lung function is impaired. It is unclear whether the presence of dyspnoea is associated with a worse course of SSc-ILD or with response to therapy.

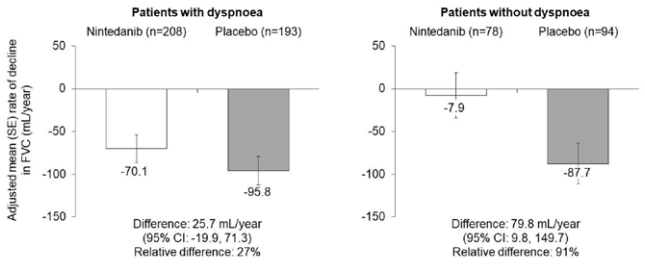
Objectives: To investigate the rate of decline in FVC in patients with SSc-ILD in the SENSCIS trial in subgroups by patient-reported dyspnoea at baseline.

Methods: The SENSCIS trial enrolled patients with SSc-ILD with first non-Raynaud symptom within ≤7 years before screening, extent of fibrotic ILD ≥10% on HRCT and FVC ≥40% predicted. Patients were randomised to receive nintedanib or placebo until the last patient reached week 52. In post-hoc analyses, we analysed the rate of decline in FVC (mL/year) over 52 weeks in patients with and without dyspnoea at baseline based on the question about dyspnoea in the St. George's Respiratory Questionnaire (SGRQ). Patients who reported having shortness of breath "most days a week", "several days a week" or "a few days a month" (rather than "only with chest infection" or "not at all") over the last month were considered to have dyspnoea at baseline. A random slope and intercept model was used to assess the rate of decline in FVC (mL/year) and an interaction test was applied to assess potential heterogeneity in the treatment effect of nintedanib between the subgroups.

Results: Of 576 patients, 69.8% had dyspnoea at baseline. At baseline, in patients with and without dyspnoea, respectively, mean (SD) extent of fibrotic ILD on HRCT was 37.7 (21.7)% and 31.6 (19.4)%; mean (SD) FVC was 71.0 (16.3) and 76.5 (16.8) % predicted; 50.7% and 44.8% were taking mycophenolate; 53.5% and 41.9% were taking corticosteroids. In the placebo group, the rate of decline in FVC (mL/year) was similar in patients with and without dyspnoea at baseline (Figure). The effect of nintedanib versus placebo on reducing the rate of decline in FVC (mL/year) was numerically more pronounced in patients without dyspnoea (difference: 79.8 [95% CI: 9.8, 149.7]) than with dyspnoea (difference: 25.7 [-19.9, 71.3]), but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect between subgroups (p=0.20).

Conclusion: In the SENSCIS trial, patients with SSc-ILD who had dyspnoea at baseline had a numerically greater extent of fibrotic ILD on HRCT and numerically lower FVC % predicted at baseline. The rate of decline in FVC in the placebo group was similar in patients with and without dyspnoea. Nintedanib had a numerically greater treatment effect in patients without dyspnoea. These data suggest that the presence of dyspnoea should not be used as a criterion for starting nintedanib in patients with SSc-ILD.

Figure. Rate of decline in FVC (mL/year) over 52 weeks in subgroups by dyspnoea at baseline in the SENSCIS trial.



Treatment-by-time-by-subgroup interaction p=0.20.
The presence of dyspnoea was based on this question from the St George's Respiratory Questionnaire: "Over the last month, I have had shortness of breath:". Patients who ticked boxes for "most days a week", "several days a week" or "a few days a month" were considered to have dyspnoea.

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OP0171 PHASE 3 TRIAL OF LENABASUM, A CB2 AGONIST, FOR THE TREATMENT OF DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (DCSSC)

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Background: Lenabasum is an oral CB2 agonist that attenuates inflammation and fibrosis in SSc animal models and showed clinical benefit with acceptable safety in a Phase 2 trial in dcSSc.

Objectives: Test efficacy and safety of lenabasum in a Phase 3 trial in dcSSc.

