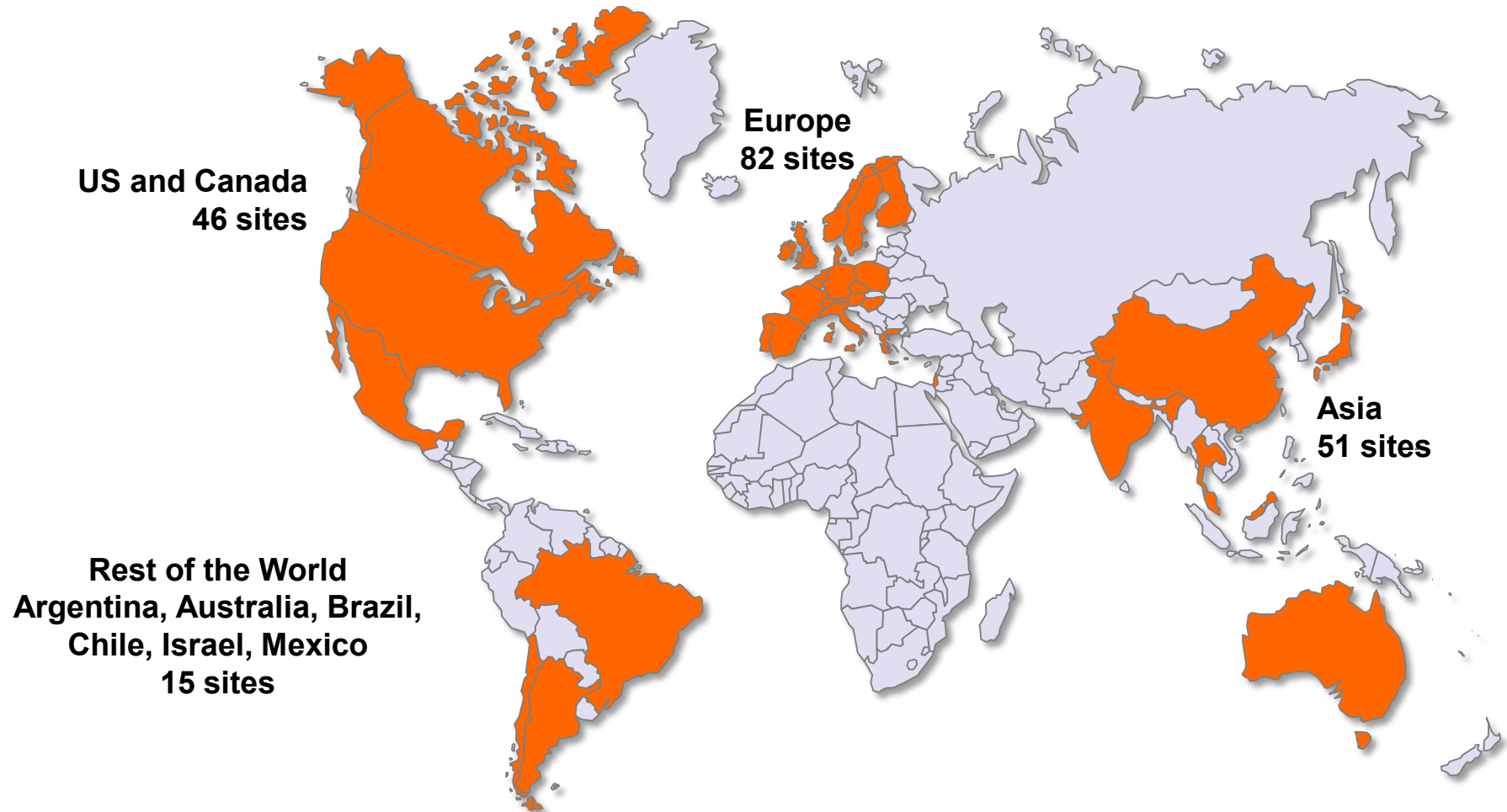
**9:15 PRO: Lung Transplant Is a Viable Treatment Option  
for Scleroderma**

