



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

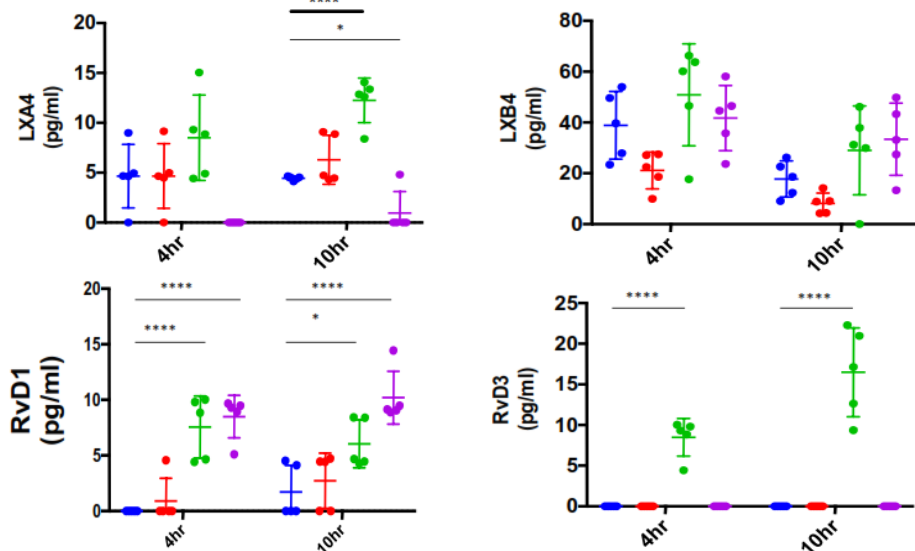
R. Spiera, L. Hummers, L. Chung, T. Frech, R. Domsic, V. Hsu, D. E. Furst, J. Gordon,
M. Mayes, R. Simms, S. Constantine, and B. White



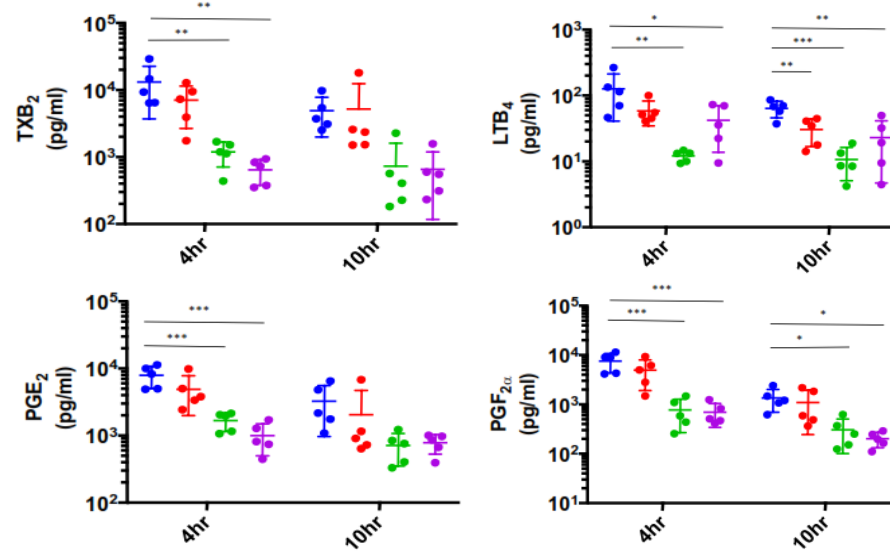
Anabasum (JBT-101)

- **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

Characteristic	Anabasum n = 27	Placebo n = 15
Female, %	85.2%	60.0%
Age, mean (SD)	48.7 (10.4)	46.5 (11.1)
Caucasian, %	81.5%	80.0%
Disease duration ¹ , months, mean (SD)	37.1 (19.0)	40.6 (19.5)
Concomitant immuno-modulating drugs, %	92.9%	80.0%
Modified Rodnan skin score, mean (SD)	23.9 (10.4)	26.2 (11.2)
Physician global assessment, mean (SD)	4.5 (1.8)	5.2 (2.1)
Patient global assessment, mean (SD)	4.8 (2.3)	4.9 (2.8)
HAQ-DI, mean (SD)	1.1 (0.8)	1.5 (0.8)
Forced vital capacity, % predicted, mean (SD)	85.9 (13.7)	79.6 (10.3)

