Safety and Efficacy of Lenabasum in Refractory Skin-Predominant Dermatomyositis Subjects Treated in an Open Label Extension of Trial JBT101-DM-001

Poster # SAT0512

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ABSTRACT

Background/Purpose: Lenabasum (aka anabasum, JBT-101) is a selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses. It is a synthetic, oral, non-immunosuppressive small molecule. Lenabasum showed acceptable safety and tolerability and evidence of clinical benefit in 22 subjects with refractory, skin-predominant dermatomyositis (DM) in Phase 2 trial JBT101-DM-001 (NCT02466243). This study evaluated safety and efficacy of open-label dosing of lenabasum in moderately-to-severely active skin-predominant DM in subjects who were refractory to or intolerant of hydroxychloroquine treatment.

Methods:. Subjects who completed the double-blind placebo-controlled (DBPC) part of JBT101-DM-001 with 12 weeks of active dosing and 4 weeks of safety follow-up were eligible to receive lenabasum 20 mg BID in an open-label extension (OLE). Safety and efficacy evaluations were done at Week 4 after the start of OLE, then every 8 weeks thereafter.

Results: 20/22 (91%) eligible subjects enrolled in the OLE and 17/20 (85%) were on baseline immunosuppressive drugs. There was a mean interval of 31 weeks (range 4-92 weeks) from the end of active DBPC dosing and the start of the OLE, during which time subjects remained on background medications prior to adding lenabasum in the OLE. At the time of OLE data cut-off, no subjects had discontinued, all 20 subjects in the OLE completed visits through Week 12 and 11 subjects completed visits through Week 28. During the 28 weeks of OLE dosing, adverse events (AEs, n = 30) occurred in 14/20 (70%) subjects. Only 1 subject had a moderate AE, all other AEs were mild. Four (20%) subjects had AEs considered related to lenabasum. The only AE that occurred in more than 1 subject was DM flare (n = 2, 10%). During the OLE, there was improvement from the beginning of the OLE dosing and from the study start in Cutaneous Dermatomyositis Activity and Severity Index (CDASI) Activity score and physician Likert assessments of global disease activity, skin disease activity and extramuscular disease activity. Similarly, there were improvements in multiple patient-reported outcomes, including patient 10-cm VAS scores of global disease activity, skin disease activity, itch and pain, as well as the Skin-dex-29 symptoms domain and PROMIS-29 physical function, fatigue, pain interference, and anxiety domains. Selected efficacy outcomes are shown in Figure 1 as change from study start during two periods: 1) "off treatment" from the end of active DBPC dosing to the start of OLE, dotted line; and 2) OLE dosing, solid line.

Conclusion: Lenabasum continues to have a favorable safety and tolerability profile in the OLE of the Phase 2 trial JBT101-DM-001 with no severe or serious AEs or study discontinuations related to lenabasum. The CDASI activity score and multiple other physician and patient-reported outcomes improved from study start and start of the OLE, although open-label nature of dosing with lenabasum is acknowledged. These data support further testing of lenabasum for the treatment of DM.

BACKGROUND

- Dermatomyositis (DM) is a serious and rare systemic autoimmune disease characterized in part by chronic activation of innate immune responses
- Current therapies for DM are frequently ineffective and include immunosuppressive drugs
- Lenabasum (JBT-101) is an oral selective CB2 agonist that activates the resolution phase of innate immune responses
- Lenabasum has shown benefit in animal models of inflammation and fibrosis and reduces interferon α, TNFα , and IL-31 production by cultured peripheral blood mononuclear cells from DM patients
- During the double-blinded placebo-controlled Part A of Phase 2 study JBT101-DM-001, lenabasum had acceptable safety and tolerability in DM subjects with active, refractory skin-predominant DM. It improved CDASI activity score and multiple patient-and physician reported outcomes
- An open-label extension of study JBT101-DM-001 was undertaken to evaluate long-term safety profile and effects on efficacy outcomes

DESIGN, SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Eligibility Criteria

- DM by Bohan and Peter's or Sontheimer's criteria
- Moderate to severely active, refractory skin-predominant DM
  - CDASI activity score ≥ 14
  - Failed or intolerant of hydroxychloroquine
  - Minimal active muscle involvement
- Adults ≥ 18 and ≤ 70 years of age
- Stable doses of concomitant medicines for DM allowed, including immunosuppressive drugs

Study Design

Double-Blind Placebo-controlled Part A of study

- 12 weeks + 4 weeks follow-up

Off-treatment

- End of double-blind dosing to start of open-label dosing.
- Mean 31 weeks off study drug

Open-label Extension (OLE)

- Subjects must complete Part A
- Lenabasum 20 mg BID

Subject Demographics	Lenabasum N = 11	Placebo N = 11	OLE N = 20
Age, mean (SD)	53.1 (9.3)	52.5 (10.4)	52.8
Female, %	91%	100%	95%
White, %	100%	91%	95%
Hispanic or Latino, %	27%	0%	13.5%
Body mass index, mean (SD)	26.4 (5.8)	27.3 (7.4)	29.9