MM Crespo, MD, Philadelphia, PA

**9:27 CON: Other Options Should Be Explored for  
Management of Scleroderma Lung Disease**

R Jablonski, MD, Chicago, IL

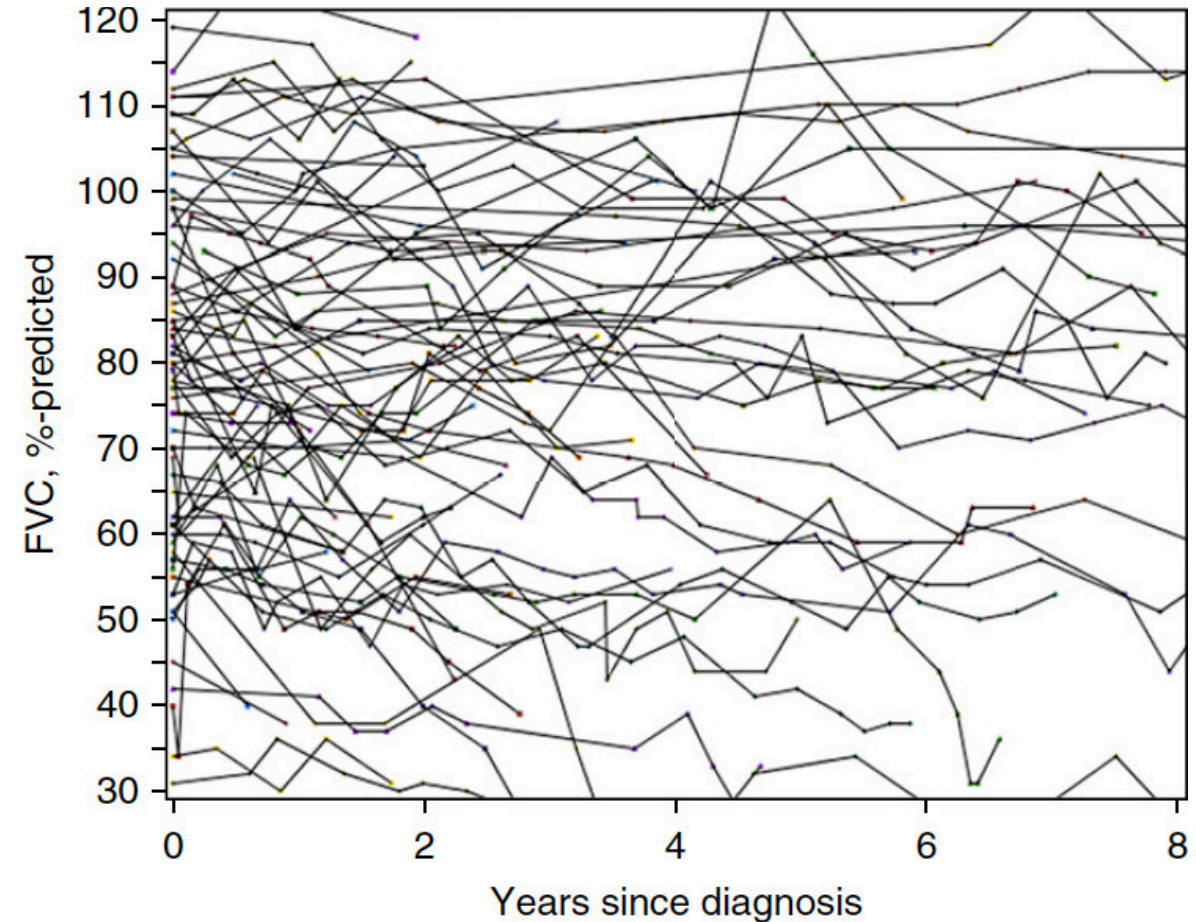
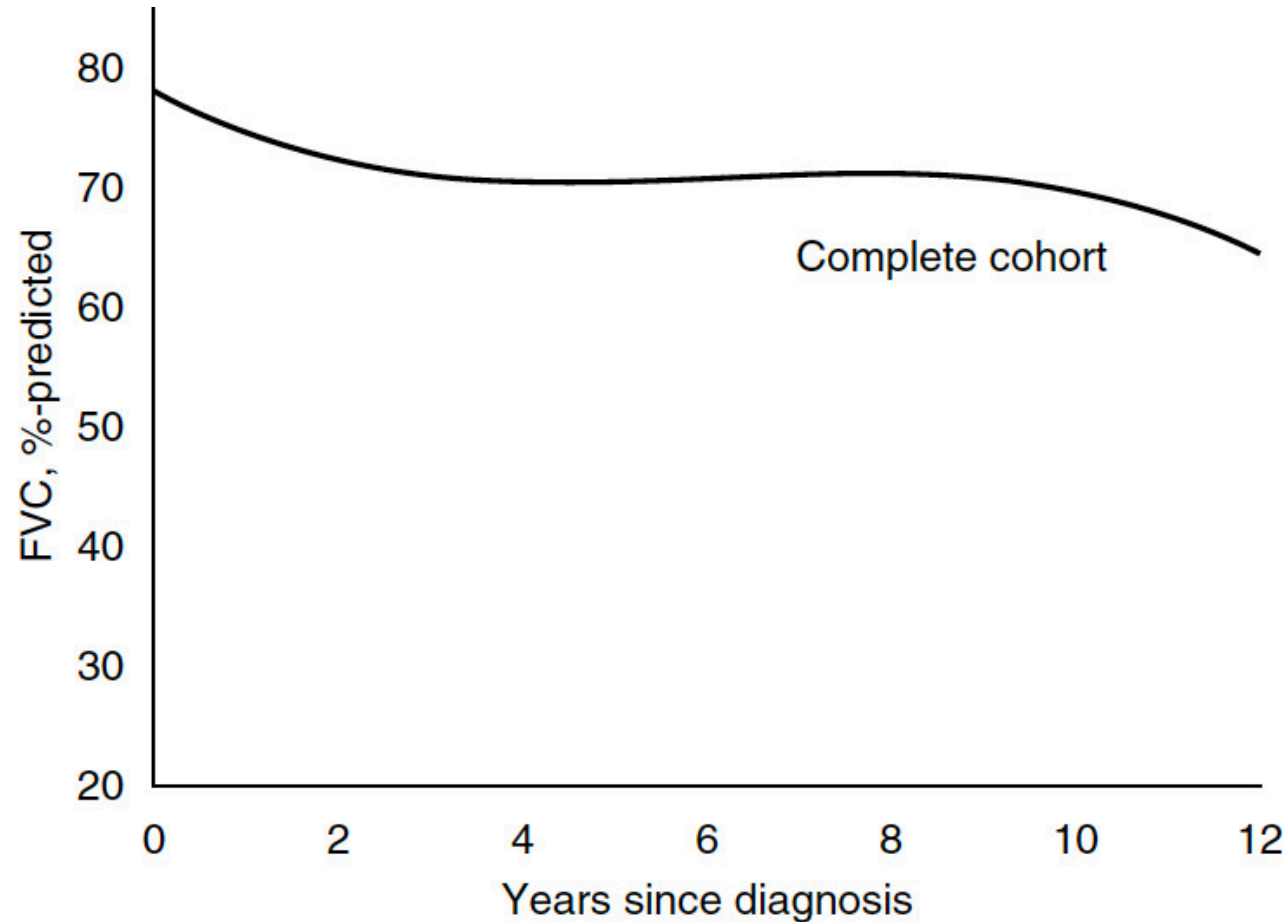
# SENSCIS



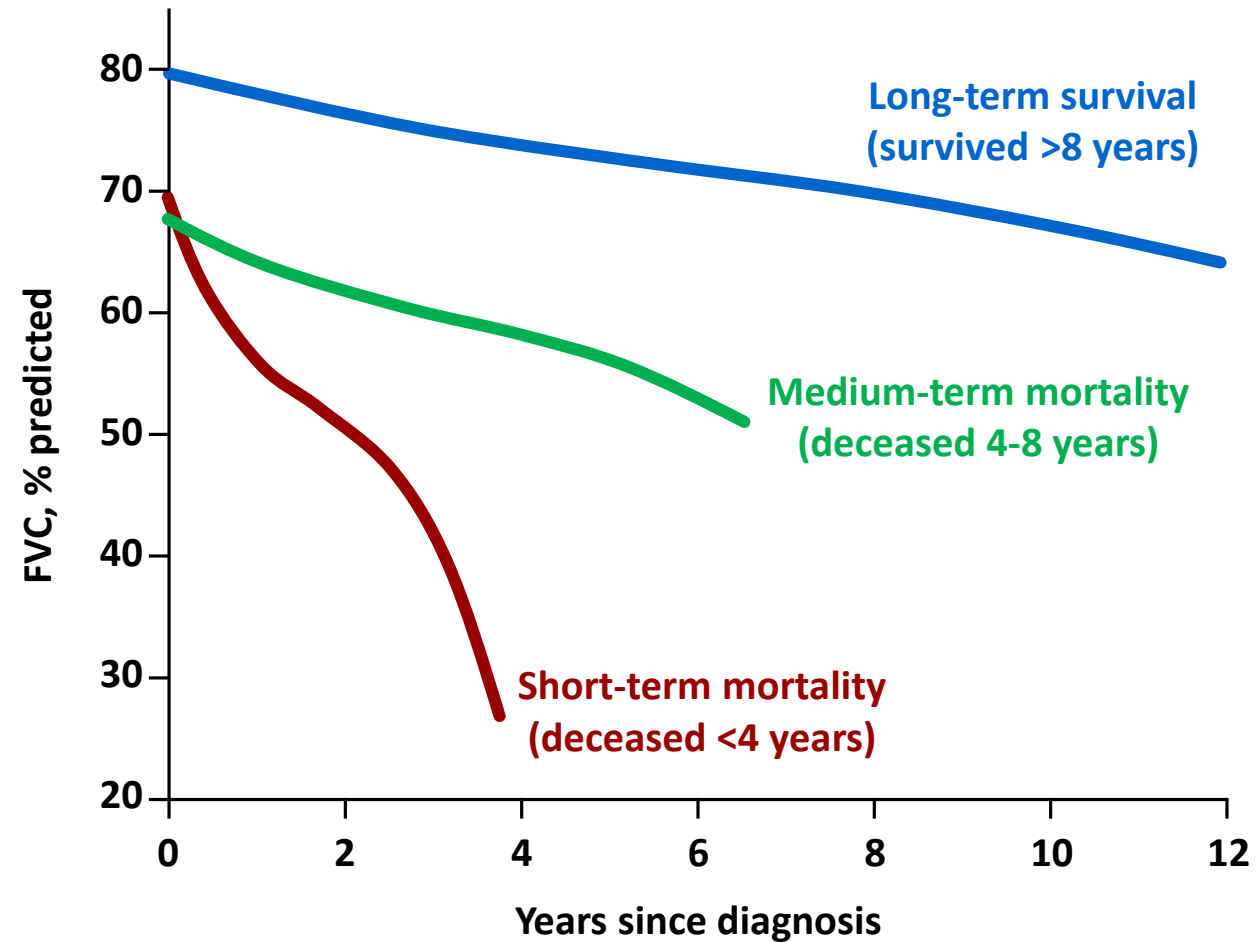
# SENSCIS

- Largest placebo-controlled trial ever conducted in SSc-ILD
- Enrolled a broad population reflective of patients treated in clinical practice
- Did not exclude patients receiving available therapies

