Safety and Efficacy of Anabasum (JBT-101) in Diffuse Cutaneous Systemic Sclerosis (dcSSc) Subjects Treated in an Open-Label Extension of Trial JBT101-SSc-001

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Poster # 725

Abstract

Background/Purpose: Anabasum (JBT-101) is a selective cannabinoid receptor type 2 agonist that activates resolution of innate immune responses and limits fibrosis in animal models of SSc. It is a synthetic, oral, non-immunosuppressive small molecule. Anabasum had acceptable safety and tolerability and showed evidence of clinical benefit in diffuse cutaneous SSc (dcSSc) in Phase 2 trial JBT101-SSc-001 (NCT02465437). The objective of this study was to provide long-term open-label safety and efficacy data in dcSSc subjects who received anabasum in that trial.

Methods: Subjects who completed the double-blind placebo-controlled (DBPC) part of JBT101-SSc-001 were eligible to receive anabasum 20 mg BID in an open-label extension (OLE).

Results: 36/38 (95%) eligible subjects enrolled in the OLE and 34/36 (94%) were on baseline immunosuppressive drugs. At the time of data cut-off, 1 subject had discontinued from the OLE, the duration of OLE dosing was median 194 days (range 25, 207 days) and total duration of DBPC + OLE dosing with anabasum was median 234 days (range 28, 295 days). All 36 subjects had at least one OLE visit ≥ 28 days post baseline. Adverse events (AEs, n = 88) occurred in 28/36 (78%) subjects in the OLE. Most AEs were mild (55/88, 62%) or moderate (30/88, 34%) in severity and unrelated to anabasum (75/88, 85%). The AEs that occurred in ≥ 10% of subjects (n, % of subjects) were mild fatigue (5, 14%) and mild/moderate upper respiratory tract infection (4, 11%). Dizziness occurred in 2 (6%) subjects. Only one subject had more than mild or moderate AEs. That subject developed renal crisis 7 days after starting 60 mg/day prednisone prescribed by a non-study physician for suspected temporal arteritis and had 2 severe and 1 life-threatening/serious AEs related to the renal crisis and deemed unrelated to anabasum. In the period between DBPC and OLE off study product (median 50 days, range 5 - 360 days), the modified Rodnan Skin Score (mRSS) was stable in all subjects, subjects treated with anabasum and subjects treated with placebo during DBPC dosing. After 10 weeks of anabasum treatment in OLE (Visit 3 in OLE), mRSS declined from baseline in these same groups of subjects.

Conclusion: In OLE of Phase 2 trial JBT101-SSc-001, anabasum continues to have acceptable safety and tolerability in dcSSc with no severe or serious AEs or study discontinuations related to anabasum. The mRSS improved, although open-label nature of dosing with anabasum is acknowledged. These data support further testing of anabasum for treatment of dcSSc.

Background

- Systemic sclerosis (SSc) is a serious and rare systemic autoimmune disease characterized in part by chronic activation of innate immune responses accompanied by fibrosis. There is an unmet need for non-immunosuppressive therapies to resolve inflammation and fibrosis in SSc.
- Anabasum (JBT-101) is an oral selective CB2 agonist that activates the resolution phase of innate immune responses to reduce tissue inflammation and fibrotic processes without immunosuppression.

JBT101-SSc-001 Trial Design

Double-blinded, Placebo-controlled Dosing
12 weeks + 4 weeks follow-up

→ **Off Treatment**
End of double-blind dosing to start of open-label dosing
Mean 20 weeks (5 - 360 days

→ **Open-label Dosing**
Mean 30 weeks
(84 – 266 days)

Eligibility Criteria
- ✓ *Diffuse cutaneous system sclerosis*
- ✓ *≥ 18 and ≤ 70 years of age*
- ✓ *Disease duration ≤ 3 years or > 3 and ≤ 6 years if mRSS ≥ 16 or high CRP or IL-6*
- ✓ *Concomitant medicines for SSc allowed, including immunosuppressive drugs*

Dosing
- ✓ *5 mg QD, 20 mg QD 20 mg BID, or placebo weeks 1-4. 20 mg BID or placebo BID weeks 5-12. Follow-up 4 weeks after end of dosing*

Safety and Efficacy Assessments
- ✓ *Day 1, then q2 weeks X 2, then q4 weeks X 4*

Eligibility Criteria
- ✓ *Subjects must complete Part A*

Dosing
- ✓ *Anabasum 20 mg BID*

Safety and Efficacy Assessments
- ✓ *Day1, 4 weeks, then q8 weeks*

Demographics and Baseline Characteristics

Characteristic	Double-blinded Dosing		Open-label Dosing
	Anabasum n = 27	Placebo n = 15	Anabasum N = 36
Female, %	85.2%	60.0%	75%
Age, mean (SD)	48.7 (10.4)	46.5 (11.1)	49.4 (11.2)
Caucasian, %	81.5%	80.0%	83%
Disease duration, months, mean (SD)	34.0 (16.6)	33.6 (17.9)	41.5 (17.5)
Concomitant immunosuppressive drugs, %	74.1%	80.0%	92%
Modified Rodnan skin score, mean (SD)	23.5 (10.4)	26.2 (11.2)	20.4 (10.9)
FVC, % predicted (SD)	86.1 (13.4)	79.6 (10.3)	82.8 (13.9)

