Assassi Shervin (Orcid ID: 0000-0002-8059-9978)
Distler Oliver (Orcid ID: 0000-0002-2413-1959)

Running head: Effect of nintedanib over 100 weeks in patients with SSc-ILD

Title: Effect of nintedanib on progression of systemic sclerosis-associated interstitial lung disease over 100 weeks: data from the SENSCIS trial

Shervin Assassi MD,[1] Oliver Distler MD,[2] Yannick Allanore MD,[3] Takashi Ogura MD,[4] John Varga MD,[5] Serena Vettori MD,[6] Bruno Crestani MD,[7] Florian Voss PhD,[8] Margarida Alves MD,[9] Susanne Stowasser MD,[9] Toby M Maher MD[10] on behalf of the SENSCIS trial investigators

[1]Division of Rheumatology and Clinical Immunogenetics, University of Texas McGovern Medical School, Houston, Texas, USA; [2]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [3]Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France; [4]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Centre, Yokohama, Japan; [5]Division of Rheumatology, University of Michigan, Ann Arbor, Michigan, USA; [6]UOC di Fisiopatologia e Riabilitazione Respiratoria, Ospedale Monaldi, Napoli, Italy; [7]Hôpital Bichat, Pneumologie, Paris, France; [8]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; [9]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [10]National Heart and Lung Institute, Imperial College London, London, UK and Keck School of Medicine, University of Southern California, Los Angeles, California, USA.

Corresponding author: Dr Shervin Assassi, Department of Internal Medicine, McGovern Medical School, 6431 Fannin, MSB 1.150, Houston, Texas 77030. Tel: +1 713 500 6900. Email: Shervin.Assassi@uth.tmc.edu.

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Abstract

Objective: In the SENSCIS trial, subjects with systemic sclerosis-associated interstitial lung disease (SSc-ILD) were randomized to receive nintedanib or placebo until the last subject reached week 52 but for ≤100 weeks. Nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% (41 mL [95% CI: 2.9, 79.0]) versus placebo. We investigated the effect of nintedanib over the whole SENSCIS trial.

Methods: The annual rate of decline in FVC (mL/year) over the whole trial was assessed descriptively using i) on-treatment data plus off-treatment data from subjects who prematurely discontinued treatment ("intent-to-treat" analysis), and ii) only on-treatment data, to assess the effect of nintedanib in subjects who remained on treatment.

Results: In the "intent-to-treat" analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was −54.9 (11.1) and −88.8 (10.9) mL/year in the nintedanib (n=287) and placebo (n=288) groups, respectively (difference 34.0 mL/year [95% CI: 3.4, 64.5]). In the on-treatment analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was −55.1 (12.3) and −94.0 (11.7) mL/year in the nintedanib (n=286) and placebo (n=288) groups, respectively (difference 38.9 mL/year [95% CI: 5.6, 72.1]). The adverse event profile of nintedanib over 100 weeks was consistent with that observed over 52 weeks.

Conclusion: Nintedanib provides a sustained benefit on slowing the progression of SSc-ILD over 100 weeks, with adverse events that are manageable for most patients.

Introduction

Systemic sclerosis (SSc) is a rare and clinically heterogeneous autoimmune disease characterized by fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common manifestation of SSc (2) and the leading cause of SSc-related death (3). Decline in forced vital capacity (FVC) in patients with SSc-ILD is indicative of disease progression and is associated with mortality (4,5,6). While there is no established definition of progression of SSc-ILD, in two recent Delphi consensus studies, physicians experienced in managing patients with SSc-ILD agreed that measurement of lung function is an effective tool for assessing progression of ILD over the long term (7,8). Further, it has been proposed that a decline in FVC of ≥10%, or a decline in FVC of 5–9% with a decline in diffusing capacity of the lungs for carbon monoxide (DLco) of ≥15%, over 1–2 years represents ILD progression (9,10).

