A Phase 2 Study of the Safety and Efficacy of Anabasum (JBT-101) in Systemic Sclerosis

Anabasum (JBT-101)

- Non-immunosuppressive selective CB2 agonist
- Activates **resolution of innate immune responses**
- Direct effects on fibroblasts
- Reduces inflammation and fibrosis in models of lung and skin disease in SSc

**Increases Pro-resolving Lipid Mediators (SPM)**

**Decreases Pro-inflammatory Lipid Mediators**
Phase 2 Study of Safety and Efficacy of Anabasum in SSc

- 16 weeks, anabasum versus placebo
- Disease duration ≤ 6 years
- Stable baseline immunosuppressive treatments allowed
- 27 subjects dosed with anabasum, 15 dosed with placebo
- 5 mg QD, 20 mg QD or 20 mg BID X 4 weeks, then 20 mg BID X 8 weeks, 4 weeks follow-up

- **Primary Efficacy Objective**
  - ACR CRISS

- **Secondary Efficacy Objectives**
  - mRSS and other ACR CRISS core measures
  - Other patient-reported outcomes
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anabasum n = 27</th>
<th>Placebo n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>85.2%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>48.7 (10.4)</td>
<td>46.5 (11.1)</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>81.5%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Disease duration¹, months, mean (SD)</td>
<td>37.1 (19.0)</td>
<td>40.6 (19.5)</td>
</tr>
<tr>
<td>Concomitant immuno-modulating drugs, %</td>
<td>92.9%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Modified Rodnan skin score, mean (SD)</td>
<td>23.9 (10.4)</td>
<td>26.2 (11.2)</td>
</tr>
<tr>
<td>Physician global assessment, mean (SD)</td>
<td>4.5 (1.8)</td>
<td>5.2 (2.1)</td>
</tr>
<tr>
<td>Patient global assessment, mean (SD)</td>
<td>4.8 (2.3)</td>
<td>4.9 (2.8)</td>
</tr>
<tr>
<td>HAQ-DI, mean (SD)</td>
<td>1.1 (0.8)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td>Forced vital capacity, % predicted, mean (SD)</td>
<td>85.9 (13.7)</td>
<td>79.6 (10.3)</td>
</tr>
</tbody>
</table>

¹ Since first non-Raynaud’s symptom
No statistically significant differences between anabasum-treated and placebo-treated subjects
EFFICACY DATA
Primary Efficacy Outcome: CRISS Scores

Primary Efficacy Outcome: CRISS Scores

Circle = subject
Median = black bar
Interquartile range = red bars

P1 = 0.044

1 Efficacy population, LOCF. Circle = individual scores, color-coded by individual. One-sided, mixed model repeated measures using rank transformed data. Model includes baseline mRSS and disease duration. No effect of immunosuppressive therapy in model.
Change in Modified Rodnan Skin Score

Change from baseline

Week

0 4 8 12 16

Change in mRSS, LS means ±SE

Anabasum - Placebo

P = 0.085

Worsening ≥ 5 points and 30% baseline

Subjects with worsening of mRSS ≥ 5 points and 30% baseline, %

0% 5% 10% 15% 20%

Week

0 4 8 12 16

1 Efficacy population. 3 Least squares mean difference, analysis of covariance model, one-sided p-value.
Change In Patient Assessments Of Skin Symptoms

**SSc SkinPRO Symptoms Questionnaire**

- **Week** vs. **Baseline**
- **JBT-101** vs. **Placebo**
- **P = 0.004**

**5-D Itch Questionnaire**

- **Week** vs. **Baseline**
- **JBT-101** vs. **Placebo**
- **P = 0.032**

*Improvement is a reduction in score*

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1 Ziemek J et al. Rheumatology 2016;55:911. 2 Elman S et al. Br J Dermatol 2010;162:587. 3 Efficacy population, least squares mean ± SE, analysis of covariance model. P-values are based on LS mean difference, one-sided p-values shown if P ≤ 0.10 (pre-specified).
Additional CRISS Score Set Outcomes (Part 1)

HAQ-DI, Change from Baseline

FVC % Predicted, Change from Baseline

1 P-values are based on LS mean difference, one-sided p-values shown if P ≤ 0.10 (pre-specified).
Additional CRISS Score Set Outcomes (Part 2)

MDGA, Change from Baseline

PtGA, Change from Baseline

1 P-values are based on LS mean difference, one-sided p-values shown if $P \leq 0.10$ (pre-specified).
Higher score = better function

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>Baseline score, mean (SD)</th>
<th>Change from baseline. LSM (SE)</th>
<th>Treatment difference (SE) (90% CI)</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JBT-101</td>
<td>Placebo</td>
<td>Week</td>
<td>JBT-101</td>
</tr>
<tr>
<td>Physical function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44.3 (8.1)</td>
<td>38.2 (6.6)</td>
<td>4</td>
<td>2.3 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>3.5 (1.1)</td>
</tr>
<tr>
<td>Social role</td>
<td>46.5 (8.9)</td>
<td>40.8 (7.3)</td>
<td>4</td>
<td>2.1 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>3.9 (1.1)</td>
</tr>
</tbody>
</table>

¹ Efficacy population, LOCF, least squares mean difference, analysis of covariance model, one-sided p-value