- No significant differences between cohorts at entry in Part A
- Mostly middle-aged white women

Baseline Disease Assessments, Study Entry, mean (SD) or n (%)	Mean (SD) Lenabasum N = 11	Mean (SD) Placebo N = 11
Physician CDASI activity score, 0 -100	**33.3** (9.7)	**35.8** (7.8)
Immunosuppressive drugs, n, %	**9** (81.8%)	**10** (90.9%)
Patient SKINdex-29 symptom score, 0-100	**61.0** (20.2)	**52.3** (24.3)
Patient SKINdex-29 functioning score, 0-100	**27.8** (15.7)	**27.3** (26.7)
Patient SKINdex-29 emotions score, 0-100	**45.0** (24.2)	**56.6** (32.1)
Patient SKINdex-29 photosensitivity, 0-100	**55.7** (31.3)	**39.8** (35.7)
Patient skin global assessment, VAS 1-10	**4.6** (2.2)	**6.4** (2.6)
Patient itch, VAS 1-10	**6.1** (2.7)	**5.1** (3.5)
Patient PROMIS-29 fatigue, 0-100	**50.3** (9.9)	**51.3** (9.9)
Patient PROMIS-29 sleep, 0-100	**54.0** (7.8)	**55.6** (7.2)
Patient PROMIS-29 physical function, 0-100	**50.6** (7.4)	**54.0** (6.7)

- No significant differences in baseline disease assessments
- At entry in Part A, subjects had severely active and symptomatic skin disease despite immunosuppressive therapy

SAFETY AND TOLERABILITY

Adverse Events	Subjects with AEs by maximum relatedness or severity, n/N (%) DBPC Part A Lenabasum N = 11	DBPC Part A Placebo N = 11	OLE Lenabasum N = 20
Total AEs	11 (100%)	9 (82%)	13 (65%)
Unrelated to study drug	3 (27%)	5 (46%)	8 (40%)
Related[1] to study drug	8 (73%)	4 (36%)	5 (25%)
Mild	7 (64%)	5 (46%)	12 (60%)
Moderate	4 (36%)	4 (36%)	5 (5%)
Severe	0 (0%)	0 (0%)	0 (0%)
Serious AE	0 (0%)	0 (0%)	0 (0%)
AEs leading to study discontinuation	0 (0%)	0 (0%)	0 (0%)

[1] *Possible, probable, or definite relationship as assessed by investigator*

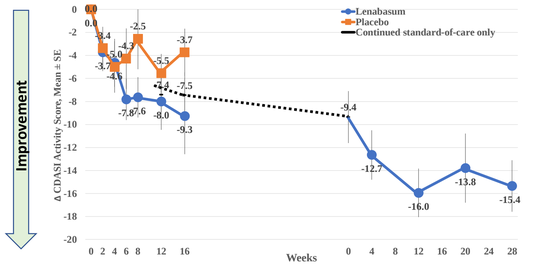
Safety profile and tolerability of lenabasum are acceptable in OLE through 28 weeks

- No serious or severe AEs related to lenabasum to date
- Proportion of subjects with AEs related to lenabasum is lower with continued dosing in OLE than during initial 12 weeks dosing in DBPC Part A
- Only AE occurring in ≥ 2 subjects during OLE was DM flare, n = 2 (10%)

IMPROVEMENT IN CDASI ACTIVITY SCORE

Stable standard-of-care drugs, including immunosuppressives

DBPC Part A N = 11 per cohort	No study drug N = 20 entering OLE	OLE Lenabasum N = 20 Weeks 0 – 20 N = 17 completed Week 28 at data cut

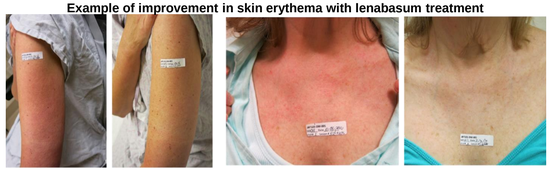


[1] *Week 0 DBPC CDASI activity score mean (SD) = 33.3 (9.74) for lenabasum and 35.8 (7.77) for placebo. P* = 0.09, p = 0.05, p = 0.28, p = 0.04, for lenabasum vs. placebo at Weeks 4, 8, 12, and 16, respectively, of DBPC Part A of study, MMRM, 2-sided*

Continued improvement in CDASI activity score during OLE

- Mean improvement of 15.4 points at Week 28
- 14/17 (82.3%) subjects achieving ≥ 10-point improvement in CDASI activity score at Week 28

Example of improvement in skin erythema with lenabasum treatment



IMPROVEMENT IN PATIENT-REPORTED OUTCOMES

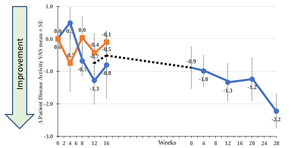
Stable standard-of-care drugs, including immunosuppressives

