Safety and Efficacy of Lenabasum (JBT-101) in an Open-Label Extension of a Phase 2 Study in Diffuse Cutaneous Systemic Sclerosis Subjects

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ABSTRACT

Background/Purpose: Lenabasum is a synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses. Lenabasum had acceptable safety and tolerability, and improved multiple efficacy outcomes in the double-blinded, randomized, placebo-controlled Part A of Phase 2 trial JBT101-SSc-001 (NCT02465437) in diffuse cutaneous SSc (dcSSc) subjects.
Objective: To provide long-term open-label safety and efficacy data in dcSSc subjects in study JBT101-SSc-001.
Methods: Subjects who completed Part A were eligible to receive oral lenabasum 20 mg BID in an open-label extension (OLE) that assessed safety and efficacy at 4 weeks, then every 8 weeks.
Results: 36/38 (95%) eligible subjects enrolled in the OLE, with mean interval of 134 (range 33-392) days or 19.1 weeks from end of dosing in Part A to start of OLE when subjects received only standard-of care drugs. 34/36 (94%) subjects were on stable doses of immunosuppressive drugs. At the time of data cut-off, 5/36 (13.9%) subjects had discontinued the OLE for reasons all unrelated to lenabasum: difficulty coming for study visits (n = 2), fatigue, inflamed tendons, and high dose steroid-induced scleroderma renal crisis. Of the remaining 31 subjects, 27 (87.1%) had already completed ≥ 1 year of dosing in OLE. Adverse events (AEs, n = 180) occurred in 33/36 (91.7%) subjects, with 7/36 (19.4%) subjects having ≥ 1 AE related to lenabasum. No subject had a serious or severe AE related to lenabasum. Three serious AEs occurred: renal crisis, thumb fracture, and digital ulcer. AEs that occurred in ≥ 10% of subjects (n, % of subjects) were: upper respiratory tract infection (8, 22.2%), skin ulcer, arthralgias, urinary tract infection (5, 13.9% each), and diarrhea (4, 11.1%). Mild dizziness occurred in 3 (8.3%) subjects.
Improvement was seen in multiple physician- and patient-reported efficacy outcomes compared to study start and start of OLE, including Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS), mRSS, HAQ-DI, Physician Global Assessment, skin symptoms, itch, and multiple PROMIS-29 domains. FVC % predicted was relatively stable. Compared to baseline at study start, the CRISS median score was 92% (23%, 100% IQR) at Week 52 and mRSS declined by mean (SD) = 9.4 (8.43) and 41.3% (32.7%) from baseline, with 35% of subjects newly achieving a low mRSS ≤ 10.
Conclusion: In OLE of Phase 2 trial JBT101-SSc-001, lenabasum continues to have acceptable safety and tolerability in dcSSc with no severe or serious AEs or study discontinuations related to lenabasum. Only about 1 in 5 subjects had an AE related to lenabasum over 1-year OLE dosing. ACR CRISS score, mRSS, Physician Global Assessment, and multiple patient-reported outcomes show continued improvement, although background therapy, potential for spontaneous improvement, and open-label dosing limit what can be definitely attributed to lenabasum.

RATIONALE, STUDY DESIGN, AND SUBJECT CHARACTERISTICS

- Systemic sclerosis (SSc) is a serious systemic autoimmune disease characterized in part by chronic activation of innate immune responses accompanied by fibrosis.
- There is a major unmet need for treatments that are more effective and safe enough to treat a broad spectrum of individuals with diffuse cutaneous SSc.
- Lenabasum (JBT-101) is an oral selective cannabinoid receptor type 2 (CB2) agonist that resolves tissue inflammation and fibrotic processes without immunosuppression.
- Lenabasum showed promising safety and efficacy in a Phase 2 trial, JBT101-SSc-001. In JBT101-SSc-001, lenabasum was tested in a double-blind, placebo-controlled (DBPC) 4 month study, which was followed by a period off study drug (mean 5 months duration), and then followed by ongoing open-label dosing.
  - ✓ **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 drugs
  - ✓ **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.
  - ✓ **OLE Dosing**: Lenabasum 20 mg BID for subjects who completed DBPC dosing with lenabasum or placebo

DBPC 4 months → Off study drug mean 5 months → **OLE** 18 months

Baseline demographics and disease characteristics

Characteristic	Double-blinded Dosing		Open-label Dosing
	Lenabasum n = 27	Placebo n = 15	Lenabasum N = 36
Female, %	85%	60%	75%
Age, mean (SD)	49 (10.4)	47 (11.1)	49 (11.2)
Caucasian, %	82%	80%	83%
Disease duration, months, mean (SD)	34 (16.6)	34 (18.0)	43 (17.5)
Concomitant immunosuppressive drugs, %	93%	87%	92%
Modified Rodnan skin score, mean (SD)	24 (10.4)	26 (11.2)	20 (10.9)

Safety and efficacy data after 18 months OLE dosing are being presented.