Nintedanib is a tyrosine kinase inhibitor that inhibits processes fundamental to the progression of lung fibrosis (11,12). Nintedanib has been approved for the treatment of idiopathic pulmonary fibrosis (IPF), other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD in many countries. In the SENSCIS trial, subjects with SSc-ILD were randomized to receive nintedanib or placebo until the last subject reached week 52 but for no longer than 100 weeks. The primary analysis showed that nintedanib reduced the rate of decline in FVC over 52 weeks versus placebo by 44% (−52.4 versus −93.3 mL/year; difference of 41.0 mL/year [95% CI: 2.9, 79.0]), with no significant difference between groups in change in modified Rodnan skin score (mRSS), and a safety profile characterized predominantly by gastrointestinal adverse events (13,14). Additional analyses investigating the proportions of patients with categorical declines in FVC of >5% and >10% predicted

over 52 weeks supported a benefit of nintedanib on slowing the progression of SSc-ILD (15). Here, we investigated the efficacy and safety of nintedanib over the whole SENSCIS trial (up to 100 weeks of treatment).

Materials and Methods

Subjects

The design of the SENSCIS trial has been published and the trial protocol is publicly available (13). Briefly, eligible subjects had SSc with onset of first non-Raynaud symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on an HRCT scan, FVC ≥40% predicted and DLco 30–89% predicted. Subjects receiving prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate.

Trial design

Subjects were randomized 1:1 to receive nintedanib 150 mg bid or placebo, stratified by the presence of anti-topoisomerase I antibody (ATA). The trial was designed to demonstrate a reduction in the rate of decline in FVC (mL/year) in subjects treated with nintedanib versus placebo over 52 weeks. Subjects could remain on randomized blinded treatment until the last subject reached week 52 but for ≤100 weeks, resulting in a variable length of follow-up depending on when the subject was randomized. A post-treatment follow-up visit, at which FVC and adverse event data were collected, was conducted 28 days after the end of treatment. Subjects who stopped treatment prematurely were asked to stay in the trial and attend visits up to 100 weeks or until the end of the trial. FVC was measured at baseline and at weeks 2, 4, 6, 12, 24, 36, 52, 68, 84 and 100. Spirometers were supplied by the

sponsor.Measurements were performed by a qualified technician and readings were confirmed centrally in accordance with American Thoracic Society/European Respiratory Society guidelines (16). The trial was conducted in accordance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation, and was approved by local authorities. All subjects provided written informed consent.

Analyses

As for the primary analysis on data over 52 weeks, the annual rate of decline in FVC over the whole trial was analyzed using random coefficient regression, with fixed effects for treatment, ATA status, sex, baseline FVC (mL), age and height, treatment-by-time and baseline-by-time interactions, and random effect of subject-specific intercept and time. Given the variable length of follow-up beyond week 52, two analytical approaches were of particular interest. The first followed an "intent-to-treat" approach in order to estimate the treatment effect regardless of premature treatment discontinuation (Figure S1a). This analysis included on-treatment data plus off-treatment data from subjects who prematurely discontinued treatment; post-treatment data from subjects who completed the planned treatment period and discontinued treatment as per the trial design (i.e. when the last subject reached week 52 or when they reached week 100) were not included. The second analysis included only on-treatment data, in order to assess the expected effect of nintedanib in subjects who remained on treatment. A pre-specified analysis, which aimed to reflect an intent-to-treat approach, was also performed based on all available data, including data collected after treatment discontinuation. However, as this analysis

included data from the post-treatment follow-up visit from subjects who had completed treatment as planned and only came off treatment at the end of the trial (as per the protocol) (Figure S1a), this analysis does not represent an intent-to-treat approach; in practice, these patients would have continued treatment. For transparency, this analysis is presented in the supplement (Figure S2b). Adjusted absolute changes from baseline in FVC over 100 weeks were analyzed using a mixed model for repeated measures, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction, age, sex and height.

