EULAR Highlights: Systemische Sklerose

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RESOLVE-1, a Phase 3 Trial of Lenabasum, a CB2 Agonist, for the Treatment of Diffuse Cutaneous Systemic Sclerosis

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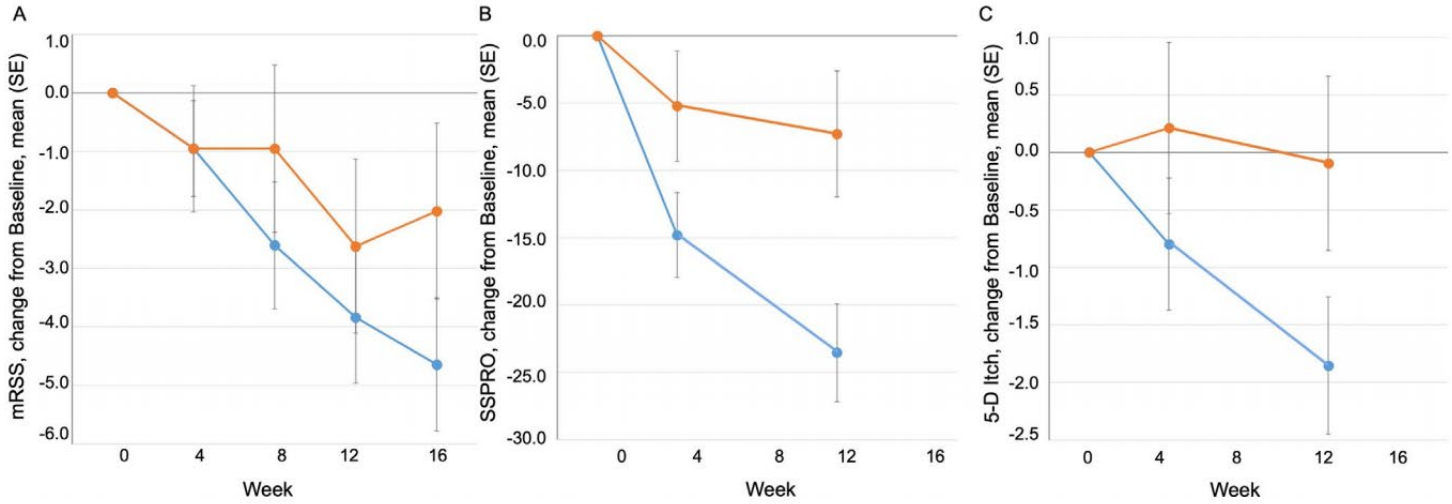
Safety and Efficacy of Lenabasum in a Phase II, Randomized, Placebo-Controlled Trial in Adults With Systemic Sclerosis

A randomized, double-blind, placebo-controlled, 9-center, multiple dose phase II study with 42 patients