Methods: Subjects ≥18 years old with disease duration ≤ 6 years were randomized 1:1:1 to lenabasum 5 mg, 20 mg, or placebo (PBO), all BID, with stable background immunosuppressant therapy (IST) allowed. The primary efficacy endpoint was ACR CRISS score, and secondary endpoints were ΔmRSS, ΔHAQ-DI, and ΔFVC, all at Week 52 for lenabasum 20 mg vs PBO.

Results: 363 adults were dosed; 37 (10%) stopped study drug early, with only 1 subject (PBO cohort) stopping due to adverse event (AE). Baseline demographics were similar among groups. Disease duration was ≤ 3 years in 60% and 66%, mean mRSS score was 22.0 and 23.3, and background IST was used by 89% and 84% of lenabasum 20 mg and PBO groups, respectively.

Safety results showed serious AEs and severe AEs occurred in 9.2% and 5.8% vs 14.6% and 13.0%, respectively, of lenabasum 20 mg and PBO groups.

Efficacy results (Table) demonstrated:

- No significant differences were seen in primary and secondary efficacy endpoints. Primary MMRM analyses with treatment-by-time-by-subgroup interactions showed that background mycophenolate (MMF) significantly influenced the outcome
- oSubjects on no IST with disease duration ≤3 years were only 7% of PBO subjects and showed little improvement on PBO, in line with other dcSSc trials in which IST was restricted. Post-hoc subgroup analyses of these subjects on no IST suggested improvement in ΔmRSS and ΔHAQ-DI, for lenabasum 20 mg vs PBO
- uUnexpectedly high improvement occurred in PBO subjects receiving IST, notably those on MMF started within 2 years of baseline
- nPost-hoc analyses of subjects on established IST (MMF or, if no MMF, ≥ 1 non-MMF IST started > 2 years before baseline)

Table 1. Primary and secondary efficacy endpoints and post-hoc analyses, Week 52

Group, by IST treatment	Cohort	N	ΔmRSS, mean (SD)	ΔFVC% mean (SD)	ΔFVC, mL mean (SD)	ΔHAQ-DI mean (SD)	ACR CRISS median
mITT population, MMRM primary analysis method							
All	Placebo	123	-8.1 (7.72)	-1.0 (8.68)	-51 (317)	-0.13 (0.468)	0.887
	Lenabasum 20 mg	120	-6.7 (6.59)	-1.6 (6.91)	-78 (265)	-0.13 (0.436)	0.888
Placebo subjects, per protocol completers, LOCF							
No IST	Placebo	16	-2.3 (9.4)	-2.8 (7.4)	-97 (244)	0.12 (0.34)	0.417
All IST	Placebo	97	-8.9 (7.07)	-1.0 (9.2)	-43 (330)	-0.17 (0.474)	0.936
MMF, no other IST	Placebo	29	-10.7 (8.1)	-0.58 (7.1)	-37 (235)	-0.12 (0.456)	0.935
MMF ≤ 2 years, no other IST	Placebo	23	-11.7 (8.1)	-0.3 (6.0)	-41 (197)	-0.13 (0.495)	0.935
Non-MMF ≤ 2 years	Placebo	24	-6.7 (6.2)	-1.4 (7.87)	-52 (281)	-0.15 (0.357)	0.931
Post-hoc comparisons, per protocol completers, LOCF							
No IST	Placebo	16	-2.3 (9.4)	-2.8 (7.4)	-97 (244)	0.12 (0.34)	0.417
	Lenabasum 20 mg	10	-6.3 (6.02)	-2.3 (5.58)	-99 (209)	-0.06 (0.498)	0.811
Established IST1	Placebo	26	-6.1 (5.35)	-4.6 (10.11)	-170 (350)	-0.17 (0.445)	0.619
	Lenabasum 20 mg	38	-7.4 (5.08)	0.4 (5.70)[2]	-21 (233)[3]	-0.07 (0.357)	0.941
Established IST, subjects with ILD	Placebo	22	-5.9 (5.28)	-3.7 (5.43)	-133 (206)	-0.10 (0.372)	0.553
	Lenabasum 20 mg	33	-7.2 (5.70)	-1.0 (10.5)	-47 (365)	-0.06 (0.391)	0.819

