Baseline Subject Demographics and Disease Characteristics in a Phase 3 Study of Safety and Efficacy of Lenabasum in Diffuse Cutaneous Systemic Sclerosis

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Abstract # 0720

Abstract

Background/Purpose: We report the baseline characteristics of a large cohort of diffuse cutaneous systemic sclerosis (dcSSc) patients enrolled in a Phase 3 trial of lenabasum, a preferential cannabinoid receptor type 2 agonist. Treatment with lenabasum, a cannabinoid receptor type 2 agonist, was safe and well-tolerated in a prior Phase 2 study in dcSSc patients and associated with improvements in ACR Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score and multiple secondary efficacy outcomes.

Methods: The RESOLVE-1 Phase 3 study was designed with input from Principal Investigators, other study investigators, and regulatory authorities in the US, EU, and Japan. An important intent of the design was to have eligibility criteria that allow testing of efficacy and safety of lenabasum in an inclusive group of dcSSc subjects to maximize relevance to patients in current practice. The study is ongoing and remains blinded.

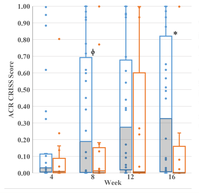
Results: Primary efficacy outcome in the US and EU is the ACR CRISS score at 12 months, comparing lenabasum 20 mg BID to placebo. Key inclusion criteria are males and females ≥ 18 years of age with dcSSc and disease duration ≤ 6 years who are on stable standard-of-care medicines, with stable immunosuppressive mediations allowed. Exceptions are concomitant treatment with > 10 mg per day prednisone or equivalent is disallowed and mRSS needs to be ≥ 15 if disease duration is > 3 to ≤ 6 years. The study enrolled 364 subjects over 15 months who received ≥ 1 dose of study drug at 77 sites in 13 countries in North America (n = 139), Europe (n = 109), and Israel (n = 37), and Asia-Pacific (n = 79), with last subject first visit on May 1, 2019. Baseline characteristics as shown in Table 1. The majority were middle-aged, female, and white, and 77% were on immunosuppressive drugs. Mycophenolate/mycophenolic acid used in 48% of subjects, and 35% of subjects took ≥ 2 concurrent immunosuppressive drugs (max = 4 concurrent). Subjects with disease duration ≤ 3 years and > 3 to ≤ 6 years otherwise had similar demographics and disease characteristics, except a higher proportion of the subjects with shorter disease duration were on methotrexate (p = 0.041, Chi-square), low dose corticosteroids (p = 0.006, Chi-square), or multiple immunosuppressive medications (p = 0.055, Chi-square). Subjects with longer disease duration had slightly lower FVC % predicted (p = 0.018, t-test).

Conclusions: This is the first Phase 3 study to use ACR CRISS as the primary efficacy outcome, a composite outcome of multiple clinically relevant measures of SSc, and the largest interventional study to date in diffuse cutaneous SSc. Benefits of having inclusive eligibility criteria are that they facilitated timely full enrollment and may make the study population more relevant to those in clinical practice. This study provides a template for Phase 3 dcSSc trials designed to show improvement in overall disease and will give valuable information on outcome with routine care as well as test efficacy of lenabasum.

Background

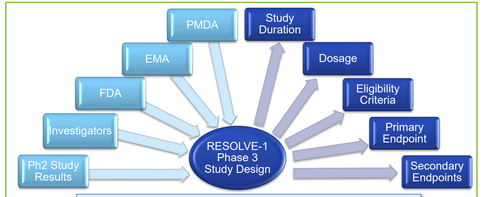
- Lenabasum is a preferential cannabinoid receptor type 2 (CB2) agonist that activates resolution of innate immune responses
- Treatment with lenabasum was safe and well-tolerated in a prior Phase 2 study in dcSSc patients, JBT101-SSc-001
- Results from JBT101-SSc-001 demonstrated that lenabasum was associated with improvements in ACR Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score and multiple secondary efficacy outcomes.

ACR CRISS Score after 16 Weeks of Lenabasum Treatment in a Phase 2 Study Diffuse Cutaneous Systemic Sclerosis Study JBT101-SSc-001



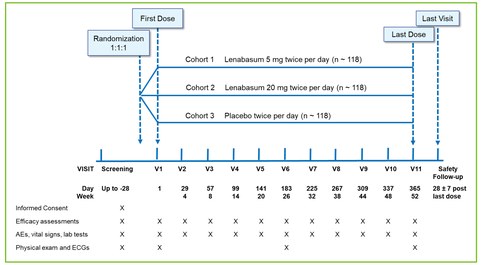
Whisker plot of ACR CRISS scores for individual participants by week. Orange = placebo; Blue = lenabasum. The solid horizontal line within each whisker plot is the median value, and the grey shaded area includes all values from minimum through median.
*P ≤ 0.05, 1-sided MMRM; P = 0.07, 2-sided MMRM
ǂ P ≤ 0.10, 1-sided MMRM.

Methods



Developing Phase 3 Trial Design for JBT101-SSc-002

Study Design



Subject Enrollment

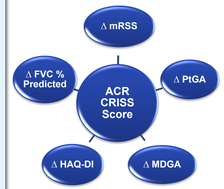
- Enrolled over 15 months; N = 364
- Last subject first visit: May 1, 2019
- Ongoing, blinded

Primary Outcome

Primary Efficacy Outcome: ACR Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) at 52 Weeks

- There is a lack of regulatory precedent for successful trials in SSc that address overall treatment benefit. mRSS is a commonly used endpoint in SSc trials. Although mRSS has been standardized through clinical trial consortia ,change in mRSS has not discriminated active drug from placebo in multiple randomized, blinded clinical trials to date.

