Title

Risk of Malnutrition in Patients With Systemic Sclerosis-Associated Interstitial Lung Disease Treated With Nintedanib in the Randomized, Placebo-Controlled SENSCIS Trial.

Journal

Arthritis Care & Research, 75(12)

Authors

Volkmann, Elizabeth
McMahan, Zsuzsanna
Smith, Vanessa
et al.

Publication Date

2023-12-01

DOI

10.1002/acr.25176

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2023 December ; 75(12): 2501–2507. doi:10.1002/acr.25176.

Risk of malnutrition in patients with systemic sclerosis-associated interstitial lung disease treated with nintedanib

Elizabeth R. Volkmann, MD, MS[1], **Zsuzsanna H. McMahan, MD, MHS**[2], **Vanessa Smith, MD, PhD**[3], **Stéphane Jouneau, MD, PhD**[4,5], **Corinna Miede, MSc**[6], **Margarida Alves, MD**[7], **Ariane L. Herrick, MD, FRCP**[8] **on behalf of the SENSCIS trial investigators**

[1]Division of Rheumatology, University of California, David Geffen School of Medicine, Los Angeles, CA, USA;

[2]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, USA;

[3]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium and Department of Internal Medicine, Ghent University, Ghent, Belgium, and Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Center (IRC), Ghent, Belgium;

[4]Department of Respiratory Medicine, Competence Centre for Rare Pulmonary Diseases, CHU Rennes, Rennes, France;

[5]Univ Rennes, CHU Rennes, Inserm, EHESP, IRSET (Institut de recherche en santé, environnement et travail), Rennes, France;

[6]mainanalytics GmbH, Sulzbach (Taunus), Germany;

[7]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany;

[8]Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, and NIHR Manchester Biomedical Research Centre, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Address correspondence to: Elizabeth R. Volkmann, University of California, David Geffen School of Medicine, Los Angeles, USA; EVolkmann@mednet.ucla.edu.

ClinicalTrials.gov **identifier:** NCT02597933

Conflict of interest: Elizabeth R. Volkmann reports grants paid to her institution from Boehringer Ingelheim (BI), Forbius, Horizon, Kadmon, the National Heart, Lung, and Blood Institute, and Prometheus; consulting fees from BI, GlaxoSmithKline, Roche; and fees for speaking from BI. Zsuzsanna H. McMahan reports grants from the Jerome L. Greene Foundation, National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases, Rheumatology Research Foundation, and Scleroderma Research Foundation; consulting fees from Triangle Insights Group; fees for speaking from Medscape; support for accommodation and meeting registration for the American College of Rheumatology (ACR) annual meeting as an AMPC Clinical Chair; and is the Chair of Finance for the ACR (unpaid). Vanessa Smith reports grants paid to her institution from the Belgian Fund for Scientific Research in Rheumatic Diseases, BI, Janssen-Cilag; payment to her institution for her role as a senior clinical investigator of the Research Foundation—Flanders (Belgium) (FWO) [1.8.029.20N]; consulting fees from BI and Janssen-Cilag; fees for speaking from BI, Galapagos, Janssen-Cilag; support for travel to the ACR congress from BI; and holds unpaid leadership or fiduciary roles with the ACR, EULAR, ERN-ReCONNET, and SCTC. Stéphane Jouneau reports grants from AIRB, BI, LVL, Novartis, Roche; fees for speaking from AIRB, AstraZeneca, BI, Bristol Myers Squibb, Chiesi, Genzyme, GlaxoSmithKline, LVL, Novartis, Pfizer, Roche, Sanofi; support for attending meetings from AIRB, BI, Roche; and has participated on a Data Safety Monitoring Board or advisory board for BI, Novartis, Roche. Corinna Miede is an employee of mainanalytics GmbH, Sulzbach (Taunus), Germany, which was contracted by BI to assist with these analyses. Margarida Alves is an employee of BI. Ariane L. Herrick reports grants from Gesynta; consulting fees from Arena, BI, Camurus, CSL Behring, Gesynta, Galderma; and fees for speaking from Janssen.

Abstract

Objective: To assess adverse events in relation to baseline body mass index (BMI) and the risk of malnutrition in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) treated with nintedanib.