ADVERSE EVENTS DURING OPEN-LABEL DOSING

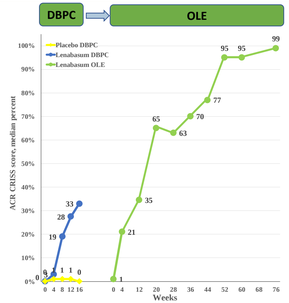
- There were no serious adverse events (AEs) related to lenabasum and no deaths in the study to date
- The only AE related to lenabasum that occurred in more than 1 subject during the OLE was dizziness, which occurred in 2 (6%) subjects to date
- 34 (94%) subjects had at least 1 AE, with 213 total AEs in the 36 subjects during the OLE to date
- By maximum severity, 5 (14%) of subjects had mild AEs, 25 (69%) had moderate AEs, 3 (8%) had severe AEs, and 1(3%) had a life-threatening AE of renal crisis caused by high-dose steroids
- By maximum relatedness, 27 (75%) of subjects had AEs unrelated to lenabasum and 7 (19%) had AEs related to lenabasum. The rate of AEs related to lenabasum decreased with time
- AEs (n, % 36 subjects) occurring in ≥ 10% of subjects during the OLE to date (18 months) were: upper respiratory tract infection 10 (28%); skin ulcer 6 (17%); urinary tract infection and arthralgia 5 (14%) each; and diarrhea 4 (11%)
- 83% of subjects who entered the OLE remained in the study at 18 months

EFFECTS ON OVERALL DISEASE

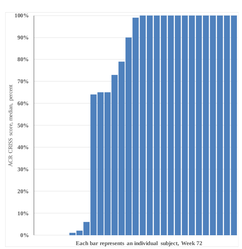
Effects of lenabasum on overall disease were evaluated with 3 outcomes:

- ACR CRISS score, a weighted composite of change from baseline in modified Rodnan skin score (mRSS), patient global assessment of health (PtGA), physician global assessment of health (MDGA), health assessment questionnaire disability index (HAQ-DI, and forced vital capacity (FVC), % predicted
- PtGA on a 10-cm visual analogue scale (VAS)
- MDGA, on a 10-cm VAS

ACR CRISS Score

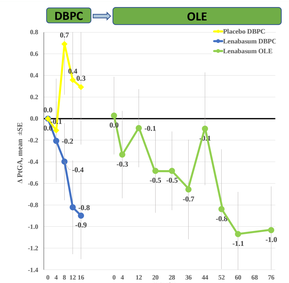


Distribution of ACR CRISS Scores by Individual Subject, OLE Month 18

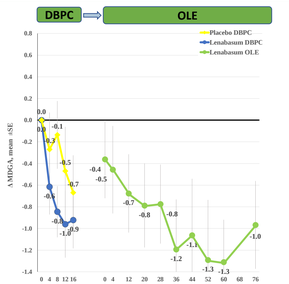


- ACR CRISS responses increased during the OLE and were durable, with median ACR CRISS score ≥ 95% from 12-18 months dosing
  - ✓ Median ACR CRISS reached 99% (6%, 100% IQR) at 18 months, stable from 95% (45%, 100% IQR) at 12 months
- About 3 in 4 subjects achieved an ACR CRISS score ≥ 60% at 18 months
- About 1 in 2 subjects achieved an ACR CRISS score = 100% at 18 months

Patient Global Assessment



Physician Global Assessment



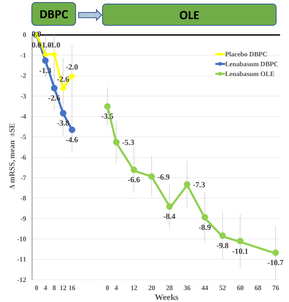
- As assessed with PtGA and MDGA, overall disease improved during the OLE, reaching a mean (SD) of -1.0 in PtGA and -1.0 in MDGA at 18 months
- Improvements were durable, with general stability in PtGA and MDGA from Months 12-18

