ACR CONVERGENCE 2026 / ORLANDO, FLORIDA

RECONNOITER-1

Reanalysis of a randomized, controlled crossover trial of AISA-021 (cilnidipine) in SSc-associated Raynaud's phenomenon



The effect of attack definition, patient population, and study design on efficacy results

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NOVEMBER 10, 2026

Disclosures

Presenter conflicts of interest and study support

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Study sponsorship

The RECONNOITER study was supported by AISA Pharma, Inc.

The unmet need in SSc-associated Raynaud's

Current vasodilator approaches can be limited by adverse events and treatment burden

Tolerability

Side effects reported in published treatment studies:

>52-64% AEs > placebo for CCBs;
~25-30% treatment withdrawals

34% AE's > placebo for PDE-5-I's
~20% treatment withdrawals

Treatment burden

Hospital-based administration may be needed for intravenous treatment.

Systemic disease complexity

Gastrointestinal and cardiovascular considerations complicate therapy in SSc

ILD treatments have little impact on Raynaud's and are costly

CLINICAL QUESTION

Can an oral agent produce clinically meaningful benefit in Raynaud's attacks while remaining well tolerated?

Del Galdo F, Ann Rheum Dis, 2024.
Herrick et al., Arthritis & Rheumatism, 2011.

AISA-021: dual L-type and N-type calcium-channel blockade

Mechanistic rationale for evaluating cilnidipine in SSc–Raynaud's phenomenon-50-500X more N-channel activity than amlodipine and nifedipine

DUAL-CHANNEL PROFILE

L-type

Vascular smooth-muscle effects

N-type

Modulation of neuronal calcium entry

BIOLOGICAL ACTIVITY CITED IN EARLIER STUDIES

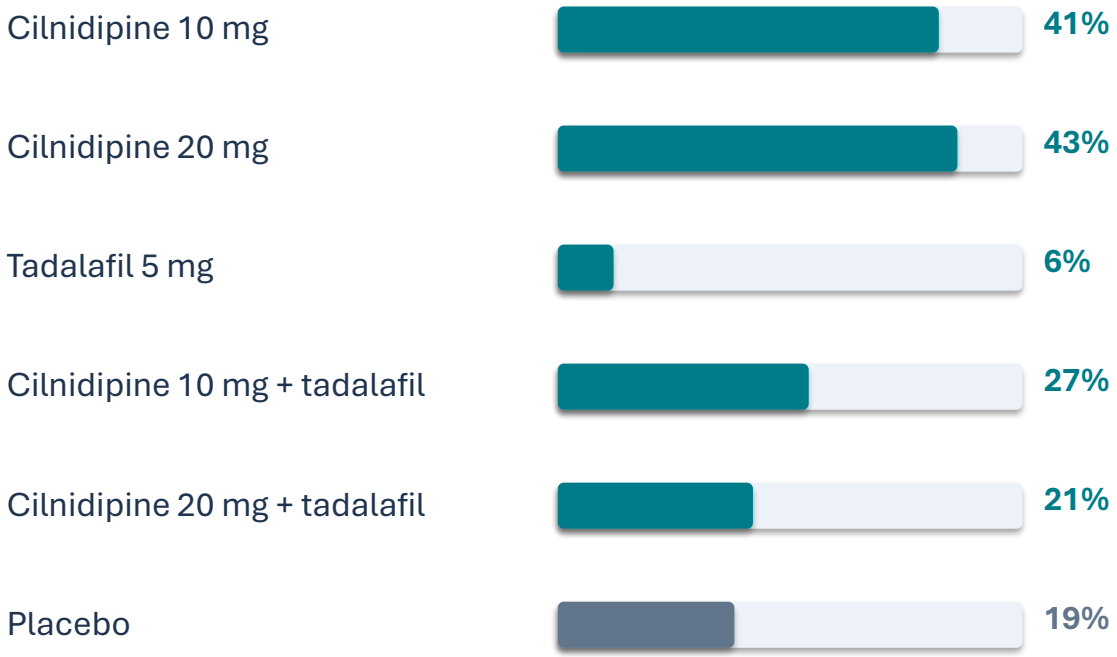
Pain / neuropathic pain	Cells, 2021
Inflammation	J Hypertens, 2012
Microvascular & endothelial effects	Eur J Pharmacol; BBRC
Renal dysfunction	Cureus, 2023
Fibrosis	Biol Pharm Bull, 2021

Investigational mechanistic hypotheses; evidence is not a demonstration of clinical benefit in SSc.