† Since first non-Raynaud's symptom No statistically significant differences between anabasum-treated and placebo-treated subjects in Part A

- > 90% subjects were on stable doses of immunosuppressive drugs started ≥ 3 months before study start
- Mean disease duration upon starting open-label dosing ~ 3½ years

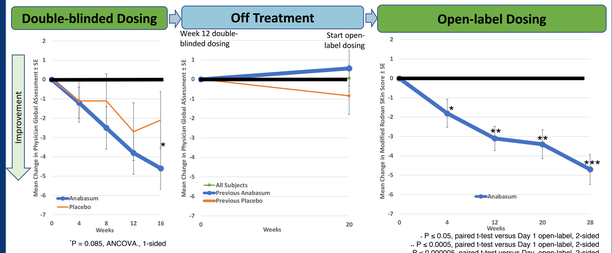
Adverse Events

Adverse Events	Subjects with AEs by Maximum Severity then Maximum Relatedness, n/N (%)								
	Double-blinded Placebo-controlled Dosing, 12 weeks						Open-label Dosing, ~28 weeks		
	Anabasum, N = 27			Placebo, N = 15			Anabasum, N = 36		
	All	Unrelated	Related†	All	Unrelated	Related†	All	Unrelated	Related†
Total AEs	17 (63%)	11 (41%)	6 (22%)	8 (53%)	5 (33%)	3 (20%)	30 (83%)	27 (75%)	3 (8%)
Mild	9 (33%)	5 (19%)	4 (15%)	6 (40%)	1(7%)	2 (13%)	8 (22%)	8 (22%)	
Moderate	8 (30%)	6 (22%)	2 (7%)	5 (33%)	3 (20%)	1 (7%)	19 (53%)	16 (44%)	3 (8%)
Severe	0	0	0	1 (7%)	1 (7%)	0	2[2] (6%)	2[2] (6%)	0
Life-threatening	0	0	0	0	0	0	1[3] (3%)	1[3] (3%)	0

† Possible, probable, or definite relationship to JBT-101 as assessed by investigator. [2] One subject had digital ischemia, 1 subject had fractures.
[3] 1 subject had developed renal crisis 7 days into a course of treatment with prednisone 60 mg per day prescribed by a non-study physician. This adverse event was judged by the investigator and Data Safety Monitoring Board not to be related to anabasum

- No severe, serious or life-threatening AEs related to anabasum to date
- AEs occurring in ≥ 10% of subjects were upper respiratory tract illness (n = 7, 19%) and urinary tract infections (n = 5, 14%). Mild dizziness, mild fatigue, digital ulcers, diarrhea, musculoskeletal pain, and fever occurred in 3 (8%) subjects each.

Modified Rodnan Skin Score, Change from Baseline



† P = 0.085, ANCOVA., 1-sided

Improvement in mRSS with anabasum treatment
- Mean change from baseline approaches a medically meaningful improvement (reduction ≥ 5 points) at end of Part A

Improvement stops when anabasum is discontinued
- Strong **negative** correction between *improvement* during double-blinded dosing and *worsening* off-treatment in subjects previously treated with anabasum (r = -0.58)

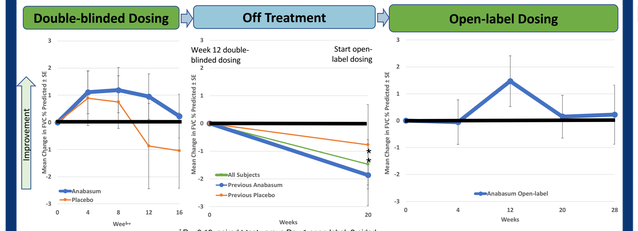
Improvement in mRSS with open-label dosing of anabasum
- Repeat improvement in subjects previously treated with anabasum
- New improvement in subjects previously treated with placebo

Change in mRSS from start of study

- 27/36 (75%) of subjects achieved a reduction in mRSS ≥ 5 and > 25% from the start of the trial. This degree of improvement that has been associated with improved survival and recently reported in 22% of similar SSc subjects receiving standard-of-care over 12 months ((Steen and Medsger, Arthritis Rheum 2001:44:2828, Dubrota et al, Ann Rheum Dis 2016: 75:1743)

At least once during open-label dosing,
- 10/36 (32%) subjects achieved a "low" mRSS ≤ 10
- 8/36 (22%) achieved a "very low" mRSS ≤ 5
- 3/36 (8%) achieved mRSS = 0 at least once during open-label dosing

