
Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS™)

O. Distler¹, K.K. Brown², J.H.W. Distler³, S. Assassi⁴, T.M. Maher⁵, V. Cottin⁶, J. Varga⁷, C. Coeck⁸, M. Gahlemann⁹, W. Sauter¹⁰, H. Schmidt¹⁰, K.B. Highland¹¹,
on behalf of the SENSCIS™ trial investigators

¹University Hospital Zurich, Switzerland; ²National Jewish Health, Denver, Colorado, USA; ³University of Erlangen-Nuremberg, Erlangen, Germany; ⁴University of Texas Houston Medical School, Houston, Texas, USA; ⁵NIHR Biomedical Research Unit Royal Brompton Hospital, London, UK and Fibrosis Research Group, National Heart and Lung Institute, Imperial College London, UK; ⁶Louis Pradel Hospital, Claude Bernard University Lyon 1, France; ⁷Feinberg School of Medicine, Chicago, Illinois, USA; ⁸SCS Boehringer Ingelheim Comm.V., Brussels, Belgium; ⁹Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; ¹⁰Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; ¹¹Cleveland Clinic, Cleveland, Ohio, USA.

Oliver Distler, MD; Kevin K. Brown, MD
Jörg H.W. Distler, MD; Shervin Assassi, MD
Toby M. Maher, MD; Vincent Cottin, MD
John Varga, MD; Carl Coeck, MD
Martina Gahlemann, MD
Wiebke Sauter, PhD; Hendrik Schmidt, PhD
Kristin B. Highland, MD

Please address correspondence to:

Dr Oliver Distler,
University Hospital Zurich,
Department of Rheumatology,
Gloriastr. 25,
Zürich 8091, Switzerland.
E-mail: Oliver.Distler@usz.ch

Received on March 31, 2017; accepted in revised form on May 5, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 106): S75-S81.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2017.

Key words: systemic sclerosis, connective tissue diseases, quality of life, respiratory function tests

Competing interests: see page S80.

ABSTRACT

Objective. Nintedanib is a tyrosine kinase inhibitor approved for the treatment of idiopathic pulmonary fibrosis (IPF). The pathological pathways involved in fibrogenesis in IPF and interstitial lung disease associated with systemic sclerosis (SSc-ILD) show commonalities; both involve fibroblast activation, myofibroblast accumulation and deposition of extracellular matrix. The SENSCIS™ trial is a randomised, placebo-controlled Phase III trial that will evaluate the efficacy and safety of nintedanib in patients with SSc-ILD (NCT02597933).

Methods. Approximately 520 patients with SSc (based on 2013 American College of Rheumatology/European League Against Rheumatism criteria) and ILD ($\geq 10\%$ fibrosis of the lungs, confirmed by central assessment of chest high resolution computed tomography), forced vital capacity (FVC) $\geq 40\%$ predicted and diffusing capacity for carbon monoxide of 30–89% predicted will be enrolled. Patients will be randomised (1:1) to nintedanib 150 mg twice daily or placebo, stratified by the presence of anti-topoisomerase I antibody. To reflect real-world management, patients receiving prednisone (≤ 10 mg/day) and/or a stable dose of mycophenolate or methotrexate, will be eligible. The primary endpoint is the annual rate of decline in FVC (mL/year) assessed over 52 weeks. Patients will remain on blinded study treatment until the last patient completes 52 weeks of treatment or for a maximum of 100 weeks of treatment. Key secondary endpoints are absolute changes from baseline in modified Rodnan skin score and St George's Respiratory Questionnaire at week 52.

Results. Recruitment for the trial began in November 2015.

Conclusion. This trial will assess the efficacy and safety of nintedanib in patients with SSc-ILD.

Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease (CTD) of unknown aetiology characterised by immune dysregulation, inflammation, widespread small vessel vasculopathy and progressive interstitial and perivascular fibrosis of the skin and internal organs (1).

Interstitial lung disease (ILD) is a major cause of morbidity and mortality in patients with SSc, accounting for approximately 1 in 3 SSc-related deaths (2, 3). The reported prevalence of SSc-ILD varies widely depending on the definition and study methodology used. In an unselected cohort of 1168 patients with SSc in the Canadian Scleroderma Research Group registry, the prevalence of ILD, defined by the presence of ground-glass attenuation, fibrotic interstitial changes or honeycombing on HRCT, was estimated to be 52% (4). As ILD is such a common and serious manifestation of SSc, it was included in the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) joint classification criteria for SSc published in 2013 (5). Most patients with SSc experience respiratory symptoms, such as exertional dyspnoea and non-productive cough (6, 7). Symptoms and lung function impairment restrict activities of daily living and have a negative impact on health-related quality of life (HRQL) (6). No drugs are licensed for the treatment of SSc-ILD. Treatment recommendations published

