Safety and Efficacy of Lenabasum in an Open-label Extension of a Phase 2 Study in Diffuse Cutaneous Systemic Sclerosis

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Abstract #OP0325

Disclosure of Robert Spiera

Research Support

- BMS
- Boehringer Ingelheim
- Chemocentryx
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- Cytori
- GSK
- Prism
- Roche-Genentech

Consulting

- Boehringer Ingelheim
- CSL Behring
- GSK
- Roche-Genentech

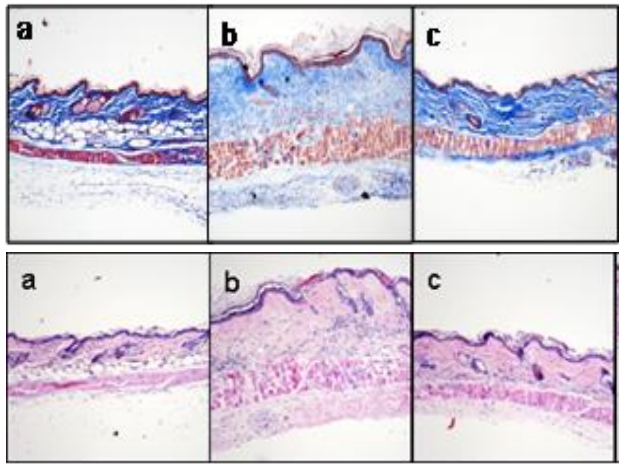
Endocannabinoid system (ECS)

Key Regulatory System

- The ECS regulates multiple physiologic functions including
  - Neurotransmission
  - Metabolism
  - Inflammation and wound healing
- Two key ECS receptors
  - Cannabinoid receptor type 1 (CB1) is highly expressed in the nervous system and also in multiple organs
  - Cannabinoid receptor type 2 (CB2) is preferentially expressed in active immune cells and hematopoietic cells
- Inflammation and fibrosis can be inhibited through CB1 inhibition or CB2 activation

Background

- Lenabasum is a preferential CB2 agonist that activates resolution of innate immune responses
- Lenabasum reduces inflammation and fibrosis in animal models of SSc and TGFβ and collagen production by isolated SSc fibroblasts



- Bleomycin intradermal injection every other day from Day 1 to Day 21
- Lenabasum administered once daily by gavage from Day 1 to Day 21