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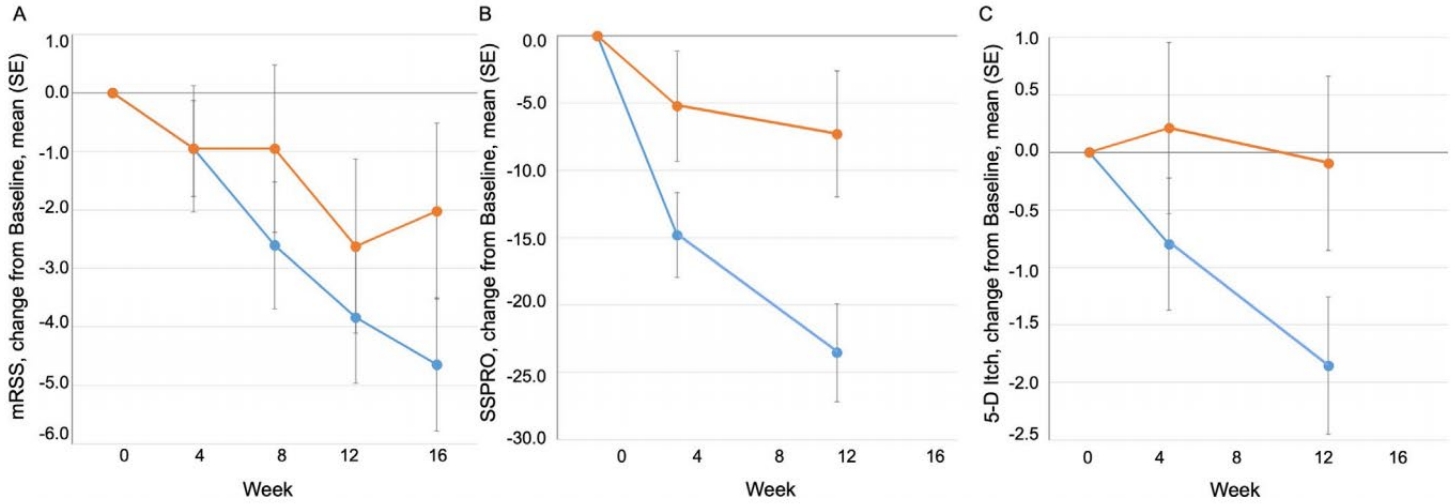

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RESOLVE-1 Phase 3 study design

PRIMARY EFFICACY ENDPOINT

ACR CRISS score

- Week 52
- Lenabasum 20 mg BID vs placebo

DESIGN

- Double-blind, randomized
- 365 dosed
- 52 weeks
- 76 sites in NA, Europe and Asia Pacific
- 1:1:1 central randomization
  - 20 mg BID
  - 5 mg BID
  - Placebo BID

SECONDARY ENDPOINTS

- Change in mRSS
- Change in HAQ-DI
- Change in FVC % predicted

ELIGIBILITY

- Diffuse cutaneous SSc
- Disease duration ≤ 6 years. If 3-6 years, then mRSS ≥ 15
- Background immunosuppressive therapies (IST) allowed if:
  - Stable for at least 8 weeks before screening
  - Corticosteroids not to exceed 10 mg prednisone per day or equivalent
- Decision to allo… immunosuppres… made to reflect … practice

Baseline disease characteristics and immunosuppressive treatments

Characteristics and treatments	Lenabasum 20 mg N = 120	Lenabasum 5 mg N = 120	Placebo N = 123
		N (%) or mean ± SD	
Disease characteristic			
Disease duration, months	32.7 (19.94)	32.2 (17.62)	30.2 (16.84)
mRSS (0 - 51)	22.1 ± 8.55	22.0 ± 7.35	23.3 ± 8.68
MDGA (0 - 10)	5.3 ± 1.46	5.4 ± 1.58	5.6 ± 1.71
HAQ-DI (0 - 3)	1.12 ± 0.782	1.07 ± 0.765	1.16 ± 0.768
PtGA (0 - 10)	5.0 ± 2.10	4.8 ± 2.16	5.0 ± 2.10
FVC, % predicted	81.3 ± 18.83	79.5 ± 16.13	78.9 ± 15.23
Immunosuppressive therapies (IST)			
Any	107 (89.2)	94 (78.3)	103 (83.7)
Mycophenolate	63 (52.5)	57 (47.5)	65 (52.8)
Corticosteroids	28 (23.3)	33 (27.5)	39 (31.7)
Methotrexate	26 (21.7)	24 (20.0)	19 (12.2)
Others	32 (26.7)	28 (23.3)	28 (22.0)
1 immunosuppressive therapy	69 (57.7)	56 (46.7)	61 (49.6)
≥ 2 immunosuppressive therapies	38 (31.7)	38 (31.7)	42 (34.1)
Treatment duration ≤ 2 years	67 (55.8)	59 (49.2)	72 (58.5)
Treatment duration > 2 years	41 (34.2)	35 (29.2)	31 (25.2)

Modified intent-to-treat (mITT) population.