by EULAR/EUSTAR in 2009 suggested that cyclophosphamide should be considered despite its known toxicities (8). This recommendation was based on the results of two trials. The first was a randomised, placebo-controlled trial of 6 months' treatment with corticosteroids and intravenous cyclophosphamide followed by azathioprine as maintenance therapy, which showed a non-significant benefit of active therapy on change in FVC % predicted at 1 year (9). The second was the randomised placebo-controlled Scleroderma Lung Study I, which demonstrated a significant but modest benefit of cyclophosphamide on change in FVC % predicted at 1 year, but with a higher rate of adverse events and premature withdrawals (10). In 2016, results from the Scleroderma Lung Study II demonstrated that 24 months' treatment with mycophenolate mofetil (MMF) was not more efficacious than 12 months' treatment with cyclophosphamide followed by 12 months' treatment with placebo; benefits on FVC % predicted over 24 months were comparable between the groups (11). There were fewer premature treatment withdrawals due to adverse events in the MMF group (11). Updated treatment recommendations published by EULAR/EUSTAR in 2016 continued to recommend that cyclophosphamide should be considered for the treatment of SSc-ILD, in particular in patients with progressive SSc-ILD (12). In addition, the updated guidelines recommended that use of autologous haematopoietic stem cell transplantation (HSCT) should be considered in selected patients with rapidly progressive SSc at risk of organ failure (12). HSCT has been associated with better long-term event-free survival than intravenous pulse cyclophosphamide in patients with early diffuse cutaneous SSc (13). For patients who have not responded to treatment and who have no extrapulmonary contraindications to transplant, lung transplant should be considered as a therapeutic option (14). Nintedanib is a potent intracellular inhibitor of tyrosine kinase receptors, including the fibroblast growth factor receptor (FGFR), platelet-derived growth

factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR), and non-receptor members of the Src family (15-17). Nintedanib has been approved for the treatment of idiopathic pulmonary fibrosis (IPF) in several countries, including the US and EU (18, 19). In the Phase II, 52-week TOMORROW trial and the two Phase III, 52-week INPULSIS® trials, nintedanib 150 mg twice daily (bid) slowed disease progression in patients with IPF by reducing the annual rate of decline in FVC (mL/year), with an adverse event profile characterised mainly by diarrhoea which was manageable for most patients (20, 21).

As in IPF, the pathological pathways involved in fibrogenesis in SSc-ILD include fibroblast activation, migration, proliferation and differentiation into myofibroblasts, culminating in excess deposition of extracellular matrix (22, 23). Transforming growth factor β (TGF- β) plays a key role: increased expression and activation of TGF- β receptors, leading to enhanced phosphorylation and downstream intracellular signalling, is characteristic of SSc fibroblasts (22). Both PDGF, a potent mitogen and activator of fibroblasts, and PDGFR are elevated in SSc fibroblasts (22). Src kinases have been implicated in processes such as fibroblast activation and the development of bleomycin-induced dermal fibrosis (24). The role of VEGF in SSc is controversial; overexpression of VEGF has been shown to have profibrotic effects in the skin of mouse models (25) and to result in disturbed vessel morphology and intractable fingertip ulcers in patients with SSc (26), but other studies suggest that VEGF may have beneficial effects via promoting wound healing and angiogenesis (27).

In vitro studies have shown that nintedanib inhibits PDGF- and TGF- β -induced proliferation and migration of human lung and dermal fibroblasts, their transformation into myofibroblasts, and the secretion of ECM (16, 17, 28). The inhibitory effects of nintedanib on PDGF, TGF- β , VEGF and Src kinases may also have beneficial effects on vascular complications of SSc, such as digital ulcer formation

(29, 30). Nintedanib has demonstrated anti-fibrotic effects in various animal models of fibrosis, irrespective of the trigger (16, 17, 28). In mouse models of bleomycin-induced and silica-induced lung fibrosis, nintedanib reduced fibrosis and collagen deposition in lung tissue (16). Nintedanib also ameliorated fibrosis in murine models of scleroderma skin disease, including the tight-skin-1 mouse and a chronic graft-versus-host disease model (28). These preclinical data, together with the efficacy and safety of nintedanib demonstrated in patients with IPF, have provided a rationale for investigating the effects of nintedanib in patients with SSc-ILD.

Materials and methods

Study design

The Phase III, multicentre, randomised, double-blind, placebo-controlled SENSICIS™ (Safety and Efficacy of Nintedanib in Systemic SCLerosIS) trial will evaluate the efficacy and safety of nintedanib for at least 52 weeks (maximum of 100 weeks) in patients with SSc-ILD (NCT02597933) (Fig. 1). Recruitment for the trial began in November 2015. Eligible patients will be randomised 1:1 to oral nintedanib 150 mg bid or placebo. As the presence of anti-topoisomerase I antibody (ATA) has been associated with the progression of ILD (31), randomised patients will be stratified by the presence of ATA. The trial will end when the last patient has completed 52 weeks of treatment and a follow-up visit 28 days later. Patients who discontinue trial drug prior to completing week 52 of treatment will be asked to attend all visits and undergo examinations as originally planned. The trial is being conducted in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. All patients will provide written informed consent prior to trial entry.

