RESOLVE-1, a Phase 3 Trial of Lenabasum, a CB2 Agonist, for the Treatment of Diffuse Cutaneous Systemic Sclerosis

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Disclosures for Robert Spiera, M.D.

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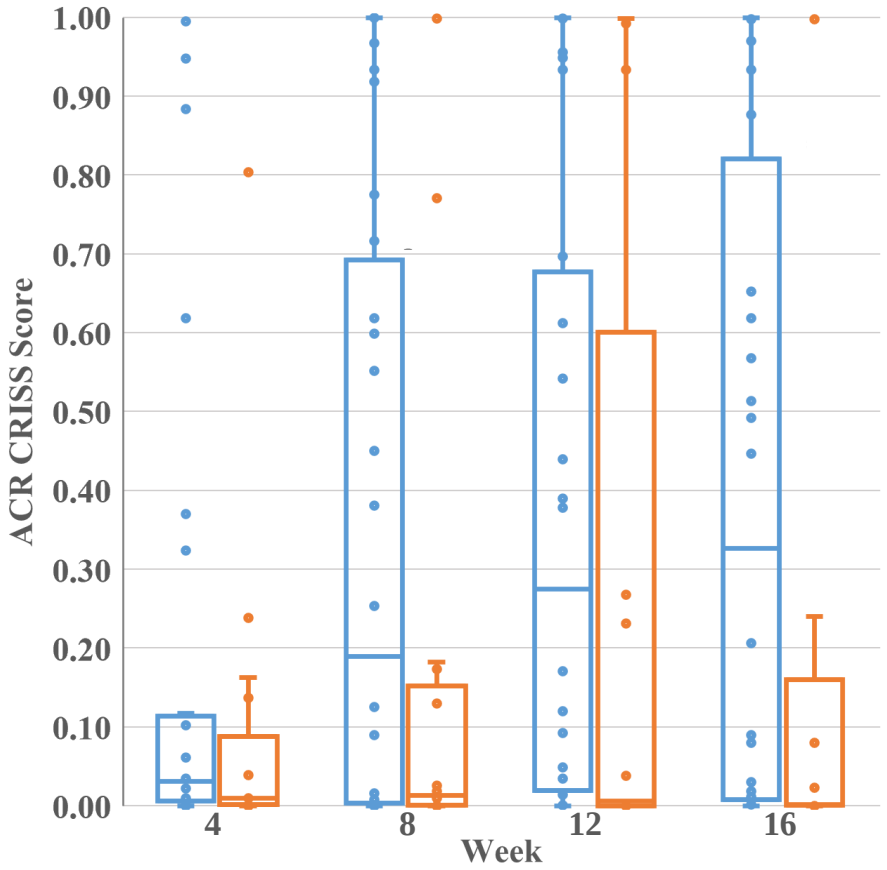
  - Janssen
  - Chemocentryx
  - Formation Biologics

Rationale

- Lenabasum is an oral, non-immunosuppressive preferential cannabinoid-2 (CB2) agonist that activates resolution of innate immune responses
- Lenabasum is active in animal models of bleomycin-induced skin and lung fibrosis
- In a 16-week, Phase 2 study of lenabasum in patients with dcSSc, treatment lenabasum was safe, well-tolerated, and was associated with greater improvement in the ACR CRISS score and improved histology and biomarkers in the skin than treatment with placebo
- The Phase 3, RESOLVE-1 study evaluated the efficacy, safety, and tolerability of lenabasum compared to placebo in patients with dcSSc

Phase 2: ACR CRISS Scores



Orange = placebo; Blue = lenabasum. A difference in ACR CRISS scores was observed between lenabasum and placebo cohorts at Week 16 [P = 0.0374, 1-sided (primary efficacy outcome); P = 0.0747, 2-sided]. At Weeks 4, 8, and 12, P = 0.1121, 0.0581, and 0.1106, respectively, 1-sided, MMRM