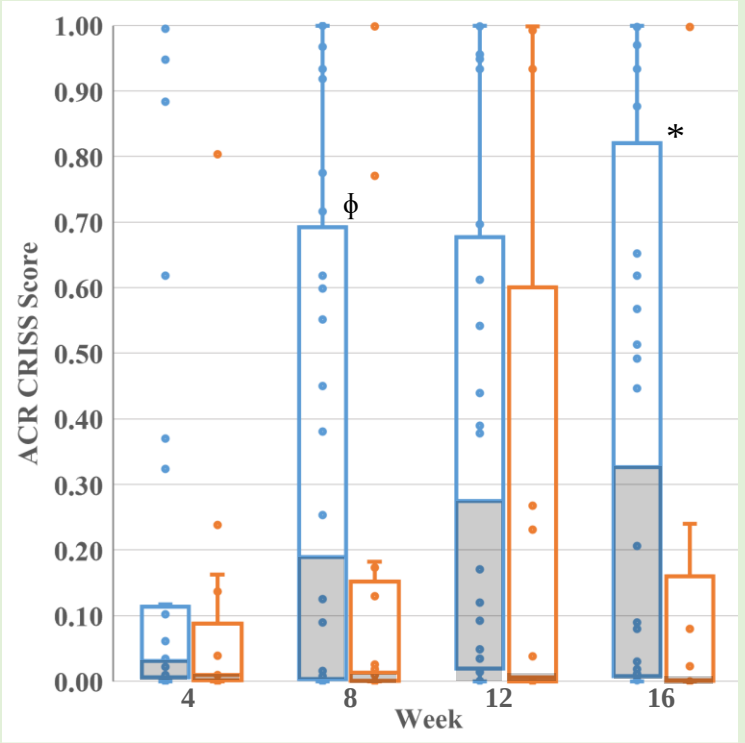
Data from John Varga

Phase 2 Study JBT101-SSc-001 of lenabasum in diffuse cutaneous SSc

Study Design

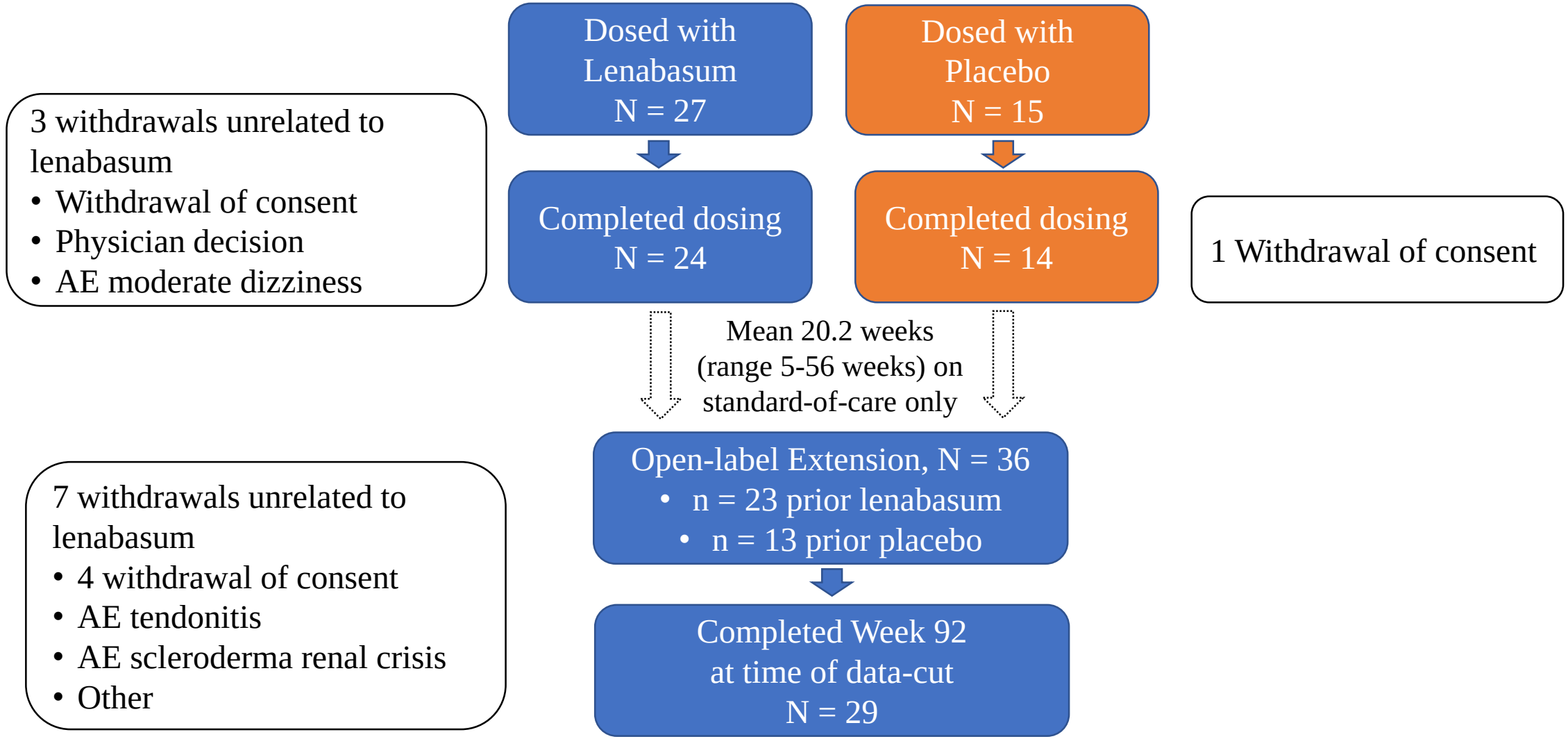
- dcSSc patients with disease duration ≤ 6 years on stable standard-of-care medications
- Initia16-week randomized, double-blinded, placebo-controlled (DBPC) part of study (Part A).
- In Part A, lenabasum treatment was associated with greater improvement than placebo in ACR CRISS scores, mRSS, patient-reported outcomes, histological inflammation and fibrosis, and gene transcripts in skin biopsies, and demonstrated acceptable safety and tolerability
- Subjects who completed the DBPC phase were offered lenabasum 20 mg BID in an open-label extension (OLE)
- In the OLE, safety and efficacy evaluations were done after 4 weeks, then every 8 weeks, with efficacy assessment every 16 weeks after Week 60
- Data through Week 92 of OLE will be presented

