OFEV® (nintedanib) Capsules for Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)

U.S. Food & Drug Administration
Arthritis Advisory Committee
July 25, 2019
Introduction

Kay Tetzlaff, MD
Medical Head, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim
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**
  - 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

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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

- **SENSCIS**
  - 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 (SENSCIS-ON)
SSc-ILD Regulatory Milestones

- **FEB**: Pre-IND written responses
- **SEP**: IND opening
- **NOV**: Phase 3 initiated
- **JUL**: Orphan drug designation
- **MAR**: Fast-track designation
- **JUN**: Type C written responses
- **MAY**: Priority review assignment
- **NOV**: Phase 3 completed
- **MAR**: sNDA submitted
- **MAY**: Priority review assignment

2015 | 2016 | 2017 | 2018 | 2019
sNDA: Proposed Indication and Dosing

- 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

- 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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<td>Susanne Stowasser, MD Boehringer Ingelheim</td>
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<td>Kevin K. Brown, MD National Jewish Health</td>
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## Advisors

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<tr>
<td>Shervin Assassi, MD, MS</td>
<td>University of Texas, Houston</td>
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<td>Kevin Carroll, PhD</td>
<td>KJC Statistics Ltd.</td>
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<td>Toby Maher, MD, PhD</td>
<td>Imperial College London</td>
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Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) Background and Unmet Medical Need

James R. Seibold, MD
Scleroderma Research Consultants
Epidemiology and Demographics of Systemic Sclerosis in United States

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

\textsuperscript{b} Barnes and Mayes. Curr Opin Rheumatol. 2012;24:165-170.
Progression of Skin and Lung Involvement in Diffuse and Limited Systemic Sclerosis

Onset of interstitial lung involvement

1-2 years after first non-RP symptom/sign

Extent of skin involvement

Time

DIFFUSE

LIMITED

Comorbid organ involvement
- Raynaud syndrome
- Digital ischemia and ulcers
- Esophageal disease
- Pulmonary hypertension

RP=Raynaud phenomenon
The Human Impact of Scleroderma

- 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

- 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

Causes of Death in Patients With SSc
EUSTAR Cohort (N=11,193)

PAH=pulmonary arterial hypertension.

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**

<table>
<thead>
<tr>
<th></th>
<th>IPF</th>
<th>SSc-ILD</th>
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<tbody>
<tr>
<td>Demographics</td>
<td>Males &gt;70 yr</td>
<td>Females 45-55 yr</td>
</tr>
<tr>
<td>Pathology</td>
<td>UIP</td>
<td>NSIP &gt;&gt; UIP</td>
</tr>
<tr>
<td>Acute exacerbations</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Progressivity</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Pace of decline in FVC</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Median survival</td>
<td>3-5 yr</td>
<td>5-8 yr</td>
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NSIP=non-specific interstitial pneumonia; UIP=usual interstitial pneumonia.
OMERACT Criteria for Outcome Assessment in CTD-ILD

- **Lung physiology/function**
  - FVC%
  - DL\textsubscript{CO}%

- **Core set measures**
  - PRO
    - HRQoL
    - Dyspnea
    - Cough
  - Survival
    - All-cause mortality
    - FVC is a surrogate
  - Lung imaging
    - Overall extent on HRCT

Forced Vital Capacity

- 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/m² BSA monthly × 6)
  - Oral mycophenolate mofetil (1500 mg bid)
  - IV or SC rituximab

bid=twice daily; BSA=body surface area; IV=intravenous; SC=sulocutaneous
Change From Baseline in FVC % Predicted at Month 12 (Primary Endpoint)
Scleroderma Lung Study I

Mean change from baseline in FVC % predicted (±SE)

Cyclophosphamide (n=73)
-1.0

Placebo (n=72)
-2.6

SE=standard error
p<0.05 for cyclophosphamide vs placebo.
FVC % Predicted Over 24 Months
Scleroderma Lung Study II

Patients, n
Cyclophosphamide 72 62 56 51 51 44 46 40 51
Mycophenolate mofetil 69 64 60 54 59 51 49 47 53

CI=confidence interval.
Time to Death or Organ Failure From Randomization
Scleroderma Lung Study I

Categorical decline in FVC % predicted ≥10% predicts survival

<table>
<thead>
<tr>
<th>Time</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>1.79 (0.98, 3.30)</td>
<td>NS</td>
</tr>
<tr>
<td>24 months</td>
<td>2.47 (1.27, 4.80)</td>
<td>&lt;0.01</td>
</tr>
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Time to Death or Organ Failure From Randomization
Scleroderma Lung Study II

Log-rank p=0.343

Categorical decline in FVC % predicted ≥10% predicts survival

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>12 months</td>
<td>8.22 (2.91, 23.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24 months</td>
<td>4.02 (1.15, 14.02)</td>
<td>&lt;0.05</td>
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SSc-ILD Current Status