Study population

Approximately 520 adults with SSc-ILD will be enrolled in the SEN-

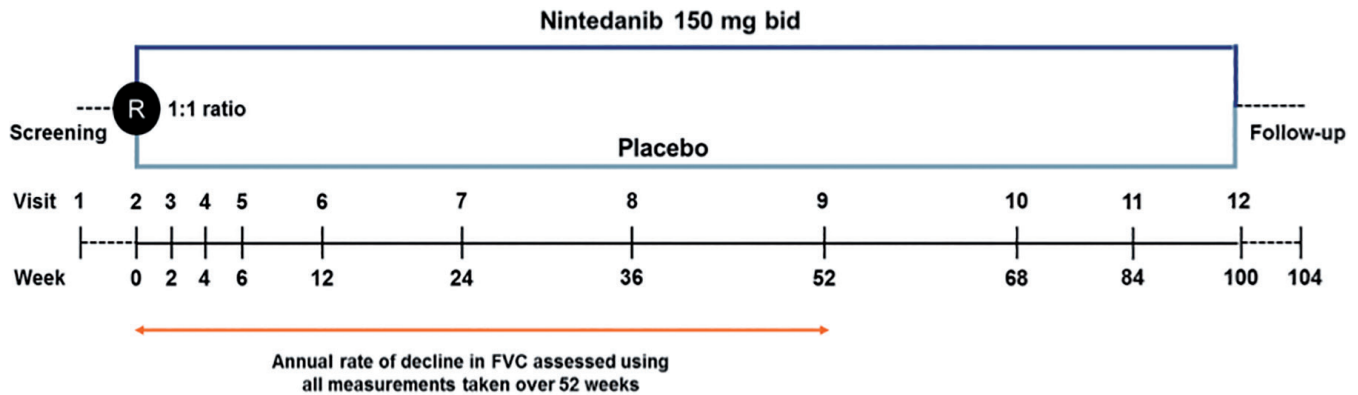


Fig. 1. Trial design. Patients will remain on blinded study treatment for up to 100 weeks or until the last patient completes 52 weeks' treatment. R: randomisation.

SCISTM trial, making it the largest prospective clinical trial in SSc-ILD to date. Patients who fulfil the 2013 ACR/EULAR classification criteria for SSc (5) with onset of disease (first non-Raynaud symptom) <7 years from screening (<5 years prior to a protocol amendment in January 2017) are eligible to participate. The likelihood of achieving clinical benefit is believed to be greatest in the years following disease onset as this is the period when the risk of progression of SSc-ILD is greatest. SSc-ILD will be confirmed by a chest HRCT scan performed within 12 months of screening and must show an extent of fibrotic disease $\geq 10\%$, assessed by central review. Features consistent with SSc-ILD will be defined by reticular abnormalities, honeycombing and ground glass opacities. Participants are required to have an FVC $\geq 40\%$ of predicted value and a diffusing capacity for carbon monoxide (DLco) 30–89% of predicted value.

Background therapy with prednisone ≤ 10 mg/day and/or stable therapy with mycophenolate (mofetil or sodium) or methotrexate (≥ 6 months) will be permitted, reflecting clinical practice. Patients will be excluded if they have taken azathioprine within 8 weeks prior to randomisation or cyclophosphamide or cyclosporine within 6 months prior to randomisation, but immunosuppressants may be used in cases of clinical deterioration, defined as an absolute decline in FVC $>10\%$ predicted from baseline, or a relative increase in modified Rodnan Skin Score (mRSS) $>25\%$ from baseline and an absolute increase in mRSS >5 points from baseline, or

clinically significant deterioration in other organ systems in the opinion of the investigator.

Key exclusion criteria include alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin >1.5 x upper limit of normal (ULN) at screening; severe renal impairment, defined as creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula; a history of scleroderma renal crisis (added in a protocol amendment in January 2017); chronic liver disease (Child Pugh A, B or C); history of myocardial infarction, severe uncontrolled hypertension, or unstable angina within 6 months of screening; significant pulmonary hypertension, defined by previous clinical or echocardiographic evidence of significant right heart failure; history of right heart catheterisation showing a cardiac index ≤ 2 L/min/m² or requiring parenteral therapy with epoprostenol/treprostinil; >3 digital ulcers or history of severe digital necrosis within 6 months of screening. Patients at known risk for bleeding (e.g., those with predisposition to bleeding or requiring fibrinolysis, full-dose anticoagulation or high-dose antiplatelet therapy) or with a history of haemorrhagic central nervous system event or thrombotic event within 12 months of screening will be excluded.