Time to absolute declines in FVC >5% predicted and >10% predicted over 100 weeks and time to relative declines in FVC (mL) >5% and >10% over 100 weeks were assessed using the intent-to-treat approach and using on-treatment data plus 1 day. Times to absolute decline in FVC >5% predicted and >10% predicted over 100 weeks were assessed post-hoc using a Cox's regression model with terms for treatment and baseline FVC % predicted, stratified by ATA status. Times to relative decline in FVC (mL) >5% and >10% over 100 weeks were assessed post-hoc using a Cox's regression model with terms for treatment, sex, baseline FVC (mL), age and height, stratified by ATA status. Percent predicted values for FVC were calculated using the Global Lung Initiative equations based on the subject's age, sex, race and height (17).

Analyses of the annual rate of decline in FVC over 100 weeks, times to absolute decline in FVC >5% predicted and >10% predicted over 100 weeks and times to relative decline in FVC (mL) >5% and >10% over 100 weeks were repeated in subgroups by mycophenolate use at baseline. Analyses of the annual rate of decline in FVC over 100 weeks were repeated in subgroups by ATA status, sex, and

SSc subtype (limited cutaneous SSc vs diffuse cutaneous SSc). Treatment-by-subgroup and treatment-by-subgroup-by-time, and subgroup and treatment-by-subgroup, were included as interaction terms in the random coefficient regression and Cox's regression models, respectively.

Adjusted absolute changes from baseline in mRSS at week 100 were analyzed using a mixed model for repeated measures, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Time to absolute increase (worsening) from baseline in mRSS ≥5 points was analyzed using a Cox's regression model with terms for treatment and baseline mRSS, stratified by ATA status.

Safety was assessed based on adverse events, reported irrespective of causality, from the first intake of trial drug to the last intake plus 28 days. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Adverse events are presented descriptively in the overall population and in subgroups based on age, sex, race, weight, ATA status and mycophenolate use at baseline. Incidence rates of adverse events were calculated as the number of subjects with the event divided by the time at risk and expressed per 100 patient–years.

Results

Subjects

A total of 576 subjects received ≥1 dose of trial drug. At baseline, mean (SD) FVC was 2500 (777) mL and 72.5 (16.7) % predicted and 279 subjects (48.4%) were taking mycophenolate. Over the whole trial, 74 subjects (25.7%) in the nintedanib group and 46 subjects (16.0%) in the placebo group prematurely discontinued trial

drug. The most common reason was adverse events: 53 (18.4%) and 33 (11.5%) subjects treated with nintedanib and placebo prematurely discontinued trial drug due to adverse events. In the nintedanib and placebo groups, respectively, 239 (83.0%) and 252 (87.5%) subjects completed the treatment period and follow-up visit, or prematurely discontinued trial drug but attended further visits as planned (Figure 1). Of those treated, 73 subjects (25.3%) in the nintedanib group and 73 subjects (25.3%) in the placebo group provided an FVC value at week 100. Median exposure to trial drug was 15.4 months in the nintedanib group and 15.6 months in the placebo group. Maximum exposure in these groups, respectively, was 23.2 and 23.8 months.

Decline in FVC

In the intent-to-treat analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was −54.9 (11.1) mL/year in the nintedanib group and −88.8 (10.9) mL/year in the placebo group (difference of 34.0 mL/year [95% CI: 3.4, 64.5]); the estimated between-group difference in FVC at week 100 was 65.3 mL (Figure 2).
In the on-treatment analysis, the adjusted mean (SE) annual rate of decline in FVC over 100 weeks was −55.1 (12.3) mL/year in the nintedanib group and −94.0 (11.7) mL/year in the placebo group (difference of 38.9 mL/year [95% CI: 5.6, 72.1]); the estimated between-group difference in FVC at week 100 was 74.7 mL (Figure 2). Curves depicting the adjusted absolute changes from baseline in FVC (mL) over 100 weeks are presented in Figure 3.

The risks of experiencing an absolute decline in FVC >5% or >10% predicted, or a relative decline in FVC (mL) >5% and >10%, over 100 weeks were numerically lower in the nintedanib group than in the placebo group (Table 1).