Methods: Among patients with SSc-ILD randomized to receive nintedanib or placebo in the SENSCIS trial, we assessed adverse events in subgroups by baseline BMI ≤20 and >20 kg/m^2, and the risk of malnutrition using a modified version of the Malnutrition Universal Screening Tool (MUST), over 52 weeks.

Results: The adverse event profile of nintedanib was similar between subgroups with baseline BMI ≤20 kg/m^2 (n=61) and >20 kg/m^2 (n=515). In these subgroups, respectively, adverse events led to treatment discontinuation in 16.7% and 15.9% of the nintedanib group and 13.5% and 8.0% of the placebo group. Based on the modified MUST, the proportions of patients who had a low risk of malnutrition at baseline and at their last assessment were 74.0% in the nintedanib group and 78.1% in the placebo group, while the proportions who were classified as at low risk at baseline but at high risk by their last assessment were 4.5% in the nintedanib group and 1.0% in the placebo group.

Conclusion: In the SENSCIS trial, most patients with SSc-ILD remained at low risk of malnutrition over 52 weeks, but the proportion at high risk was higher in patients treated with nintedanib than placebo. Management of disease manifestations and adverse events that may be associated with weight loss is important to reduce the risk of malnutrition in patients with SSc-ILD.

INTRODUCTION

Systemic sclerosis (SSc) is a complex and heterogeneous autoimmune disease characterized by immune dysregulation and progressive fibrosis of the skin and internal organs (1). Gastrointestinal involvement is common in patients with SSc and can lead to a myriad of symptoms, including reflux, nausea, bloating, diarrhoea and/or constipation (2–5). Among 402 patients with SSc at a UK hospital, 94% reported upper gastrointestinal symptoms and 79% reported lower gastrointestinal symptoms (2). Gastrointestinal complications and increased disease severity are associated with an increased risk of weight loss and malnutrition (6–9). Malnutrition has also been associated with increased mortality in patients with SSc (10–12), but it is unclear to what extent this reflects a direct impact of malnutrition on the risk of mortality versus the higher prevalence of malnutrition in patients with greater disease severity.

In addition to the underlying SSc, some of the drugs used to treat SSc or SSc-associated interstitial lung disease (SSc-ILD) are associated with gastrointestinal adverse events (13–16). The adverse event profile of nintedanib, which is licensed for the treatment of SSc-ILD, as well as for idiopathic pulmonary fibrosis (IPF) and progressive fibrosing ILDs of any aetiology, is characterized mainly by gastrointestinal adverse events, particularly diarrhoea (17–19). In the randomized, placebo-controlled SENSCIS trial of nintedanib in patients with SSc-ILD, a greater proportion of patients treated with nintedanib than placebo reported diarrhoea over 52 weeks (76% vs 32%) (15). Most cases of diarrhoea were of mild or

moderate intensity and did not lead to permanent discontinuation of nintedanib (18). It remains unclear whether treatment with nintedanib is associated with an increased risk of malnutrition in patients with SSc-ILD. Thus, we performed a post-hoc analysis of data from the SENSCIS trial to evaluate the risk of malnutrition over 52 weeks of treatment using a screening tool, and to assess adverse events in subgroups by body mass index (BMI) at baseline.

PATIENTS AND METHODS

The design of the SENSCIS trial has been described and the protocol is publicly available (15). Briefly, eligible patients had SSc with their first non-Raynaud symptom in the prior ≤7 years, extent of fibrotic ILD (assessed in the whole lung) of ≥10% on high-resolution computed tomography (HRCT), forced vital capacity (FVC) ≥40% predicted, and diffusing capacity of the lung for carbon monoxide (DLco) 30–89% predicted. Patients taking prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months were allowed to participate. Patients were randomized 1:1 (stratified by the presence of anti-topoisomerase I antibody) to receive nintedanib 150 mg twice daily (bid) or placebo until the last patient had reached week 52 but for ≤100 weeks. Treatment interruptions (for ≤4 weeks for adverse events considered related to trial medication or ≤8 weeks for other adverse events) and dose reductions to 100 mg bid were allowed to manage adverse events. After resolution of the adverse event, treatment could be reintroduced or the dose increased back to 150 mg bid. For diarrhoea with an increase of <4 stools per day, anti-diarrhoeal medicines were recommended; for diarrhoea with an increase of 4 to 6 stools per day that persisted despite symptomatic care, or with an increase of ≥7 stools per day, incontinence, or life-threatening consequences, treatment interruption and/or dose adjustment was recommended (in addition to symptomatic care) (18).