Efficacy endpoints

The primary endpoint is the annual rate of decline in FVC (mL/year) assessed over 52 weeks. Key secondary endpoints are the absolute change from baseline in mRSS and St George's Respiratory Questionnaire (SGRQ) total

score at week 52. The mRSS evaluates a patient's skin thickness according to clinical palpation of the 17 surface anatomic areas of the body rated using a 0–3 scale (0, normal skin; 1, mild thickness; 2, moderate thickness; 3, severe thickness with inability to pinch the skin into a fold), with the sum of the individual scores defined as the total score (32). The SGRQ is a self-administered questionnaire comprising three domains: symptoms, activity and impact (33). Each domain score, as well as the total score, ranges from 0 to 100, with higher scores indicating worse HRQL. Exploratory endpoints are listed in Table I.

Three optional sub-studies at dedicated sites will assess changes in quantitative lung fibrosis score by HRCT (centrally reviewed), changes in skin biopsies (histology and protein and RNA biomarkers), and changes in vascular density by nailfold capillary microscopy (centrally reviewed).

Safety and tolerability

Safety will be assessed by physical examination, vital signs, 12-lead electrocardiogram, echocardiography (in patients with a history of pulmonary hypertension), laboratory measurements and the recording of adverse events (coded using the Medical Dictionary for Regulatory Activities). The intensity of adverse events will be rated by the investigators as mild (easily tolerated), moderate (enough discomfort to cause interference with usual activity) or severe (incapacitating or causing inability to work or to perform usual activities). Adverse events of hepatic

Table I. Efficacy endpoints.

Primary endpoint	Annual rate of decline in FVC (mL/year) 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
Exploratory secondary endpoints	Annual rate of decline in FVC % predicted Absolute change from baseline in FVC (mL) at week 52 Relative change from baseline (%) in mRSS at week 52 Time to all-cause mortality Absolute change from baseline in DLco % predicted at week 52 Absolute change from baseline in digital ulcer net burden at week 52 Absolute change from baseline in CRISS index score at week 52 (changed from exploratory further endpoint in a protocol amendment in January 2017) Absolute change from baseline in HAQ-DI score at week 52 Absolute change from baseline in FACIT dyspnoea score at week 52
Exploratory further endpoints	Proportion of patients with a relative decline from baseline in FVC (mL) >5% at week 52 Proportion of patients with a relative decline from baseline in FVC (mL) >10% at week 52 Absolute change from baseline in SpO ₂ (%) at rest at week 52 Proportion of patients with absolute change from baseline in mRSS ≥5 points at week 52 Absolute change from baseline in SHAQ domain scores (individual VAS scores) at week 52 Absolute change from baseline in FACIT functional limitation score at week 52 Absolute change from baseline in SGRQ domain scores at week 52 Absolute change from baseline in EQ-5D-5L VAS score at week 52 Absolute change from baseline in patient global VAS score at week 52 Absolute change from baseline in physician global VAS score at week 52 Proportion of patients with disease progression at week 52* Efficacy data collected beyond week 52

*Any of the following: absolute decline from baseline in FVC >10%; relative change from baseline in mRSS >25% and absolute change >5 points; death.

CRISS: Combined Response Index for Systemic Sclerosis; EQ-5D-5L: European Quality of Life-5 Dimensions 5-level classification system; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire Disability Index; SHAQ: Scleroderma Health Assessment Questionnaire; SpO₂: oxygen saturation; VAS: visual analogue score.

injury and gastrointestinal perforation are of special interest, based on known effects of VEGF(R) inhibitors (34). Hepatic injury will be assessed based on: ALT and/or AST ≥8 x ULN; ALT and/or AST ≥3 x ULN and total bilirubin ≥2 x ULN; ALT and/or AST ≥3 x ULN and unexplained international normalised ratio >1.5; ALT and/or AST ≥3 x ULN and unexplained eosinophilia (>5%); ALT and/or AST ≥3 x ULN and fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, or rash.

Dose reductions from 150 mg bid to 100 mg bid and treatment interruptions will be permitted to manage adverse events, using the same regimen as in the Phase III INPULSIS® trials in patients with IPF (21, 35). Specific recommendations for the management of diarrhoea and hepatic enzyme elevations have been provided to investiga-

tors (Fig. 2 and Fig. 3). In summary, diarrhoea should be managed as early as possible with adequate hydration and standard anti-diarrhoeal treatment, *e.g.* loperamide. If diarrhoea persists, dose reduction to 100 mg bid or treatment interruption should be considered.

An adjudication committee will review medical documentation to adjudicate cases suspected to be major adverse cardiovascular events and deaths due to cardiac and respiratory causes.