¹ Since first non-Raynaud's symptom

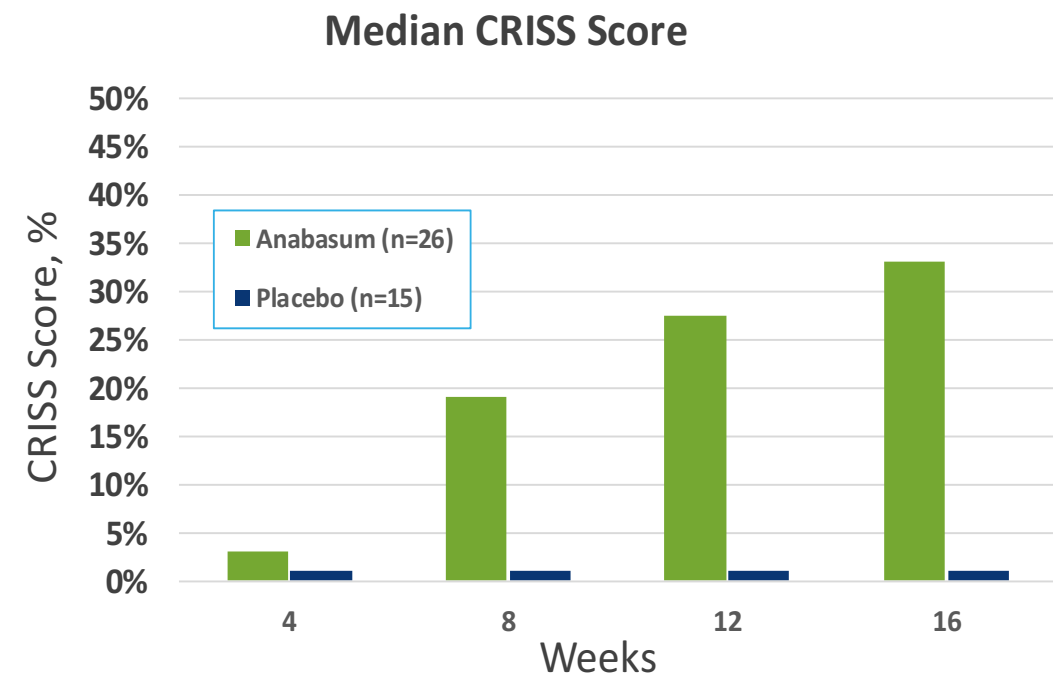
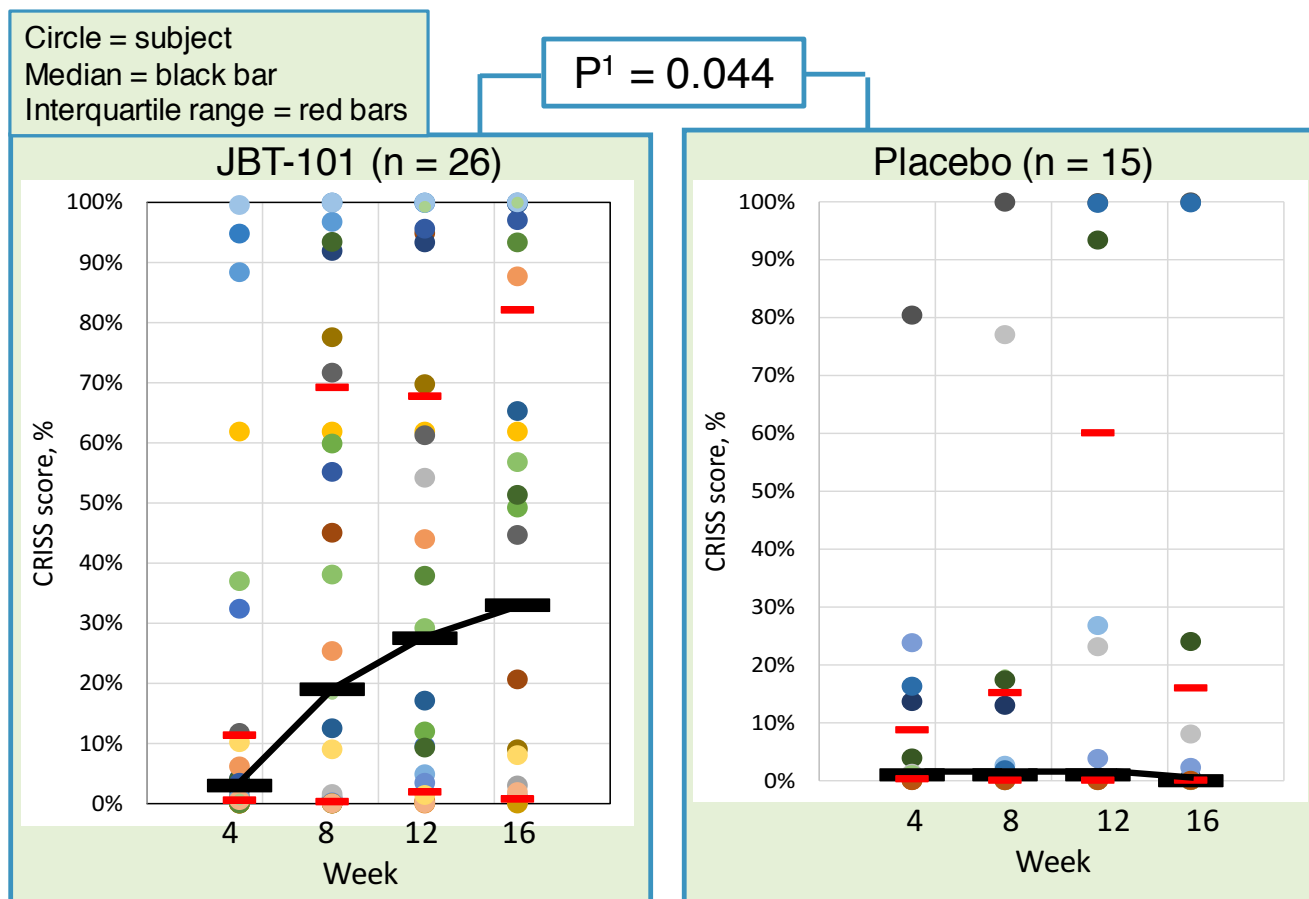
No statistically significant differences between anabasum-treated and placebo-treated subjects