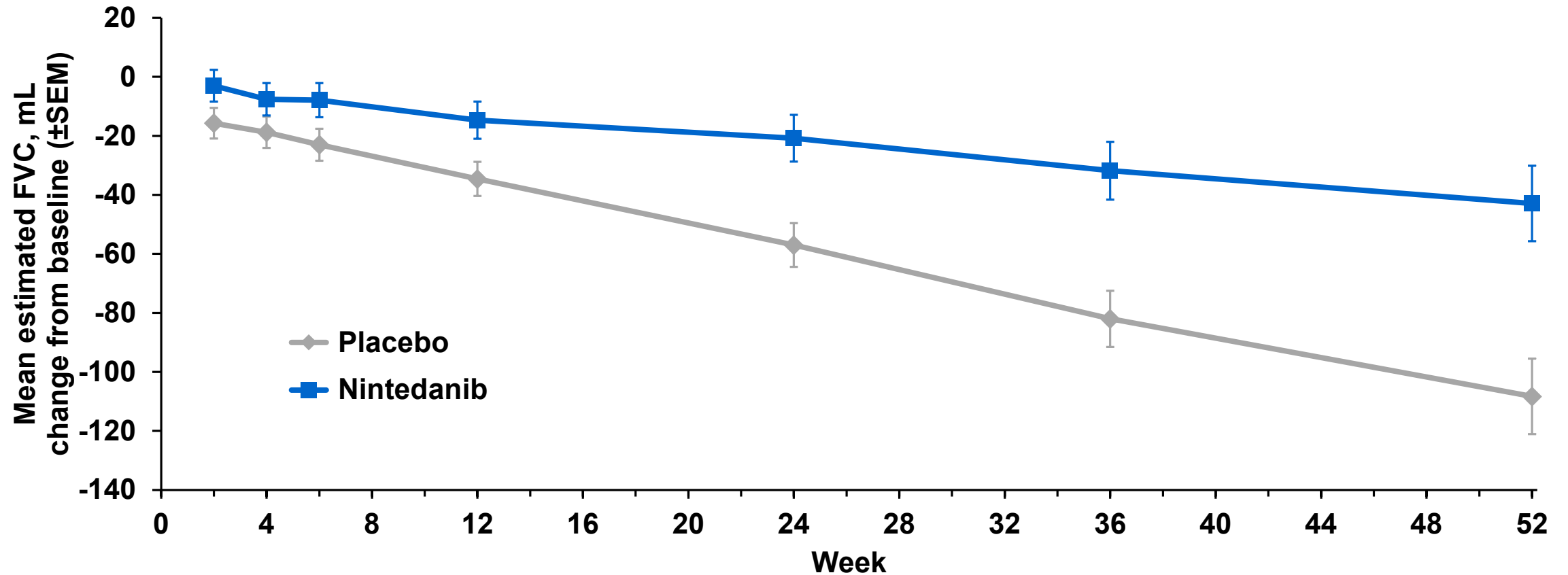
# FVC Decline Precedes Mortality in SSc-ILD