RESOLVE-1 Phase 3 study design

PRIMARY EFFICACY ENDPOINT

ACR CRISS score

- Week 52
- Lenabasum 20 mg BID vs placebo

DESIGN

- Double-blind, randomized
- 365 dosed
- 52 weeks
- 76 sites in NA, Europe and Asia Pacific
- 1:1:1 central randomization

20 mg BID | 5 mg BID | Placebo BID

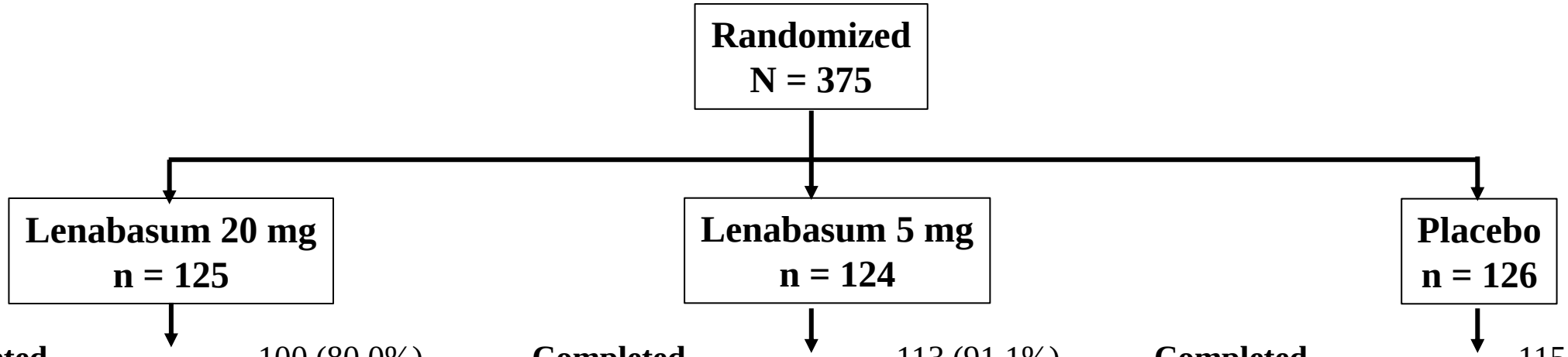
SECONDARY ENDPOINTS

- Change in mRSS
- Change in HAQ-DI
- Change in FVC % predicted

ELIGIBILITY

- Diffuse cutaneous SSc
- Disease duration ≤ 6 years. If 3-6 years, then mRSS ≥ 15
- Background immunosuppressive therapies (IST) allowed if:
  - Stable for at least 8 weeks before screening
  - Corticosteroids not to exceed 10 mg prednisone per day or equivalent
- Decision to allow background immunosuppressive therapies was made to reflect current clinical practice

Subject disposition and reasons for discontinuation



	Lenabasum 20 mg n = 125	Lenabasum 5 mg n = 124	Placebo n = 126
Completed	100 (80.0%)	113 (91.1%)	115 (91.3%)
Discontinued	25 (20.0%)	11 (8.9%)	11 (8.7%)
• Death	2 (1.6%)	0	1 (0.8%)
• Any adverse event	5 (4.0%)	1 (0.8%)	6 (4.8%)
• Related adverse event	0	0	1 (0.8%)
• Lack of efficacy	0	2 (1.6%)	0
• Consent withdrawn	10 (8.0%)	3 (2.4%)	1 (0.8%)
• Lost to follow up	1 (0.8%)	1 (0.8%)	0
• Physician decision	2 (1.6%)	0	0
• Non-compliance	0		
• Noncompliance		2 (1.6%)	0
• Other*	5 (4.0%)	2 (1.6%)	3 (2.4%)

* Other includes 10 subjects who were randomized but never dosed. N = 365 in safety population. N = 363 in mITT population with 2 subjects in lenabasum 5 mg BID cohort who were dosed but had no efficacy follow-up