- 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

Susanne Stowasser, MD
Associate Head Medicine, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim
Rationale for Clinical Development of Nintedanib in SSc-ILD

- 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.
Clinical Development of Nintedanib in Fibrosing Interstitial Lung Diseases

Fibrosing Interstitial Lung Diseases

- Idiopathic Pulmonary Fibrosis (IPF)
  - INPULSIS: Approved

- Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)
  - SENSICIS: Under review

- Progressive Fibrosing ILDs
  - INBUILD: Ongoing
The Nintedanib Program in IPF Is the Foundation for Development in SSc-ILD

Phase 2 trial

TOMORROW (N=428)\textsuperscript{a}

Dose-finding efficacy and safety
52 weeks

Open-label extension studies

INPULSIS-1 (N=513)\textsuperscript{b}
INPULSIS-2 (N=548)
Confirmatory efficacy and safety
52 weeks

Phase 3 trials

1199.35 (N=198)\textsuperscript{c}
Safety and efficacy

INPULSIS-ON (N=734)\textsuperscript{d}
Safety

Long-term exposure up to 68 months\textsuperscript{e}

\textsuperscript{e} For patients treated with nintedanib in INPULSIS and INPULSIS-ON.
Key Commonalities Across IPF and SSc-ILD Phase 3 Studies

- 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

AE=adverse event.
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\(^a\)
- In SSc-ILD, FVC decline is associated with mortality\(^b,c,d,e\)
- FVC is the primary outcome in SSc trials that assess ILD progression\(^f\)
- OMERACT CTD-ILD working group proposes FVC as the preferred outcome measure in trials of 1-year duration\(^g,h\)

Annual Rate of Decline in FVC (Primary Endpoint)
INPULSIS Studies in IPF

Adjusted Change From Baseline in FVC
INPULSIS Studies in IPF (Pooled)

Difference: 110.6 mL (56%)
(95% CI: 83.2, 137.9); p < 0.001

Adjusted Change From Baseline in FVC

Nintedanib 150 mg bid
Placebo

Week
0 4 8 12 16 20 24 28 32 36 40 44 48 52

Adjusted mean change from baseline in FVC, mL (SE)

Patients, n
Nintedanib 626 616 613 604 587 569 519
Placebo 417 408 407 403 395 383 345

a Adjusted mean difference vs placebo at Week 52.
Building on the IPF Experience
SENSCIS Phase 3 Study in SSc-ILD

- Nintedanib addresses the same underlying pathophysiology in IPF and SSc-ILD
- SENS CIS 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

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.

US and Canada
46 sites

Europe
82 sites

Asia
51 sites

Rest of the World
Argentina, Australia, Brazil, Chile, Israel, Mexico
15 sites
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

Variable treatment duration beyond 52 weeks

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

- 52-week treatment period for primary endpoint
- Treatment period beyond 52 weeks but ≤100 weeks

FPE=first patients enrolled; FPI=first patient in; LPI=last patient in.
Key Inclusion Criteria
SENSCIS

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

Key Exclusion Criteria

SENSCIS

- ALT or AST or bilirubin >1.5×ULN
- Bleeding risk (e.g., 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\(^a\)
- History of scleroderma renal crisis
- \(\text{FEV}_1/\text{FVC} < 70\%\)

ALT=alanine transaminase; AST=aspartate transaminase; FEV\(_1\)=forced expiratory volume in 1 second; ULN=upper limit of normal.

\(^a\) Defined as previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization showing a cardiac index ≤2 L/min/m\(^2\), or pulmonary hypertension requiring parenteral therapy with epoprostenol/treprostinil.
Main Concomitant Medications at Baseline

- **Permitted**
  - Prednisone (≤10 mg/day or equivalent)
  - Stable therapy with mycophenolate or methotrexate for ≥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

\[mRSS=\text{modified Rodnan skin score (scores ranges from 0-51); }\]
\[SGRQ=\text{St George’s Respiratory Questionnaire (scores ranges from 0-100).}\]
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

ATA=anti-topoisomerase antibody.
Disposition of Patients Over 52 Weeks
SENSCIS

Screened (n=819)
Randomized (n=580)
Treated (n=576)

Placebo (n=288)
- 89% remained on study drug (n=257)
- 11% prematurely discontinued study drug (n=31)
  - Did not complete visits up to Week 52 (n=13)
  - 95% completed visits up to Week 52 (n=275)

Nintedanib 150 mg bid (n=288)
- 81% remained on study drug (n=232)
- 19% prematurely discontinued study drug (n=56)
  - Did not complete visits up to Week 52 (n=24)
  - 92% completed visits up to Week 52 (n=264)
Handling of Missing FVC Measurements at Week 52