# FVC Decline Precedes Mortality in SSc-ILD



# SENSCIS: Mean Absolute Change in FVC

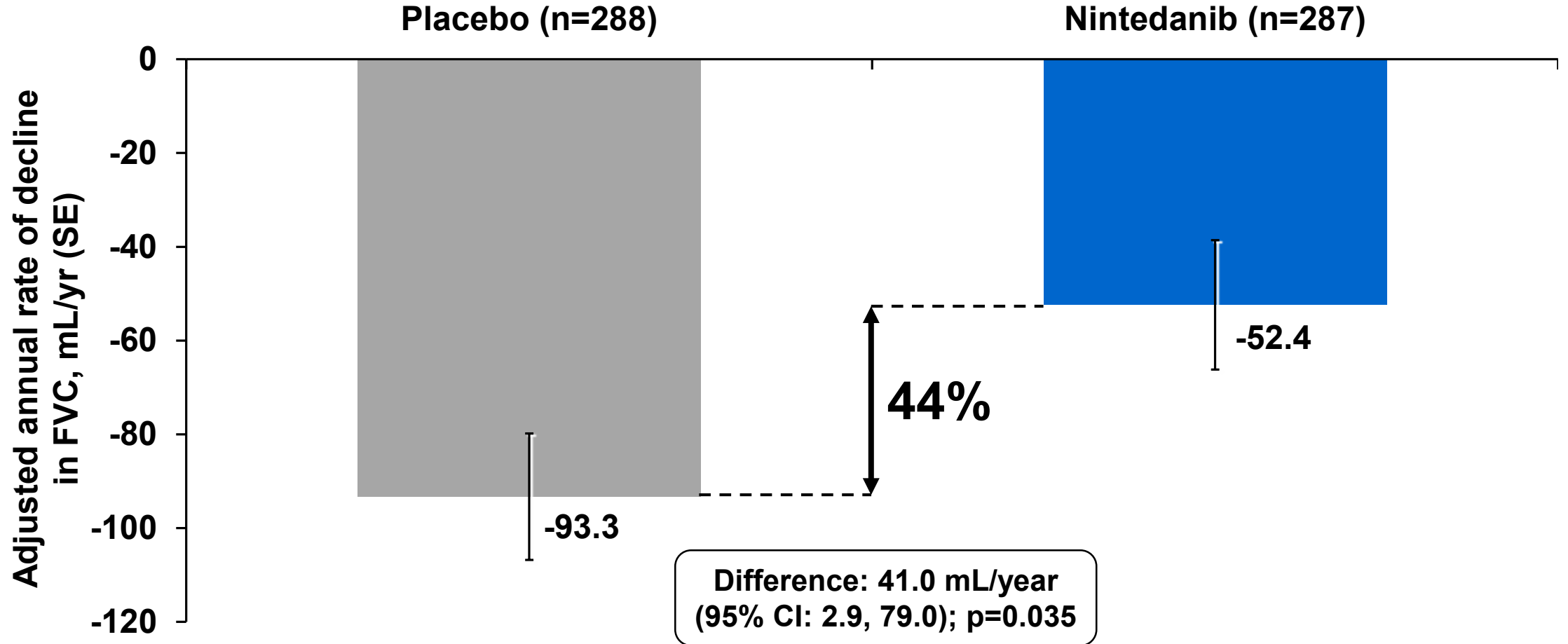


Patients, n

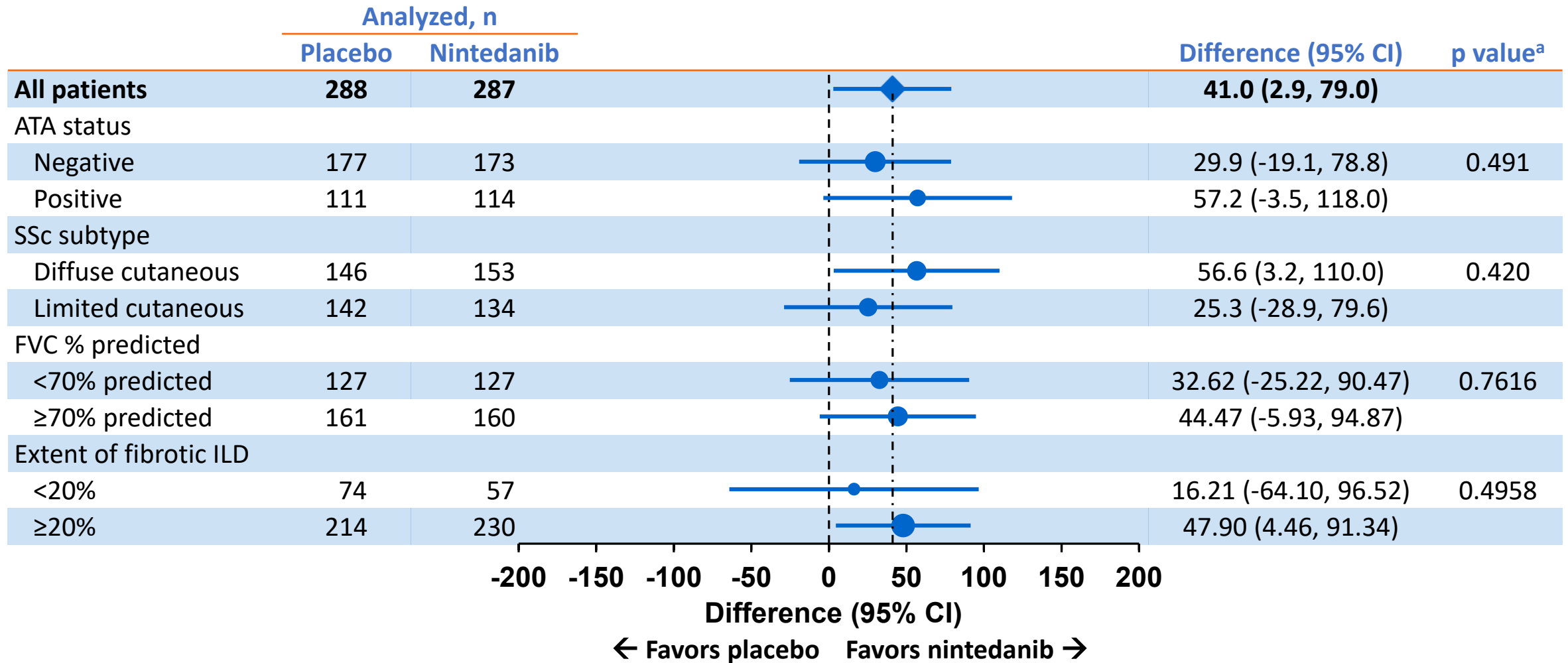
Placebo	288	283	281	280	283	280	268	257
Nintedanib	288	283	281	273	278	265	262	241



# SENSCIS: Adjusted Annual Rate of FVC Decline

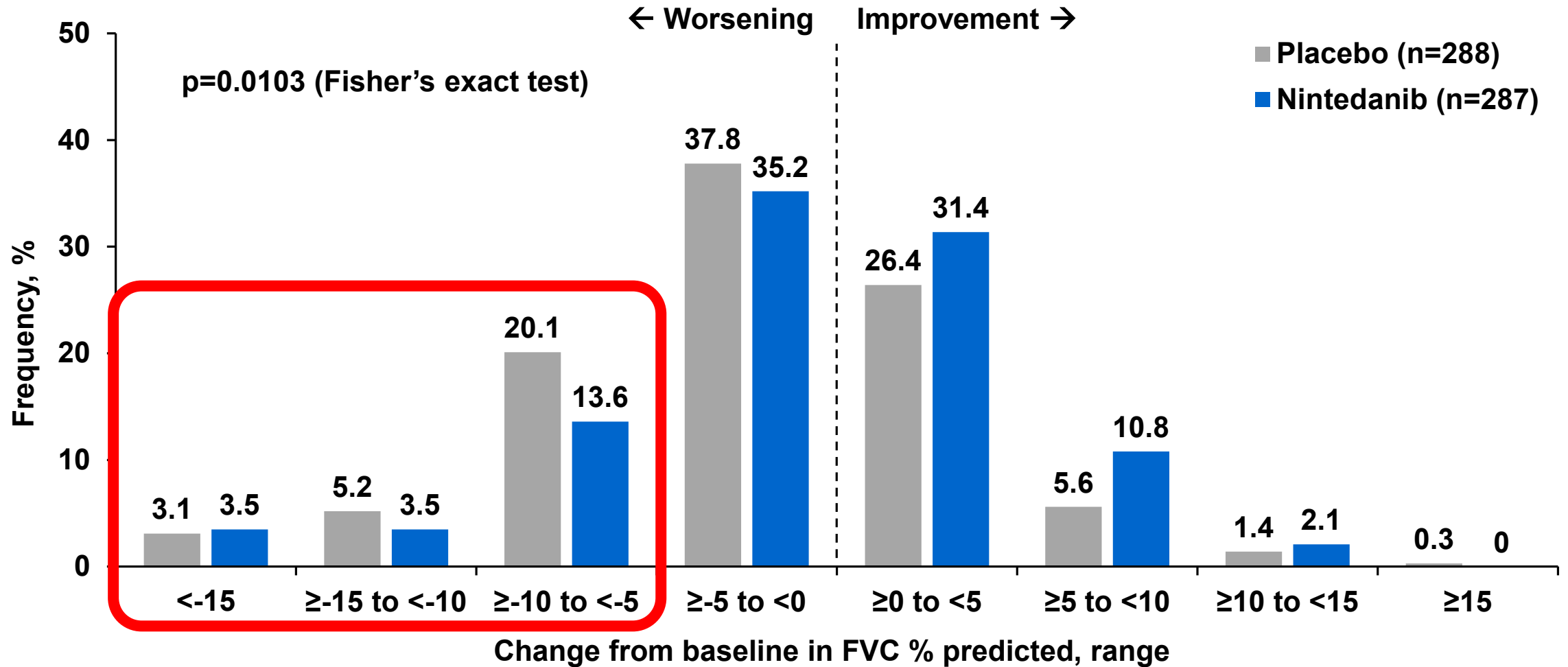


# SENSCIS: Additional Subgroup Analyses of Primary Endpoint



<sup>a</sup> Treatment-by-time-by-subgroup interaction.

# SENSCIS: Categorical Analysis



## SSc-ILD—Where We Are...

- Patients with scleroderma are affected in the prime of their lives. They are parents, children, siblings, employers, employees, and caregivers. Their major personal relationships, quality of life, and functional status are all adversely affected
- Lung fibrosis is the leading cause of death
- No approved therapies are available for SSc-ILD
  - Unapproved immunosuppressive therapies may provide short-term benefit in selected subsets
- As with IPF, prevention or slowing of disease progression, as measured by FVC, is a therapeutic goal
- Effective antifibrotic therapy is needed

# Medication Use for Hypertension / PAH

## SENSCIS – 52 Weeks

Customized drug grouping Preferred name	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Antihypertensives	204 (70.8)	210 (72.9)
Nifedipine	66 (22.9)	60 (20.8)
Amlodpine	30 (10.4)	34 (11.8)
Amlodpine besilate	23 (8.0)	23 (8.0)
Bosentan	23 (8.0)	21 (7.3)
Sildenafil	18 (6.3)	20 (6.9)
Sildenafil citrate	13 (4.5)	14 (4.9)
Diltiazem hydrochloride	15 (5.2)	13 (4.5)
Iloprost trometamol	8 (2.8)	8 (2.8)
Iloprost	7 (2.4)	6 (2.1)
Epoprostenol	0	1 (0.3)