EFFICACY DATA



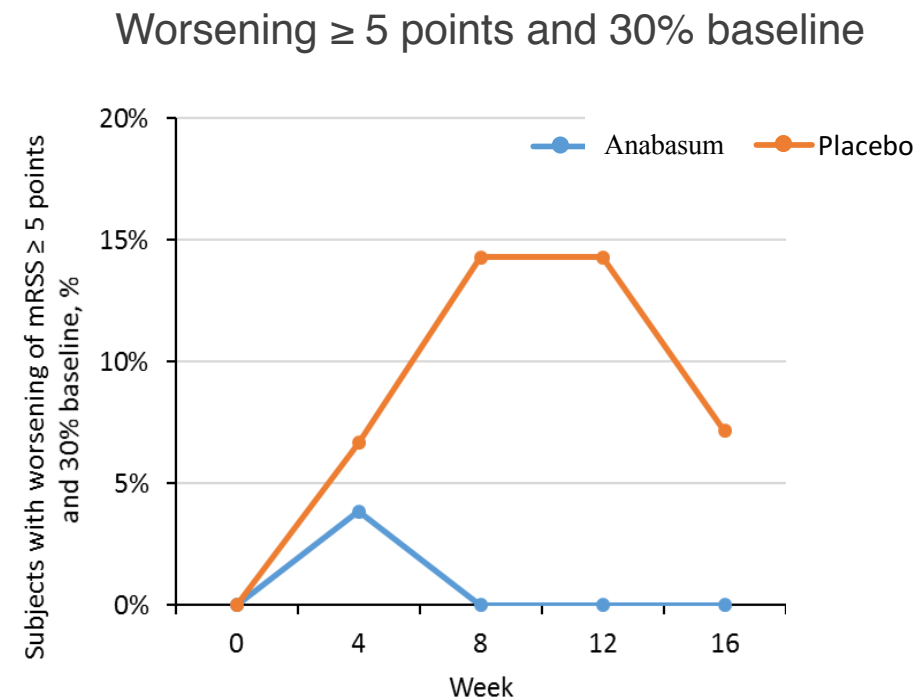
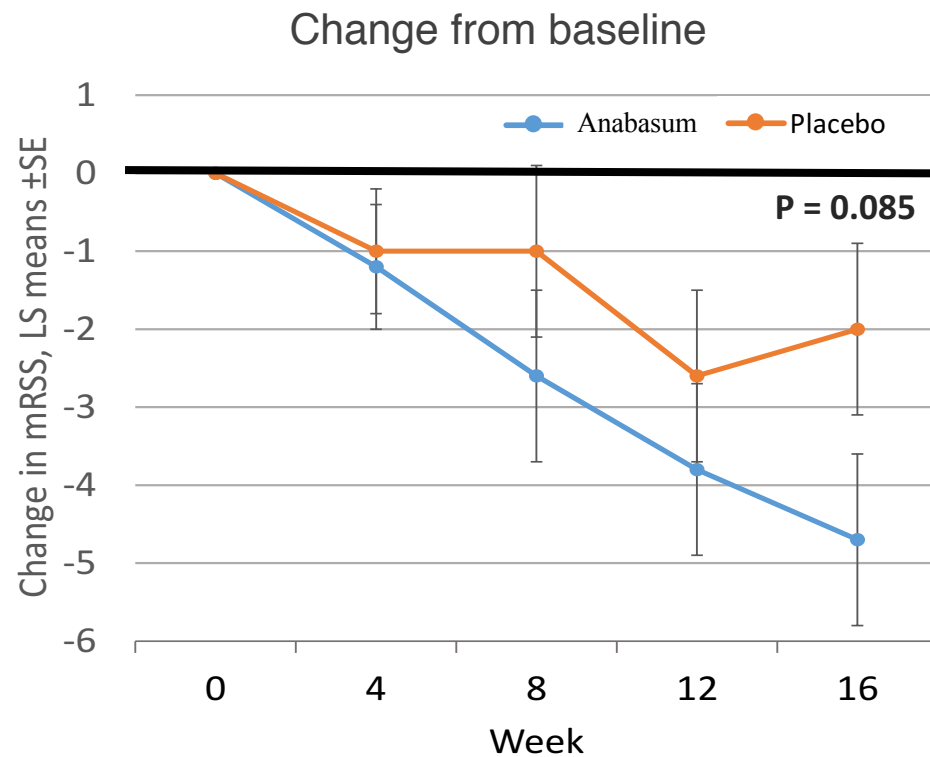
Primary Efficacy Outcome: CRISS Scores



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

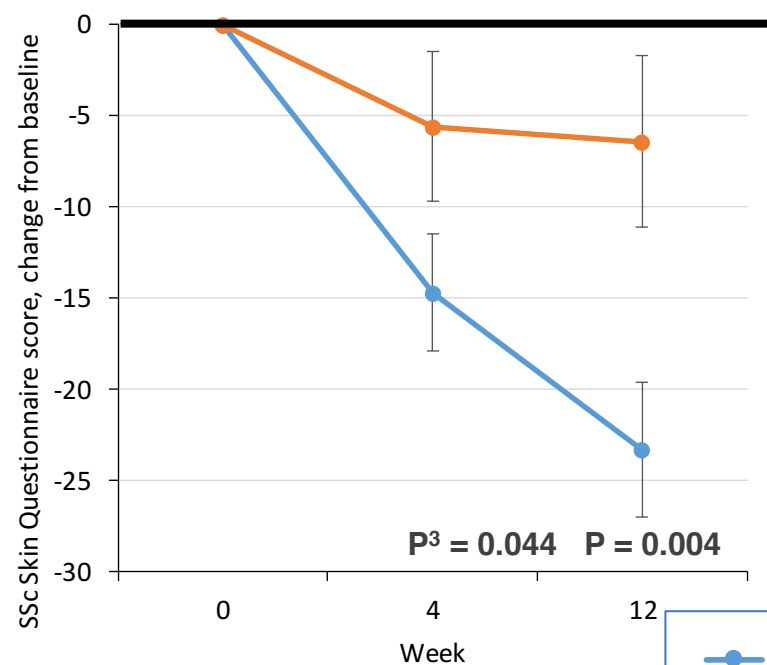


¹ Efficacy population. ³ Least squares mean difference, analysis of covariance model, one-sided p-value.