ACR CRISS Score during Part A



Whisker plot of ACR CRISS scores for individual participants by week. Orange = placebo; blue = lenabasum. The solid horizontal line within each whisker plot is the median value, and the grey shaded area includes all values from minimum through median

Subject disposition



Subject baseline demographics and disease characteristics in OLE

Characteristic	Open-label N = 36
Female, %	75%
Age, mean (SD)	48 (11.1)
Caucasian, %	83%
Disease duration, months, mean (SD)	41 (17.4)
Concomitant immunomodulating drugs, %	92%
Modified Rodnan skin score (mRSS), mean (SD)	20 (11.0)
Health Assessment Questionnaire Disability Index (HAQ-DI), mean (SD)	1.2 (0.8)
Physician Global Assessment, mean (SD)	4.4 (2.2)
Patient Global Assessment, mean (SD)	4.8 (2.8)
FVC % predicted, mean (SD)	83 (14.4)

Adverse events

- 35/36 (97%) of subjects had ≥ 1 AE during ≥ 92-weeks dosing the OLE, for a total of 249 AEs in the OLE through March 5, 2019

- **7 serious AEs**, all unrelated to lenabasum, occurred in 5 (14%) subjects: scleroderma renal crisis with thrombocytopenic microangiopathy related to high dose corticosteroids, iron deficiency anemia, multiple fractures, herpes zoster, and ischemic digital ulcers (n = 2).

- **AEs leading to study discontinuation**, both unrelated to lenabasum, occurred in 2 (6%) subjects: tendonitis and scleroderma renal crisis

- **AEs related to lenabasum** occurred in 7/36 (19%) subjects. Three (8%) subjects had AEs judged by the investigator to be probably or definitely related to lenabasum: 1 had mild fatigue, 1 had a moderate skin ulcer and moderate lymph node pain, and 1 had mild disturbance in attention, mild lethargy, and moderate feeling abnormal

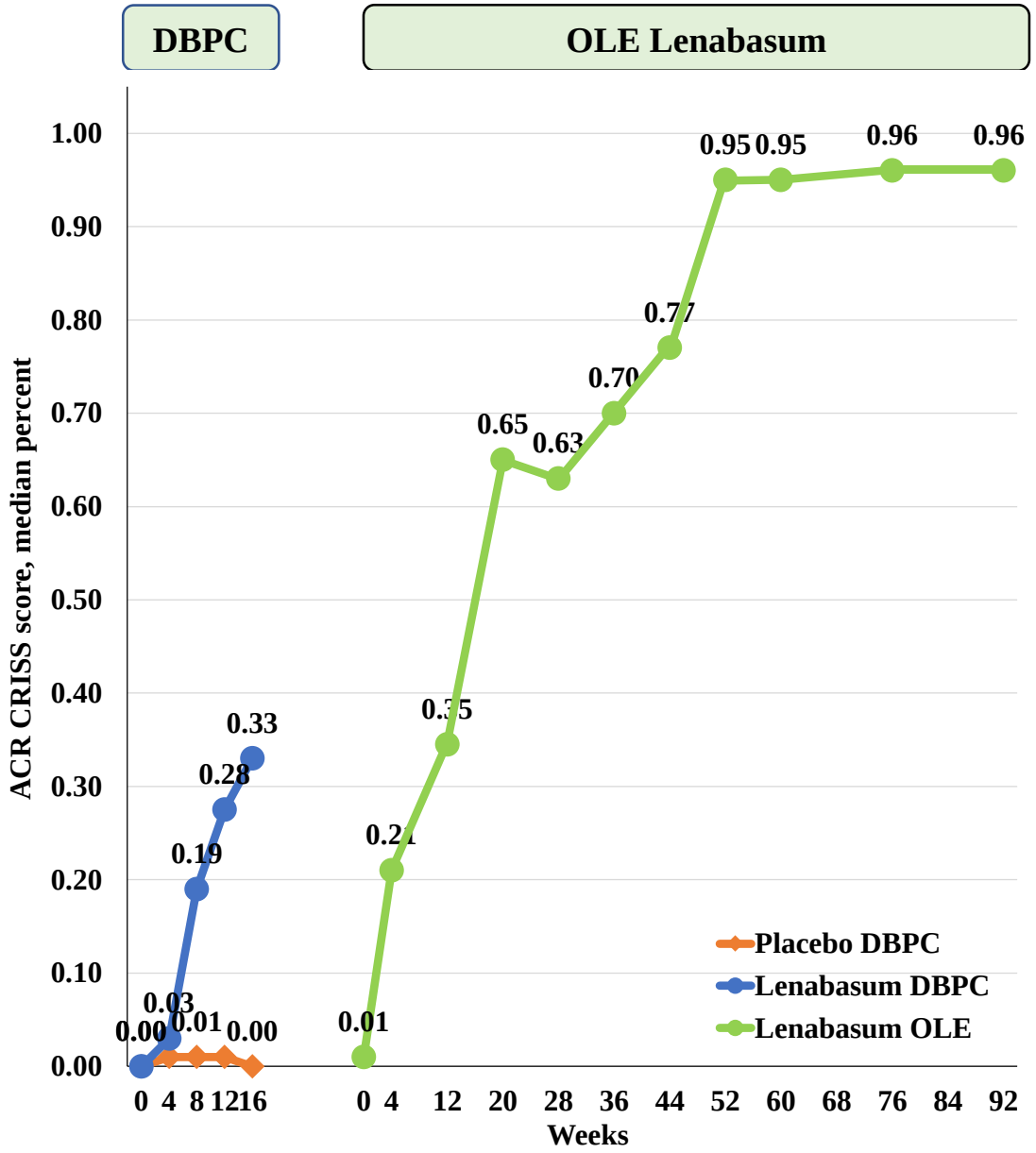
- No severe AEs or study discontinuations related to lenabasum to date