Adverse events were reported by the investigators irrespective of causality and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Weight was measured at baseline and at weeks 2, 4, 6, 12, 24, 36 and 52. A modified version of the Malnutrition Universal Screening Tool (MUST), a tool developed to identify adults at risk of malnutrition (20), was used to assess the risk of malnutrition at baseline and weeks 12, 24, 36 and 52. The MUST, which takes account of BMI, unplanned weight loss, and acute disease likely to affect nutritional intake, has been used to assess the risk of malnutrition in several studies in patients with SSc (6,9,11,21) and has been recommended for this purpose by expert groups (22,23). In the modified MUST, we calculated scores using BMI, weight loss and a surrogate for acute disease effect (any serious adverse event that led to hospitalization between weight assessments and for which the patient received medication from the WHO classification code “solutions for parenteral nutrition” for ≥5 days) (Figure 1). At baseline, the modified MUST score was based solely on BMI, as no data were available to assess weight loss and acute disease effect. The MUST score ranged from 0 to 6. As in the original MUST, we regarded scores of 0, 1 and ≥2 as indicating a low, medium and high risk of malnutrition, respectively.

To investigate whether adverse events were reported more frequently in patients with a low BMI at baseline, we assessed adverse events reported over 52 weeks in subgroups by

baseline BMI ≤20 and >20 kg/m^2. We assessed mean MUST scores; the proportions of patients at low, medium and high risk of malnutrition based on MUST scores at baseline and weeks 12, 24, 36 and 52; and the risk of malnutrition based on MUST scores at baseline and at last assessment. All analyses were descriptive and performed in patients who received ≥1 dose of trial drug.

The SENSCIS trial was carried out in compliance with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation. The trial was performed at 194 sites in 32 countries and was approved by an independent ethics committee or institutional review board at every site. The sites are listed in Section A of the supplementary appendix to the primary manuscript on the trial results (15). Patients provided written informed consent before trial entry.

RESULTS

Characteristics of subgroups by BMI at baseline

Among 576 patients, 61 patients (10.6%) had a BMI ≤20 kg/m^2 at baseline. Compared with patients with a baseline BMI >20 kg/m^2 at baseline, those with BMI ≤20 kg/m^2 had a lower mean age (48.6 vs 54.6 years) and a higher (worse) mean modified Rodnan skin score (16.1 vs 10.5). A greater proportion of patients with a baseline BMI ≤20 kg/m^2 than >20 kg/m^2 were female (83.6% vs 74.2%) and had diffuse cutaneous SSc (62.3% vs 50.7%), while a lower proportion were taking mycophenolate (39.3% vs 49.5%) (Supplementary Table 1). The proportions of patients positive for anti-topoisomerase 1, anti-centromere, anti-nuclear, or anti-RNA polymerase III antibodies was similar between the subgroups (Supplementary Table 1). The proportions of patients with oesophageal or stomach involvement, constipation, diarrhoea, or hypertension at screening were lower or similar in those with BMI ≤20 kg/m^2 compared to BMI >20 kg/m^2 (Supplementary Table 2). Greater proportions of patients with BMI ≤20 kg/m^2 than >20 kg/m^2 had pulmonary hypertension, joint contractures, digital ulcers, friction rubs, and atrophy (Supplementary Table 2).

Adverse events in subgroups by BMI at baseline

The adverse event profile of nintedanib was similar between subgroups by BMI ≤20 and >20 kg/m^2 at baseline (Table 1). Diarrhoea was the most common adverse event, reported in 79.2% of patients with BMI ≤20 kg/m^2 and 75.4% of patients with BMI >20 kg/m^2 at baseline. The frequencies of nausea and vomiting were also similar between the subgroups by BMI. Weight loss adverse events were less frequent in patients with BMI ≤20 than >20 kg/m^2 (4.2% vs 12.5%), but abdominal pain was more frequent in patients with BMI ≤20 than >20 kg/m^2 (20.8% vs 10.6%). Serious adverse events were more frequent in patients with BMI ≤20 than >20 kg/m^2 (33.3% vs 23.1%). The frequencies of adverse events leading to dose reduction, and of adverse events leading to discontinuation of nintedanib, were similar in patients with BMI ≤20 and >20 kg/m^2 at baseline.

