SESSION 15 - THERAPY

OC.55

RECONNOITER-1: A PHASE 2, PROSPECTIVE, BLINDED, RANDOMIZED, PARALLEL-GROUP AND CROSSOVER CLINICAL TRIAL EVALUATING AISA-021, A NOVEL CCB, IN SUBJECTS WITH RAYNAUD'S PHENOMENON (SSC-RP)

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Introduction: There are no FDA-approved treatments for Raynaud phenomenon (RP), the major life-altering symptom of SSc, affecting >95% of SSc patients. While CCBs treat SSc-RP, marginal efficacy, side effects and intolerance limit use. CCB's may reduce ILD and fibrosis (Jang.; Resp Med 237(2025)), (Zheng; Nature Biomed Engin (2025). We studied AISA-021(cilnidipine), a dual N + L-type CCB approved for hypertension in Japan in 1995 for SSc-RP.

Material and Methods: The Phase 2 RCT was a 65 patient, double-blind, placebo-controlled study evaluating daily oral AISA-021 for moderate to severe RP. In Part A, 27 patients from two sites were randomized into six groups of 10 mg, 20 mg with/without tadalafil 5mg and placebo. 20 mg dosing provided best efficacy and safety. In Part B, 20 mg vs placebo was studied via crossover. 35 of 38 patients have been enrolled, with 28 evaluable patients required for 80% power. Enrollment targeted 38 patients because of ~30% dropouts in previous CCB trials. Results of treatment in 33 patients and mITT population of 32 patients are reported (SSc-RP(n=30), SLE-RP(n=1), RA-RP(n=1). Efficacy, safety, and impact on SSc using SHAQ PRO were assessed.

Results: Treatment assignments remain blinded. In Part B average median weekly attacks decreased from 14 at baseline to 8 and from 13 to 10 in Groups 1 and 2 (42.9% versus 23.3%). Group 1 had numerically superior responses in all domains compared to Group 2(Table 1). Treatments were well-tolerated and safe, with comparable AEs (Group 1 46.9%, Group 2 45.2%). Key secondary efficacy endpoints favor Group 1. Median change in attack frequency, MID on RCS, mean RP severity, percent attack-free days, all-cause pain, and median GI distress reached clinically meaningful response in Group 1 compared to Group 2. Complete attack resolution differed (6% Group 1 and 3% Group 2) and >50% attack resolution (44% Group 1 and 29% Group 2).

Conclusions: In this first-in-class clinical trial for CTD-RP, significant impact on symptoms with

Parameter	Baseline Period(n=32) in Groups 1, 2	Treatment Group 1 (% difference) (n=32)	Treatment Group 2 (% difference) (n=31)
Median and Mean (SD) Weekly Raynaud's attack frequency	14,13 15.5, 15.3 (8.0)	8 (42.9%) 11.05(28.7%)	10(23.1%) 10.97(28.4%)
Median and Mean(SD) Duration of attacks (mins)	35.1, 37.0 64.6, 65.6(118)	19.6 (44.2%) 27.0(58.2%)	25.4(31.3%) 35.9(45.3%)
Median and Mean(SD) Severity of attacks (0-10)	4.18, 4.24 4.0,4.0 (2.1)	2.6(43.6%) 2.7 (31.3%)	2.7(37.0%) 3.0(24.9%)
Median and Mean (SD) RCS(0-10) Mean Change in RCS(SD)	4.32, 4.18 4.3,4.2(2.1)	1.95(54.9%) 2.7(37.2%) 1.56 (1.75)	2.35(43.8%) 2.9(30.9%) 1.34(1.51)
Median and Mean (SD) Raynaud's Pain Score(0-10)	2.78, 2.64 3.1,3.0(2.3)	0.74(72.0%) 1.9 (38.7%)	1.53(42.0%) 2.1(30.0%)
Median and Mean (SD) Proportion of attack-free days (%)	0, 0 4.0,4.2(9.1)	8.7 (∞) 20.2(505%)	0, (0%) 12.0(286%)
Median and Mean (SD) SHAQ alt. disability (0-10)	0.63 0.7,0.7(0.6)	0.63(0) 0.61 (16.4%)	0.5(20.1%) 0.6(14.9%)
Median and Mean (SD) SHAQ Pain (0-100)	22.5, 20.0 30.9, 29.5 (26.5)	15(33.3%) 22.9(26.0%)	25(-25%) 27.4(7.1%)
Median and Mean (SD) SHAQ GI dysfunction (0-100)	15,10 27.1,26.1(30.4)	5(66.7%) 17.7(34.6%)	10(0%) 17.8(31.8%)
Median and Mean (SD) SHAQ Breathing Problems (0-100)	2.5, 0 19.2, 17.1(27.6)	0(100%) 6.7(65.1%)	0(0%) 9.1(46.8%)
Treatment-emergent adverse events		46.9% Mild (37.5%) Moderate (9.4%) Severe (0%) Withdrawal (3.1%)	45.2% Mild (35.3%) Moderate (9.7%) Severe (0) Withdrawal (0%)

Clinically meaningful improvement (>25%) in only Group 1

minimal side effects was found. Dual N- and L-type channel blocking actions, versus primarily L-type activity of approved CCBs, may explain this. CCB's exacerbate GI symptoms and were improved here. Placebo group positive response occurred as in previous SSc-RP trials. Unblinded results will be presented at the Congress Meeting, but data with adequate power is presented here. Comparable safety to placebo, and reduced dropouts distinguish AISA-021. We plan to advance AISA-021 into pivotal studies as it may be an efficacious, safe addition for SSc-RP and perhaps SSc.