Adverse events occurring in ≥ 10% of subjects in OLE

Adverse Event, Preferred Term	Subjects with AEs, n/36 (%)		
	All	Unrelated	Related
Upper respiratory tract infection	12 (33%)	12 (33%)	
Urinary tract infection	6 (17%)	6 (17%)	
Skin ulcer	6 (17%)	5 (14%)	1 (3%)
Arthralgia	6 (17%)	6 (17%)	
Nasopharyngitis/pharyngitis	5 (14%)	5 (14%)	
Diarrhoea	4 (11%)	4 (11%)	
Cough	4 (11%)	4 (11%)	
Fatigue	4(11%)	3 (8%)	1 (3%)

- The following AEs occurred in 3 (8%) of subjects each: abdominal pain, anaemia, dizziness, headache, pain in extremity, musculoskeletal pain (unrelated), dysphagia, nausea, constipation, rash, road traffic accident, and pyrexia. All of these AEs were considered unrelated except dizziness (2 possibly related), headache (1 possibly related), and constipation (1 possibly related).
- No laboratory test abnormalities or vital sign abnormalities related to lenabasum

ACR CRISS score

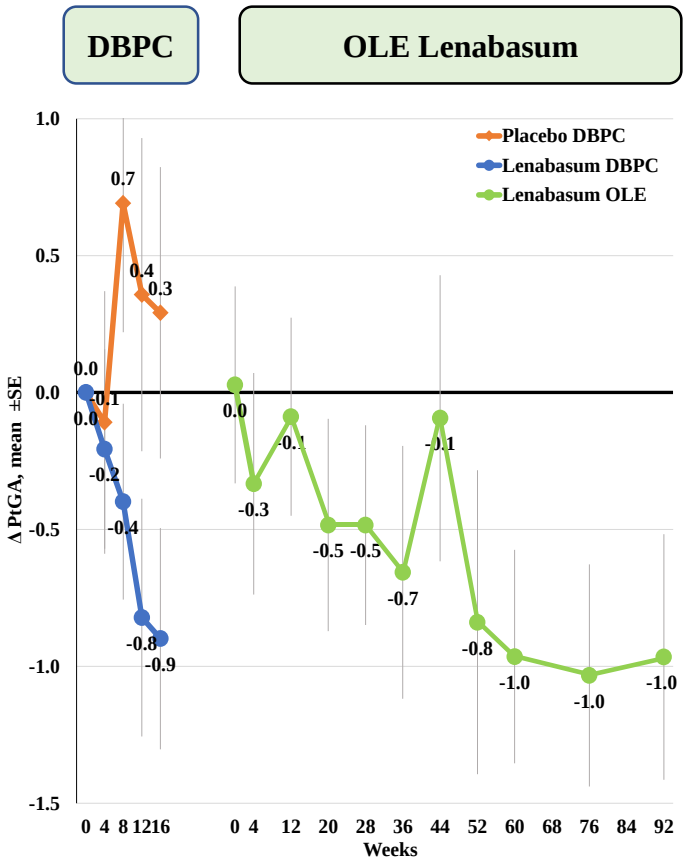


Composite measure of probability of improvement from baseline, combines change in mRSS, MDGA, PtGA, HAQ-DI, and FVC % predicted

- Increases through 1st year in OLE
- Improvement maintained thereafter

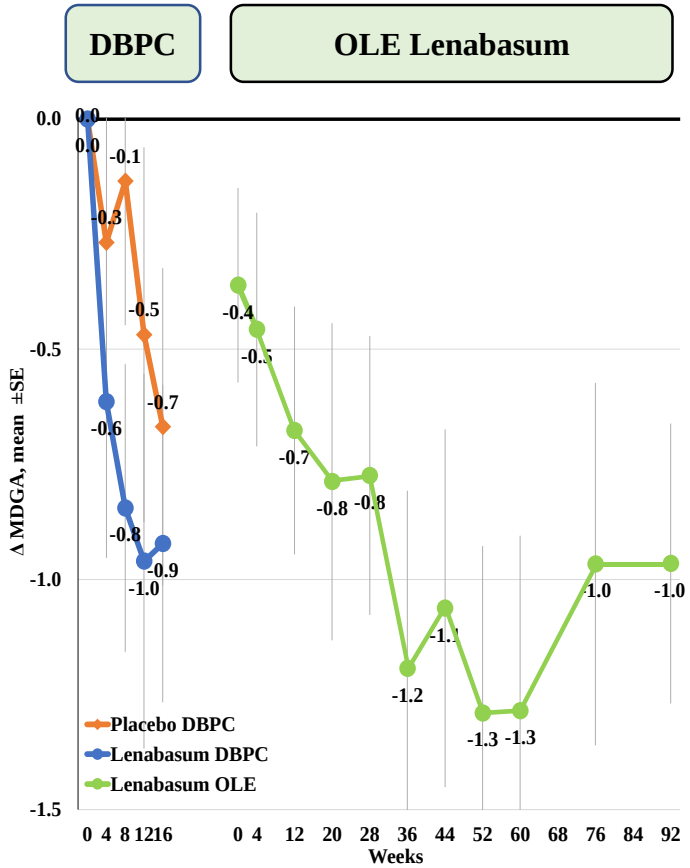
Patient and Physician Global Assessments of health related to SSc

PtGA



Baseline PtGA mean (SD) = 4.9 (2.3) for lenabasum arm and 4.8 (2.8) for placebo arm in Part A and 4.9 (2.8) for all subjects at start of open-label dosing