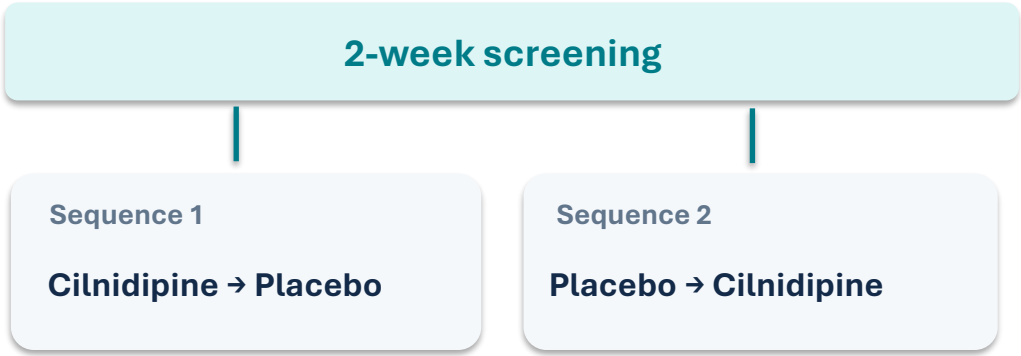
RECONNOITER*: randomized trial design

Part A dose exploration followed by a Part B randomized crossover study

PART A / DOSE FINDING / 27 PATIENTS/ NET ATTACK REDUCTION



PART B / CROSSOVER / 37 PATIENTS (33 SSC–RP)



4-day washout between 2-week periods

1-month safety follow-up

.*Randomized Evaluation of the Benefit of Cilnidipine Dose on the Nature, Observational Indices, Temperature Changes, and Overall Effect in Secondary Raynaud's Disease

Baseline SSc demographics and disease characteristics

Part B: source-reported group characteristics; treatment-group denominators to be verified

Characteristic	AISA-021 (n=32)	Placebo (n=31)
Age, years (SD)	63 (9.0)	61 (14)
Female, n (%)	15 (88%)	13 (72%)
Disease duration, years (SD)	16 (12.2)	13.3 (8.6)
Baseline RCS (SD)	4.6 (1.9)	3.8 (2.2)
ANA, n (%)	14 (82%)	14 (78%)
ENA, n (%)	2 (11.8%)	2 (11.1%)
Anti-Scl-70, n (%)	10 (59%)	10 (56%)
Weekly attacks at baseline (SD)	17.1 (8.9)	15.2 (7.5)

One patient withdrew after non-related diagnosis of breast CA within 2 days of randomization; one patient withdrew after AISA-021 for non-related vestibular neuritis

Safety on top of standard-of-care treatment

Part B: comparable overall adverse-event incidence versus placebo

45.7%

Any AE, cilnidipine

16 of 35 exposed

45.5%

Any AE, placebo

15 of 33 exposed

0

Grade 3–4 AEs

Reported for both treatment conditions

Safety outcome	AISA-021 (n=35)	Placebo (n=33)
Serious adverse event	1 (2.9%)	1 (2.9%)
Discontinuation due to drug	1 (2.9%)	0 (0%)
Drug-related treatment-emergent AE	5 (14.3%)	6 (18.2%)

Initial analysis: significance of efficacy depended on endpoint selection

World Congress results, March 2026 • Attack = any patient-reported color change lasting >30 seconds

WEEKLY ATTACK FREQUENCY

n = 32

AISA-021	Placebo
−22.1%	−12.4%

p = 0.21

SSc Disease population

ATTACK-FREE DAYS

n = 32

AISA-021	Placebo
−20.1%	−8.3%

p = 0.02

What constitutes a clinically meaningful Raynaud's attack?