- 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**

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<thead>
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<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
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<tbody>
<tr>
<td><strong>Mean age, years (SD)</strong></td>
<td>53.4 (12.6)</td>
<td>54.6 (11.8)</td>
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<tr>
<td><strong>Female, n (%)</strong></td>
<td>212 (73.6)</td>
<td>221 (76.7)</td>
</tr>
<tr>
<td><strong>Mean weight, kg (SD)</strong></td>
<td>70.0 (16.4)</td>
<td>69.4 (15.4)</td>
</tr>
<tr>
<td><strong>Mean body mass index, kg/m² (SD)</strong></td>
<td>25.8 (5.1)</td>
<td>25.9 (4.8)</td>
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<tr>
<td>**Race, n (%)**a</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>186 (64.6)</td>
<td>201 (69.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>81 (28.1)</td>
<td>62 (21.5)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>16 (5.6)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>American Indian/Alaska Native/ Native Hawaiian/other Pacific Islander</td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
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SD=standard deviation.

*a Data from patients who selected one race. Four patients ticked two boxes.
### Baseline Disease Characteristics

**SENSCIS**

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<th>Nintedanib n=288</th>
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<tr>
<td><strong>Type of SSc, n (%)</strong></td>
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<tr>
<td>Diffuse cutaneous</td>
<td>146 (50.7)</td>
<td>153 (53.1)</td>
</tr>
<tr>
<td>Limited cutaneous</td>
<td>142 (49.3)</td>
<td>135 (46.9)</td>
</tr>
<tr>
<td><strong>mRSS, mean (SD)</strong></td>
<td>10.9 (8.8)</td>
<td>11.3 (9.2)</td>
</tr>
<tr>
<td><strong>Years since onset of first non-Raynaud symptom, median (minimum, maximum)</strong></td>
<td>3.5 (0.4, 7.2)</td>
<td>3.4 (0.3, 7.1)</td>
</tr>
<tr>
<td><strong>Anti-topoisomerase antibody positive, n (%)</strong></td>
<td>177 (61.5)</td>
<td>173 (60.1)</td>
</tr>
<tr>
<td><strong>Taking mycophenolate, n (%)</strong></td>
<td>140 (48.6)</td>
<td>139 (48.3)</td>
</tr>
<tr>
<td><strong>Taking corticosteroids, n (%)</strong></td>
<td>135 (46.9)</td>
<td>152 (52.8)</td>
</tr>
<tr>
<td><strong>Taking methotrexate, n (%)</strong></td>
<td>15 (5.2)</td>
<td>23 (8.0)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>Nintedanib</td>
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<tr>
<td></td>
<td>n=288</td>
<td>n=288</td>
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<tr>
<td><strong>Mean extent of fibrotic ILD on HRCT, (SD)</strong></td>
<td>35.2 (20.7)</td>
<td>36.8 (21.8)</td>
</tr>
<tr>
<td><strong>HRCT features, n (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Reticulation</td>
<td>272 (94.4)</td>
<td>266 (92.4)</td>
</tr>
<tr>
<td>Ground glass opacities</td>
<td>246 (85.4)</td>
<td>241 (83.7)</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>45 (15.6)</td>
<td>44 (15.3)</td>
</tr>
<tr>
<td><strong>Mean FVC, mL (SD)</strong></td>
<td>2541 (816)</td>
<td>2459 (736)</td>
</tr>
<tr>
<td><strong>Mean FVC, % predicted (SD)</strong></td>
<td>72.7 (16.6)</td>
<td>72.4 (16.8)</td>
</tr>
<tr>
<td><strong>Mean DLco, % predicted (SD)</strong></td>
<td>53.2 (15.1)</td>
<td>52.9 (15.1)</td>
</tr>
<tr>
<td><strong>Mean SpO2, % (SD)</strong></td>
<td>97.5 (2.5)</td>
<td>97.6 (1.9)</td>
</tr>
</tbody>
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SpO2=peripheral capillary oxygen saturation.

a Qualitative assessment by central review by expert radiologist.

b Corrected for hemoglobin.
Study Results
Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

SENSCIS

-93.3
-93.3
-52.4

Adjusted annual rate of decline in FVC, mL/yr (SE)

Placebo (n=288)

Nintedanib (n=287)

Difference: 41.0 mL/year
(95% CI: 2.9, 79.0); p=0.035
Rate of Decline in FVC % Predicted Over 52 Weeks

SENSCIS

Placebo (n=288)
Nintedanib (n=287)

Difference: 1.2
(95% CI: 0.1, 2.2)

Adjustment annual rate of decline
in FVC % predicted (SE)

46%

Difference: 1.2
(95% CI: 0.1, 2.2)
Absolute Change From Baseline in FVC (mL) at Week 52

SENSCIS

Placebo (n=288)

Nintedanib (n=288)

Adjusted mean change from baseline in FVC, mL (SE)

Difference: 46.4 mL
(95% CI: 8.1, 84.7)