MDGA

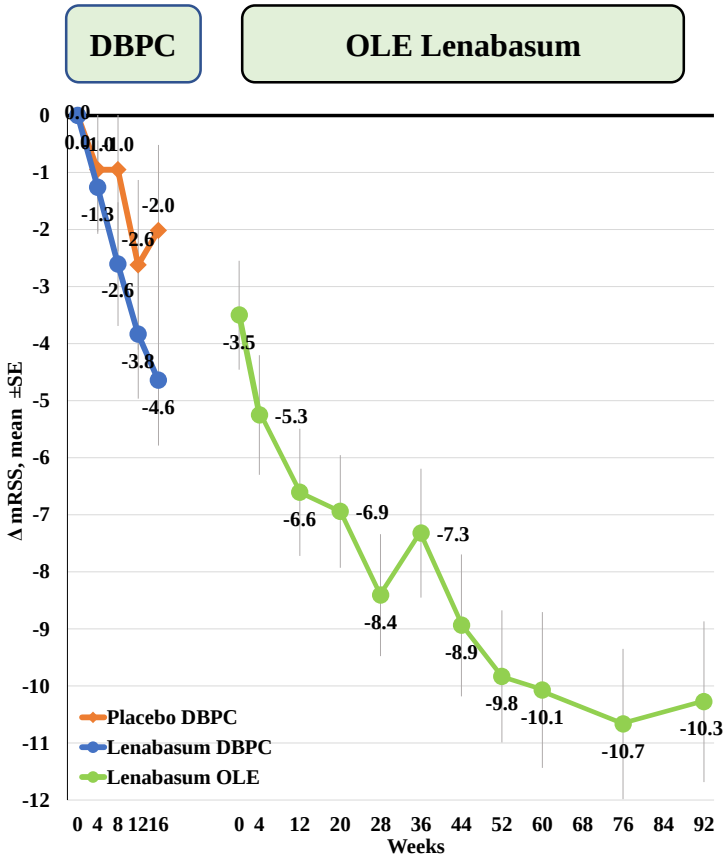


Baseline MDGA mean (SD) = 4.9 (2.3) for lenabasum arm and 4.8 (2.8) for placebo arm in Part A and 4.9 (2.8) for all subjects at start of open-label dosing

- Improvement increases during first year in OLE
- Improvement maintained thereafter in OLE