Baseline demographic characteristics

Demographic characteristics	Lenabasum 20 mg N = 120	Lenabasum 5 mg N = 120	Placebo N = 123
	N (%) or mean ± SD		
Age, years	49.7 ± 12.9	49.7 ± 13.5	51.9 ± 12.4
Female	96 (80.0)	88 (73.3)	91 (74.0)
BMI, kg/m^2	25.0 ± 5.6	24.5 ± 5.0	25.1 ± 5.2
Location			
North America	46 (38.3)	47 (39.1)	47 (38.2)
Europe, Israel, Australia	52 (43.3)	53 (44.2)	54 (43.9)
Asia	22 (18.3)	20 (16.7)	22 (17.9)
Race			
White	84 (70.0)	80 (66.7)	88 (71.5)
Asian	24 (20.0)	24 (20.0)	26 (21.1)
Black/African American	6 (5.0)	8 (6.7)	4 (3.3)
Other	6 (5.0)	8 (6.7)	5 (4.1)

Modified intent-to-treat (mITT) population

Baseline disease characteristics and immunosuppressive treatments

Characteristics and treatments	Lenabasum 20 mg N = 120	Lenabasum 5 mg N = 120	Placebo N = 123
		N (%) or mean ± SD	
Disease characteristic			
Disease duration, months	32.7 (19.94)	32.2 (17.62)	30.2 (16.84)
mRSS (0 - 51)	22.1 ± 8.55	22.0 ± 7.35	23.3 ± 8.68
MDGA (0 - 10)	5.3 ± 1.46	5.4 ± 1.58	5.6 ± 1.71
HAQ-DI (0 - 3)	1.12 ± 0.782	1.07 ± 0.765	1.16 ± 0.768
PtGA (0 - 10)	5.0 ± 2.10	4.8 ± 2.16	5.0 ± 2.10
FVC, % predicted	81.3 ± 18.83	79.5 ± 16.13	78.9 ± 15.23
Immunosuppressive therapies (IST)			
Any	107 (89.2)	94 (78.3)	103 (83.7)
Mycophenolate	63 (52.5)	57 (47.5)	65 (52.8)
Corticosteroids	28 (23.3)	33 (27.5)	39 (31.7)
Methotrexate	26 (21.7)	24 (20.0)	19 (12.2)
Others	32 (26.7)	28 (23.3)	28 (22.0)
1 immunosuppressive therapy	69 (57.7)	56 (46.7)	61 (49.6)
≥ 2 immunosuppressive therapies	38 (31.7)	38 (31.7)	42 (34.1)
Treatment duration ≤ 2 years	67 (55.8)	59 (49.2)	72 (58.5)
Treatment duration > 2 years	41 (34.2)	35 (29.2)	31 (25.2)

Modified intent-to-treat (mITT) population.

Primary and secondary efficacy outcomes

Outcome	Lenabasum 20 mg BID N = 100	Lenabasum 5 mg BID N = 113	Placebo BID N = 115
Primary			
ACR CRISS Step 1 = 0	n = 1, 1 ILD	N = 4, 1 CHF, 3 ILD	N = 4, 1 renal crisis, 3 ILD
ACR CRISS score, median (IQR)	0.8880 (0.9360)	0.8270 (0.9180)	0.8870 (0.0710, 0.9990)
P-value - Ranked Score, MMRM	0.4972	0.3486	
Secondary			
Change in mRSS, mean (SD)	-6.7 (6.59)	-7.1 (6.24)	-9.1 (7.72)
Change in HAQ-DI, mean (SD)	-0.133 (0.4363)	-0.060 (0.3917)	-0.127 (0.4677)
Change in FVC, %, L, mean (SD)	-1.602 (6.9106)	-2.248 (6.2099)	-0.993 (8.6840)

Modified intent-to-treat (mITT) population. Missing visits or ACR CRISS score core items due to COVID-19 were imputed using LOCF. Other missing data for any core items were imputed using Markov Chain Monte Carlo multiple imputation technique prior to calculating the score, but missing visits are not imputed. Combined inference statistics. Each imputation was analyzed using mixed model repeated measures (MMRM) on the ranked ACR CRISS score with region, disease duration, baseline mycophenolate use, visit, treatment, and treatment-by-visit interaction as the fixed effects and baseline mRSS as a covariate. Secondary outcomes were similarly analyzed, but using MMRM without ranked score.