Primary and secondary efficacy outcomes

Outcome	Lenabasum 20 mg BID N = 100	Lenabasum 5 mg BID N = 113	Placebo BID N = 115
Primary			
ACR CRISS Step 1 = 0	n = 1, 1 ILD	N = 4, 1 CHF, 3 ILD	N = 4, 1 renal crisis, 3 ILD
ACR CRISS score, median (IQR)	0.8880 (0.9360)	0.8270 (0.9180)	0.8870 (0.0710, 0.9990)
P-value - Ranked Score, MMRM	0.4972	0.3486	
Secondary			
Change in mRSS, mean (SD)	-6.7 (6.59)	-7.1 (6.24)	-9.1 (7.72)
Change in HAQ-DI, mean (SD)	-0.133 (0.4363)	-0.060 (0.3917)	-0.127 (0.4677)
Change in FVC, %, L, mean (SD)	-1.602 (6.9106)	-2.248 (6.2099)	-0.993 (8.6840)

Modified intent-to-treat (mITT) population. Missing visits or ACR CRISS score core items due to COVID-19 were imputed using LOCF. Other missing data for any core items were imputed using Markov Chain Monte Carlo multiple imputation technique prior to calculating the score, but missing visits are not imputed. Combined inference statistics. Each imputation was analyzed using mixed model repeated measures (MMRM) on the ranked ACR CRISS score with region, disease duration, baseline mycophenolate use, visit, treatment, and treatment-by-visit interaction as the fixed effects and baseline mRSS as a covariate. Secondary outcomes were similarly analyzed, but using MMRM without ranked score.

- **Improvement in placebo group far exceeded expectations based on literature and expert**
- **Unable to discern treatment effect on top of placebo effect**

Pre-specified analysis: Background mycophenolate (MMF) had statistically significant effect on ACR CRISS score

Pre-specified: Impact of pre-specified fixed effects on MMRM model for ACR CRISS score. Also prespecified analysis for each core item of ACR CRISS score

Effect	P value
Baseline MMF (Yes, No)	< 0.0177
Visit	< 0.0001
Baseline MMF*Visit	0.0290
Study drug treatment	0.8590
Study drug treatment*Visit	0.9980
Baseline mRSS (≤ 25, > 25)	0.4627
Region (US, non-US)	0.5395
Disease duration (≤ 2 years, > 2 years)	0.3946

Post-hoc observation: Efficacy was greater when duration of MMF treatment was shorter at baseline. All subjects.

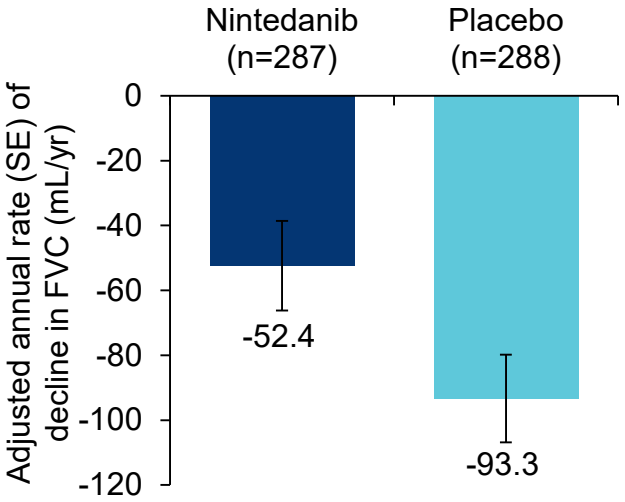
	N	ACR CRISS Score (IQR)	Change in mRSS (SD)
No IST	49	0.352 (0.001, 0.919)	-4.5 (6.75)
All MMF	173	0.936 (0.308, 0.999)	-8.61 (7.15)
≤ 6 months	51	0.992 (0.537, 1.000)	-10.8 (8.58)
≤ 1 year	95	0.975 (0.454, 1.000)	-9.9 (7.90)
≤ 2 years	112	0.956 (0.361, 1.000)	-9.3 (7.75)
> 2 years	57	0.856 (0.219, 0.989)	-7.1 (5.22)