# Post-hoc Responder Analyses for Absolute Decline From Baseline in FVC % Predicted

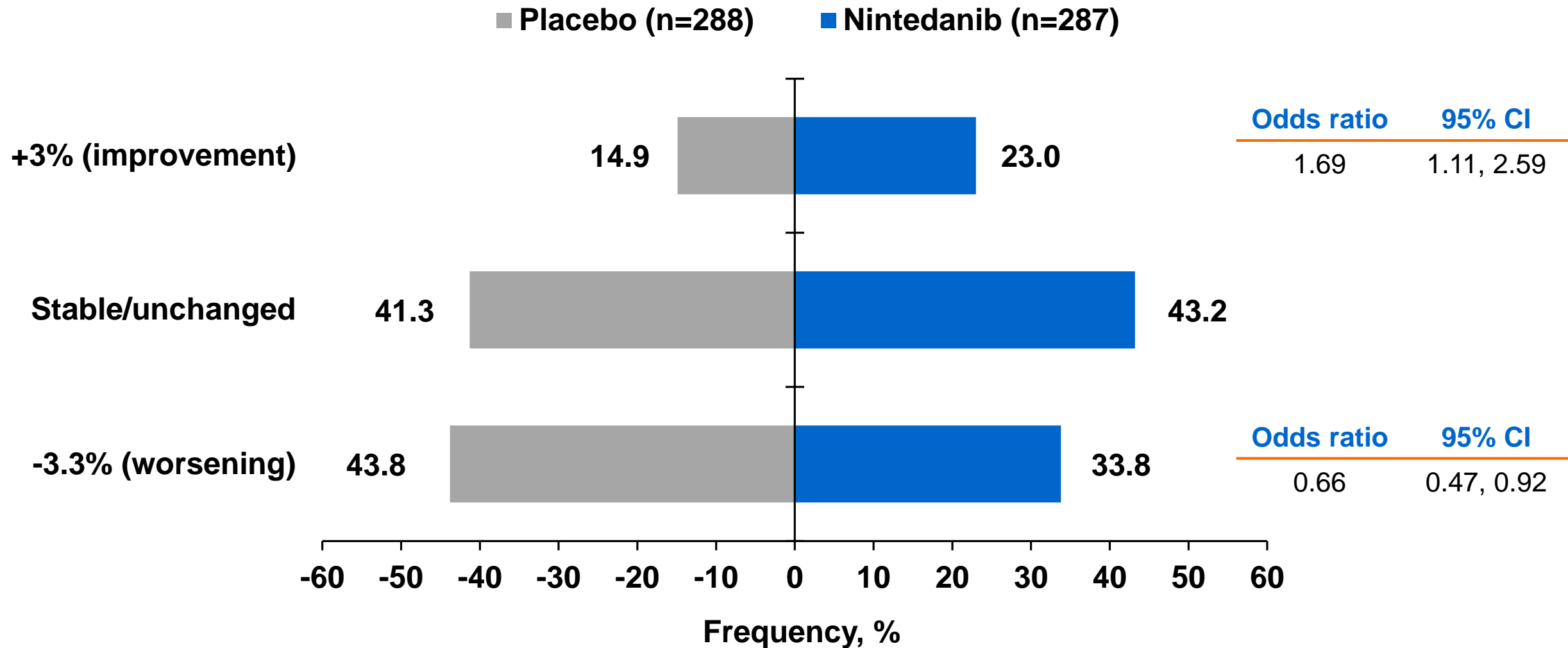
## SENSCIS (Worst Value Carried Forward)

	Nintedanib	Placebo
Analyzed, n	287	288
Absolute decline in FVC % predicted at Wk 52, n (%)		
<b>&gt;5% predicted</b>	<b>59 (20.6)</b>	<b>82 (28.5)</b>
Odds ratio (95% CI)	0.65 (0.44, 0.96)	
p value	0.0287	
<b>&gt;10% predicted</b>	<b>20 (7.0)</b>	<b>24 (8.3)</b>
Odds ratio (95% CI)	0.82 (0.44, 1.52)	
p value	0.5342	

**Percent of patients with disease worsening lower in nintedanib treatment group**

# Responder Analysis<sup>a</sup>

## Change From Baseline in FVC % Predicted at 52 Weeks



<sup>a</sup> Worst observation carried forward.

# Restricted Medication Use

## SENSCIS – 52 Weeks

	Patients, n (%)			
	Initiated during study treatment		Initiated post treatment	
	Placebo n=288	Nintedanib n=288	Placebo n=288	Nintedanib n=288
Mycophenolate (mofetil, acid, sodium)	4 (1.4)	4 (1.4)	2 (0.7)	2 (0.7)
Methotrexate	1 (0.3)	1 (0.3)	0	1 (0.3)
<b>Added first restricted medication</b>	<b>9 (3.1)</b>	<b>11 (3.8)</b>	<b>5 (1.7)</b>	<b>10 (3.5)</b>
Cyclophosphamide	2 (0.7)	5 (1.7)	2 (0.7)	7 (2.4)
Azathioprine	3 (1.0)	0	1 (0.3)	0
Rituximab	1 (0.3)	3 (1.0)	1 (0.3)	1 (0.3)
Tocilizumab	0	1 (0.3)	0	2 (0.7)
Tacrolimus	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)



# Defintion of Clinically Significant Deterioration

## SENSCIS

Clinically significant deterioration is defined as

- ▶ Absolute decline since baseline in FVC percent predicted  $>10\%$  (in the absence of other causes for FVC deterioration<sup>a</sup>)
- ▶ Relative change from baseline in mRSS of  $>25\%$  and an absolute change from baseline of  $>5$  patients
- ▶ Clinically significant deterioration in other organ systems or clinical parameters at the discretion of the investigator

Initiation of additional therapy, including immunosuppressants, was allowed as deemed necessary by the investigator

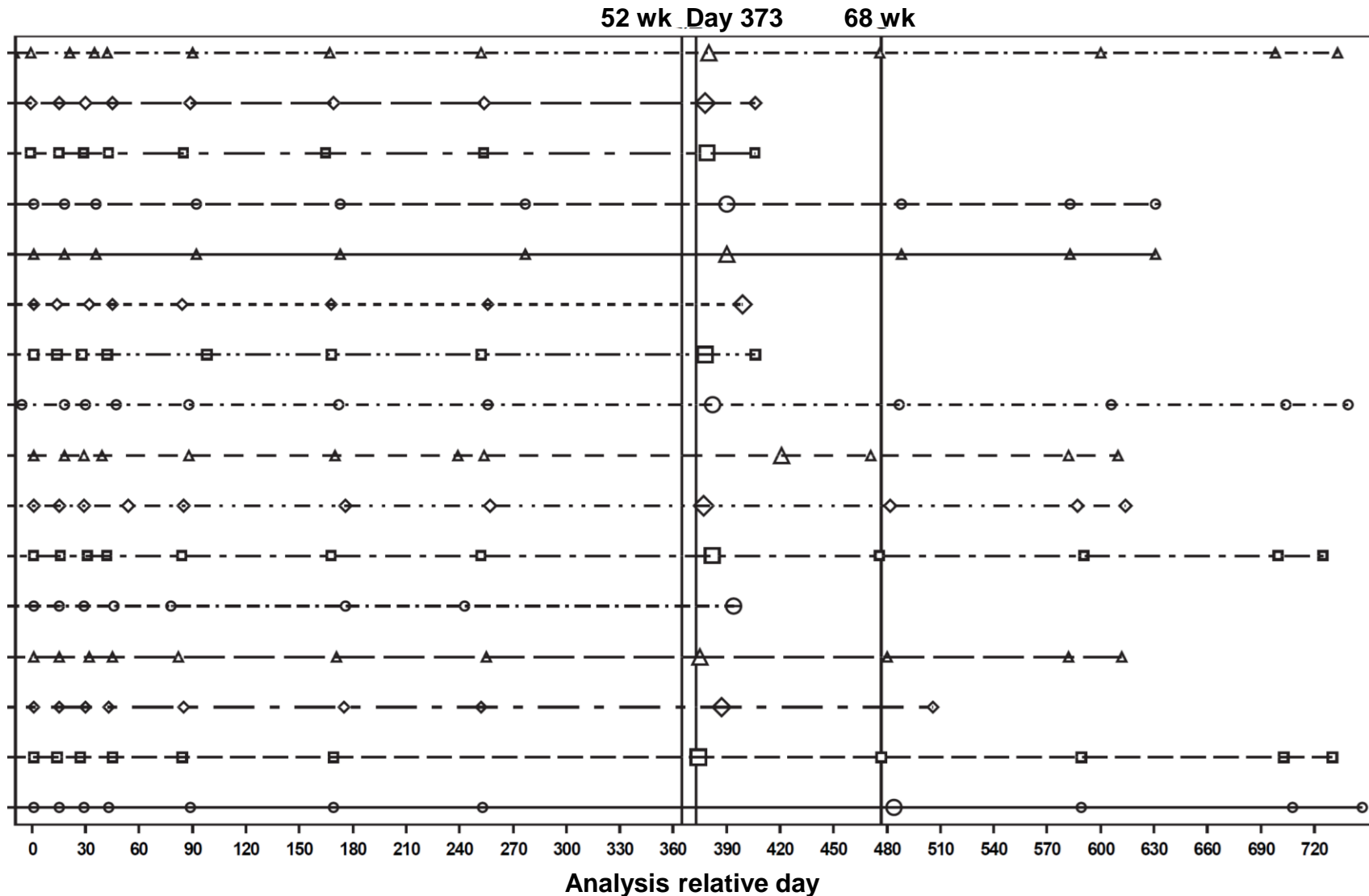
<sup>a</sup> Other causes for FVC decline (ie, respiratory tract infection) should be excluded.