- **Improvement in placebo group far exceeded expectations based on literature and expert opinions**
- **Unable to discern treatment effect on top of placebo effect**

Pre-specified analysis: Background mycophenolate (MMF) had statistically significant effect on ACR CRISS score

Pre-specified: Impact of pre-specified fixed effects on MMRM model for ACR CRISS score. Also prespecified analysis for each core item of ACR CRISS score

Effect	P value
Baseline MMF (Yes, No)	< 0.0177
Visit	< 0.0001
Baseline MMF*Visit	0.0290
Study drug treatment	0.8590
Study drug treatment*Visit	0.9980
Baseline mRSS (≤ 25, > 25)	0.4627
Region (US, non-US)	0.5395
Disease duration (≤ 2 years, > 2 years)	0.3946

Post-hoc observation: Efficacy was greater when duration of MMF treatment was shorter at baseline. All subjects.

	N	ACR CRISS Score (IQR)	Change in mRSS (SD)
No IST	49	0.352 (0.001, 0.919)	-4.5 (6.75)
All MMF	173	0.936 (0.308, 0.999)	-8.61 (7.15)
≤ 6 months	51	0.992 (0.537, 1.000)	-10.8 (8.58)
≤ 1 year	95	0.975 (0.454, 1.000)	-9.9 (7.90)
≤ 2 years	112	0.956 (0.361, 1.000)	-9.3 (7.75)
> 2 years	57	0.856 (0.219, 0.989)	-7.1 (5.22)

Mycophenolate (MMF) = mycophenolate mofetil, mycophenolic acid, or mycophenolate sodium

- **MMF had statistically significant effect on ACR CRISS score that increased with visit. Other pre-specified baseline factors of mRSS score, region, and disease duration did not have a statistically significant effect on ACR CRISS score**
- **Duration of MMF treatment influenced efficacy results, with lower ACR CRISS scores and change in mRSS with longer treatment duration (> 2 years at baseline)**

Pre-specified analysis: Background mycophenolate (MMF) had statistically significant effect on FVC

Pre-specified: Impact of pre-specified fixed effects on MMRM model for change in FVC % predicted

Effect	P value
Baseline MMF (Yes, No)	0.05
Visit	< 0.0001
Baseline MMF*Visit	0.05
Study drug treatment	0.93
Study drug treatment*Visit	0.67
Baseline FVC	< 0.0001
Region (US, non-US)	0.23
Disease duration (≤ 2 years, > 2 years)	0.43

Post-hoc observation: Efficacy was greater when duration of MMF treatment was shorter at baseline. All subjects.