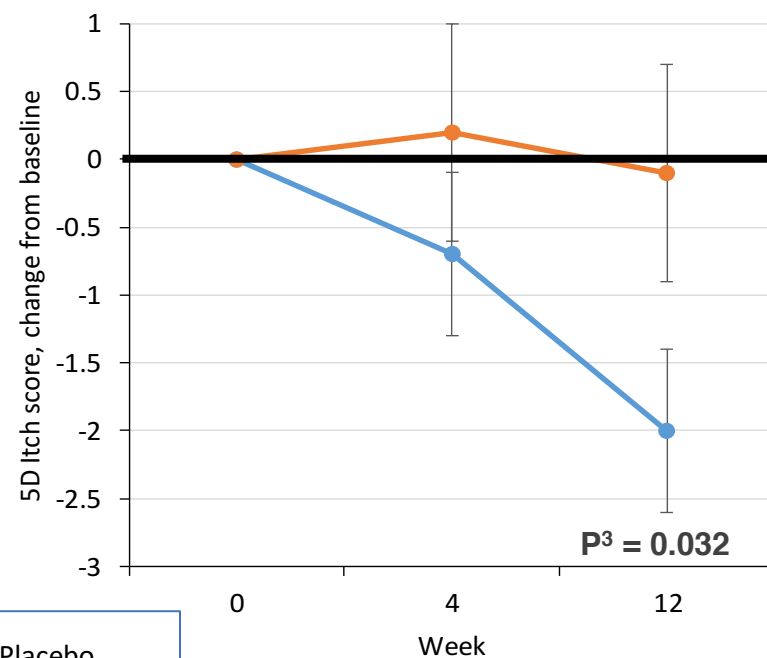


Change In Patient Assessments Of Skin Symptoms

SSc SkinPRO Symptoms Questionnaire¹



5-D Itch Questionnaire²



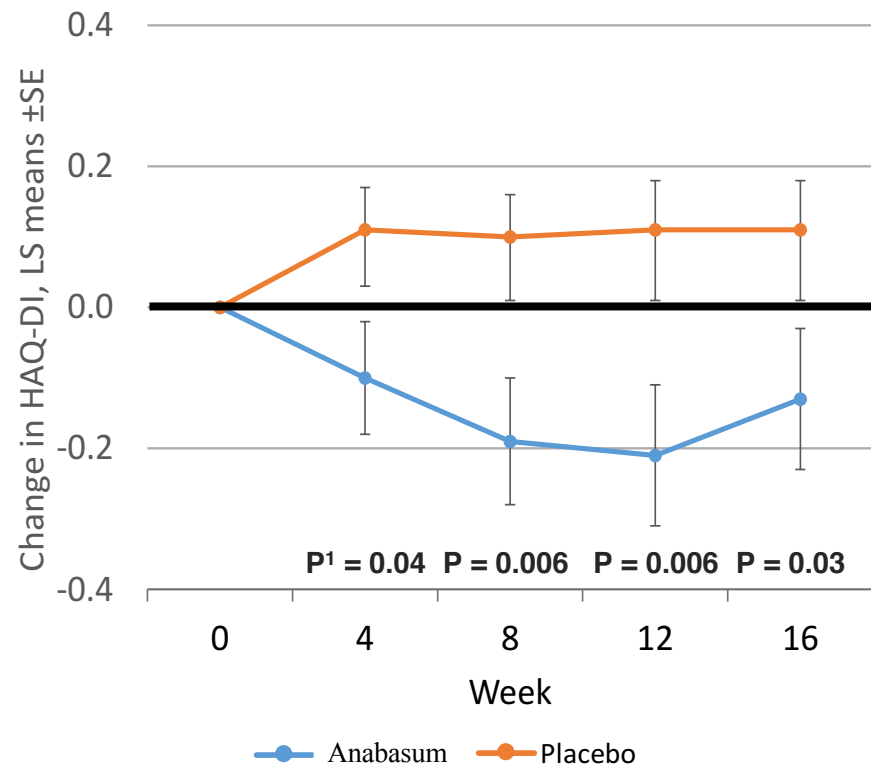
—●— Anabasum —●— Placebo
Improvement is a reduction in score

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 \pm SE, analysis of covariance model. P-values are based on LS mean difference, one-sided p-values shown if $P \leq 0.10$ (pre-specified).