EFFECTS ON SKIN

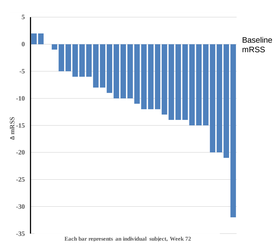
Effects of lenabasum on skin involvement were evaluated with 3 outcomes:

- mRSS, change from baseline
- SSPRO-18 – a patient-reported outcome of impact on skin on quality of life
- 5-D Itch score – questionnaire that assess severity of itch in skin diseases

Modified Rodnan Skin Score

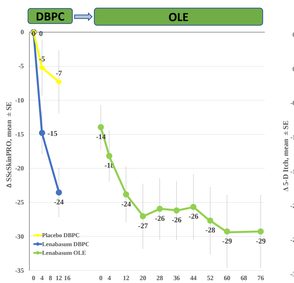


Distribution of change from Baseline by Individual Subject, OLE Month 18

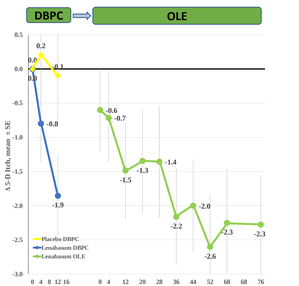


- mRSS scores improved during the OLE and were durable, with mean mRSS score about -10 points from months 12-18
- About half (47%) of subjects achieved a low absolute mRSS of ≤ 10 points
- 60% of subjects achieved a change from Baseline in mRSS score of ≤ -10 points at 18 months
- 87% achieved a minimal important difference in change from Baseline in mRSS score of ≤ -5 points at 18 months

SSPRO-18 Score



5-D Itch score



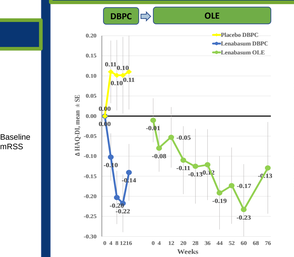
- As assessed with two patient-reported outcomes, SSPRO-18 and 5-D Itch score, skin involvement improved steadily during the OLE
- Improvements were durable, with general stability in PtGA and MDGA from Months 12-18

EFFECTS ON FUNCTION

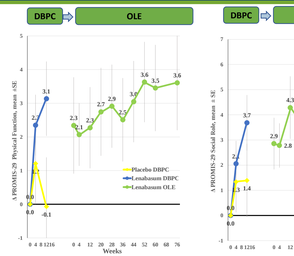
Effects of lenabasum patient were evaluated with 3 outcomes:

- HAQ-DI, a measure of patient-reported disability
- PROMIS-29 Physical function domain
- PROMIS-29 Social role domain, a measure of social functioning

HAQ-DI



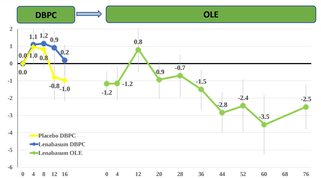
PROMIS-29 Physical Function



PROMIS-29 Social Role

- All three measures of patient-reported function improved during the OLE
- Mean improvement in HAQ-DI at 18 months exceeded reported 18-month MID of -0.10

Forced Vital Capacity



- FVC % predicted stable from beginning of OLE through Month 9
- Small decrease in mean FVC % predicted seen after Month 9; compared to beginning of OLE, mean FVC % predicted decreased by 1.3% predicted at 12 months.

CONCLUSIONS

- Safety and tolerability profile of lenabasum in dcSSc remained very favorable after 18 months dosing in the OLE
- Subjects improved with lenabasum treatment in the OLE, as assessed by measures of overall disease, skin involvement, and patient function.
- Generally, improvement increased over time in the first 12 months of the OLE, then was stable thereafter, showing a durable response. A slight decrease was seen in FVC % predicted.
- The limitations of assessing efficacy with open-label dosing are acknowledged, as is the potential impact of any change in concomitant medications

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 Drs. Phillip Clements, Virginia Steen and Richard Silver**

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