Safety and Efficacy of Lenabasum at 21 Months in an Open-Label Extension of a Phase 2 Study in Diffuse Cutaneous Systemic Sclerosis (dcSSc) Subjects

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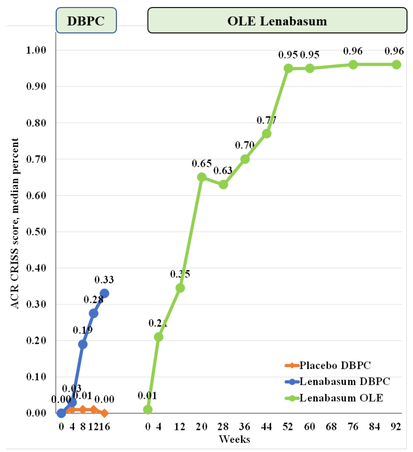
Abstract

Background: Lenabasum is a non-immunosuppressive, selective CB2 agonist that limits inflammation and fibrosis in animal models of SSc. Lenabasum was safe and well-tolerated and improved efficacy outcomes in dcSSc subjects in the double-blinded, randomized, placebo-controlled Part A of Phase 2 trial JBT101-SSc-001 (NCT02465437).
Materials and methods: Subjects who completed Part A were eligible to receive lenabasum 20 mg BID in an open-label extension (OLE) that assessed safety and efficacy at 4 weeks, then every 8 weeks.
Results: Thirty-six/38 (95%) eligible subjects enrolled in the OLE and as of March 2019, 29/36 (81%) patients completed ≥ Week 92. Reasons for subject discontinuation included: withdrawal of consent (N=4), AEs unrelated to lenabasum (N=2; tendonitis and scleroderma renal crisis), and other reasons (N=1). Thirty-five (97%) subjects experienced ≥1 AE, with 249 total AEs. Seven (19%) subjects had ≥ 1 AE considered related to lenabasum. Three (8%) had AEs judged to be probably or definitely related to lenabasum: mild fatigue (N=1); moderate skin ulcer and lymph node pain (N=1); and mild disturbance in attention and lethargy and moderate feeling abnormal (N=1). Most subjects experienced AEs that were mild (n=6, 17%) to moderate (n=23, 64%) in maximum severity. Six (17%) had severe AEs and 1 (3%) had a life-threating AE of renal crisis associated with exposure to high-dose steroids. AEs in ≥ 10% of subjects were: upper respiratory tract infection (n=11, 31%); skin ulcer, urinary tract infection, and arthralgia (each n=6, 17%); and diarrhea, nasopharyngitis, and cough (each n=4, 11%). Dizziness and fatigue occurred in 3 (8%) subjects each. Multiple efficacy outcomes showed stable improvement from about 1 year in the OLE or continued improvement in some cases. Median ACR CRISS score was 0.96 and mean (SE) change in mRSS was –10.3 (1.4) at Week 92.
Conclusions: Lenabasum continues to be safe and well-tolerated to date in the OLE of Phase 2 trial JBT-101-SSc-001, with no serious AEs or study discontinuations related to lenabasum. Improvement in efficacy outcomes have been durable. Background therapy, natural history of the disease, and open-label dosing limit what efficacy can be definitely attributed to lenabasum.

ACR CRISS Score

ACR CRISS Score: Composite measure of probability of improvement from baseline. Score is calculated using an exponential formula the incorporates change from baseline in mRSS, MDGA, PtGA, HAQ-DI, and FVC % predicted in a weighted manner.



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

Adverse Events During Open-Label Dosing

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%)

Table 2. Adverse events occurring in ≥ 10% of subjects in OLE

- 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

Background

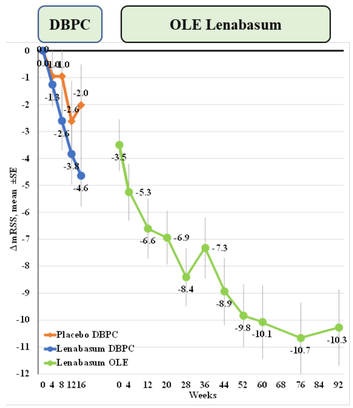
- Systemic sclerosis (SSc) is a serious systemic autoimmune disease characterized in part by chronic activation of innate immune responses accompanied by fibrosis.
- Lenabasum is an oral selective cannabinoid receptor type 2 (CB2) agonist that has shown promising safety and efficacy profiles to date in a two-part Phase 2 trial, JBT101-SSc-001.
  - Part A: 16-week, randomized, double-blind, placebo-controlled (DBPC)
  - Part B: Open-label extension (OLE)
- Skin biopsies from subjects in Part A showed improvement in inflammation and fibrosis at Week 12 compared to study start.
- **Subjects:** Adults with dcSSc. Disease duration ≤ 3 years or > 3 and ≤ 6 years if mRSS ≥ 16 or high CRP or IL-6. Stable doses of concomitant medicines allowed, including immunosuppressive drug
- **DBPC Dosing:** Month 1: Lenabasum 5 mg QD, 20 mg QD 20 mg BID, or placebo. Months 2-3: 20 mg BID or placebo. Month 4: Safety and efficacy assessments continued
- **Off Study Drug:** Background immunosuppressant medications continued, but no study drug was given (Mean 20.2 Weeks).
- **OLE Dosing:** Lenabasum 20 mg BID for subjects who completed DBPC dosing with lenabasum or placebo