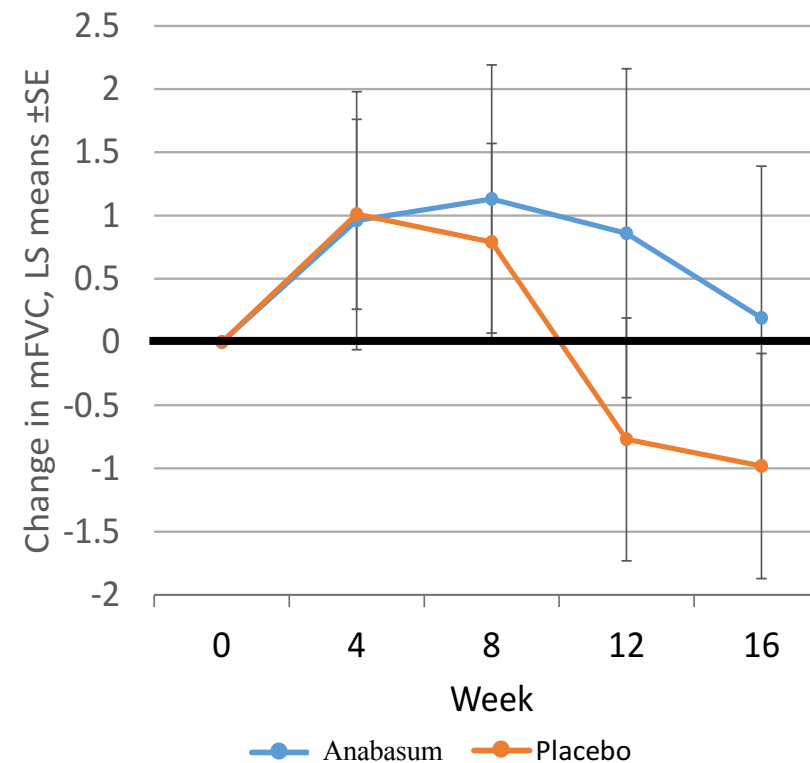


Additional CRISS Score Set Outcomes (Part 1)

HAQ-DI, Change from Baseline



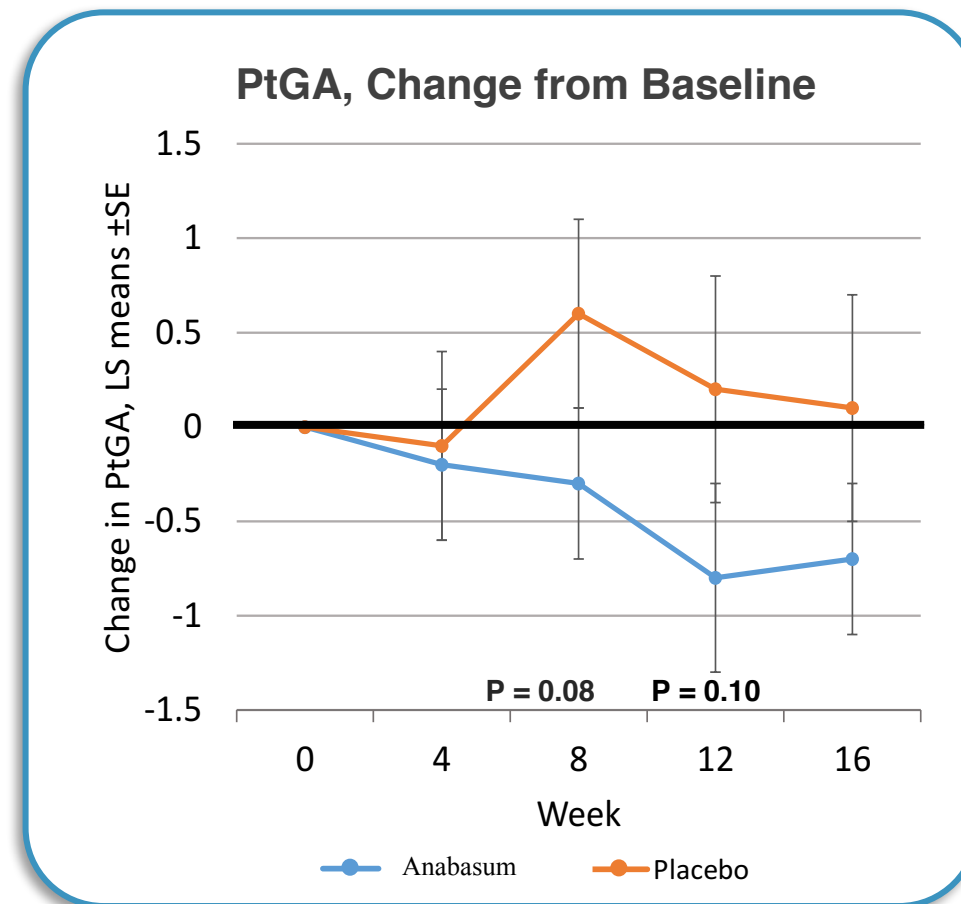
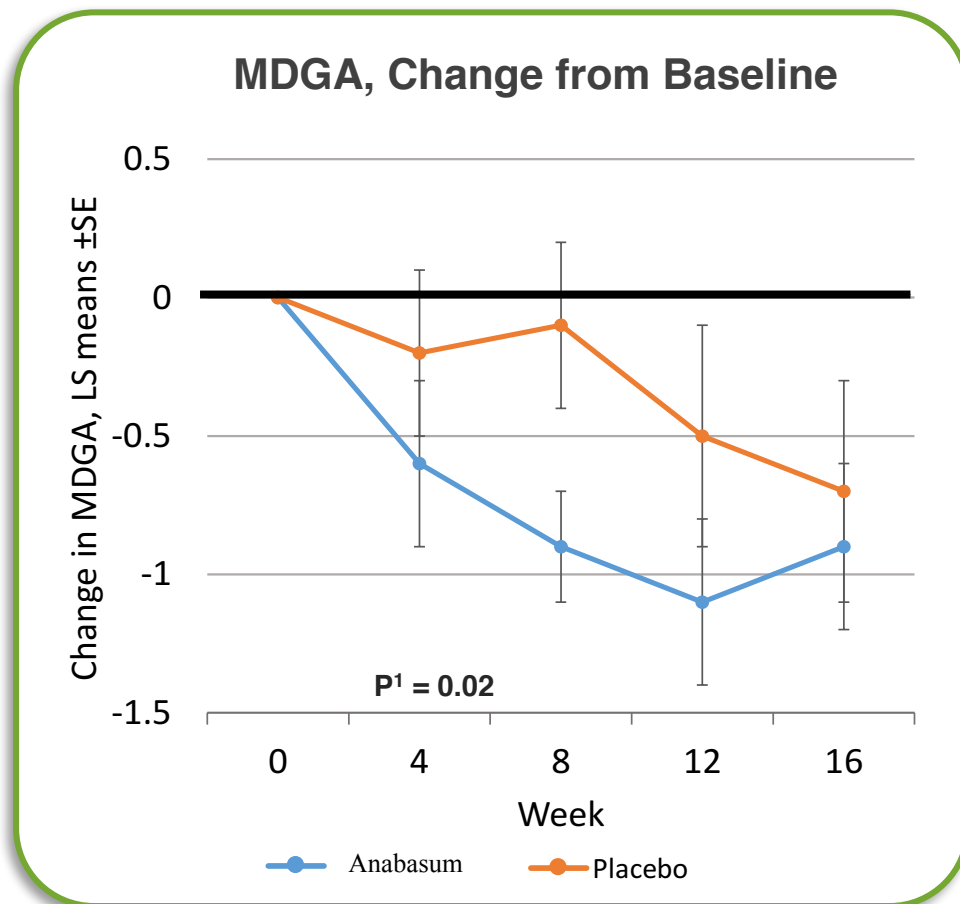
FVC % Predicted, Change from Baseline