Results of the subgroup analyses by mycophenolate use at baseline are presented in Table 2 and Figure S3. In both the intent-to-treat and on-treatment analyses, the effect of nintedanib on the annual rate of decline in FVC over 100 weeks was numerically smaller in subjects who were taking mycophenolate at baseline than in those who were not (Table 2). The exploratory interaction p-values for heterogeneity in the effect of nintedanib on the annual rate of FVC decline between the subgroups were p=0.072 in the intent-to-treat analysis and p=0.45 in the on-treatment analysis. The risks of experiencing an absolute decline in FVC >5% or >10% predicted, or a relative decline in FVC (mL) >5% and >10%, over 100 weeks were numerically lower in the nintedanib group than in the placebo group in both subgroups by mycophenolate use (Figure S3). The exploratory interaction p-values for heterogeneity in the effect of nintedanib ranged from p=0.21 to p=0.56. The treatment effect of nintedanib between subgroups by mycophenolate use at baseline showed some variability across the FVC-based endpoints; however, taking into account all the analyses and the widely overlapping confidence intervals, the results did not indicate a heterogeneous effect of nintedanib between these subgroups. The adjusted mean annual rates of decline in FVC over 100 weeks in subgroups by ATA status, sex and SSc subtype, based on the intent-to-treat analysis, are presented in Tables S1–3. The exploratory interaction p-values did not indicate a heterogeneous effect of nintedanib across these subgroups.

Changes in mRSS

Small reductions (improvements) in mRSS were observed in both treatment groups. A numerically smaller proportion of subjects treated with nintedanib than placebo

experienced an increase from baseline in mRSS ≥5 points over 100 weeks (13.9% vs 16.7%) (Table S4).

Adverse events

The most frequent adverse event over up to 100 weeks of treatment was diarrhea, which was reported in 76.4% of subjects treated with nintedanib and 32.6% of subjects who received placebo; 7.6% and 0.3% of subjects in the nintedanib and placebo groups, respectively, permanently discontinued trial drug due to diarrhea (Table 3). Serious adverse events were reported in 30.6% of subjects treated with nintedanib and 27.4% of subjects treated with placebo; fatal adverse events were reported in 2.1% and 1.7% of subjects in the nintedanib and placebo groups, respectively. Elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN) were reported in 5.6% of subjects in the nintedanib group and 0.7% of subjects in the placebo group. No subjects met criteria for Hy's law (ALT and/or AST ≥3 × ULN and bilirubin ≥2 × ULN). The proportions of subjects with major adverse cardiovascular events, myocardial infarction, and bleeding adverse events are shown in Table S5. Major adverse cardiovascular events were reported in a smaller proportion of subjects treated with nintedanib than placebo. No subjects treated with nintedanib had a myocardial infarction. Bleeding adverse events were balanced between treatment groups.

The adverse event profile of nintedanib over up to 100 weeks of treatment was generally consistent across subgroups based on age, sex, race, weight, ATA status and mycophenolate use at baseline (Tables S6–S11).

Discussion

We evaluated the efficacy and safety of nintedanib in subjects with SSc-ILD over the whole SENSCIS trial. Our results, based on data from up to 100 weeks of treatment, suggested that the effect of nintedanib on slowing the progression of SSc-ILD observed over the first 52 weeks persisted beyond that period. The annual rate of decline in FVC over 100 weeks was lower in subjects treated with nintedanib than placebo across all the analytical methods used. In the analysis that used an intent-to-treat approach, which we consider to be the most relevant, nintedanib reduced the annual rate of decline in FVC (mL/year) over 100 weeks by 38%, similar to the 44% relative reduction observed over 52 weeks (13). It would be expected that the relative reduction in the rate of FVC decline with nintedanib versus placebo observed over 100 weeks would be slightly lower than that observed over 52 weeks, as more data from patients who prematurely discontinued nintedanib (and so lost the effect of treatment) are included. These results were supported by time-to-event analyses based on categorical declines in FVC and applying standard censoring rules. Of note, our findings were obtained in a patient population of whom almost half were taking mycophenolate at baseline. The treatment effects of nintedanib on FVC endpoints showed some variability between the subgroups by mycophenolate use at baseline, and the effect on the annual rate of decline in FVC was numerically smaller in patients taking than not taking mycophenolate.