Attack definition and disease characteristics influence signal detection

Symptoms and classification

-Biphasic to triphasic color change

-Localized numbness, tingling, pain, burning or coldness

-Acrocyanosis vs prolonged episodes of diminished perfusion

Advanced vascular disease

-Frequent ischemic color changes may not reflect classic vasospasm

-Structural vascular change may limit vasodilator response.

Trial design and analysis

-Regression to the mean in all trials, initial effect is strongest

-Crossover vs parallel design

-Treatment duration and sequence
-Baseline attack burden

The choice of attack definition is not merely semantic: it changes which episodes the endpoint counts.

Audience poll

Which definition best identifies a Raynaud's attack for a clinical trial?

A Any patient-reported digital color change, any duration

B Biphasic color change >30 seconds and <4 hours

C Biphasic color change >30 seconds plus any other symptom

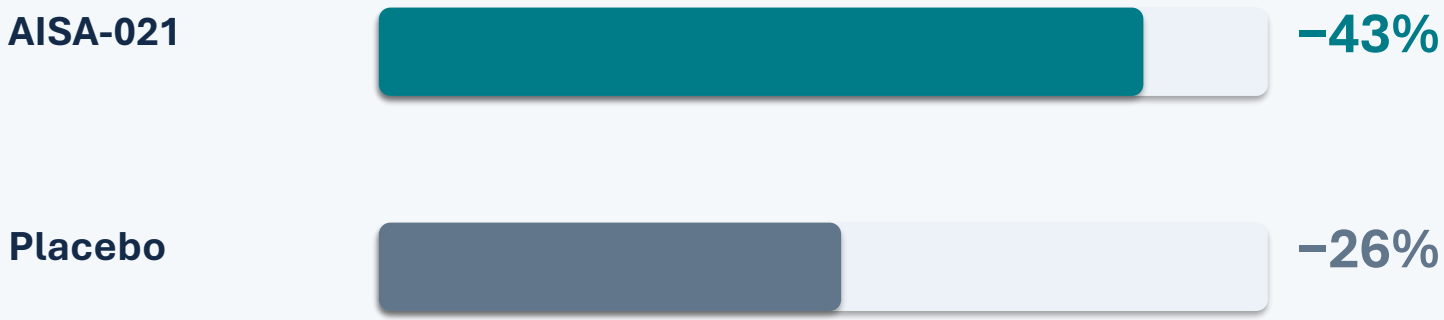
D Biphasic extremity color change >30 seconds plus localized numbness, tingling, pain, burning or coldness

Audience response • select A, B, C, or D

Qualified symptomatic attacks reveal a stronger treatment signal

Biphasic color change plus localized numbness, tingling or pain

MEAN REDUCTION IN QUALIFIED ATTACKS (N = 32)



p = 0.028

1.93

fewer attacks per week
vs placebo (as reported)