Anabasum subjects had greater improvement in physical function and social role at Week 12
**PROMIS-29 Sleep, Fatigue and Pain Domains Show Improvement**

Lower score = less symptoms

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>Baseline score, mean ± SD</th>
<th>Change from baseline. LSM ± SE</th>
<th>Treatment difference ± SE (90% CI)</th>
<th>P-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JBT-101</td>
<td>Placebo</td>
<td>Week</td>
<td>JBT-101</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>52.2 ± 7.3</td>
<td>52.7 ± 7.2</td>
<td>4</td>
<td>-2.7 ± 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>-3.9 ± 2.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57.0 ± 12.6</td>
<td>59.8 ± 8.5</td>
<td>4</td>
<td>-1.3 ± 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>-2.3 ± 1.2</td>
</tr>
<tr>
<td>Pain interference</td>
<td>57.7 ± 8.6</td>
<td>62.9 ± 8.9</td>
<td>4</td>
<td>-3.4 ± 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>-3.9 ± 2.2</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>4.5 ± 2.6</td>
<td>4.7 ± 2.8</td>
<td>4</td>
<td>-0.6 ± 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>-1.0 ± 0.4</td>
</tr>
</tbody>
</table>

¹ Efficacy population, LOCF, least squares mean difference, analysis of covariance model, one-sided p-value

**Anabasum subjects had greater improvement in sleep and pain interference at Week 12**
TRANSLATIONAL DATA
Analyses of Skin Histology

- Skin biopsies collected on Day 1 and Week 12
- Analyzed for cellular infiltrates and fibrosis
- Slides read in pairs by Robert Lafyatis, who was blinded to treatment assignment

Myofibroblasts and Hyalinized Collagen as Markers of Skin Disease in Systemic Sclerosis

Eugene Y. Kissin, Peter A. Merkel, and Robert Lafyatis
Anabasum Improves Inflammation in the Skin

Change after 12 weeks of treatment

**Placebo**
- Improved: 15%
- Unchanged: 16%
- Worsened: 69%

\[ \Delta \text{mRSS} = -1.2 \]

**Anabasum**
- Improved: 38%
- Unchanged: 48%
- Worsened: 14%

\[ \Delta \text{mRSS} = -5.1 \]

*P = 0.008  
Fisher’s exact test two-sided*
Anabasum Improves Fibrosis in the Skin

Change after 12 weeks of treatment

**Placebo**
- Improved: 39%
- Unchanged: 46%
- Worsened: 15%
  \( \Delta \text{mRSS} = -1.8 \)

**Anabasum**
- Improved: 43%
- Unchanged: 9%
- Worsened: 48%
  \( \Delta \text{mRSS} = -4.0 \)

\( P = 0.049 \)  
Fisher’s exact test two-sided
Anabasum Reduces Expression of Genes Associated with Inflammation and Fibrosis Pathways in the Skin

- Skin biopsies collected on Day 1 and Week 12
- Data analyzed blinded to treatment assignment

<table>
<thead>
<tr>
<th>Gene Expression Data Collection</th>
<th>Bioinformatic Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabasum, N = 46</td>
<td>Differential Expression pre- and post-treatment</td>
</tr>
<tr>
<td>Placebo, N = 26</td>
<td>Pathway Analysis pre- and post-treatment</td>
</tr>
</tbody>
</table>

1937 genes (FDR < 5%) modulated in anabasum arm

**Decreased**
- ECM organization
- Collagen metabolism
- Inflammatory response
- Response to cytokine
- Angiogenesis
Anabasum Treatment Significantly Inhibits Expression of Inflammatory Response Genes in Skin Biopsies

EXAMPLE:

- Average expression per patient of 47 genes that map to the Inflammatory Response pathway (example genes include CCL1, CCL2, CCL5, CXCL10, IL4R, ICAM1, multiple interferon-induced genes, and TLR9)

p-values calculated by paired t-test
SAFETY DATA
Safety and Tolerability

• No serious or severe anabasum-related AEs
• Most common AEs:
  - Dizziness (22% in anabasum-treated subjects vs. 13% in placebo-treated subjects)
  - Fatigue (19% in anabasum-treated subjects vs. 7% in placebo-treated subjects)
• No increase in psychiatric AEs (11% in anabasum-treated subjects vs. 13% in placebo-treated subjects)
• No differences from placebo in change from baseline in Addiction Research Center Inventory-Marijuana scores
• No differences from placebo in laboratory tests or ECGs
Conclusions

- Consistent efficacy in multiple clinical outcomes

- Histology and gene expression data show on-target effects of anabasum in skin

- Acceptable safety profile with no evidence of immunosuppression

- These data support Phase 3 development of anabasum for treatment of SSc
Thank You

• The participants who took part in our Phase 2 study
• The investigators and site study teams for their commitment to complete the study
Subject Disposition

Intent to Treat
N = 43

Safety Population
N = 42

Efficacy Population
N = 41

Completer Population
N = 38

43 Randomized

27 Dosed with JBT-101
1 withdrawn by physician decision
1 withdrew consent
1 withdrew for AE of moderate dizziness

26 Completed ≥ 1 efficacy evaluation

24 Completed study

15 Dosed with Placebo

15 Completed ≥ 1 efficacy evaluation

14 Completed study

1 withdrew consent