Modified MUST scores

In the nintedanib group, the mean ± SD MUST score increased (worsened) slightly from 0.3 ± 0.6 at weeks 12 and 24 to 0.4 ± 0.7 at weeks 36 and 52. In the placebo group, the mean ± SD MUST score was 0.2 ± 0.5 at weeks 12, 24 and 36 and 0.2 ± 0.6 at week 52.

At baseline, the proportions of patients at low, medium and high risk of malnutrition based on MUST score were 91.7%, 5.9% and 2.4% in the nintedanib group, and 87.2%, 8.0% and 4.9%, respectively, in the placebo group (Figure 2). Between week 12 and week 52, the proportions of patients classified as at low risk of malnutrition based on the MUST ranged from 72.9% to 81.8% in the nintedanib group and from 80.8% to 88.3% in the placebo group. Over the same period, the proportions of patients classified as at high risk of malnutrition ranged from 5.6% to 9.6% in the nintedanib group and from 4.3% to 5.4% in the placebo group (Figure 2).

MUST scores suggested that the proportion of patients who remained at low risk of malnutrition between baseline and their last measurement was numerically lower in the nintedanib group than in the placebo group (74.0% vs 78.1%) (Table 2). The proportion of patients who were at low risk of malnutrition at baseline and developed a high risk by their last measurement was higher in the nintedanib group than the placebo group (4.5% vs 1.0%) (Table 2).

Discussion

In these post-hoc analyses of data from the SENSCIS trial, the adverse event profile of nintedanib, including the frequency of adverse events leading to treatment discontinuation, were similar between patients with a low BMI (≤20 kg/m^2) and a higher BMI at baseline. Nintedanib was associated with an increased risk of gastrointestinal adverse events and weight loss versus placebo, but patients with a low BMI at baseline did not appear to be at a greater risk of experiencing these events. Based on a modified version of the MUST, most patients had a low risk of malnutrition at baseline. However, the proportion of patients who had a low risk of malnutrition at baseline and remained at low risk at their last assessment over 52 weeks was lower in patients treated with nintedanib versus placebo (74.0% vs 78.1%). The proportion of patients who were classified as at high risk of malnutrition at week 52 was greater in patients who received nintedanib than placebo (9.6% vs 5.4% at week 52). There is some evidence to suggest that the risks of various types of gastrointestinal involvement, and their severity, vary between patients with SSc with different characteristics related to sex (24,25), autoantibody profile (25–29), duration of SSc (25,27), SSc subtype (diffuse cutaneous SSc vs limited cutaneous SSc) (25,29), manifestations of SSc such as myopathy (24,25), and medication use (29,30). A number of factors have been associated with malnutrition in patients with SSc, such as a greater number of gastrointestinal complaints (6), the presence of oral aperture or microstomia (6,31), and greater disease severity (6,7,9). Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes such as fibroblast proliferation, migration and activation and the deposition of extracellular matrix (32,33). The exact mechanism/s by which nintedanib causes gastrointestinal side effects is unknown, but it may be that inhibition of the vascular endothelial growth factor receptor (VEGFR) causes morphometric changes in the bowel

mucosa, altering motility (34). At present, it is not possible to predict gastrointestinal side effects, or their severity, in an individual patient treated with nintedanib.

Our findings illustrate the importance of monitoring for gastrointestinal problems, weight loss and malnutrition in patients with SSc-ILD who are treated with nintedanib and ensuring that patients receive nutritional counselling when needed. Indeed, monitoring weight and nutritional status should be part of the care of all patients with SSc (22,23,35,36). An expert panel recommended that all patients with SSc be screened for malnutrition using a tool such as the MUST, combined with laboratory tests and detailed questioning of the patient about gastrointestinal problems, and that patients with SSc should weigh themselves monthly (22). Patients with SSc-ILD treated with nintedanib should be informed about the risk of gastrointestinal side-effects and how these should be managed through dose adjustment, treatment interruption, and/or the use of therapies to relieve symptoms. Involvement of a gastroenterology team may be helpful, particularly when it is unclear whether gastrointestinal symptoms are due to the underlying SSc, comorbidities, or medication use (37).