46%
Change From Baseline in FVC (mL) Over 52 Weeks

SENSCIS

Patients, n

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<tr>
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<td>8</td>
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<tr>
<td>12</td>
<td>280</td>
<td>273</td>
</tr>
<tr>
<td>16</td>
<td>268</td>
<td>278</td>
</tr>
<tr>
<td>20</td>
<td>257</td>
<td>265</td>
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<tr>
<td>28</td>
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<td>36</td>
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<tr>
<td>40</td>
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<td></td>
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<tr>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean estimated FVC, mL change from baseline (±SEM)

Based on primary analysis model.
Categorical Analysis—Change in FVC % Predicted at 52 Weeks

- Worsening
  - p=0.0103 (Fisher’s exact test)

- Improvement
  - Nintedanib (n=287)
  - Placebo (n=288)

Frequency, %

Change from baseline in FVC % predicted:

- 
  - < -15
  - ≥ -15 to < -10
  - ≥ -10 to < -5
  - ≥ -5 to < 0
  - ≥ 0 to < 5
  - ≥ 5 to < 10
  - ≥ 10 to < 15
  - ≥ 15

a Worst observation carried forward.
Additional Responder Analysis
Change From Baseline in FVC % Predicted at 52 Weeks


<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Placebo (n=288)</th>
<th>Nintedanib 150 mg bid (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3.3% decline (deterioration)</td>
<td>n=126</td>
<td>n=97</td>
</tr>
<tr>
<td>OR (95% CI):</td>
<td>0.66 (0.47, 0.92)</td>
<td>1.69 (1.11, 2.59)</td>
</tr>
<tr>
<td>≥3% increase (improvement)</td>
<td>n=43</td>
<td>n=66</td>
</tr>
</tbody>
</table>

a Worst observation carried forward.
Subgroup Analyses of Primary Endpoint 1/2
SENSCIS Treated Set

<table>
<thead>
<tr>
<th>Analyzed, n</th>
<th>Placebo</th>
<th>Nintedanib</th>
<th>Difference (95% CI)</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>288</td>
<td>287</td>
<td>41.0 (2.9, 79.0)</td>
<td></td>
</tr>
<tr>
<td>ATA status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>177</td>
<td>173</td>
<td>29.9 (-19.1, 78.8)</td>
<td>0.491</td>
</tr>
<tr>
<td>Positive</td>
<td>111</td>
<td>114</td>
<td>57.2 (-3.5, 118.0)</td>
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</tr>
<tr>
<td>SSc subtype</td>
<td></td>
<td></td>
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<tr>
<td>Diffuse cutaneous</td>
<td>146</td>
<td>153</td>
<td>56.6 (3.2, 110.0)</td>
<td>0.420</td>
</tr>
<tr>
<td>Limited cutaneous</td>
<td>142</td>
<td>134</td>
<td>25.3 (-28.9, 79.6)</td>
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<tr>
<td>FVC % predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70% predicted</td>
<td>127</td>
<td>127</td>
<td>32.6 (-25.2, 90.5)</td>
<td>0.762</td>
</tr>
<tr>
<td>≥70% predicted</td>
<td>161</td>
<td>160</td>
<td>44.5 (-5.9, 94.9)</td>
<td></td>
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<tr>
<td>Extent of fibrotic ILD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;20%</td>
<td>74</td>
<td>57</td>
<td>16.2 (-64.1, 96.5)</td>
<td>0.496</td>
</tr>
<tr>
<td>≥20%</td>
<td>214</td>
<td>230</td>
<td>47.9 (4.5, 91.3)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment-by-time-by-subgroup interaction.
Subgroup Analyses of Primary Endpoint 2/2

**SENSCIS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Analyzed, n</th>
<th>Placebo</th>
<th>Nintedanib</th>
<th>Difference in annual rate of decline in FVC (95% CI)</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td>288</td>
<td>287</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td>229</td>
<td>224</td>
<td>44.4 (1.4, 87.4)</td>
<td>0.730</td>
</tr>
<tr>
<td>≥65 years</td>
<td></td>
<td>59</td>
<td>63</td>
<td>28.1 (-54.2, 110.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>212</td>
<td>220</td>
<td>34.6 (-9.3, 78.4)</td>
<td>0.594</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>76</td>
<td>67</td>
<td>58.6 (-18.0, 135.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td></td>
<td>186</td>
<td>200</td>
<td>45.8 (-0.8, 92.5)</td>
<td>0.725</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>81</td>
<td>62</td>
<td>44.5 (-32.9, 121.9)</td>
<td></td>
</tr>
<tr>
<td>Black/African Am.</td>
<td></td>
<td>16</td>
<td>20</td>
<td>-20.4 (-176.7, 136.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td>126</td>
<td>139</td>
<td>39.7 (-16.6, 95.9)</td>
<td>0.277</td>
</tr>
<tr>
<td>Canada and US</td>
<td></td>
<td>73</td>
<td>69</td>
<td>10.3 (-65.6, 86.1)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td>71</td>
<td>59</td>
<td>43.4 (-37.0, 123.8)</td>
<td></td>
</tr>
<tr>
<td>Rest of world</td>
<td></td>
<td>18</td>
<td>20</td>
<td>178.4 (28.1, 328.7)</td>
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<tr>
<td>Mycophenolate</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>140</td>
<td>138</td>
<td>26.3 (-27.9, 80.6)</td>
<td>0.452</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>148</td>
<td>149</td>
<td>55.4 (2.3, 108.5)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment-by-time-by-subgroup interaction.
Prespecified Subgroup Analyses of Primary Endpoint by Mycophenolate Use