DBPC Part A N = 11 per cohort	No study drug N = 20 entering OLE	Open-label Lenabasum N = 20 Weeks 0 – 20, N = 17 completed Week 28 at data cut

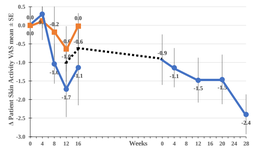
Blue solid = lenabasum
- 20 mg QD Weeks 0 -4 in DBPC
- 20 mg BID thereafter

Orange solid = placebo
Black dotted = SOC only

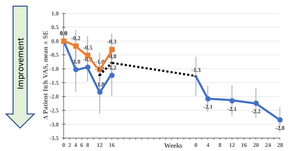
Δ 10-cm Patient Disease Activity VAS



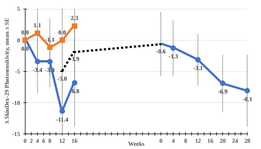
Δ 10-cm Patient Skin Activity VAS



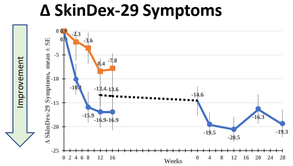
Δ SkinDex-29 Photosensitivity



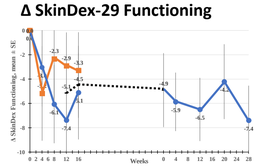
Δ 10-cm Patient Itch VAS



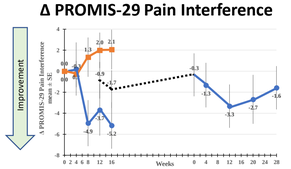
Δ SkinDex-29 Symptoms



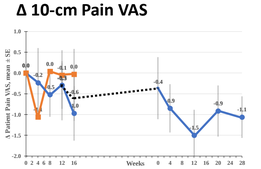
Δ SkinDex-29 Functioning



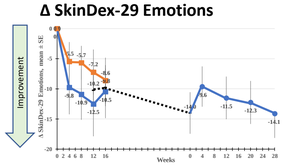
Δ PROMIS-29 Pain Interference



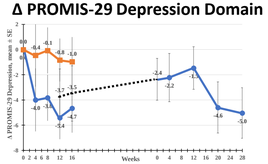
Δ 10-cm Pain VAS



Δ SkinDex-29 Emotions



Δ PROMIS-29 Depression Domain



IMPROVEMENT IN PHYSICIAN-REPORTED OUTCOMES

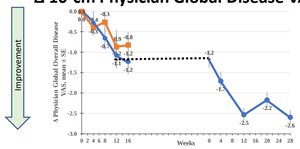
Stable standard-of-care drugs, including immunosuppressives

DBPC Part A N = 11 per cohort	No study drug N = 20 entering OLE	Open-label Lenabasum N = 20 Weeks 0 – 20, N = 17 completed Week 28 at data cut

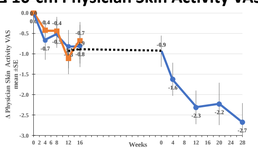
Blue solid = lenabasum
- 20 mg QD Weeks 0 -4 in DBPC
- 20 mg BID thereafter

Orange solid = placebo
Black dotted = SOC only

Δ 10-cm Physician Global Disease VAS

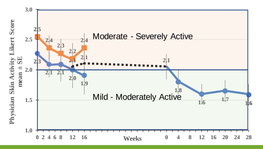


Δ 10-cm Physician Skin Activity VAS



CDASI Low Skin Disease Activity (≤ 14)

Physician Skin Activity Likert Scale



SUMMARY AND CONCLUSIONS

- 95% enrollment in OLE shows excellent patient and physician acceptance of lenabasum
- In the OLE to date, lenabasum:
  - ✓ Has a favorable safety profile and is well-tolerated despite concomitant treatment with immunosuppressive drugs in most subjects
  - ✓ Is associated with improvement in multiple measures of skin involvement
  - ✓ Is associated with improvement in multiple patient-reported measures of quality of life
  - ✓ Shows a consistent pattern of effect across many outcomes
    - Greater improvement than placebo during the DBCP Part A of the study
    - Limited improvement when lenabasum is stopped and only standard-of-care drugs are continued
    - Resumption of improvement in subjects who previously received lenabasum, stopped lenabasum temporarily, then restarted lenabasum
    - New improvement in subjects who previously received placebo
- Limitations of assessing safety and efficacy during the OLE are acknowledged
- The degree and consistency of improvement in efficacy outcomes combined with a favorable safety profile to date support further clinical testing of lenabasum for treatment of DM

THANK YOU

❖ **To the individuals with DM who participated in this study**

❖ **To the study staff who are executing this trial**

❖ **To Data Safety Committee Chairperson Dr. Philip Cohen**

❖ **To NIH/NIAMS for funding for this study**

This study was funded in part and sponsored by Corbus Pharmaceuticals, Inc.