Baseline Characteristics

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)

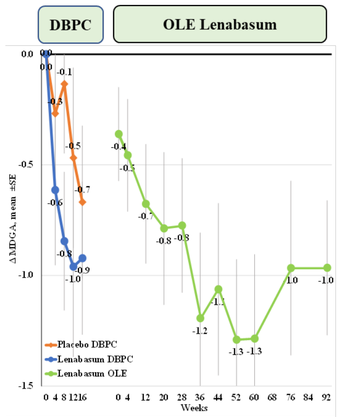
Table 1. Baseline demographics and disease characteristics

mRSS



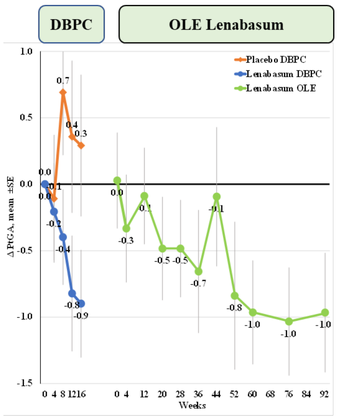
Baseline mRSS mean (SD) = 23.6 (10) for lenabasum arm and 26 (11) for placebo arm in Part A and 20.4 (11) for all subjects at start of open-label dosing

MDGA



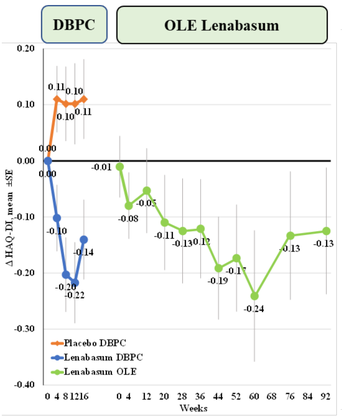
Baseline MDGA mean (SD) = 4.9 (2.3) for lenabasum arm and 4.8 (2.8) for placebo arm in Part A and 4.9 (2.8) for all subjects at start of open-label dosing

PtGA



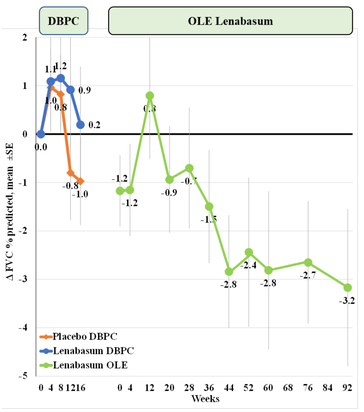
Baseline PtGA mean (SD) = 4.9 (2.3) for lenabasum arm and 4.8 (2.8) for placebo arm in Part A and 4.9 (2.8) for all subjects at start of open-label dosing

HAQ-DI



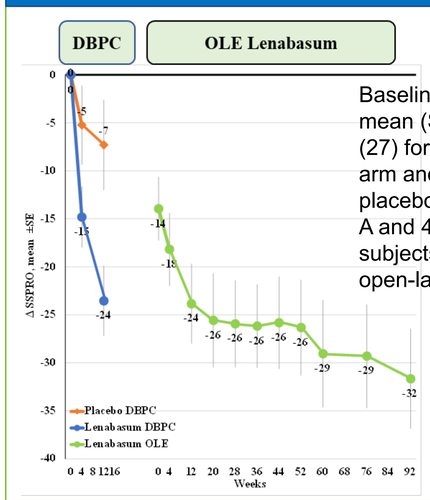
Baseline HAQ-DI mean (SD) = 1.1 (0.8) for lenabasum arm and 1.5 (0.8) for placebo arm in Part A and 1.2 (0.8) for all subjects at start of open-label dosing

FVC % predicted



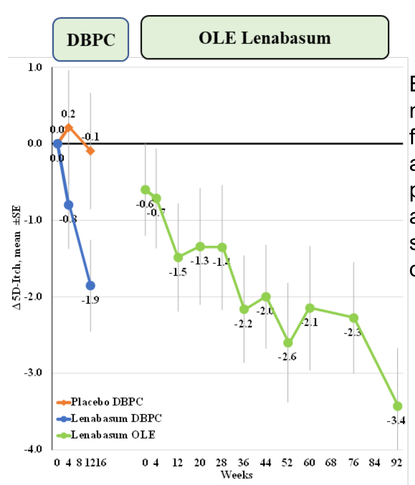
Baseline FVC % predicted mean (SD) = 86% (13) for lenabasum arm and 81% (9) for placebo arm in Part A and 83% (14) for all subjects at start of open-label dosing

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

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

- To the people with SSc who participated and are participating in this study
- To the investigators and study staff that are successfully executing this trial
- To our DSMB members

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