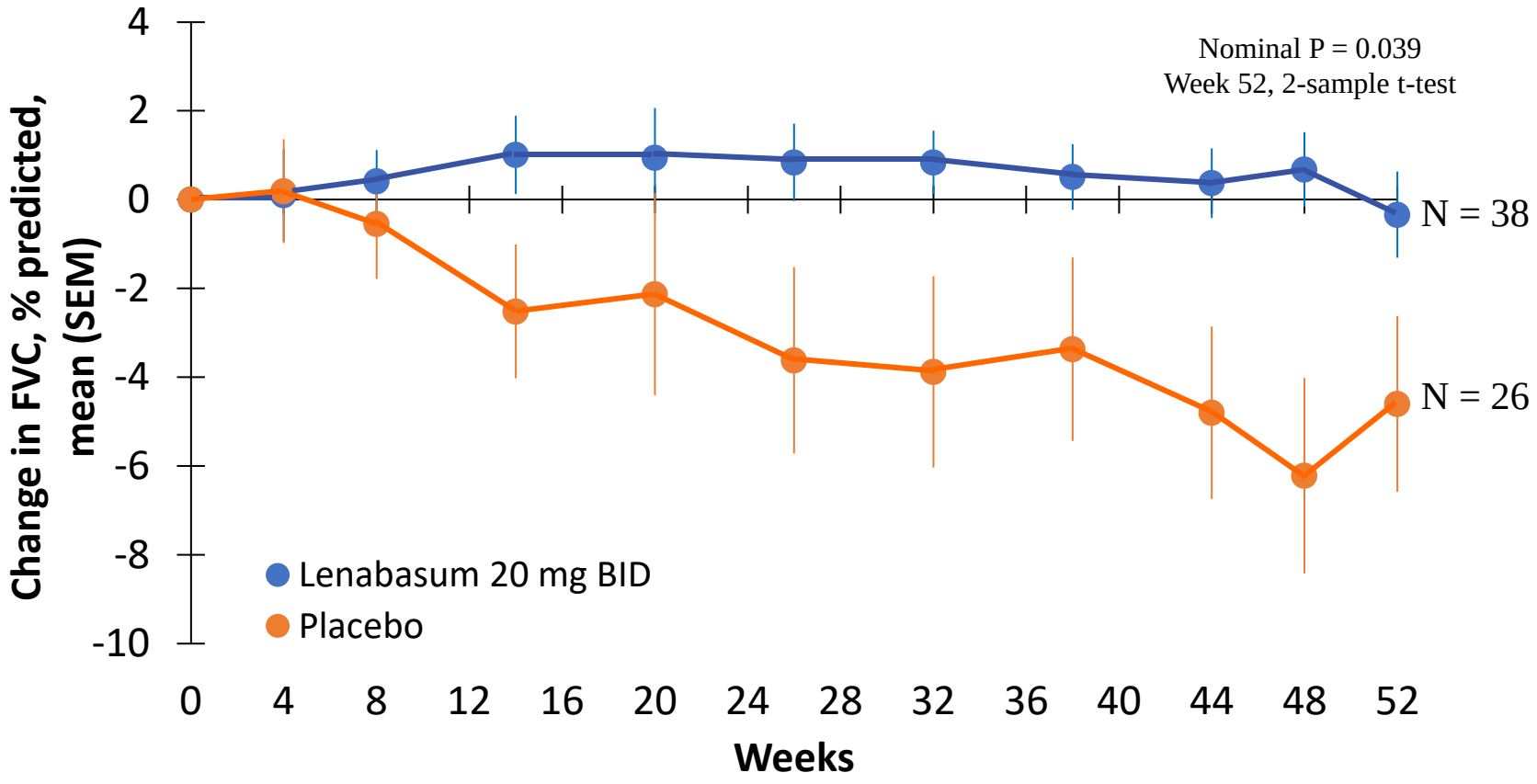
	N	FVC, mL (SD)	FVC, % predicted (SD)
No IST	45	-145 (246)	-3.89 (6.95)
All MMF	154	-49 (268)	-0.71 (6.86)
≤ 6 months	45	45 (306)	1.98 (7.851)
≤ 1 year	87	0 (267)	0.68 (7.11)
≤ 2 years	103	-16 (256)	0.25 (6.79)
> 2 years	51	-117 (277)	-2.7 (6.58)

Mycophenolate (MMF) = mycophenolate mofetil, mycophenolic acid, or mycophenolate sodium

- **Baseline FVC % predicted and MMF at baseline had a significant effect on change in FVC, % predicted, whereas region or disease duration did not, in the MMRM model. MMF effect has an interaction with time**
- **Duration of MMF treatment at baseline also influenced results, with greater benefit on FVC with shorter treatment duration. After 2 years treatment with MMF, subsequent decline in FVC began to approach that of subjects on no immunosuppressive therapies**

Post-hoc analysis: Subjects treated with lenabasum 20 mg BID added to established IST (> 2 years duration) had stable FVC % predicted