## Timing of FVC in Patients With FVC Data After Week 52

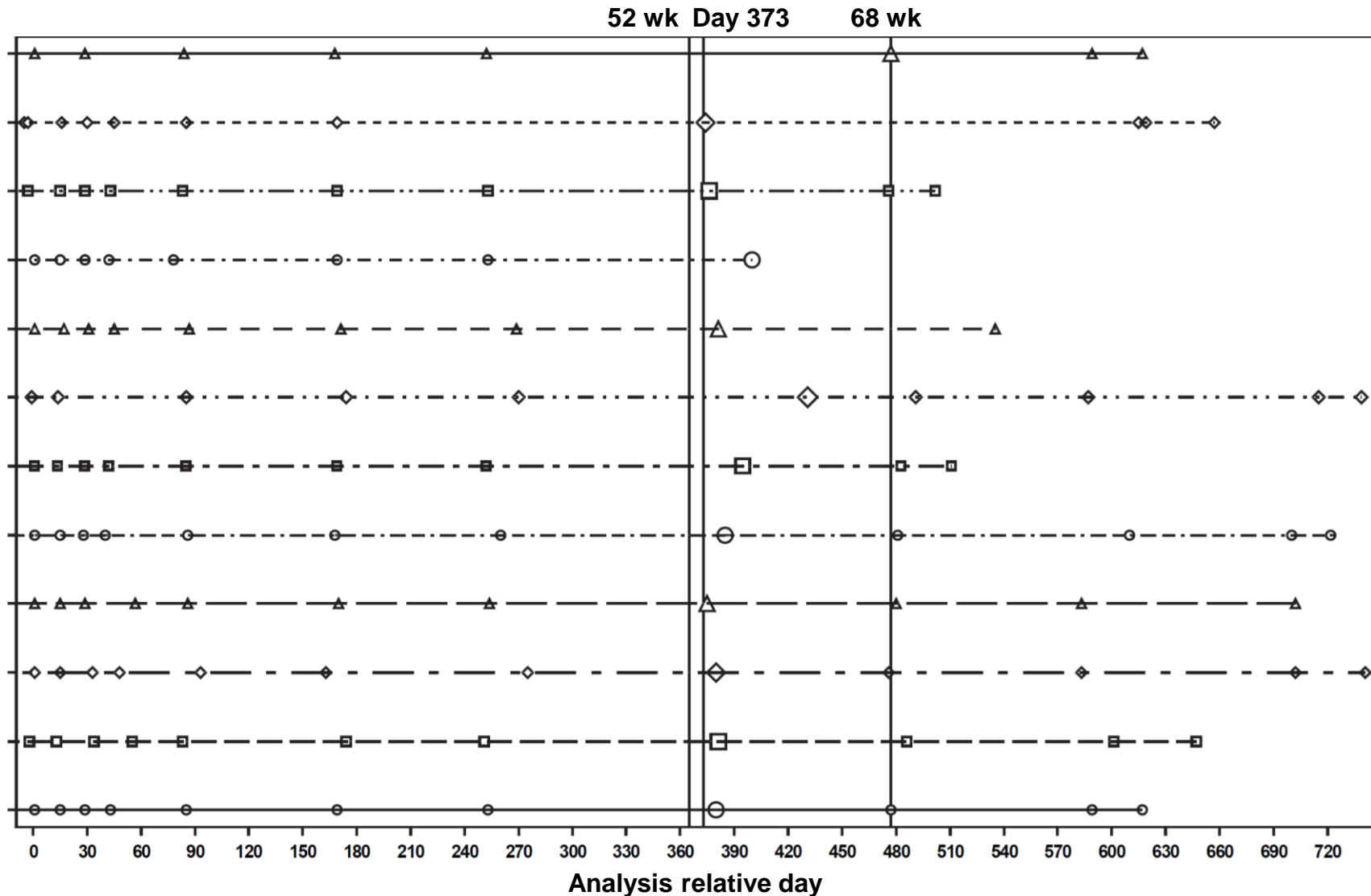
- ▶ Time (days) between end of 52 week time window and FVC assessment

	<b>Placebo n=12</b>	<b>Nintedanib n=16</b>
Q1	5.0	5.0
Median	8.0	9.0
Q3	24.5	19.0
Timing ≤28 days, n (%)	10 (83)	14 (88)