Mycophenolate (MMF) – mycophenolate mofetil, mycophenolic acid, or mycophenolate sodium

- **MMF had statistically significant effect on ACR CRISS score that increased with visit. Other baseline factors of mRSS score, region, and disease duration did not have a statistically signifi ACR CRISS score**
- **Duration of MMF treatment influenced efficacy results, with lower ACR CRISS scores and ch with longer treatment duration (> 2 years at baseline)**

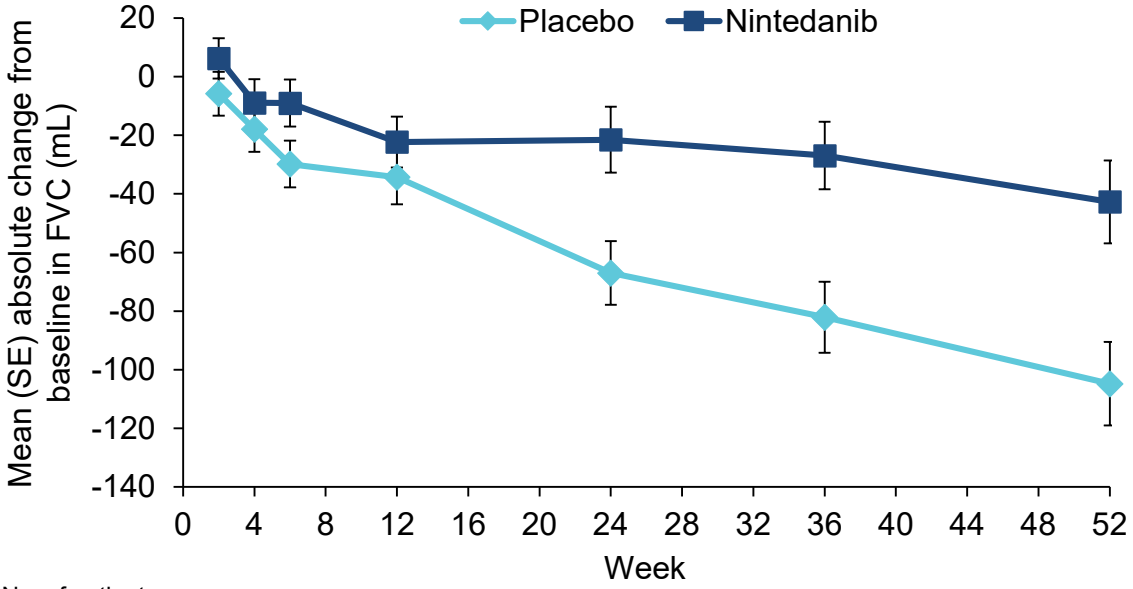
Senscis: Primary endpoint: Decline in FVC over 52 weeks

Annual rate of decline in FVC (mL/yr) (primary endpoint)



Difference: 41.0 mL/yr
(95% CI: 2.9, 79.0); p=0.04
Relative reduction: 44%

Change from baseline in FVC (mL) over 52 weeks



No. of patients

Nintedanib	288	283	281	273		278		265		262			241
Placebo	288	283	281	280		283		280		268			257

Distler O, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1903076.