Statistical analysis

The primary endpoint will be analysed based on all measurements taken over 52 weeks using a random coefficient regression model. The slope of decline, assumed to be linear, as in the INPULSIS® trials in patients with IPF (21), will be calculated for every patient and the average compared between the nintedanib and placebo groups. The stratification

factor, *i.e.*, presence of ATA (positive or negative), and other covariables, such as baseline FVC in mL, will be included in the model. Sensitivity analyses, using multiple imputation methods estimating the effect of nintedanib under differing assumptions around the persistence of efficacy after treatment discontinuation, will be undertaken.

The two key secondary endpoints will be analysed using a restricted maximum likelihood (REML) based repeated measures approach. Both will be tested under a hierarchical test strategy that protects the type-1 error. If the results of the primary endpoint reach statistical significance, test results of change from baseline in mRSS at week 52 will be confirmatory. If these test results are statistically significant, test results of change from baseline in SGRQ total score at week 52 will be confirmatory. If any of the previous steps do not reach statistical significance, the analyses of the key secondary endpoints will be exploratory.

Analyses will be conducted using two-sided tests, with *p*-values <5% signalling statistical significance.

All other endpoints will be analysed in an exploratory fashion using similar models as for the primary or key secondary endpoints or will be summarised descriptively. A Cox proportional hazards model will be used to estimate the hazard ratio for nintedanib versus placebo for all-cause mortality.

All efficacy and safety analyses will be based on patients who were randomised and received ≥1 dose of trial medication. All measurements performed within the first 52 weeks will be used for the efficacy analyses, even if a patient prematurely discontinues treatment (intent-to-treat principle).

The difference in the absolute change from baseline in FVC (mL) at week 52 between the nintedanib and placebo groups is assumed to be between 70 and 110 mL (10, 21). A standard deviation of 245 mL in both treatment groups is assumed. Assuming a small number of patients without analysable data, a sample size of 260 patients per treatment group will achieve 90% power to detect a difference between groups of 70 mL/year in the primary endpoint.

Fig. 2. Recommendations for management of diarrhoea in the SENSICIS™ trial.