- The ACR CRISS score incorporates 5 clinically relevant efficacy outcomes in SSc, including change from baseline in measures of skin and lung disease, patient and physician global assessment of health relates to SSc, and patient-reported function[1]
- Use of ACR CRISS score may reduce risk of a false negative study. The approach to and measurement of the mRSS can be variable, especially among raters with more limited experience.[2,3] This variability can reduce the size of treatment effect, when change in mRSS is used by itself to assess improvement. ACR CRISS has shown a statistically significant treatment effect in studies in which change in mRSS has not
- Experts in SSc are increasingly recognizing ACR CRISS score as an acceptable efficacy outcome for clinical trials that focus on overall treatment of SSc



Key Eligibility Criteria

dcSSc
- Males and Females ≥ 18 years of age
- Fulfills the 2013 ACR criteria for SSc[4]
- Skin thickening on upper arms proximal to the elbows, upper legs proximal to the knees or trunk

Active Disease
- Disease duration ≤ 6 years from the first non-Raynaud's symptom
- mRSS ≥ 15 for those with disease duration of > 3 to ≤ 6 years*
  *Limited to no more than 1/3rd of subjects

Medications
- Stable standard of care medicines allowed
- Immunosuppressive medications allowed
- **Exclusion**: concomitant treatment with > 10 mg per day prednisone

Eligibility criteria allow testing of efficacy and safety of lenabasum in an inclusive group of dcSSc subjects to maximize relevance to patients in current practice.

Subject Demographics and Baseline Characteristics

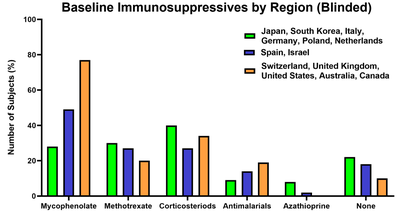
Demographics and Baseline Disease Characteristics (Blinded)

Characteristic at First Dose	Mean (SD) or %		
	Disease duration		
	0 to ≤ 6 years	0 to ≤ 3 years	> 3 to ≤ 6 years
	N = 365 (100%)	N = 242 (66.3%)	N = 123 (33.7%)
Years of age	50 ± 12.9	51 ± 12.6	49 ± 13.5
Female	76%	73%	81%
ILD[1]	49%	41%	64%
Caucasian	249 (68.2%)	166 (68.6%)	83 (67.5%)
Asian	78 (21.4%)	53 (21.9%)	25 (20.3%)
Black	18 (4.9%)	11 (4.6%)	7 (5.7%)
Other[2]	20 (5.5%)	12 (5.0%)	8 (6.5%)
mRSS[3]	22.5 (8.20)	22.3 (8.82)	22.9 (6.84)
MDGA	5.4 (1.58)	5.4 (1.63)	5.5 (1.48)
PtGA	4.9 (2.12)	5.0 (2.09)	4.7 (2.16)
HAQ-DI[4]	1.1 (0.77)	1.1 (0.79)	1.1 (0.74)
FVC % predicted	80.1 (17.08)	81.7 (16.59)	77.0 (17.64)
Any immunosuppressive drug	84%	87%	80%
≥ 2 immunosuppressive drugs	44%	48%	38%
Mycophenolate	55%	56%	53%
Corticosteroids	35%	38%	28%
Methotrexate	25%	29%	17%
Other[5]	35%	36%	33%

[1] ILD per Scleroderma Medical History, Chest-CT
[2] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Other
[3] Based on the mRSS – primary score
[4] Includes all subjects' scores regardless of aids/devices used
[5] Includes abatacept, apremilast, azathioprine, cyclophosphamide, etanercept, hydroxychloroquine, immunoglobulin, rituximab, tacrolimus, tocilizumab

- The majority of enrolled subjects are White, middle-aged, and female
- Subjects with disease duration ≤ 3 years and > 3 to ≤ 6 years had similar demographics and disease characteristics
- Subjects with longer disease duration also had slightly lower FVC % predicted (p = 0.013, t-test)
- 44% of subjects took ≥ 2 concurrent immunosuppressive drugs (max = 5 concurrent)
- A higher proportion of the subjects with shorter disease duration were on methotrexate (p = 0.020, Fishers exact), low dose corticosteroids (p = 0.064, Fishers exact), or multiple immunosuppressive medications (p = 0.096, Fishers exact)

Baseline Immunosuppressives by Region (Blinded)



Region	Average Number of Immunosuppressives
Japan, South Korea, Italy, Germany, Poland, Netherlands	1.3
Spain, Israel	1.5
Australia, Canada, Switzerland, United Kingdom, United States	1.7

Conclusions

- This is the first Phase 3 study to use ACR CRISS as the primary efficacy outcome, a composite outcome of multiple clinically relevant measures of SSc. It is the largest interventional study to date in diffuse cutaneous SSc.
- The majority of patients were female, Caucasian, and on background immunosuppressive medications.
- Despite a high rate of background off-label concomitant treatment with immunosuppressive drugs, the SSc disease burden is significant as reflected in baseline mRSS, HAQ-DI, PtGA, and MDGA.
- Benefits of having inclusive eligibility criteria are that they facilitated timely, full enrollment and will make the study population representative of patients in clinical practice.
- This study provides a template for Phase 3 dcSSc trials that are testing improvement in overall disease in SSc and will give valuable information on outcome with routine care as well as test efficacy of lenabasum.

References

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Presenting Author Disclosures

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