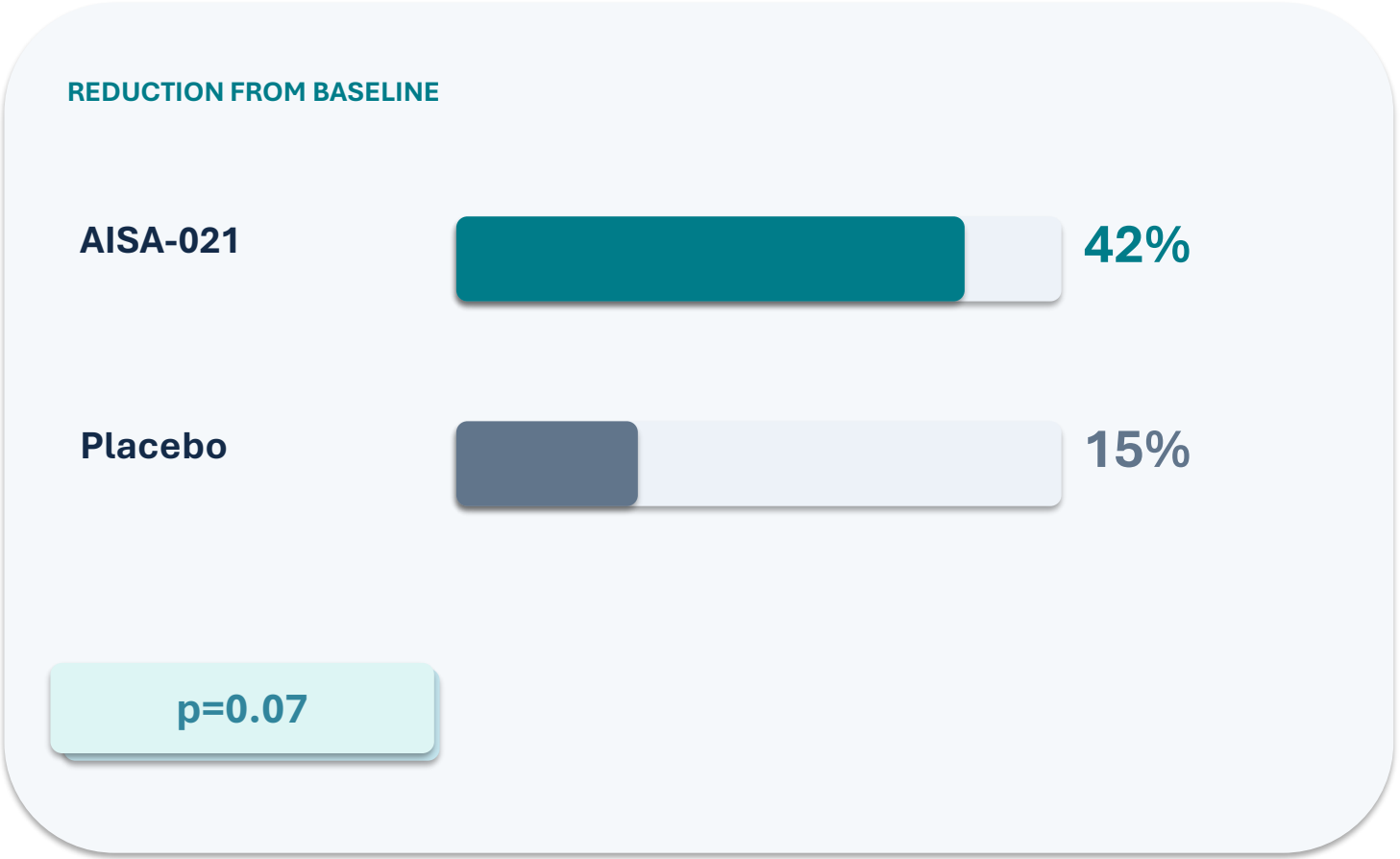
FIRST TREATMENT PERIOD

−41.7% vs −14.2%

n = 17 vs 14 • p = 0.028

Pain improved numerically with AISA-021

Exploratory Scleroderma Health Assessment Questionnaire pain assessment



Interpretation

Numerical signal favoring cilnidipine; not statistically significant at the conventional 0.05 threshold.

N-type antagonism effect is a mechanistic hypothesis, not proof of a pain effect.

Disease duration may influence responsiveness

Exploratory subgroup comparison of weekly attack reductions

Raynaud's duration	n	Cilnidipine –vs-placebo	Paired t-test p
<7 years	6	−5.50 attacks/week	0.05
7–14 years	9	−2.22 attacks/week	0.13
>14 years	15	−1.20 attacks/week	0.37

Hypothesis

Earlier disease may show a larger treatment effect.

Interpret with caution

Very small subgroups; exploratory and not statistically significant.