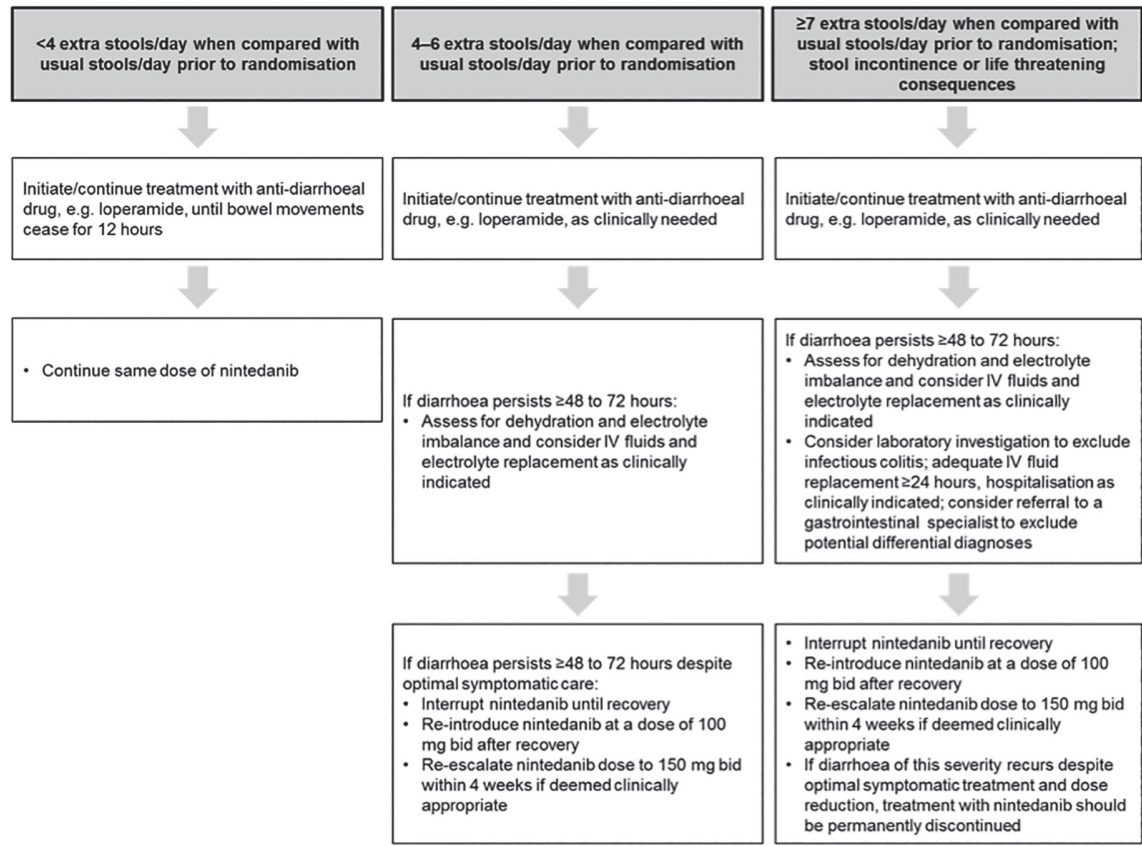
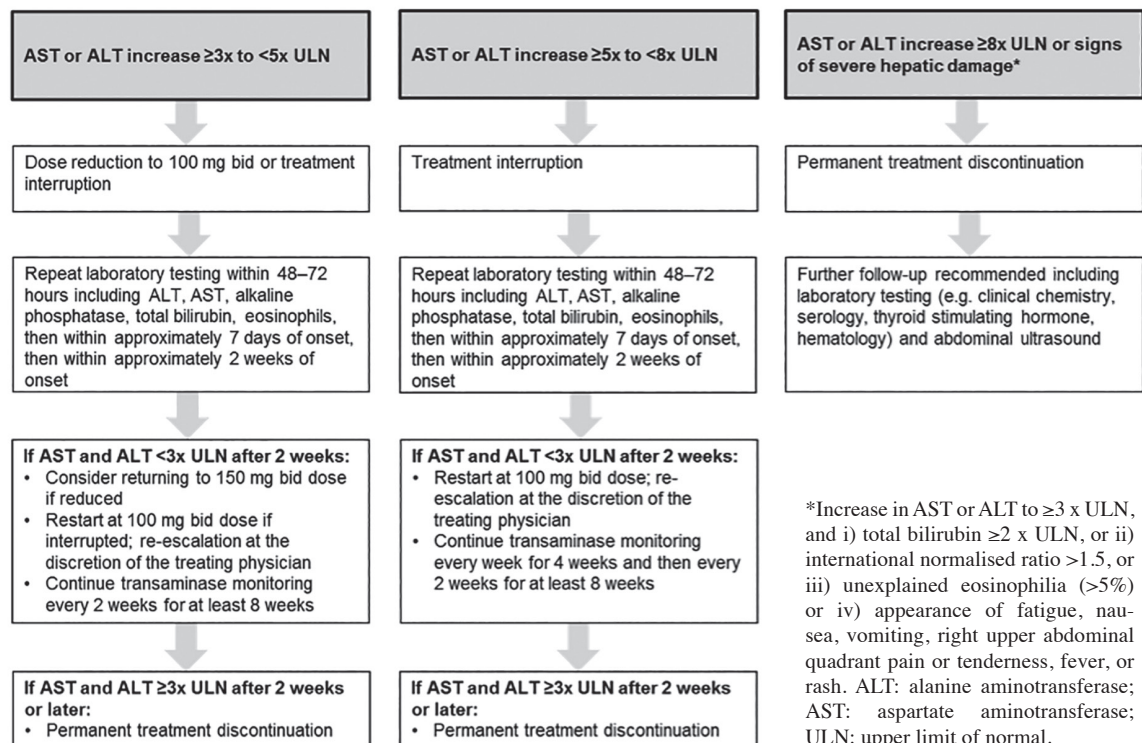


Fig. 3. Recommendations for management of hepatic enzyme elevations in the SENSICIS™ trial.



Discussion

Data from preclinical studies suggesting inhibitory effects of nintedanib on pathological processes active in SSc and ILD, as well as the established ef-

ficacy and safety of nintedanib in the treatment of IPF, provide a scientific rationale for the investigation of nintedanib as a treatment for SSc-ILD. The Phase III, multicentre, randomised,

placebo-controlled, SENSICIS™ trial will determine the efficacy and safety of nintedanib 150 mg bid in patients with SSc-ILD. As in the TOMORROW and INPULSIS® trials in patients with

IPF, the primary endpoint in the SENS-CIS™ trial is the annual rate of decline in FVC assessed over 52 weeks. Change in FVC has been widely used as an outcome in clinical trials in patients with SSc-ILD (9-11, 36) and the Outcome Measures in Rheumatology (OMERACT) CTD-ILD working group identified change in FVC as the preferred efficacy measure for clinical trials in patients with SSc-ILD with 1-year duration (37). The annual rate of decline in FVC uses all the FVC values collected during the trial, making this endpoint more robust than using only the FVC values at baseline and week 52. The option of a flexible dosing regimen, allowing treatment interruption and/or dose reduction from 150 mg bid to 100 mg bid for the management of adverse events, has been provided to reduce permanent treatment discontinuations. As in the INPULSIS® trials, patients who prematurely discontinue trial medication will be asked to attend all visits as planned to minimise missing data.