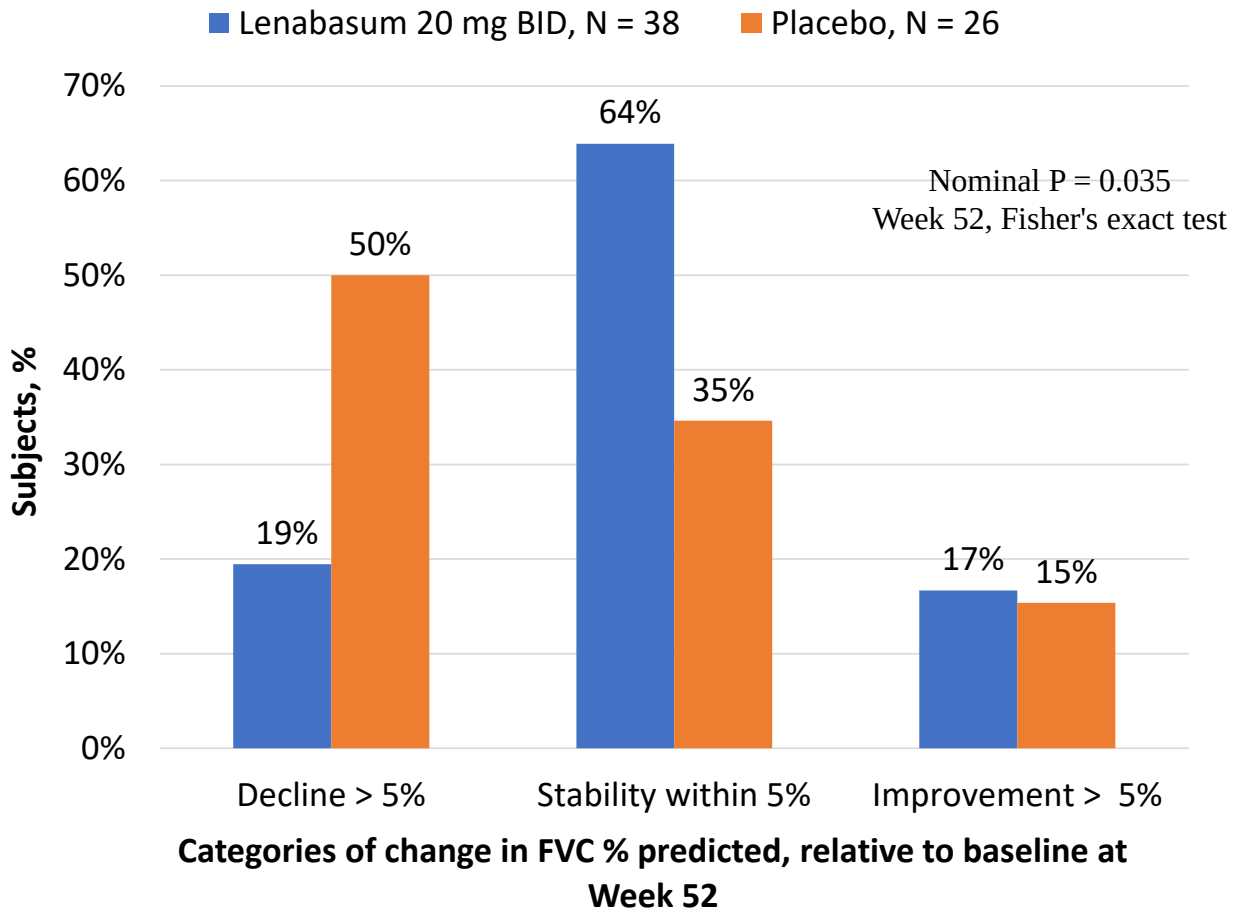
Subjects treated with lenabasum 20 mg BID added to established IST had stable FVC % predicted over 1 year



IST = immunosuppressant therapies. Post-hoc analyses, per protocol population of subjects who completed study drug and Week 52, LOCF for any missing values. Subjects were receiving at least 1 background IST for greater than 2 years treatment duration at baseline, and any MMF treatment must be > 2 years duration

Post-hoc analysis: Subjects treated with lenabasum 20 mg BID added to established IST had less decline and more stability in FVC % predicted

A lower proportion of subjects treated with lenabasum 20 mg BID added to established immunosuppressive therapies had worsening lung function and a higher proportion had stable lung function, compared to subjects treated with placebo