SENSCIS

Taking mycophenolate at baseline

- Placebo
- Nintedanib

Adjusted rate of decline in FVC, mL/yr (SE)

-66.5
-40.2

Taking mycophenolate at baseline

- Placebo
- Nintedanib

Adjusted rate of decline in FVC, mL/yr (SE)

-119.3

Not taking mycophenolate at baseline

- Placebo
- Nintedanib

Adjusted rate of decline in FVC, mL/yr (SE)

-63.9

Treatment-by-time-by-subgroup interaction p=0.452

26.3 mL/year (95% CI: -27.9, 80.6)

55.4 mL/year (95% CI: 2.3, 108.5)
Responder Analysis for US/Canada

Worst Observation Carried Forward was used for missing data at Week 52.
Key Secondary Endpoints
## Key Secondary Endpoints

**SENSCIS**

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

- No treatment differences in mRSS or SGRQ between treatment groups

SGRQ=St. George’s Respiratory Questionnaire; Scores range from 0 (no impairment) to 100 (worst possible impairment);
MCIDs in IPF are estimated between 5-8 points
## Time to Death Over Whole Trial

**SENSCIS**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyzed, n</td>
<td>288</td>
<td>288</td>
</tr>
<tr>
<td>Patients with event, n (%)</td>
<td>9 (3.1)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.16 (0.47, 2.84)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.754</td>
<td></td>
</tr>
</tbody>
</table>

- No treatment differences in mortality between treatment groups

Data from randomization to last contact date on case report form.
Points of Interest

- Sensitivity analysis of primary endpoint
- Tipping point analysis
- Available data over 100 weeks
### Annual Rate of Decline in FVC

#### Prespecified and Revised Sensitivity Analyses

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nintedanib</th>
<th>Analyzed, n</th>
<th>Difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
<td>288</td>
<td>287</td>
<td></td>
<td>41.0 (2.9, 79.0)</td>
<td>0.035</td>
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<tr>
<td><strong>Multiple imputation sensitivity analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prespecified (missing n=78)</td>
<td>288</td>
<td>288</td>
<td></td>
<td>30.0 (-6.2, 66.2)</td>
<td>0.105</td>
</tr>
<tr>
<td></td>
<td>288</td>
<td>288</td>
<td></td>
<td>32.9 (-3.2, 69.1)</td>
<td>0.074</td>
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<tr>
<td></td>
<td>288</td>
<td>288</td>
<td></td>
<td>33.9 (-2.0, 69.8)</td>
<td>0.064</td>
</tr>
<tr>
<td>Revised (missing n=50)</td>
<td>288</td>
<td>288</td>
<td></td>
<td>34.3 (-1.8, 70.5)</td>
<td>0.063</td>
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<tr>
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<td>288</td>
<td>288</td>
<td></td>
<td>36.9 (0.8, 72.9)</td>
<td>0.045</td>
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<tr>
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<td>288</td>
<td>288</td>
<td></td>
<td>37.7 (1.9, 73.5)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

---

**Legend**

- **Favors placebo**
- **Favors nintedanib**

---

**Notes**

- The table presents the annual rate of decline in FVC for the primary analysis and multiple imputation sensitivity analyses.
- The difference in percentage change (95% CI) and p value is calculated for both placebo and nintedanib groups.
- The analyses consider prespecified (missing n=78) and revised (missing n=50) scenarios.
Tipping Point Analysis

- **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$^a$)

- 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)

$^a$ 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 SENSICS 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

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

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

## SENSCIS

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exposure through 52 weeks, mo (SD)</td>
<td>11.4 (2.4)</td>
<td>10.5 (3.4)</td>
</tr>
<tr>
<td>Mean exposure over entire trial, mo (SD)</td>
<td>15.7 (5.7)</td>
<td>14.5 (6.7)</td>
</tr>
</tbody>
</table>

Categorical exposure over entire trial, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 months</td>
<td>93.4</td>
<td>85.8</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>67.4</td>
<td>60.4</td>
</tr>
<tr>
<td>&gt;18 months</td>
<td>37.8</td>
<td>36.8</td>
</tr>
</tbody>
</table>