The effect of nintedanib on skin will be investigated using the mRSS, a frequently used and reproducible measure of skin fibrosis in patients with SSc (32, 38), which has been shown to correlate with skin thickness in biopsies (39). Changes in HRQL will be assessed using the SGRQ. Although originally developed for use in patients with chronic obstructive pulmonary disease and asthma, the SGRQ has been shown to have acceptable psychometric properties in patients with IPF (40,41), has demonstrated construct validity in patients with SSc-ILD (42), and has been endorsed by the OMERACT CTD-ILD working group to measure HRQL in clinical trials in SSc-ILD (37). In addition to these key secondary endpoints, results from a large number of exploratory endpoints will provide insights into the effects of nintedanib in patients with SSc-ILD and the clinical course of the disease.

Conclusions

The Phase III, multicentre, randomised, placebo-controlled SENS-CIS™ trial is evaluating the efficacy and safety of nintedanib in patients with SSc-ILD.

The results of this study will illuminate the effects of nintedanib on a number of clinically relevant outcomes in patients with SSc-ILD, a disease for which there are currently no licensed treatments. In addition, the SENS-CIS™ trial will provide a wealth of data on the clinical course of SSc-ILD and its impact on patients.

Acknowledgments

Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Julie Fleming and Wendy Morris of FleishmanHillard Fishburn, London, UK, during the preparation of this article. The authors were fully responsible for all content and editorial decisions, and were involved at all stages of manuscript development and have approved the final version.

Competing interests

O. Distler has/had provided consultancy to and/or received research funding from Actelion, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sanofi, Sinoxa and UCB in the area of potential treatments of SSc and its complications. He also has a patent mir-29 for the treatment of SSc.

K.K. Brown provided consultancy to Boehringer Ingelheim.

J.H.W. Distler has conducted preclinical studies with Boehringer Ingelheim. He is also a member of a speaker's bureau, has served on advisory boards and is the PI for Germany (SENS-CIS trial). S. Assassi has served on advisory boards and has received consultancy fees from Boehringer Ingelheim.

T. Maher is supported by a NIHR Clinician Scientist Fellowship (NIHR Ref: CS-2013-13-017). Relevant to this manuscript he has received fees for consultancy and speaking from Boehringer Ingelheim. He has also received industry academic research funding from GSK R&D, UCB and Novartis and has received fees for consultancy and speaking from AstraZeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, DOSA, Galapagos,

GSK R&D, ProMetic, Roche (and previously InterMune), Sanofi Aventis and UCB.

V. Cottin has received personal fees from Actelion, Boehringer Ingelheim, Bayer, Biogen Idec, Gilead, GSK, MSD, Novartis, Roche and Sanofi, and grants from Boehringer Ingelheim, GSK, Actelion, Roche and Promedior. J. Varga has received support for clinical trials from Boehringer Ingelheim.

C. Coeck, M. Gahlemann, W. Sauter, and H. Schmidt are employees of Boehringer Ingelheim, the sponsor of the study.

K.B. Highland is a member of a speaker's bureau and has received research funding from Boehringer Ingelheim.

References

- VARGA J, ABRAHAM D: Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest* 2007; 117: 557-67.
- STEEN VD, MEDSGER TA: Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; 66: 940-4.
- TYNDALL AJ, BANNERT B, VONK M *et al.*: Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69: 1809-15.
- STEELE R, HUDSON M, LO E *et al.*: Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. *Arthritis Care Res (Hoboken)* 2012; 64: 519-24.
- VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al.*: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.
- BARON M, SUTTON E, HUDSON M *et al.*: The relationship of dyspnoea to function and quality of life in systemic sclerosis. *Ann Rheum Dis* 2008; 67: 644-50.
- THEODORE AC, TSENG CH, LI N, ELASHOFF RM, TASHKIN DP: Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study. *Chest* 2012; 142: 614-21.
- KOWAL-BIELECKA O, LANDEWÉ R, AVOUAC J *et al.*: EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009; 68: 620-8.
- HOYLES RK, ELLIS RW, WELLSBURY J *et al.*: A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; 54: 3962-70.
- TASHKIN DP, ELASHOFF R, CLEMENTS PJ *et al.*: Cyclophosphamide versus placebo