It is interesting to note that 52% of subjects in the placebo group experienced an absolute decline in FVC of >5% predicted over 100 weeks, suggesting that although the inclusion criteria for the SENSCIS trial did not require that patients had recent evidence of ILD progression, and almost half were taking mycophenolate at baseline, the majority of patients enrolled in the trial exhibited progressive ILD. Considering the age of onset of SSc, and the association between FVC decline and

mortality in patients with SSc-ILD (4,5,6), the observed reduction in the rate of decline in FVC in subjects who received nintedanib in the SENSCIS trial is clinically relevant. These data are supported by those of INPULSIS-ON, the long-term extension of the INPULSIS trials in subjects with IPF, which suggested that the effect of nintedanib on slowing the rate of decline in FVC persisted beyond 4 years (18). An ongoing open-label extension of the SENSCIS trial, SENSCIS-ON (NCT03313180), will provide long-term data on the effects of nintedanib in patients with SSc-ILD.

The safety and tolerability profile of nintedanib observed over 100 weeks was consistent with that observed over 52 weeks (13,14), and with the profile established in patients with IPF and other chronic fibrosing ILDs (18,19,20). A comparison of the permanent treatment discontinuations that occurred over 100 weeks with those that occurred over 52 weeks (13) shows that only four patients discontinued nintedanib after 52 weeks of treatment, of whom two discontinued due to diarrhea. As observed over 52 weeks of treatment (21), although mycophenolate is also associated with gastrointestinal adverse events, permanent discontinuations of nintedanib over 100 weeks were not more frequent compared to placebo in subjects taking concomitant mycophenolate than in subjects taking nintedanib alone, supporting the tolerability of this combination.

Strengths of our analyses include the broad population of patients enrolled in the SENSCIS trial, the standardized collection and reading of FVC data, the high proportion of subjects who completed the trial in both treatment groups, and the consistent results obtained using different statistical methods to investigate the effect of nintedanib on FVC decline. Given that the SENSCIS trial was designed to demonstrate a reduction in the rate of FVC decline over 52 weeks, our analyses also have limitations, including the post-hoc nature of the intent-to-treat and on-treatment

analyses; missing FVC data, particularly, due to the trial design, at the later time-points; and selection bias in the patients who continued longer in the trial. Thus, the analyses of the data beyond 52 weeks should be considered exploratory. We were unable to investigate changes in St. George's Respiratory Questionnaire (SGRQ) score over 100 weeks, as after week 52, the SGRQ was only completed at the end of treatment visit.

In conclusion, these analyses suggest that the effect of nintedanib on slowing the progression of SSc-ILD observed over 52 weeks persisted over the duration of the SENSCIS trial. The results of the SENSCIS trial suggest that nintedanib provides a sustained benefit on slowing the progression of SSc-ILD, with adverse events that are manageable for most patients.

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Data sharing

A data availability statement can be found in the supplement.

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Table 1. Absolute and relative declines in FVC over 100 weeks (assessed as time to event)

	Nintedanib (n=288)	Placebo (n=288)
"Intent-to-treat" analysis		
Absolute decline in FVC >5% predicted, n (%)	130 (45.1)	150 (52.1)
HR (95% CI)	0.83 (0.66, 1.05)	
p-value	0.12	
Absolute decline in FVC >10% predicted, n (%)	52 (18.1)	67 (23.3)
HR (95% CI)	0.79 (0.55, 1.13)	
p-value	0.19	
Relative decline in FVC (mL) >5%, n (%)	171 (59.4)	201 (69.8)
HR (95% CI)	0.80 (0.65, 0.99)	
p-value	0.04	
Relative decline in FVC (mL) >10%, n (%)	103 (35.8)	117 (40.6)
HR (95% CI)	0.88 (0.67, 1.14)	
p-value	0.33	
On-treatment analysis		
Absolute decline in FVC >5% predicted, n (%)	117 (40.6)	144 (50.0)
HR (95% CI)	0.80 (0.63, 1.02)	
p-value	0.07	
Absolute decline in FVC >10% predicted, n (%)	46 (16.0)	65 (22.6)
HR (95% CI)	0.75 (0.51, 1.09)	
p-value	0.13	
Relative decline in FVC (mL) >5%, n (%)	156 (54.2)	194 (67.4)