*Entire trial represents up to 100 weeks.*
## Summary of Adverse Events
**SENSCIS and INPULSIS – 52 Weeks**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>SENSCIS Placebo n=288</th>
<th>SENSCIS Nintedanib n=288</th>
<th>INPULSIS 1 and 2 Placebo n=423</th>
<th>INPULSIS 1 and 2 Nintedanib n=638</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>95.8</td>
<td>98.3</td>
<td>89.6</td>
<td>95.5</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>8.7</td>
<td>16.0</td>
<td>13.0</td>
<td>19.3</td>
</tr>
<tr>
<td>SAE</td>
<td>21.5</td>
<td>24.0</td>
<td>30.0</td>
<td>30.4</td>
</tr>
<tr>
<td>AE resulting in death</td>
<td>1.4</td>
<td>1.7</td>
<td>7.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

SAE=serious adverse event.
# Most Common AEs >10%

## SENS CIS and INPULSIS – 52 Weeks

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>SENS CIS</th>
<th>INPULSIS 1 and 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=288</td>
<td>Nintedanib n=288</td>
<td>Placebo n=423</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31.6</td>
<td>75.7</td>
<td>18.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.5</td>
<td>31.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.4</td>
<td>24.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>17.4</td>
<td>18.4</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17.0</td>
<td>12.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Cough</td>
<td>18.1</td>
<td>11.8</td>
<td>13.5</td>
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<tr>
<td>Weight decrease</td>
<td>4.2</td>
<td>11.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7.3</td>
<td>11.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12.2</td>
<td>11.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.9</td>
<td>10.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4.2</td>
<td>9.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8.7</td>
<td>7.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8.3</td>
<td>5.6</td>
<td>10.6</td>
</tr>
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</table>
## Safety Topics of Special Interest

**SENSCIIS and INPULSIS – 52 Weeks**

<table>
<thead>
<tr>
<th>Safety topics</th>
<th>SENSCIIS</th>
<th></th>
<th>INPULSIS 1 and 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=288</td>
<td>Nintedanib n=288</td>
<td>Placebo n=423</td>
<td>Nintedanib n=638</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31.6</td>
<td>75.7</td>
<td>18.4</td>
<td>61.6</td>
</tr>
<tr>
<td>Hepatic eventsa</td>
<td>4.9</td>
<td>17.4</td>
<td>4.5</td>
<td>17.7</td>
</tr>
<tr>
<td>Bleeding eventsb</td>
<td>8.3</td>
<td>11.1</td>
<td>7.8</td>
<td>10.3</td>
</tr>
<tr>
<td>MACEc</td>
<td>1.7</td>
<td>1.4</td>
<td>2.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*a Combination of 4 hepatic disorder SMQ searches.

b SMQ of hemorrhage terms, excluding laboratory.

c 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**

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.

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>91 (31.6)</td>
<td>218 (75.7)</td>
</tr>
<tr>
<td>Mild</td>
<td>61 (21.2)</td>
<td>108 (37.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (9.4)</td>
<td>98 (34.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (1.0)</td>
<td>12 (4.2)</td>
</tr>
<tr>
<td>SAEs</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td><strong>Clinical consequence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2 (0.7)</td>
<td>57 (19.8)</td>
</tr>
<tr>
<td>Premature treatment discontinuation</td>
<td>1 (0.3)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>Recovered</td>
<td>86/91 (94.5)</td>
<td>202/218 (92.7)</td>
</tr>
</tbody>
</table>
## Hepatic Events
### SENS CIS – 52 Weeks

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

<table>
<thead>
<tr>
<th>Hepatic events</th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AEs</strong></td>
<td>14 (4.9)</td>
<td>50 (17.4)</td>
</tr>
<tr>
<td><strong>SAEs</strong></td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Clinical consequence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2 (0.7)</td>
<td>11 (3.8)</td>
</tr>
<tr>
<td>Premature treatment discontinuation</td>
<td>1 (0.3)</td>
<td>6 (2.1)</td>
</tr>
</tbody>
</table>

*a Combination of 4 hepatic disorder SMQ searches.
Liver Enzymes and Bilirubin
SENSCIS – 52 Weeks

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST ≥1.5×ULN</td>
<td>11 (3.8)</td>
<td>52 (18.1)</td>
</tr>
<tr>
<td>ALT and/or AST ≥3×ULN</td>
<td>2 (0.7)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>ALT and/or AST ≥5×ULN</td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>ALT and/or AST ≥8×ULN</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hy’s Law lab constellation(^a)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

> Transaminase abnormalities resolved on dose reduction or discontinuation

\(^a\) ALT and/or AST ≥3x ULN and bilirubin ≥2x ULN.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.
## Bleeding Events
### SENSCIS – 52 Weeks

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

- All patients continued study medication uninterrupted

---

*aSMQ of hemorrhage terms, excluding laboratory.*
## Cardiovascular Events
### SENSUSIC – 52 Weeks

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong>a</td>
<td>5 (1.7)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Fatal cardiovascular events</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Adjudicated MACE</strong></td>
<td>3 (1.0)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