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



Additional CRISS Score Set Outcomes (Part 2)



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



PROMIS-29 Physical Function and Social Role Scores Improve

Higher score = better function

DOMAIN	Baseline score, mean (SD)		Change from baseline. LSM (SE)			Treatment difference (SE) (90% CI)	P-value ¹
	JBT-101	Placebo	Week	JBT-101	Placebo		
Physical function	44.3 (8.1)	38.2 (6.6)	4	2.3 (0.9)	1.2 (1.2)	1.1 (1.5) (-1.4, 3.6)	0.22
			12	3.5 (1.1)	-1.1 (1.4)	4.6 (1.8) (1.5, 7.7)	0.009
Social role	46.5 (8.9)	40.8 (7.3)	4	2.1 (0.9)	1.3 (1.2)	0.7 (1.6) (-1.9, 3.4)	0.32
			12	3.9 (1.1)	1.3 (1.5)	2.7 (1.9) (-0.6, 5.9)	0.09

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

DOMAIN	Baseline score, mean \pm SD		Change from baseline. LSM \pm SE			Treatment difference \pm SE (90% CI)	P-value ¹
	JBT-101	Placebo	Week	JBT-101	Placebo		
Sleep disturbance	52.2 \pm 7.3	52.7 \pm 7.2	4	-2.7 \pm 1.5	1.5 \pm 1.9	-4.3 \pm 2.3 (-8.1, -0.4)	0.03
			12	-3.9 \pm 2.2	2.0 \pm 1.8	-5.3 \pm 2.3 (-9.2, -1.4)	0.01
Fatigue	57.0 \pm 12.6	59.8 \pm 8.5	4	-1.3 \pm 1.2	-0.04 \pm 1.6	-1.3 \pm 2.1 (-4.5, 3.0)	0.25
			12	-2.3 \pm 1.2	-2.2 \pm 1.9	-0.1 \pm 2.4 (-4.2, 4.0)	0.49
Pain interference	57.7 \pm 8.6	62.9 \pm 8.9	4	-3.4 \pm 1.2	-1.4 \pm 1.6	-2.0 \pm 2.1 (-5.4, 1.5)	0.17
			12	-3.9 \pm 2.2	-0.6 \pm 1.8	-3.9 \pm 2.2 (-7.7, -0.2)	0.04
Pain intensity	4.5 \pm 2.6	4.7 \pm 2.8	4	-0.6 \pm 0.3	0.0 \pm 0.4	-0.6 \pm 0.6 (-1.5, 0.4)	0.16
			12	-1.0 \pm 0.4	-0.2 \pm 0.6	-0.8 \pm 0.7 (-2.0, 0.4)	0.14

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

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

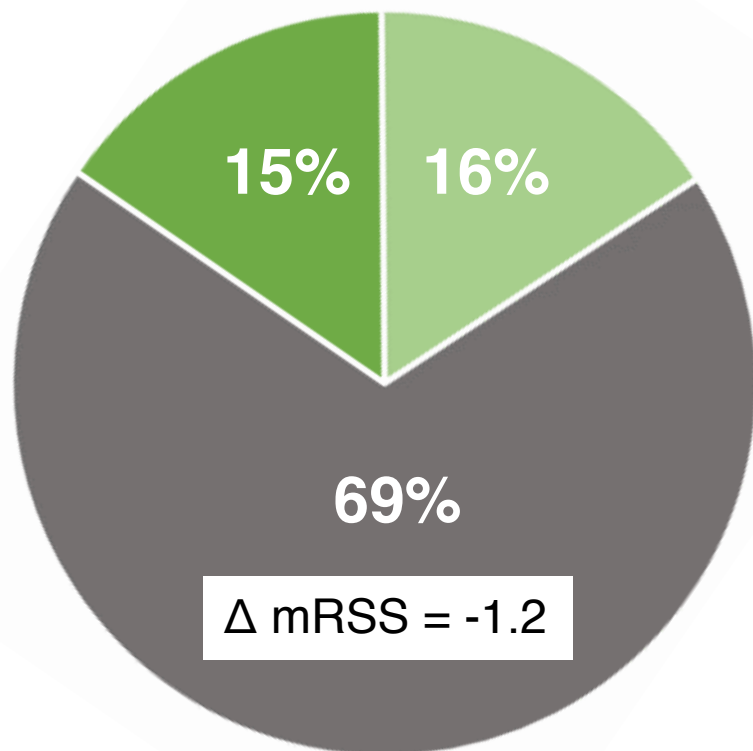
Eugene Y. Kissin, Peter A. Merkel, and Robert Lafyatis