Previous analyses of data from the SENSCIS trial suggested that gastrointestinal adverse events associated with nintedanib were not more frequent in patients with a predisposition to gastrointestinal problems based on medical history and/or the presence of certain gastrointestinal problems at baseline (18). Further, although mycophenolate may be associated with gastrointestinal side-effects, the proportion of patients with gastrointestinal adverse events, and the proportion who prematurely discontinued nintedanib, were similar between patients taking and not taking mycophenolate at baseline (16). Analyses of pooled data from clinical trials of nintedanib in patients with a variety of ILDs have indicated that its adverse event profile is generally similar between male and female patients, but that nausea, vomiting and hepatic adverse events, and the use of dose reductions and treatment interruptions to manage adverse events, are more frequent in female patients (38). Weight loss associated with nintedanib therapy does not appear to be a greater problem in patients with SSc-ILD than in patients with other ILDs. The proportion of nintedanib-treated patients who experienced weight loss adverse events over 52 weeks of the SENSCIS trial (11.8%) (15) was similar to that observed in the INPULSIS trials in patients with IPF (9.7%) (17) and the INBUILD trial in patients with progressive fibrosing ILDs other than IPF (12.3%) (39). Data from the open-label extension of the SENSCIS trial, SENSCIS-ON, suggest that the safety and tolerability profile of nintedanib, including the risk of weight loss, is similar over longer-term use (40,41).

Strengths of our analyses include the large cohort of patients included and the standardization of data collection in the setting of a clinical trial. Limitations of our analyses include that they were *post-hoc* and that the follow-up period was only 52 weeks so the long-term consequences of weight loss or malnutrition could not be assessed. Information on weight loss and nutritional status prior to inclusion in the trial were not available. The number of patients with BMI ≤20 kg/m^2 at baseline was quite small (n=61). The MUST was not developed to evaluate the risk of malnutrition in patients with SSc. Tools developed specifically for patients with SSc, such as the PREdictor of MAlnutrition in Systemic Sclerosis (PREMASS) score (42), may be valuable for future research.

In conclusion, in the SENSCIS trial in patients with SSc-ILD, the adverse event profile of nintedanib was similar between subgroups by BMI ≤20 and >20 kg/m^2 at baseline. Scores based on a modified MUST indicated that most patients remained at low risk of malnutrition over 52 weeks of treatment, but the proportion of patients who were classified as at high risk of malnutrition was higher in patients treated with nintedanib than placebo. Management of disease manifestations and gastrointestinal adverse events that may be associated with weight loss is important to reduce the risk of malnutrition in patients with SSc-ILD treated with nintedanib.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the patients who participated in the SENSCIS trial. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment for development of this manuscript. Elizabeth Ng and Wendy Morris of FleishmanHillard, London, UK, provided writing assistance, which was contracted and funded by BI. BI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Funding:

The SENSCIS trial was supported by Boehringer Ingelheim International GmbH

Data availability

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, BI grants all external authors access to relevant clinical study data. In adherence with the BI Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use https://vivli.org/ to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Significance and Innovations

- Nintedanib is a licensed treatment for SSc-ILD that may be associated with gastrointestinal adverse events.
- In patients with SSc-ILD, the adverse event profile of nintedanib was similar between subgroups by body mass index (BMI) ≤20 and >20 kg/m^2 at baseline.
- Based on a modified version of the Malnutrition Universal Screening Tool (MUST), the proportion of patients classified as having a high risk of malnutrition over 52 weeks was small, but was greater in patients treated with nintedanib than placebo.
- These findings highlight the importance of managing disease manifestations and gastrointestinal adverse events that may be associated with weight loss in patients with SSc-ILD.