### Other cardiovascular events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>3 (1.0)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>4 (1.4)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (1.4)</td>
<td>11 (3.8)</td>
</tr>
</tbody>
</table>

*a 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

- 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

Kay Tetzlaff, MD
Medical Head, Therapeutic Area Respiratory Diseases
Boehringer Ingelheim
Benefit/Risk of Nintedanib in SSc-ILD

- 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative effect size, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INPULSIS 1</td>
<td>52.21 (32.43, 71.99)</td>
</tr>
<tr>
<td>INPULSIS 2</td>
<td>45.21 (21.66, 68.76)</td>
</tr>
<tr>
<td>SENSCIS</td>
<td>43.89 (3.18, 84.60)</td>
</tr>
<tr>
<td>Combined analysis</td>
<td>48.66 (34.46, 62.85)</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2=0\%$, $\tau^2=0$, $p=0.88$
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

Images from K Brown, National Jewish Health.
SSc-ILD

Images from K Brown, National Jewish Health.
One Individual’s History of Lung Function Loss

Image from of K Brown, National Jewish Health.
ILD Shortens Survival in Scleroderma

Survival and SSc Organ Involvement

The Presence of ILD Is Associated With Mortality
Nationwide Norwegian SSc Cohort

Anti-inflammatory Therapy Has Not Altered Long-term Survival

Survival at 10 years ~50%-60%

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

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 Jabonski, MD, Chicago, IL
US and Canada
46 sites

Europe
82 sites

Asia
51 sites

Rest of the World
Argentina, Australia, Brazil, Chile, Israel, Mexico
15 sites
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

Placebo (n=288)

Adjusted annual rate of decline in FVC, mL/yr (SE)

Nintedanib (n=287)

Difference: 41.0 mL/year (95% CI: 2.9, 79.0); p=0.035
### SENSCIS: Additional Subgroup Analyses of Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Analyzed, n</th>
<th>Difference (95% CI)</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td>41.0 (2.9, 79.0)</td>
</tr>
<tr>
<td>ATA status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>177/173</td>
<td>29.9 (-19.1, 78.8)</td>
<td>0.491</td>
</tr>
<tr>
<td>Positive</td>
<td>111/114</td>
<td>57.2 (-3.5, 118.0)</td>
<td></td>
</tr>
<tr>
<td>SSc subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse cutaneous</td>
<td>146/153</td>
<td>56.6 (3.2, 110.0)</td>
<td>0.420</td>
</tr>
<tr>
<td>Limited cutaneous</td>
<td>142/134</td>
<td>25.3 (-28.9, 79.6)</td>
<td></td>
</tr>
<tr>
<td>FVC % predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70% predicted</td>
<td>127/127</td>
<td>32.62 (-25.22, 90.47)</td>
<td>0.7616</td>
</tr>
<tr>
<td>≥70% predicted</td>
<td>161/160</td>
<td>44.47 (-5.93, 94.87)</td>
<td></td>
</tr>
<tr>
<td>Extent of fibrotic ILD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>74/57</td>
<td>16.21 (-64.10, 96.52)</td>
<td>0.4958</td>
</tr>
<tr>
<td>≥20%</td>
<td>214/230</td>
<td>47.90 (4.46, 91.34)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment-by-time-by-subgroup interaction.
SENSCIS: Categorical Analysis

Change from baseline in FVC % predicted, range

Worsening

Improvement

Placebo (n=288)

Nintedanib (n=287)

p=0.0103 (Fisher’s exact test)
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
## SENS CIS – 52 Weeks

<table>
<thead>
<tr>
<th>Customized drug grouping</th>
<th>Patients, n (%)</th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td></td>
<td>204 (70.8)</td>
<td>210 (72.9)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
<td>66 (22.9)</td>
<td>60 (20.8)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
<td>30 (10.4)</td>
<td>34 (11.8)</td>
</tr>
<tr>
<td>Amlodipine besilate</td>
<td></td>
<td>23 (8.0)</td>
<td>23 (8.0)</td>
</tr>
<tr>
<td>Bosentan</td>
<td></td>
<td>23 (8.0)</td>
<td>21 (7.3)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td></td>
<td>18 (6.3)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>Sildenafil citrate</td>
<td></td>
<td>13 (4.5)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Diltiazem hydrochloride</td>
<td></td>
<td>15 (5.2)</td>
<td>13 (4.5)</td>
</tr>
<tr>
<td>Iloprost trometamol</td>
<td></td>
<td>8 (2.8)</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Iloprost</td>
<td></td>
<td>7 (2.4)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
### Post-hoc Responder Analyses for Absolute Decline From Baseline in FVC % Predicted