[2] P = 0.0386 two-sample t-test; [3] P = 0.0481 two-sample t-test; other comparisons were not significant

suggested improvement in ΔFVC% (nominal P = 0.0386) and ΔFVC mL (nominal P = 0.0481) for lenabasum 20 mg vs PBO. Improvement in FVC was also seen in subjects on established IST who had ILD at baseline, lenabasum 20 mg vs PBO

- mACR CRISS score demonstrated a ceiling effect and correlated most highly with ΔmRSS (r = -0.739) and moderately with MDGA (-0.432), HAQ-DI (-0.362), FVC% (0.366), and PtGA (-0.288)

Conclusion: Lenabasum was safely used in this study. Unexpectedly high improvement on background IST, especially MMF, has not been previously reported at this level. The primary endpoint was not met. Post-hoc analyses showed greater improvement in lenabasum- vs PBO-treated subjects who were not on background IST and those on established IST, including subjects with ILD.

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OP0172

BRENTUXIMAB VEDONTIN FOR SKIN INVOLVEMENT IN REFRACTORY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS, INTERIM RESULTS OF A PHASE IIB OPEN-LABEL TRIAL

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Background: Systemic sclerosis (SSc) is an autoimmune disease affecting multiple organs causing morbidity and mortality. Treatments targeting SSc skin often have limited success. The presence of CD30+ lymphocytes in skin biopsies and increased levels of serum CD30 have been reported in SSc patients[1]. This could constitute a new therapeutic target.

Objectives: To explore the efficacy and safety of brentuximab vedotin, a chimeric anti-CD30 antibody drug conjugate, in patients with severe active diffuse cutaneous SSc who failed multiple treatments.

Methods: This Phase IIb, single center, open-label, investigator-initiated trial will recruit 10 patients. Brentuximab vedotin 0.6 mg/Kg was infused intravenously every 3 weeks for 48 weeks. Inclusion criteria were age ≥18 years, meeting the 2013 ACR/EULAR SSc classification criteria, modified Rodnan skin score (mRSS) ≥15 with <5 years since the first non-Raynaud's symptom and/or skin worsening despite immunosuppression. Patients were allowed to continue their standard of care medications for SSc except for rituximab. Patients with severe cardiac or pulmonary SSc involvement, severe infections, significant peripheral neuropathy, or active malignancy were excluded. The primary objective was a decrease in mRSS of ≥8 at 48 weeks. The main secondary endpoint was MRSS at 24 weeks. Differences were assessed by paired t tests. Data were compared to 16 age, disease duration, mRSS and past/present use of immunosuppressors-matched controls (ratio 2-3:1) from the Canadian Scleroderma Research Group (CSRG) registry.

Results: Eight of 10 patients have been recruited to date; two are in the first 8 weeks and one was withdrawn at her request after developing influenza at week 12. Five subjects (60% female) have reached week 24, and 3 have completed 48 weeks. The mRSS is shown in Table 1. The ΔMRSS for patients treated with brentuximab between weeks 0 and 24 was 8.2 ([CI 95% 2.8, 13.6], p = 0.013) and from 0 to 48 was 15.3 ([CI 95% 8.2, 22.5], p = 0.012). Whereas, the ΔMRSS for the CSRG controls was 3.1 ([CI 95% -2, 8.2], p = 0.211) at 48 weeks. Assuming that mRSS would at least be the same from week 24 to 48 in the 2 cases who are between 24 and 48 weeks with brentuximab, we compared the 5 cases vs controls (Figure 1). ΔMRSS for Brentuximab was 12.2 ([CI 95% 5.9, 18.5], p = 0.006. No cases have developed a peripheral neuropathy and only one SAE (influenza).

Table 1.

N (SD)	N	Age	Disease duration	mRSS week 0	mRSS week 24	mRSS week 48	mRSS week 48**
Case	5	60.2 (9.3)	4.5 (2.1)	33 (5.2)	24.8 (6)	15.7 (3)	20.8 (8.3)
Control	16	58.5 (8.3)	4.9 (2.1)	31.3 (5.9)	N/D	28.1 (7.5)	28.1 (7.5)
p		0.731	0.775	0.559	N/D	0.013	0.079

mRSS = modified Rodnan skin score, N/D = no data, ** = comparisons including 5 cases, assuming stability in MRSS from week 24 to 48 in cases 5 and 6