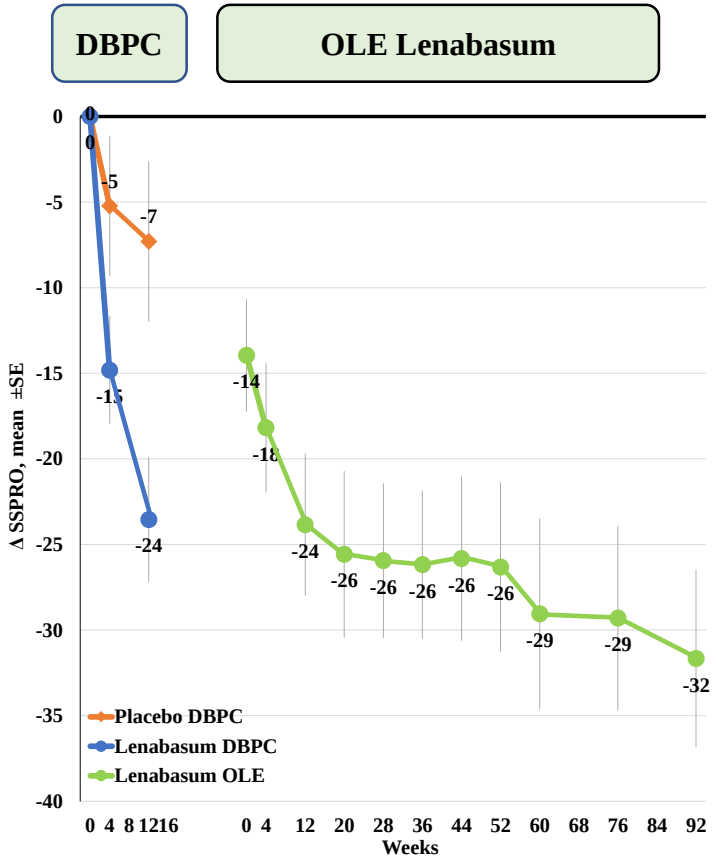
Skin involvement

mRSS



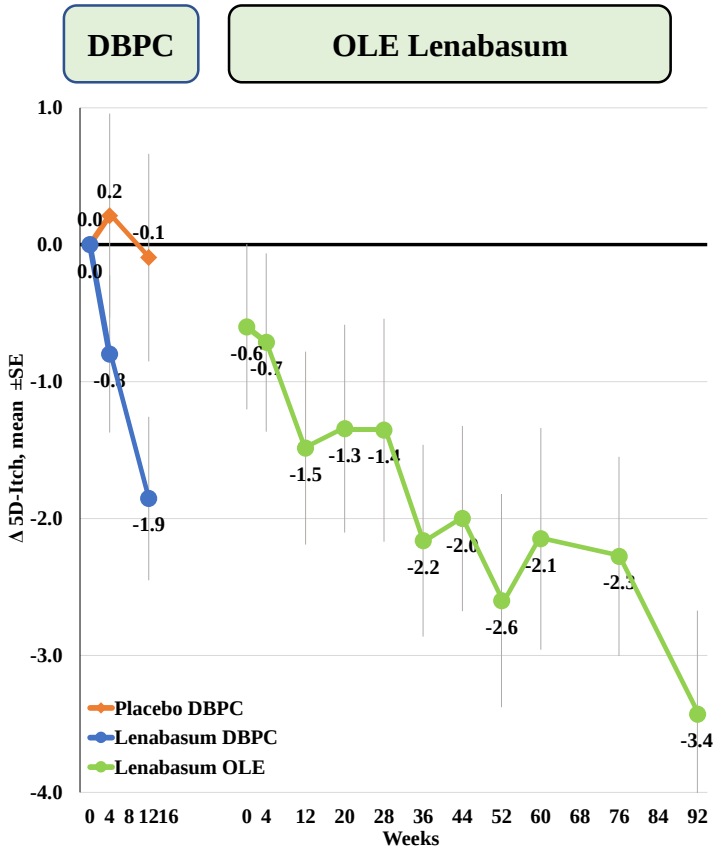
Baseline mRSS mean (SD) = 23.6 (10) for lenabasum arm and 26 (11) for placebo arm in Part A and 20.4 (11) for all subjects at start of open-label dosing