**SENSCIS (Worst Value Carried Forward)**

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

Percent of patients with disease worsening lower in nintedanib treatment group

Missing values at Week 52 were imputed using a worst value carried forward approach.
Responder Analysis\textsuperscript{a}
Change From Baseline in FVC % Predicted at 52 Weeks

\[\begin{array}{c|cc}
\text{Frequency, %} & \text{Placebo (n=288)} & \text{Nintedanib (n=287)} \\
\hline
+3\% \text{ (improvement)} & 14.9 & 23.0 \\
\hline
\text{Stable/unchanged} & 41.3 & 43.2 \\
\hline
-3.3\% \text{ (worsening)} & 43.8 & 33.8 \\
\hline
\end{array}\]

\text{Odds ratio} & 1.69 & 0.66  \\
95\% CI & 1.11, 2.59 & 0.47, 0.92

\textsuperscript{a} Worst observation carried forward.
### Restricted Medication Use

**SENSCIS – 52 Weeks**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycophenolate (mofetil, acid, sodium)</strong></td>
<td>4 (1.4)</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>2 (0.7)</td>
<td>5 (1.7)</td>
<td>2 (0.7)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>3 (1.0)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
Clinically significant deterioration is defined as

- Absolute decline since baseline in FVC percent predicted >10% (in the absence of other causes for FVC deterioration)
- 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

*a 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

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

Analysis relative day

52 wk  Day 373  68 wk
0  30  60  90  120  150  180  210  240  270  300  330  360  390  420  450  480  510  540  570  600  630  660  690  720
**Annual Rate of Decline in FVC**

**INPULSIS and INPULSIS-ON**

### Adjusted annual rate of decline in FVC, mL/year (±SE)

- **INPULSIS (52 weeks)**
  - Placebo: n=423
  - Nintedanib: n=638
  - Nintedanib: -113.6

- **INPULSIS-ON (192 weeks)**
  - Continued nintedanib: n=430
  - Initiated nintedanib: n=304
  - Nintedanib: -145.0
  - Nintedanib: -119.7

---

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

SENSCIS

Adjusted annual rate of decline in FVC, mL/yr (SE)

-93.3

Placebo overall n=288

Overall n=287

Dose Intensity ≤90% n=105

Dose Reduction n=117

Treatment Interruption n=109

Reduction/ Interruption n=139

Nintedanib

-52.4

-44.3

-39.7

-60.9

-47.1

44%

Placebo

Nintedanib
PRO Strategy

- At the time of the SENSCIS 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.

Figure adapted from Khanna D, et al. *J Rheumatol.* 2015;42(11):2168-2171; DOI: https://doi.org/10.3899/jrheum.141182
## Treatment Interruptions, Reductions and Discontinuations
### SENSCIS – 52 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=288</th>
<th>Nintedanib n=288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment interruption</td>
<td>33 (11.5)</td>
<td>109 (37.8)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>13 (4.5)</td>
<td>117 (40.6)</td>
</tr>
<tr>
<td>Dose increase after reduction</td>
<td>2 (0.7)</td>
<td>25 (8.7)</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>0</td>
<td>13 (4.5)</td>
</tr>
<tr>
<td>Premature treatment discontinuation</td>
<td>31 (10.8)</td>
<td>56 (19.4)</td>
</tr>
</tbody>
</table>
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 | FVC decline >5 and ≤10% predicted | FVC decline >2% and ≤5% predicted | FVC |Δ| ≤2% and ≤5% predicted | FVC increase >2% and ≤5% predicted | FVC increase >5 and ≤10% predicted | FVC increase >10% predicted | p Value |
|-------------|-----------------------------------|-----------------------------------|-----|------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---------|
| (n=37)      | (n=81)                            | (n=95)                            | (n=178) | (n=66) | (n=33) | (n=9) |
| 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\(^a\) to GI Events
SENCSIS – 52 Weeks

<table>
<thead>
<tr>
<th>MedDRA PT</th>
<th>Without predisposition to GI events</th>
<th>With predisposition to GI events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=53</td>
<td>Nintedanib n=54</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (20.8)</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (7.5)</td>
<td>17 (31.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3.8)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Abdominal pain(^b)</td>
<td>3 (5.7)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>GERD</td>
<td>1 (1.9)</td>
<td>2 (3.7)</td>
</tr>
</tbody>
</table>

\(^a\) Predisposition to GI events: Patients with reported underlying GERD, esophageal dysphagia, malabsorption, SSc-related diarrhea or constipation.

\(^b\) MedDRA high-level term (related preferred terms grouped by anatomy, pathology, physiology, aetiology, or function).
### FVC Over Entire Trial – Treatment Policy Strategy

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

Based on slopes derived from random slope and intercept model as for the primary analysis. Analysis including all off-treatment data of patients who discontinued treatment prematurely.
Primary Endpoint: Annual Rate of Decline in FVC (mL/yr) Over 52 Weeks

SENSCIS

ST-45

Adjusted annual rate of decline in FVC, mL/yr (SE)

Placebo (n=288)

Nintedanib (n=287)

Difference: 42.6 mL/year (95% CI: 5.04, 80.07); p=0.0263
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.

N=136
N=122