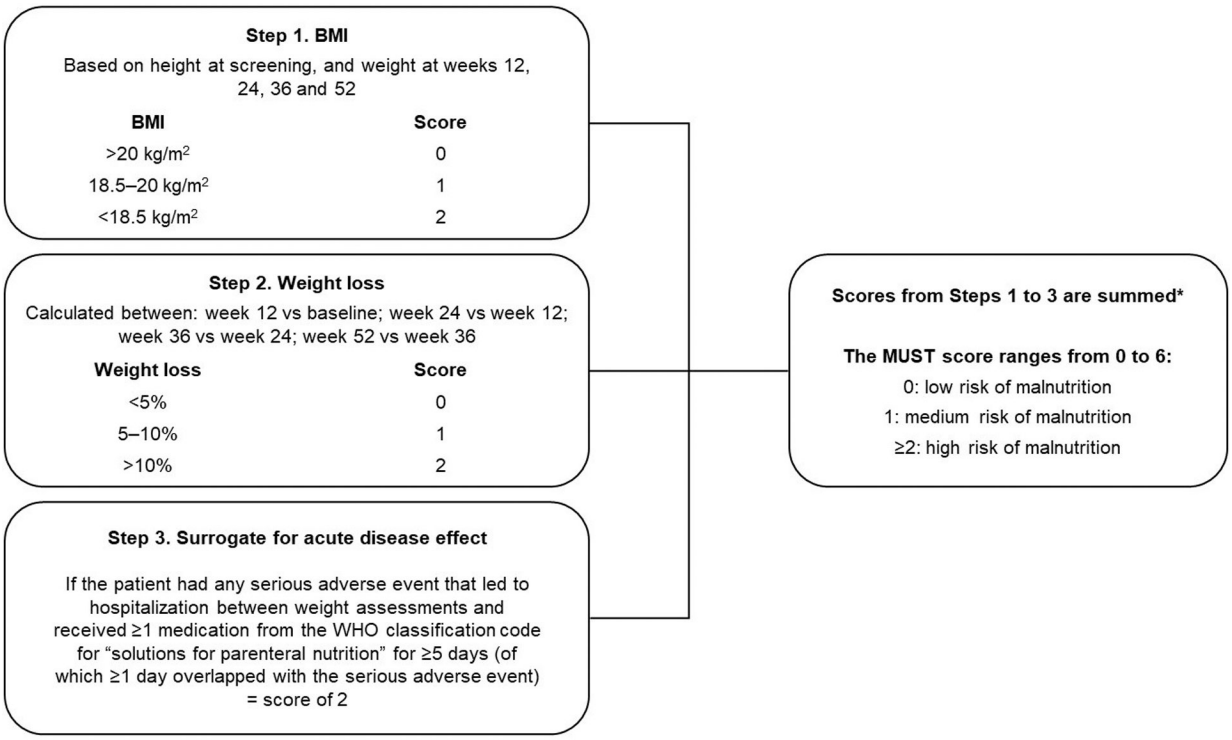

Figure 1.
The modified Malnutrition Universal Screening Tool (MUST).