Decline in forced vital capacity (FVC) in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) with and without dyspnoea: data from the SENSCIS trial

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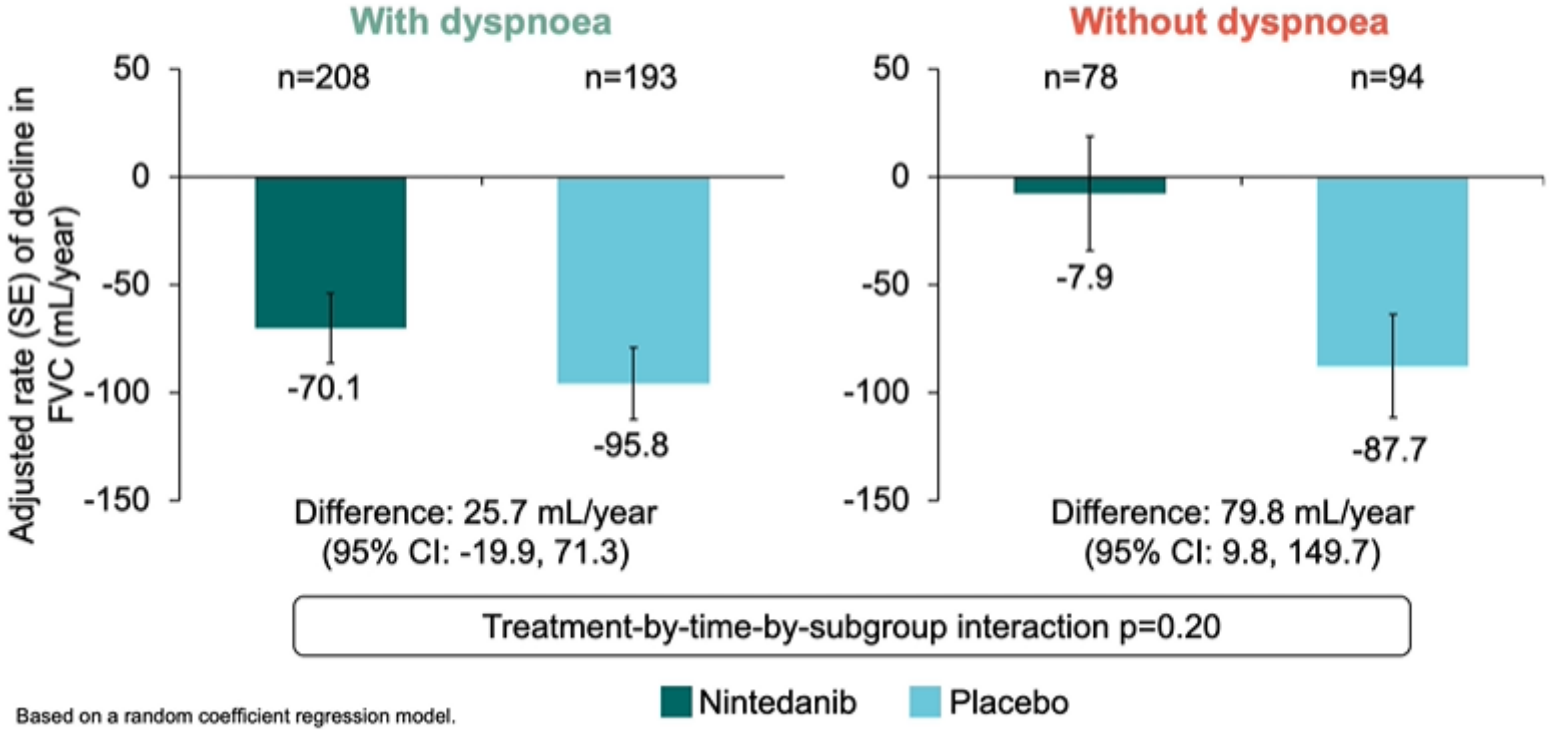
Subgroups by dyspnoea at baseline

Rate of decline in FVC (mL/year) over 52 weeks in subgroups by dyspnoea at baseline



Based on a random coefficient regression model.