Skin Symptoms (SSPRO)



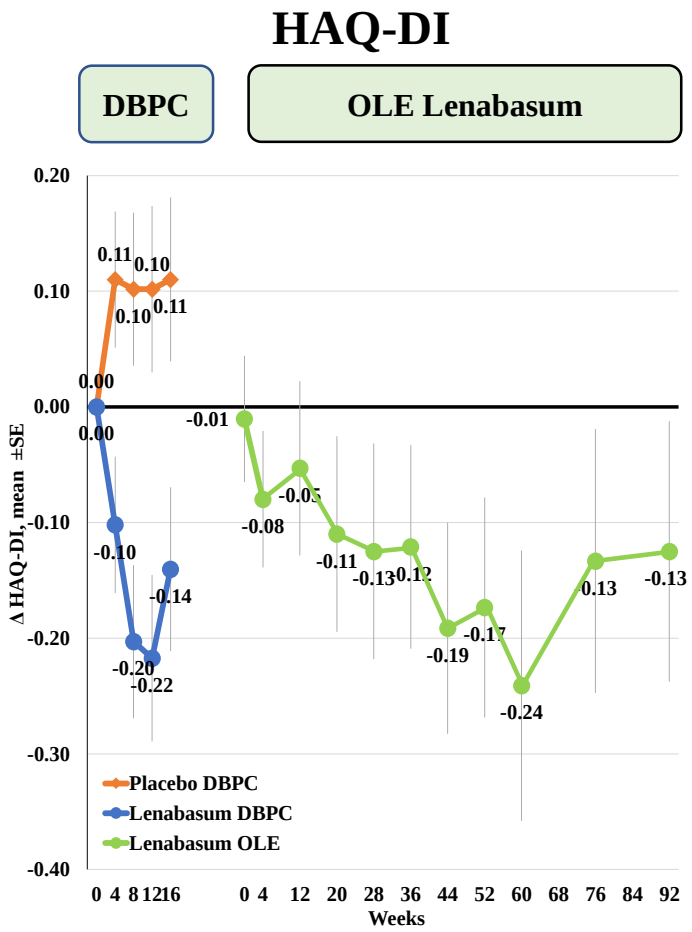
Baseline SSPRO mean (SD) =73 (27) for lenabasum arm and 83 (33) for placebo arm in Part A and 47 (11) for all subjects at start of open-label dosing