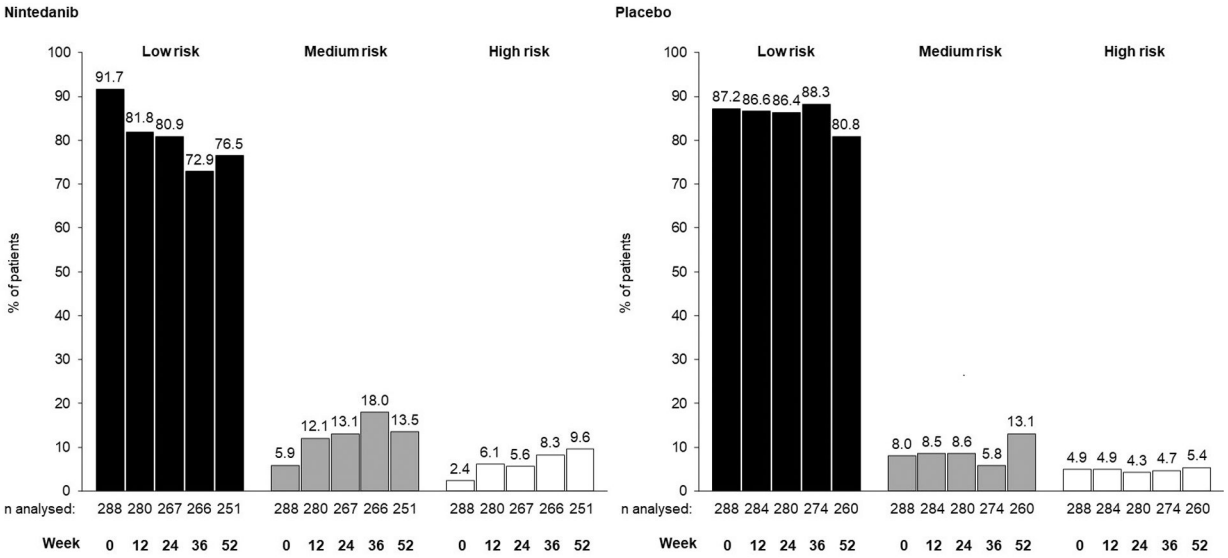

Figure 2.

Risk of malnutrition based on a modified Malnutrition Universal Screening Tool (MUST) at baseline and weeks 12, 24, 36 and 52 in the SENSCIS trial.

Table 1.

Adverse events in subgroups by body mass index (BMI) at baseline in the SENSCIS trial

	BMI ≤20 kg/m^2		BMI >20 kg/m^2	
	Nintedanib (n=24)	**Placebo (n=37)**	**Nintedanib (n=264)**	**Placebo (n=251)**
Any adverse event(s)	24 (100)	34 (91.9)	259 (98.1)	242 (96.4)
Most frequent adverse events*				
Diarrhoea	19 (79.2)	8 (21.6)	199 (75.4)	83 (33.1)
Nausea	6 (25.0)	1 (2.7)	85 (32.2)	38 (15.1)
Vomiting	5 (20.8)	2 (5.4)	66 (25.0)	28 (11.2)
Skin ulcer	10 (41.7)	13 (35.1)	43 (16.3)	37 (14.7)
Cough	1 (4.2)	5 (13.5)	33 (12.5)	47 (18.7)
Nasopharyngitis	3 (12.5)	3 (8.1)	33 (12.5)	46 (18.3)
Upper respiratory tract infection	3 (12.5)	6 (16.2)	30 (11.4)	29 (11.6)
Abdominal pain	5 (20.8)	2 (5.4)	28 (10.6)	19 (7.6)
Fatigue	1 (4.2)	0	30 (11.4)	20 (8.0)
Weight decreased	1 (4.2)	0	33 (12.5)	12 (4.8)
Adverse event(s) leading to treatment discontinuation	4 (16.7)	5 (13.5)	42 (15.9)	20 (8.0)
Adverse event(s) leading to dose reduction	9 (37.5)	2 (5.4)	89 (33.7)	8 (3.2)
Serious adverse event(s)†	8 (33.3)	8 (21.6)	61 (23.1)	54 (21.5)
Fatal adverse event(s)	2 (8.3)	2 (5.4)	3 (1.1)	2 (0.8)

Values are number (%) of patients with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52).

*Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities. Adverse events reported in >10% of patients in either treatment group in the overall population are shown.

†Event that resulted in death, was life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed serious for any other reason.

Table 2.

Risk of malnutrition based on a modified Malnutrition Universal Screening Tool (MUST) at baseline and at last assessment over 52 weeks in the SENSCIS trial.

		Nintedanib				Placebo			
		Baseline risk				Baseline risk			
		Low	Medium	High	Total	Low	Medium	High	Total
Last assessment of risk	Low	213 (74.0)	1 (0.3)	0	214 (74.3)	225 (78.1)	7 (2.4)	0	232 (80.6)
	Medium	31 (10.8)	8 (2.8)	0	39 (13.5)	20 (6.9)	14 (4.9)	4 (1.4)	38 (13.2)
	High	13 (4.5)	8 (2.8)	7 (2.4)	28 (9.7)	3 (1.0)	2 (0.7)	10 (3.5)	15 (5.2)
	Missing	7 (2.4)	0	0	7 (2.4)	3 (1.0)	0	0	3 (1.0)
	Total	264 (91.7)	17 (5.9)	7 (2.4)	288 (100)	251 (87.2)	23 (8.0)	14 (4.9)	288 (100)

Values are number (%) of patients.