HR (95% CI)	0.78 (0.63, 0.96)	
p-value	0.02	
Relative decline in FVC (mL) >10%, n (%)	91 (31.6)	113 (39.2)
HR (95% CI)	0.82 (0.62, 1.09)	
p-value	0.17	

Table 2. Annual rate of decline in FVC (mL/year) over 100 weeks in subgroups by mycophenolate use at baseline

	Subjects taking mycophenolate at baseline		**Subjects not taking mycophenolate at baseline**	
	Nintedanib	**Placebo**	**Nintedanib**	**Placebo**
"Intent to treat" analysis, n	138	140	149	148
Adjusted mean (SE) annual rate of decline in FVC (mL/year)	−54.4 (15.7)	−59.8 (15.5)	−55.1 (15.6)	−116.4 (15.2)
Difference (95% CI)	5.4 (−37.9, 48.8)		61.3 (18.6, 104.0)	
Treatment-by-time-by-subgroup interaction p-value	0.072			
On-treatment analysis, n	138	140	148	148
Adjusted mean (SE) annual rate of decline in FVC (mL/year)	−45.0 (17.2)	−70.7 (16.6)	−65.2 (17.4)	−116.3 (16.3)
Difference (95% CI)	25.7 (−21.3, 72.7)		51.1 (4.3, 98.0)	
Treatment-by-time-by-subgroup interaction p-value	0.45			

Table 3. Adverse events

	Nintedanib (n=288)		Placebo (n=288)	
	N (%)	Incidence rate (per 100 patient–years)	N (%)	Incidence rate (per 100 patient–years)
Any adverse event(s)	283 (98.3)	1156.1	281 (97.6)	456.3
Most frequent adverse events*				
Diarrhea	220 (76.4)	201.7	94 (32.6)	32.5
Nausea	96 (33.3)	35.9	41 (14.2)	11.6
Vomiting	78 (27.1)	26.9	33 (11.5)	8.9
Skin ulcer	57 (19.8)	18.2	56 (19.4)	16.0
Nasopharyngitis	43 (14.9)	13.0	56 (19.4)	15.9
Cough	41 (14.2)	12.1	63 (21.9)	18.5
Upper respiratory tract infection	39 (13.5)	11.5	44 (15.3)	12.2
Weight decreased	39 (13.5)	11.5	15 (5.2)	3.9
Abdominal pain	36 (12.5)	10.6	21 (7.3)	5.6

Headache	34 (11.8)	10.0	28 (9.7)	7.5
Fatigue	33 (11.5)	9.8	21 (7.3)	5.6
Urinary tract infection	29 (10.1)	8.4	28 (9.7)	7.5
Dyspnea	27 (9.4)	7.7	31 (10.8)	8.2
Severe adverse event(s)†	62 (21.5)	18.8	44 (15.3)	11.7
Adverse event(s) leading to permanent discontinuation of trial drug	50 (17.4)	13.9	29 (10.1)	7.3
Most frequent adverse events leading to permanent discontinuation of trial drug‡				
Diarrhea	22 (7.6)	6.0	1 (0.3)	0.3
Nausea	6 (2.1)	1.6	0	0
Vomiting	4 (1.4)	1.1	1 (0.3)	0.3

Data are n (%) of subjects with ≥1 such adverse event. *Adverse events reported in >10% of subjects in either treatment group are shown, coded according to preferred terms in the Medical Dictionary for Regulatory activities (MedDRA). †Events that were incapacitating or that caused an inability to work or to perform usual activities. ‡Adverse events that led to permanent discontinuation in >1% of subjects in either treatment group are shown.

Figure legends

Figure 1. Disposition of subjects over the SENSCIS trial

Figure 2. Annual rate of decline in FVC (mL/year) over 100 weeks

Figure 3. Adjusted absolute changes from baseline in FVC over 100 weeks