5D-Itch



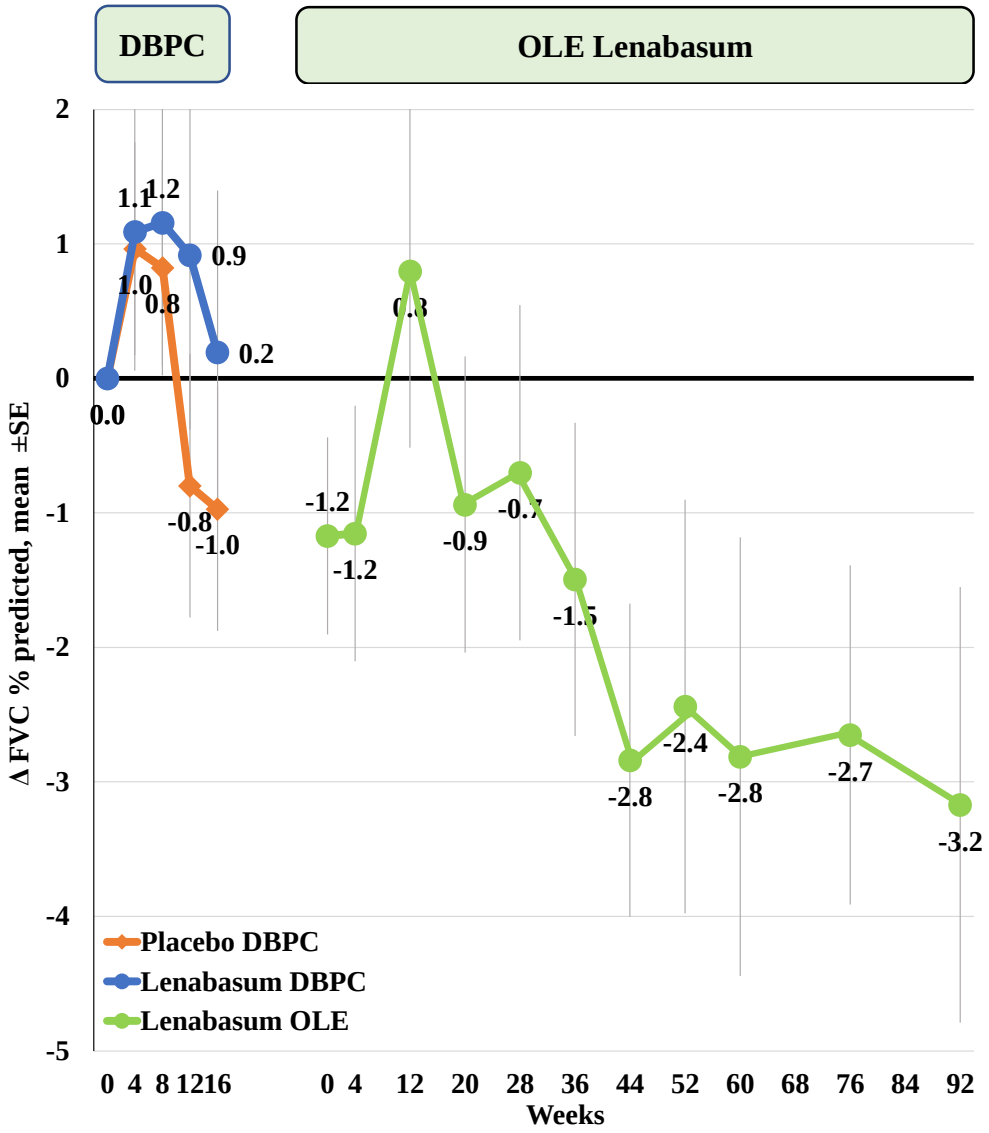
Baseline 5D-itch mean (SD) = 11 (4.4) for lenabasum arm and 13 (5.1) for placebo arm in Part A and 11 (4.9) for all subjects at start of open-label dosing

Patient-reported function: HAQ-DI



Baseline HAQ-DI mean (SD) = 1.1 (0.8) for lenabasum arm and 1.5 (0.8) for placebo arm in Part A and 1.2 (0.8) for all subjects at start of open-label dosing

FVC percent predicted



- Stable through 9 months in OLE
- Slight decline thereafter

Baseline FVC % predicted mean (SD) = 86 (13) for lenabasum arm and 81 (9) for placebo arm in Part A and 83 (14) for all subjects at start of open-label dosing

Summary and Conclusions

- Lenabasum has been safe and well-tolerated in study JBT101-SSc-001 through Week 92 of the OLE. There have been no severe AEs and no study discontinuations related to lenabasum to date
- Improvement in multiple efficacy outcomes was observed through year 1 in the OLE, with stability or continued improvement thereafter
- Limitations of ascribing efficacy to lenabasum during the OLE are acknowledged
- A Phase 3 study testing safety and efficacy of lenabasum in SSc is ongoing

Thank you

- The participants who took part in our Phase 2 study
- The investigators and site study teams for their commitment during the study

Investigators and study coordinators

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