Forced Vital Capacity % Predicted, Change from Baseline



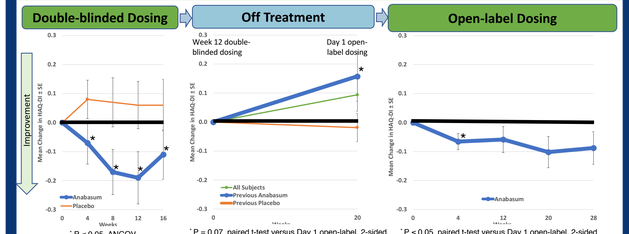
† P = 0.10, paired t-test versus Day 1 open-label, 2-sided

Stability of FVC % predicted with anabasum treatment
- Subjects not selected for restrictive lung defect

Slight worsening of FVC % predicted off treatment
- Expected from natural history of SSc

Stability of FVC % predicted with open-label dosing
- Unexpected stability of mean FVC % predicted during both double-blinded and open-label dosing of anabasum
- Change in FVC at Week 28 open-label dosing from start of study was 0.4 ± 1.6 % predicted

Health Assessment Questionnaire Disability Index (HAQ-DI)



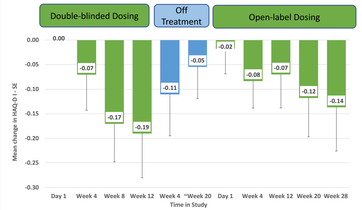
* P ≤ 0.05, ANCOV
† P = 0.07, paired t-test versus Day 1 open-label, 2-sided
‡ P ≤ 0.05, paired t-test versus Day 1 open-label, 2-sided

Improvement in HAQ-DI with anabasum treatment
- Exceeds MID at Week 8

Worsening of HAQ-DI off treatment

Improvement in HAQ-DI with open-label dosing
- Repeat improvement in subjects previously treated with anabasum
- New improvement in subjects previously treated with placebo

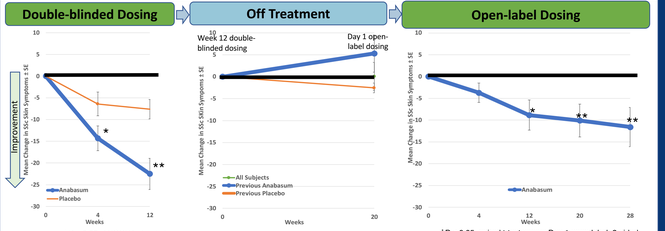
Change in HAQ-DI from start of study



Improvement in mean HAQ-DI from start of study exceeds minimally important difference (> -0.10) in both double-blinded an dosing periods
- At Week 28 in open-label dosing, improvement in HAQ-DI = -0.14 ± 0.09

At least once during open-label dosing,
- 11/28 (39%) achieved a reduction in HAQ-DI ≥ -0.050

Skin Symptoms



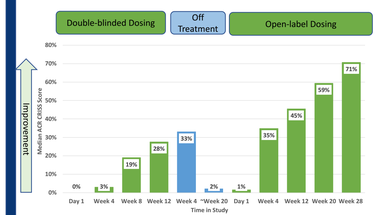
* P ≤ 0.05, ANCOVA, 1-sided
** P ≤ 0.005, ANCOVA, 1-sided
† P ≤ 0.05, paired t-test versus Day 1 open-label, 2-sided
†† P ≤ 0.005, paired t-test versus Day 1 open-label, 2-sided

Improvement in skin symptoms with anabasum treatment
- Using SSc SkinPrO instrument (see **abstract # 738**)

Improvement stops when anabasum is discontinued
- Moderate **negative** correction between *improvement* in skin symptoms during double-blinded dosing and *worsening* off treatment in subjects previously treated with anabasum (r = -0.40)

Improvement in skin symptoms and PtGA with open-label dosing
- Repeat improvement in subjects previously treated with anabasum
- New improvement in subjects previously treated with placebo
- 14/32 (44%) subjects achieved a "low" level of SSc skin symptoms with score of ≤ 30 points during open-label dosing

ACR CRISS Score



ACR CRISS achieves median 71% at Week 28 in open-label dosing
- Improvement during both double-blinded and open-label dosing
- Improvement in Patient and Physician Global Assessments were seen similar to other outcomes reported here (data not shown) and contributed to ACR CRISS scores
- Repeat improvement in subjects previously treated with anabasum
- New improvement in subjects previously treated with placebo
- ACR CRISS scores by Week 28
  - 75% had ACR CRISS ≥ 30%
  - 53% had ACR CRISS ≥ 50%
  - 44% had ACR CRISS ≥ 70%
  - 36% had ACR CRISS ≥ 90%

Note: ACR CRISS scores are not normally distributed

Conclusions

- **95% participation in open-label dosing indicates excellent patient and physician acceptance of anabasum**
- **Favorable safety profile with no severe or serious adverse events related to anabasum**
- **Cessation of improvement off treatment is consistent with efficacy of anabasum**
- **Improvement in multiple outcomes with open-label dosing is consistent with efficacy of anabasum, acknowledging limitations of open-label dosing**

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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