Subclinical ILD is frequent and progresses across different connective tissue diseases

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Patient cohort and ILD definitions

All CTD patients, including **systemic sclerosis (SSc), anti-synthetase syndrome (ASS)** and **mixed connective tissue disease (MCTD)** from the Oslo University Hospital diagnosed were included and ILD assessed by semi-quantitative assessment[1]

Subclinical ILD

ILD extent <5% by semi-quantitative assessment

Preserved lung function with FVC >80% predicted

No respiratory symptoms

Clinical ILD

ILD extent >5% on HRCT

ILD extent <5% on HRCT

-with respiratory symptoms

-with FVC<80%

[1]Hoffmann-Vold et al. Arthritis Rheumatol. 2015 May;67(8):2205-12

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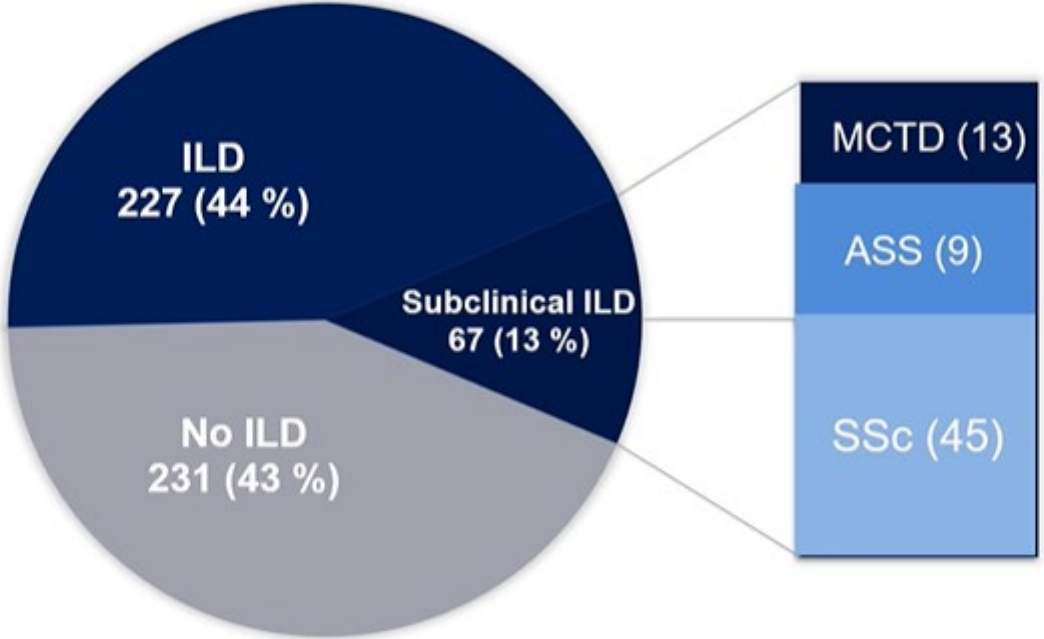
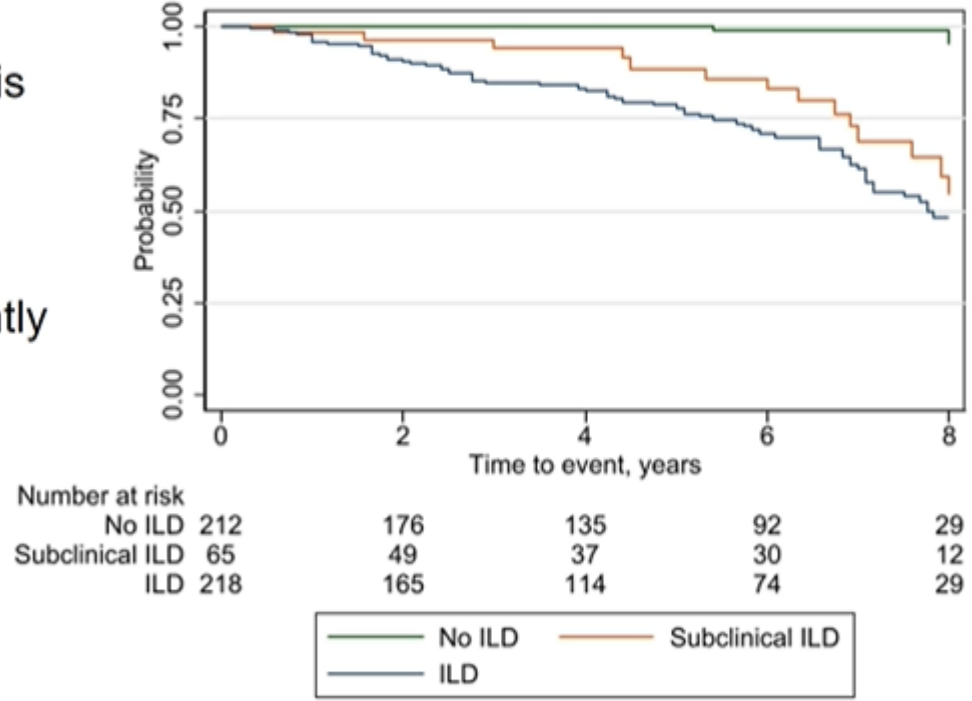
The prevalence of subclinical ILD varied between 10% in MCTD and ASS and 15% in SSc