Disease classification and response to AISA-021

Weekly Raynaud's attacks by SSc subtype | paired crossover analysis

SSc diagnosis	N	Placebo attacks/week	Cilnidipine attacks/week	Mean reduction attacks/week	95% CI for reduction	Paired t-test p value
All SSc combined	31	9.74	7.55	2.19	0.40 to 3.99	**0.0283**
Limited	23	10.17	7.48	2.70	0.45 to 4.94	**0.0206**
Diffuse	5	8.40	7.60	0.80	−4.92 to 6.52	0.7174
Unknown subtype	3	8.67	8.00	0.67	−7.32 to 8.65	0.7538

INTERPRETATION

Overall and limited-subtype reductions favored cilnidipine; diffuse and unknown subgroups were small and inconclusive.

Crossover versus parallel-arm trial design

Design implications for future confirmation of the efficacy signal

Consideration	Crossover	Parallel arm
Sample size	Often smaller; within-patient control	Usually larger
Washout and carryover	Potential concern	Not a crossover issue
Progressive disease	May complicate interpretation	Often more suitable
Detectable treatment effects	May affect blinding	May affect blinding
Treatment-sequence effects	Must be evaluated	Not applicable

SOURCE-REPORTED SEQUENCE ANALYSIS / WEEKLY ATTACKS

Assigned treatment sequence	N with both periods	Period-1 mean change	Period-2 mean change
Placebo → cilnidipine	17	Placebo: –14.22%	Cilnidipine: –49.87%
Cilnidipine → placebo	14	Cilnidipine: –41.73%	Placebo: –29.78%

Clinical interpretation: efficacy incremental to existing best therapy

RECONNOITER assessed incremental benefit in patients with long-standing disease

11.7

Median SSc duration

years

14.7

Median Raynaud's duration

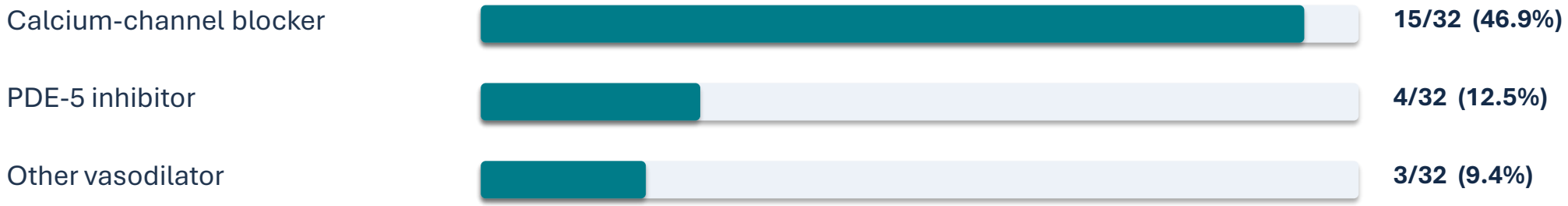
years

Add-on

Therapy design

Existing Raynaud's medications continued during treatment

BACKGROUND THERAPIES AT BASELINE (N=32)



*Categories may overlap; summed counts do not establish the number of unique patients. No untreated-placebo arm was studied.

Planned development pathway

Forward-looking milestones from the source presentation; dates are targets, not commitments



Proposed indication: treatment of Raynaud's phenomenon in patients with systemic sclerosis

Acknowledgments

RECONNOITER investigators, advisors, and study team

FLINDERS MEDICAL CENTER / ADELAIDE, AUSTRALIA

Michael Shanahan, MD (PI)
Julie Weston, RN • Erin Morton
Kelly Loffler, PhD • Jenny Walker, MD
Mihir Wechalekar, MD

AISA ADVISORS

Robyn Domsic, MD • Tracy Frech, MD
John Pauling, MD • Jerry Molitor, MD • Francesco Del Galdo, MD

SPONSOR TEAM

Meredith Todd • Angela Hansen • Andrew Sternlicht, MD



Thank you