- in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655-66.
11. TASHKIN DP, ROTH MD, CLEMENTS PJ *et al.*: Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708-19.
 12. KOWAL-BIELECKA O, FRANSEN J, AVOUAC J *et al.*: Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2016. Epub ahead of print.
 13. VAN LAAR JM, FARGE D, SONT JK *et al.*: Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014; 311: 2490-8.
 14. WEILL D, BENDEN C, CORRIS PA *et al.*: A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; 34: 1-15.
 15. HILBERG F, ROTH GJ, KRSSAK M *et al.*: BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res* 2008; 68: 4774-82.
 16. WOLLIN L, MAILLET I, QUESNIAUX V *et al.*: Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J Pharmacol Exp Ther* 2014; 349: 209-20.
 17. WOLLIN L, WEX E, PAUTSCH A *et al.*: Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1434-45.
 18. BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. (2014). OFEV™ (nintedanib) prescribing information. Available at: <http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ofev/ofev.pdf>. Accessed 1 June 2016.
 19. BOEHRINGER INGELHEIM (2015). OFEV (nintedanib) Summary of Product Characteristics. February 2015. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003821/human_med_001834.jsp&mid=WC0b01ac058001d124. Accessed 1 June 2016.
 20. RICHELDI L, COSTABEL U, SELMAN M *et al.*: Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365: 1079-87.
 21. RICHELDI L, DU BOIS RM, RAGHU G *et al.*: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071-82.
 22. USATEGUI A, DEL REY MJ, PABLOS JL: Fibroblast abnormalities in the pathogenesis of systemic sclerosis. *Expert Rev Clin Immunol* 2011; 7: 491-8.
 23. BAGNATO G, HARARI S: Cellular interactions in the pathogenesis of interstitial lung diseases. *Eur Respir Rev* 2015; 24: 102-14.
 24. SKHIRTLADZE C, DISTLER O, DEES C *et al.*: Src kinases in systemic sclerosis: central roles in fibroblast activation and in skin fibrosis. *Arthritis Rheum* 2008; 58: 1475-84.
 25. MAURER B, DISTLER A, SULIMAN YA *et al.*: Vascular endothelial growth factor aggravates fibrosis and vasculopathy in experimental models of systemic sclerosis. *Ann Rheum Dis* 2014; 73: 1880-7.
 26. DISTLER O, DISTLER JH, SCHEID A *et al.*: Uncontrolled expression of vascular endothelial growth factor and its receptors leads to insufficient skin angiogenesis in patients with systemic sclerosis. *Circ Res* 2004; 95: 109-16.
 27. ALLIPOUR BIRGANI S, MAILÄNDER M, WASLE I *et al.*: Efficient therapy of ischaemic lesions with VEGF121-fibrin in an animal model of systemic sclerosis. *Ann Rheum Dis* 2016; 75: 1399-406.
 28. HUANG J, BEYER C, PALUMBO-ZERR K *et al.*: Nintedanib inhibits fibroblast activation and ameliorates fibrosis in preclinical models of systemic sclerosis. *Ann Rheum Dis* 2016; 75: 883-90.
 29. IOANNOU M, PYRPASOPOULOU A, SIMOS G *et al.*: Upregulation of VEGF expression is associated with accumulation of HIF-1 α in the skin of naïve scleroderma patients. *Mod Rheumatol* 2013; 23: 1245-8.
 30. LIAKOULI V, CIPRIANI P, MARRELLI A *et al.*: Angiogenic cytokines and growth factors in systemic sclerosis. *Autoimmun Rev* 2011; 10: 590-4.
 31. ASSASSI S, SHARIF R, LASKY RE *et al.*: Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. *Arthritis Res Ther* 2010; 12: R166.
 32. CLEMENTS PJ, LACHENBRUCH PA, SEIBOLD JR *et al.*: Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. *J Rheumatol* 1993; 20: 1892-6.
 33. JONES PW, QUIRK FH, BAVEYSTOCK CM: The St George's Respiratory Questionnaire. *Respir Med* 1991; 85: 25-31.
 34. SCHMIDINGER M: Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. *EJC Suppl* 2013; 11: 172-91.
 35. CORTE T, BONELLA F, CRESTANI B *et al.*: Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. *Respir Res* 2015; 16: 116.
 36. KHANNA D, MITTOO S, AGGARWAL R *et al.*: Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) - Report from OMERACT CTD-ILD Working Group. *J Rheumatol* 2015; 42: 2168-71.
 37. SAKETKOO LA, MITTOO S, HUSCHER D *et al.*: Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. *Thorax* 2014; 69: 428-36.
 38. MERKEL PA, CLEMENTS PJ, REVEILLE JD *et al.*: OMERACT 6: Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. *J Rheumatol* 2003; 30: 1630-47.
 39. FURST DE, CLEMENTS PJ, STEEN VD *et al.*: The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. *J Rheumatol* 1998; 25: 84-8.
 40. SWIGRIS JJ, ESSER D, CONOSCENTI CS, BROWN KK: The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. *Health Qual Life Outcomes* 2014; 12: 124.
 41. SWIGRIS JS, ESSER D, WILSON H *et al.*: Psychometric properties of the St. George's Respiratory Questionnaire in patients with IPF. *Eur Respir J* 2017; 18: 49 (1).
 42. BERETTA L, SANTANIELLO A, LEMOS A *et al.*: Validity of the Saint George's Respiratory Questionnaire in the evaluation of the health-related quality of life in patients with interstitial lung disease secondary to systemic sclerosis. *Rheumatology (Oxford)* 2007; 46: 296-301.