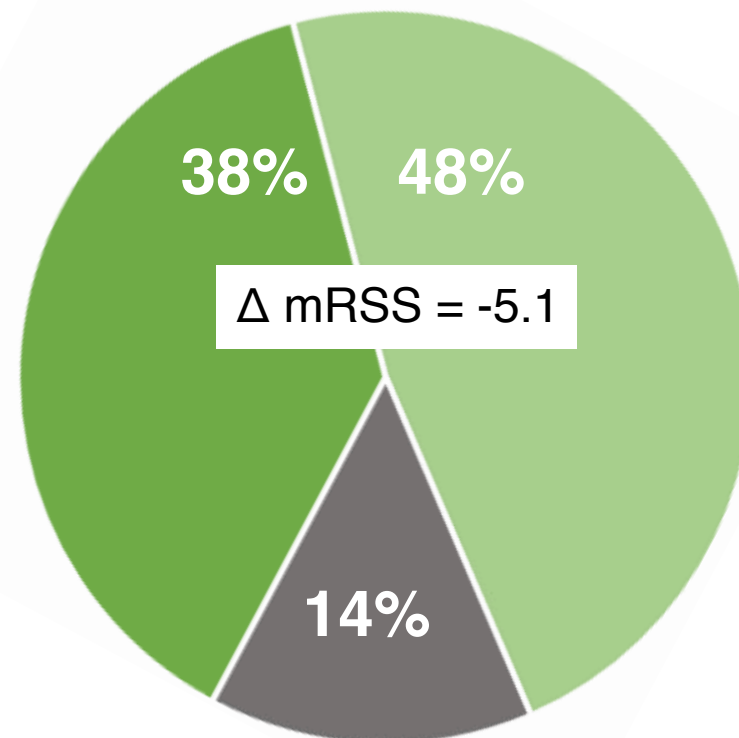
Anabasum Improves Inflammation in the Skin