IST = immunosuppressant therapies. Post-hoc analyses, per protocol population of subjects who completed study drug and Week 52, LOCF for any missing values. Subjects were receiving at least 1 background IST for greater than 2 years treatment duration at baseline, and any MMF treatment must be > 2 years duration

Lenabasum's safety profile remained favorable in RESOLVE-1

Lenabasum's safety profile was favorable, with fewer serious and severe AEs in lenabasum groups compared to placebo

Lenabasum was well-tolerated with no potentially or definitely-related TEAE leading to study drug discontinuation

Treatment-emergent Adverse Events (TEAE)	Lenabasum 20 mg N = 120, n (%)	Lenabasum 5 mg N = 120, n (%)	Placebo N = 123, n (%)
Any TEAE	110 (91.7)	110 (90.2)	106 (86.2)
Any Serious TEAE	11 (9.2)	10 (8.2)	18 (14.6)
Any TEAE by Maximum Severity			
Mild	55 (45.8)	47 (38.5)	44 (35.8)
Moderate	48 (40.0)	59 (48.4)	46 (37.4)
Severe	7 (5.8)	4 (3.3)	16 (13.0)
Any TEAE by Strongest Relationship	36 (30.0)	35 (28.7)	41 (33.3)
Unrelated	27 (22.5)	34 (27.9)	30 (24.4)
Unlikely	42 (35.0)	36 (29.5)	33 (26.8)
Possible	4 (3.3)	5 (4.1)	2 (1.6)
Probable	1 (0.8)	0	0
Definite			
Any TEAE Leading to Study Drug Discontinuation	5 (4.2)	2 (1.6)	7 (5.7)
Potentially Related TEAEs Leading to Study Drug Discontinuation	0	0	1 (0.8)
Any TEAE Leading to Death		0	1 (0.8)

Safety population of 365 subjects receiving at least 1 dose of study drug. Deaths during active treatment were unrelated to study drug. Death in the placebo group was from rapidly progressing SSc with respiratory and renal failure. Death in the lenabasum 20 mg group was from myocarditis leading to heart and respiratory failure.

Adverse events occurring in at least 3% more of lenabasum 20 mg BID group, compared to placebo

Likely class effects of dizziness, headache, dry mouth and somnolence occurred more frequently in lenabasum groups than placebo

No increase in neutropenia, opportunistic infections, or malignancies was seen to suggest immunosuppression

System Organ Class	Lenabasum 20 mg BID N = 120, n (%)	Lenabasum 5 mg BID N = 122, n (%)	Placebo N = 123, n (%)
Dizziness	22 (18.3)	11 (9.0)	6 (4.9)
Nasopharyngitis	18 (15.0)	25 (20.5)	9 (7.3)
Headache	17 (14.2)	4 (11.5)	10 (8.1)
Nausea	17 (14.2)	5 (4.1)	13 (10.6)
Vomiting	15 (12.5)	7 (5.7)	7 (5.7)
UTI	13 (10.8)	10 (8.2)	6 (4.9)
Dry mouth	6 (5.0)	7 (5.7)	2 (1.6)
Hematuria	6 (5.0)	4 (3.3)	0
Somnolence	5 (4.2)	1 (0.8)	0

Safety population of 365 subjects receiving at least 1 dose of study drug

Summary and Conclusions

- The primary analysis of this study did not demonstrate efficacy for lenabasum in dcSSc patients receiving standard treatments including immunosuppressive therapies
- Efficacy outcomes in the placebo rate far exceeded what was expected
- Mycophenolate significantly affected the results, with greater improvement in subjects who received MMF
  - Less improvement from MMF if duration of MMF therapy was < 2 years at baseline
- Evidence for an effect of lenabasum in on FVC was obtained from post-hoc analyses that considered the effect of background immunosuppressive therapies on outcomes
- Results from the post-hoc analyses will require confirmation in additional studies to determine the potential of lenabasum for treating patients with SSc
- Treatment with lenabasum was safe and well-tolerated in this study