# Timing of FVC in Patients with FVC Data After Week 52 Nintedanib Group

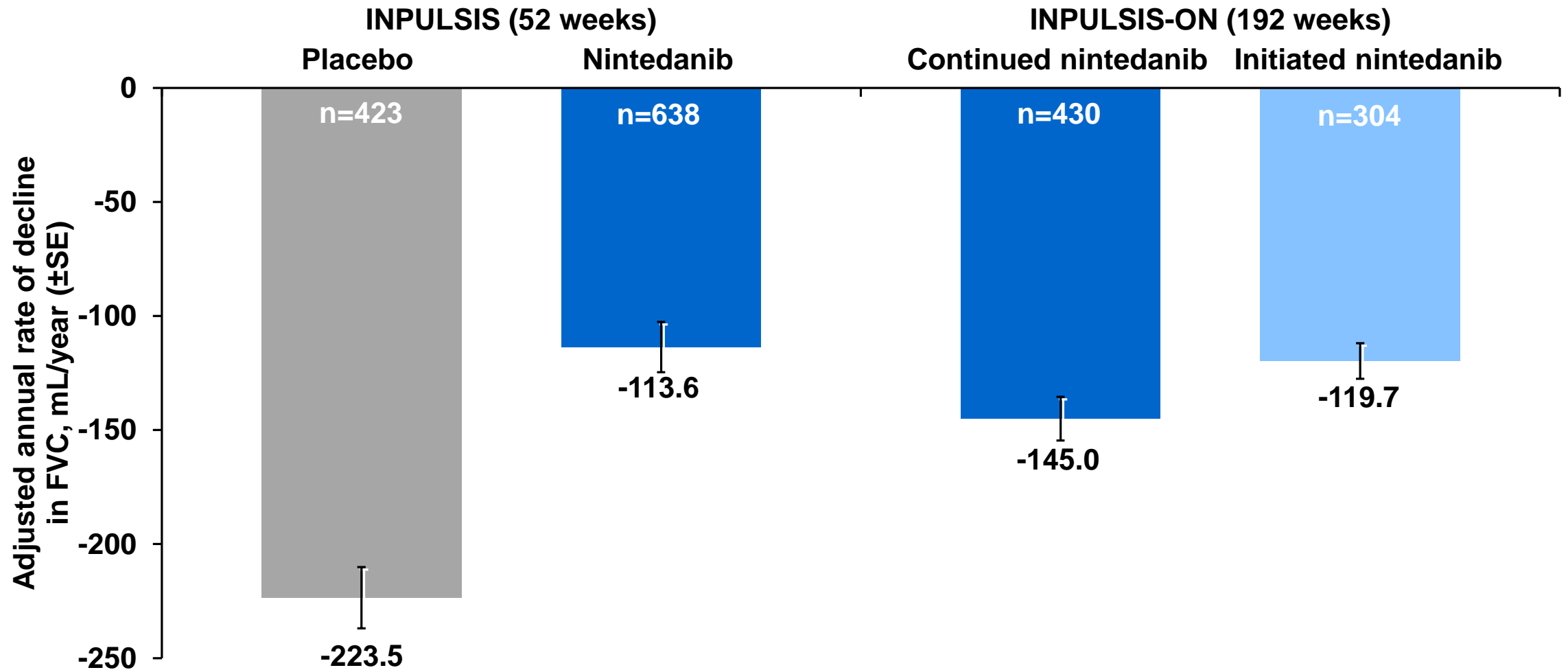


# Timing of FVC in Patients with FVC Data After Week 52 Placebo Group



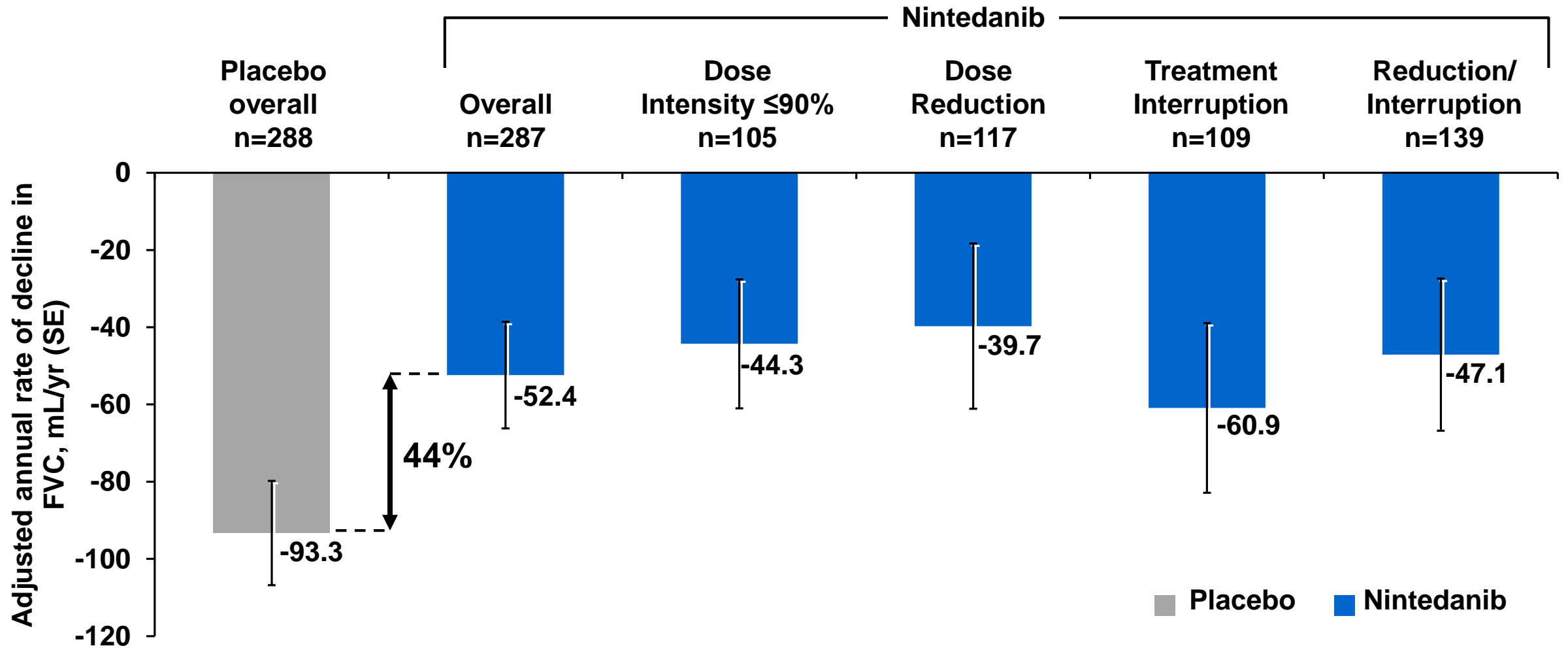
# Annual Rate of Decline in FVC

## INPULSIS and INPULSIS-ON



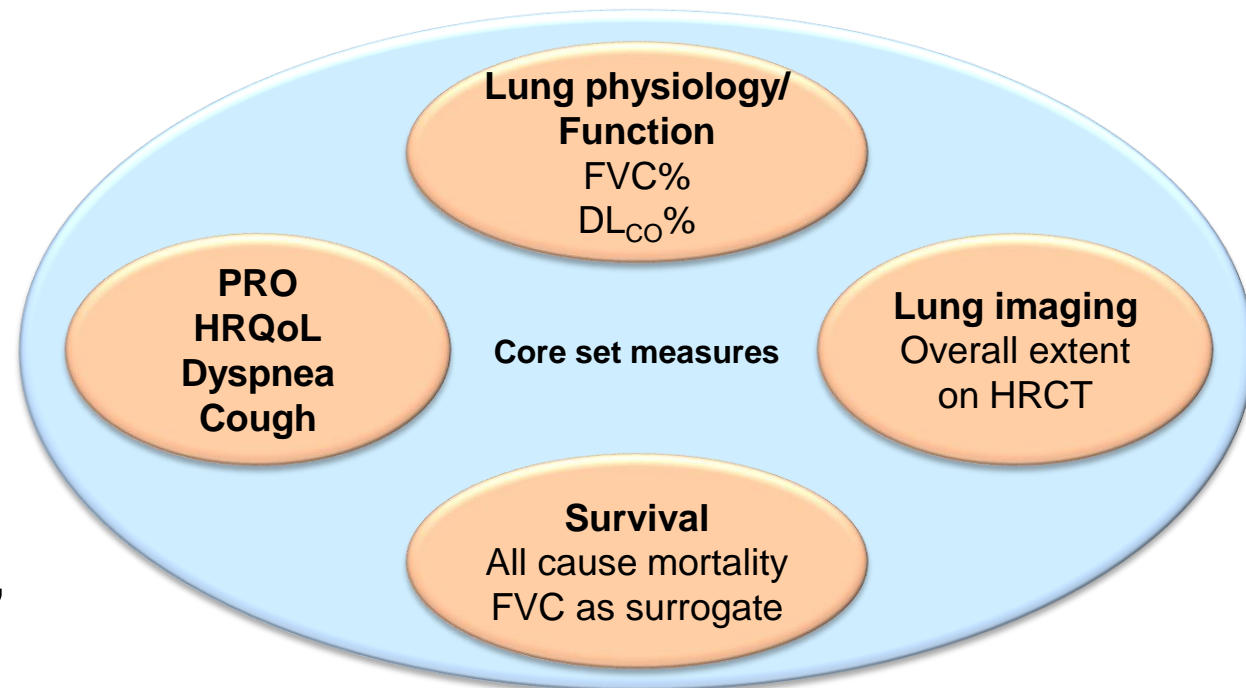
# Rate of Decline in FVC (mL/yr) over 52 Weeks by Dose Reductions and Treatment Interruptions