Subclinical ILD progressed in 38% of patients with CTD

- Over a median time of 4.5 years 95/395 (24%) showed lung fibrosis progression
  - 72 (26%) SSc
  - 23 (19%) MCTD patients
- Disease progression was frequently present in
  - subclinical ILD (38%)
  - ILD (51%) patients



How should patients with SSc be screened for ILD?

Interdisciplinary consensus statements on SSc-ILD

All patients should be screened at baseline using HRCT[1–3]

Pulmonary function testing provides baseline parameters[4–6]

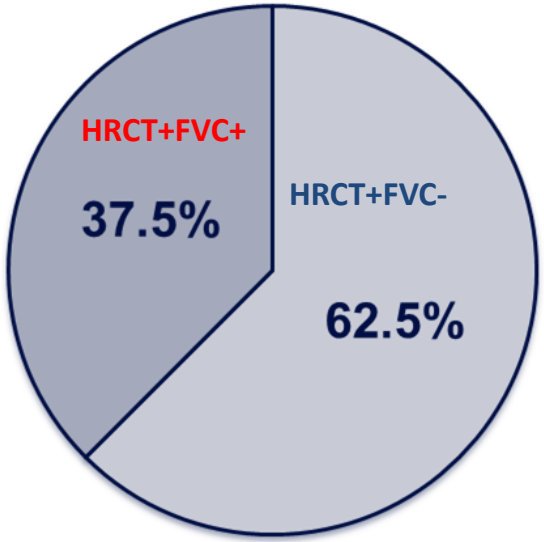
- Forced vital capacity (FVC)
- Diffusing capacity of the lungs for carbon monoxide (DL_{CO})
- Auscultation

Hoffmann-Vold et al, Lancet Rheum 2020

Pulmonary function testing alone misses the majority of patients with SSc-ILD

102 SSc patients (Zurich cohort)

- 64/102 (63%) with significant ILD on HRCT
- 27/102 (26%) with FVC <80% predicted
- 20/64 (38%) with significant ILD and FVC <80% predicted



Suliman YA, Dobrota R et al. Arthritis Rheumatol 2015

Take home messages SSc

- Lenabasum (Cannabinoid-Receptor-Agonist): After a successful phase 2 trial, a completely negative phase 3 trial is presented. Secondary analysis with effects of MMF on overall disease (CRISS).
- SSc patients with meaningful ILD do not need to be symptomatic.
- These «preclinical» ILD patients progress and respond to therapy similar to patients with symptoms
- Lung function is insufficient to detect ILD
- Therefore, all patients with SSc need to be screened with HRCT to detect ILD