Change after 12 weeks of treatment

Placebo



Anabasum



P = 0.008
Fisher's exact test
two-sided

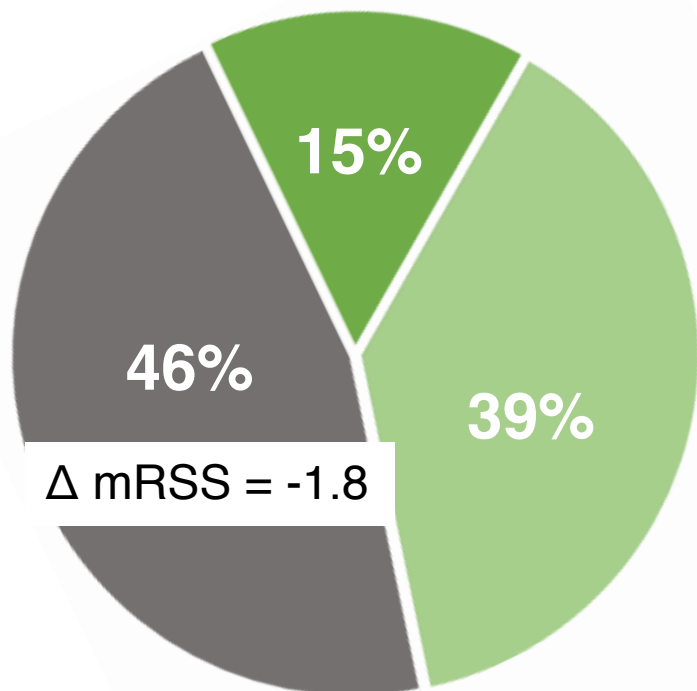
■ Improved ■ Unchanged ■ Worsened



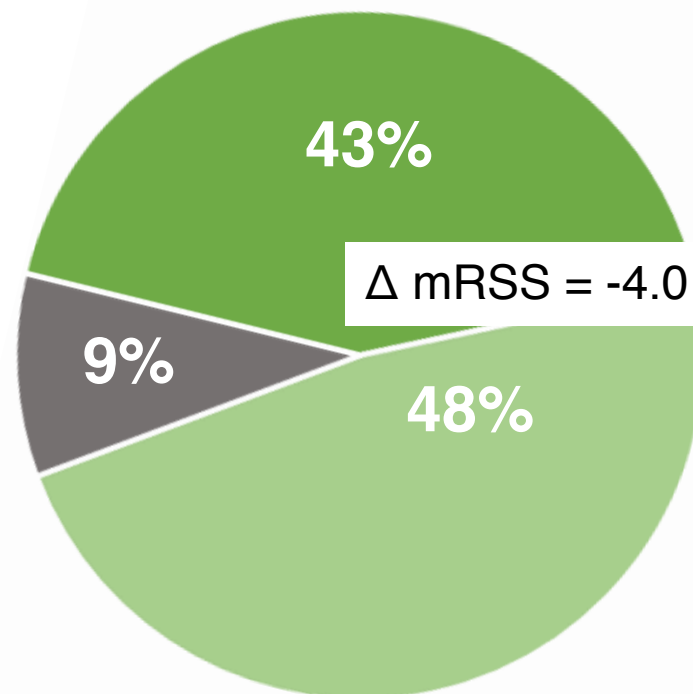
Anabasum Improves Fibrosis in the Skin

Change after 12 weeks of treatment

Placebo



Anabasum



P = 0.049
Fisher's exact test
two-sided

■ Improved ■ Unchanged ■ Worsened



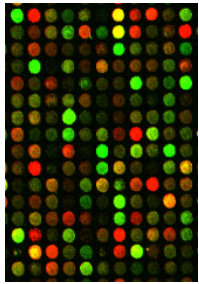
Anabasum Reduces Expression of Genes Associated with Inflammation and Fibrosis Pathways in the Skin

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

Gene Expression Data Collection

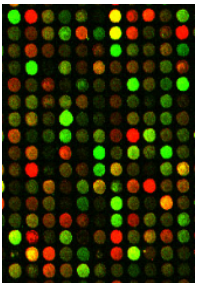
Bioinformatic Analyses

Anabasum, N = 46



Differential Expression
pre- and post-treatment

Placebo, N = 26



Pathway Analysis
pre- and post-treatment

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

Decreased

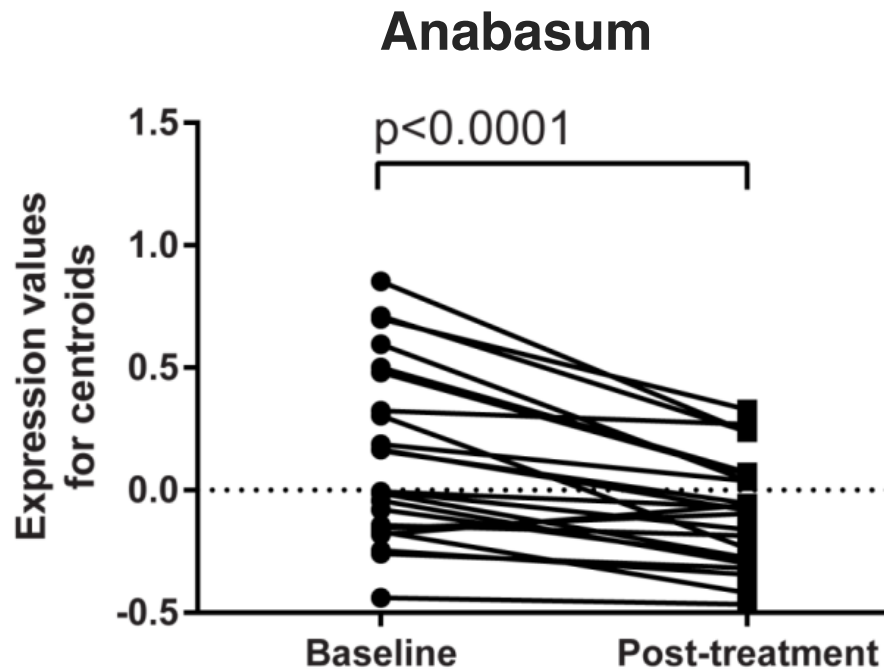
- *ECM organization*
- *Collagen metabolism*
- *Inflammatory response*
- *Response to cytokine*
- *Angiogenesis*



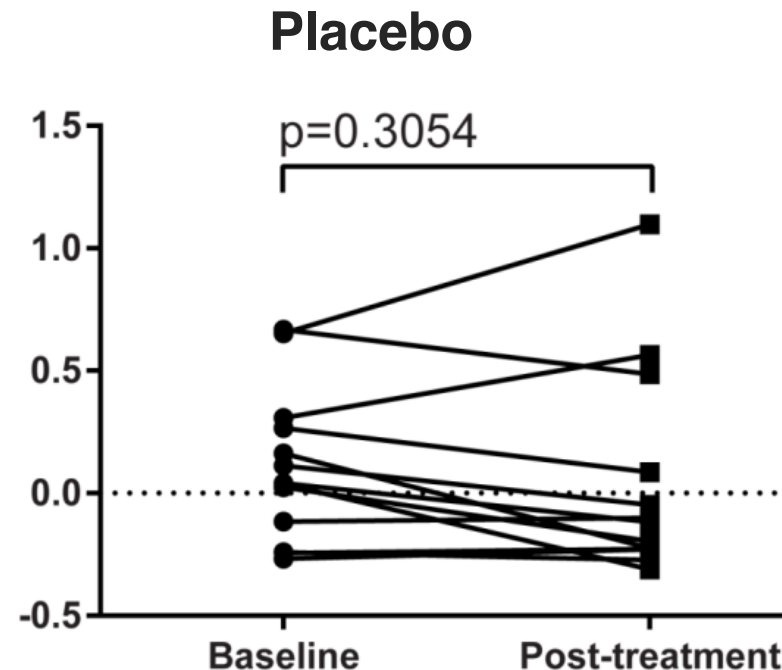
Anabasum Treatment Significantly Inhibits Expression of *Inflammatory Response* Genes in Skin Biopsies

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