SENSCIS



# PRO Strategy

- ▶ At the time of the SENSICIS trial no disease-specific PRO measures were available for SSc-ILD.
- ▶ Selection of PRO measures informed by recommendations from the **OMERACT CTD-ILD working group**
- ▶ Core patient-reported **outcome domains: Health-related quality of life (HRQL), dyspnea, cough, and functional status**
- ▶ In the absence of disease-specific measures, PROs developed for other conditions were utilized to measure these key domains: e.g. SGRQ, FACIT-Dyspnea



# Treatment Interruptions, Reductions and Discontinuations

## SENSCIS – 52 Weeks

	Patients, n (%)	
	Placebo n=288	Nintedanib n=288
Treatment interruption	33 (11.5)	109 (37.8)
Dose reduction	13 (4.5)	117 (40.6)
Dose increase after reduction	2 (0.7)	25 (8.7)
Second dose reduction	0	13 (4.5)
Premature treatment discontinuation	31 (10.8)	56 (19.4)



# PRO-Scores: Ability to Detect Change

Mean Change in SGRQ and FACIT-Dyspnea at Week 52 by change in FVC% predicted status (SENSCIS Treated Set)

	FVC decline >10% predicted (n=37)	FVC decline >5 and ≤10% predicted (n=81)	FVC decline >2% and ≤5% predicted (n=95)	FVC  Δ  ≤2% predicted (n=178)	FVC increase >2% and ≤5% predicted (n=66)	FVC increase >5 and ≤10% predicted (n=33)	FVC increase >10% predicted (n=9)	p Value
SGRQ Total Score	5.5 (17.9)	1.4 (13.8)	-0.6 (15.6)	-1.1 (14.3)	-1.8 (15.6)	-3.4 (11.1)	-3.8 (6.91)	0.1210
FACIT-Dyspnea	3.1 (7.59)	0.9 (6.25)	1.0 (6.75)	-0.0 (6.86)	0.2 (6.81)	-1.2 (6.33)	0.4 (6.17)	0.1786

**Changes in SGRQ and FACIT Dyspnea scores do not differ significantly in patients with different responses in FVC**

Analysis of variance models (ANOVAs) were used to examine whether mean change in the respective PRO score from Baseline to Week 52 was significantly different among patients in the varying responder groups. SGRQ scores range from 0 (no impairment) to 100 (worst possible impairment). FACIT Dyspnea scale scores range from 27.7 (raw score=0) to 75.9 (raw score=30). Higher scores represent worse dyspnea or increased functional limitation.

# GI AEs by Predisposition<sup>a</sup> to GI Events

## SENSCIS – 52 Weeks

MedDRA PT	Patients, n (%)			
	Without predisposition to GI events		With predisposition to GI events	
	Placebo n=53	Nintedanib n=54	Placebo n=235	Nintedanib n=234
Diarrhea	11 (20.8)	38 (70.4)	80 (34.0)	180 (76.9)
Nausea	4 (7.5)	17 (31.5)	35 (14.9)	74 (31.6)
Vomiting	2 (3.8)	11 (20.4)	28 (11.9)	60 (25.6)
Abdominal pain <sup>b</sup>	3 (5.7)	9 (16.7)	29 (12.3)	44 (18.8)
GERD	1 (1.9)	2 (3.7)	21 (8.9)	10 (4.3)

<sup>a</sup> Predisposition to GI events: Patients with reported underlying GERD, esophageal dysphagia, malabsorption, SSc-related diarrhea or constipation.

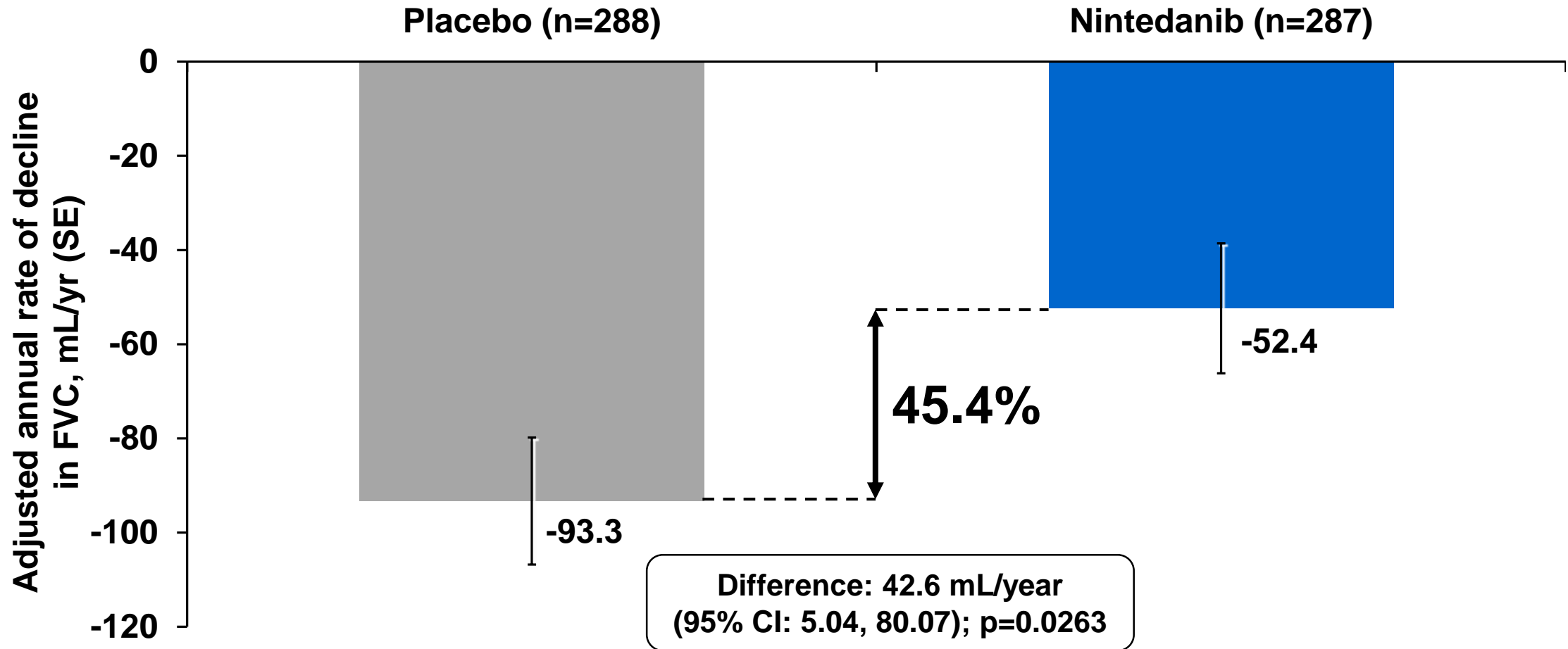
<sup>b</sup> MedDRA high-level term (related preferred terms grouped by anatomy, pathology, physiology, aetiology, or function).

# FVC Over Entire Trial – Treatment Policy Strategy

	<b>Adjusted annual rate of decline, mL/yr (SE)</b>	<b>Adjusted difference at 100 weeks, mL (95% CI)</b>
Placebo (n=288)	-88.8 (10.9)	65.3 (6.6, 124.1)
Nintedanib (n=287)	-54.9 (11.1)	

# Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

## SENSCIS



# Similar Nintedanib Plasma Exposure Between Patients With and Without Mycophenolate Co-treatment

Dose-normalized steady state trough plasma concentrations of nintedanib after multiple oral administration twice daily in patients with SSc-ILD without (No) compared to with (Yes) Mycophenolate comedication.

