Abnormal Vascular Contraction in Response to Cold Exposure is Common and Concerning in People with Raynaud's or Cold Sensitivity and Likely Can be Prevented and Treated with a Novel Calcium Channel Blocker

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Introduction

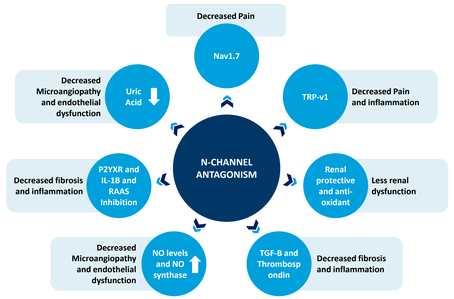
- Raynaud's prevalence in the general population is 5% and higher in women. Cold sensitivity affects 10-30% off the population, with pain, tingling, numbness, chills, stiffness, weakness, swelling or skin color changes. Military prevalence is somewhat less. Cold-induced dysfunction affects dexterity, strength, decision-making and cognitive ability and mood. More that 50% of military operations are conducted in temperatures below 50°F at which these effects can be demonstrated.
- While CCBs are used off-label to treat Raynaud's and cold sensitivity, efficacy is modest and side effects common. Cold-related injury is mitigated by cold-induced vasodilation (CIVR), but **currently approved CCBs do not affect CIVR, nor the cold pressor response**.
- **Cilnidipine** has been used for 30 years to treat hypertension in Asian countries but is not approved elsewhere. It has unique potency compared to other CCBs at inhibiting the N-type channel, increasing NO, and also has analgesic effects. Importantly and uniquely amongst CCBs, it also **inhibits the cold pressor response**. Finger temperature during and after exposure to cold does not increase with CCBs versus placebo but may with cilnidipine which has separate vasodilatory effects from increased local NO effect.
- Currently approved CCBs have marginal efficacy and high adverse events (>45%) and frequent (33%) treatment discontinuations **We are exploring Cilnidipine use for Raynaud's in a Phase 2 trial.** due to intolerance. Preliminary results are presented here.
- **Cilnidipine in clinical use for Raynaud's in Japanese patients appears to be better tolerated than other calcium channel blockers in patients without hypertension** with lower adverse events in healthy volunteers, minimal changes in blood pressure in normotensive patients and little to no increase in heart rate.
- It is **conceivable that prophylactic use of cilnidipine, prior to extreme cold exposure, might convey a degree of protection against frostbite and cold related injury**, and also might **reduce the consequences of cold-induced dysfunction**, improving overall tolerance to cold amongst cold-sensitive individuals and mitigating reductions in dexterity, strength, cognitive ability and mood.
- A simple proposed study prospective randomized and blinded study (ARCTIC) in 60 volunteers, might provide additional support for this hypothesis.

Methods

- Our Phase 2 study, RECONNOITER is a Phase 2 prospective, double-blind, randomized, placebo-controlled trial in 65 patients with Secondary Raynaud's primarily due to Scleroderma. Part A was dose finding, and parallel arm design, while Part B, is a prospective, double-blind, randomized, placebo-controlled, two-way crossover design trial with >80% power to determine whether cilnidipine has a >25% effect on reducing the weekly frequency of Raynaud's episodes in patients with frequent Raynaud's attacks.
- Patients were allowed to remain on stable doses of other medications for Raynaud's and other conditions.
- Study endpoints included weekly frequency of attacks(1º), several Raynaud's specific and scleroderma specific assessments, EndoPAT® endothelial function, and thermography.
- Data on the first 27 patients enrolled in Part A were reviewed by a DSMB and declared cilnidipine to be apparently safe and well-tolerated with an adverse event rate lower than their experiences using other CCBs to treat SSc-RP. They also noted a dose-effect and that efficacy similarly appeared greater compared with current CCB use and advised proceeding to Part B of the study without enrolling remaining patients
- Part B , studying 20 mg of cilnidipine versus placebo daily, remains blinded, but preliminary safety results in the firt 32 patients who have completed dosing are presented here.
- Data on cold-induced dysfunction from published studies is also presented here.
- A trial design schematic for a study called ARCTIC, to evaluate cilnidipine prophylactic use to treat cold-induced dysfunction is also presented.

"Cilnidipine appears to have improved efficacy and seems safer than currently used calcium antagonists in reducing Raynaud's attack frequency, in this preliminary study…" RECONNOITER DSMB

[Abnormal Vascular Contraction in Respo]

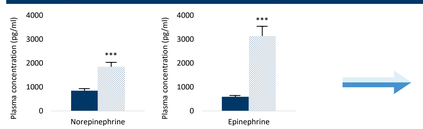


SSC Disease Contributors	Available CCBs	Cilnidipine
Vasoconstriction	+	+
Endothelial Dysfunction	-	+
Pain	-	+
Arterial and venous disease	-	+
Fibrosis	-	+
Autonomic Dysfunction	-	+
Actions at Nav1.7 receptor	-	+
Actions at TRPv-1 receptor	-	+

Parameter	10 mg Cilnidipine (n=4)	20 mg Cilnidipine (n=3)	Placebo (n=3)
Weekly attack Frequency If baseline RCS<3.5	-41% -27%	-43% -42%	-19% -18%
Duration	20%	-20%	-12%
Severity	-16%	-36%	16%
Daily RCS Change	12% (n=3)	-28%	-5%
Average Raynaud's Pain	-27%	12%	4%
Safety	1 AE (in combo with T); no withdrawals (n=9)	1 AE (HA-mild); 1 withdrawal (n=8)	1 AE (increase in GERD)
Subgroup: attack frequency	<10 baseline: -55% (n=2) >10 baseline: -28% (n=2)	<10 baseline: -29% (n=2) >10 baseline: -50% (n=2)	<10 baseline: 43% (n=1) >10 baseline: -39% (n=2)
Subgroup: Baseline RCS	<3.5 baseline: -27% (n=3) 3.5-7.5 baseline: -86% (n=1)	<3.5 baseline: -42% (n=1) >3.5-7.5 baseline: -43% (n=2)	<3.5 baseline: -18% (n=3) 3.5-7.5 baseline: -32% (n=3)

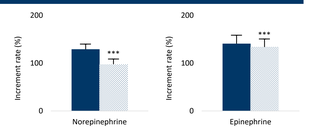
Parameter	Pooled Cilnidipine (n=7)	Cilnidipine 20 mg (n=3)	Placebo (n=4)
% change in Pain	-31%	-53%	+7%
% change in Standard Disability Index	-25%	-50%	-16%
% change in Alternative Disability Index	-13%	-42%	-13%
% improvement in Breathing	41% (median)	67% (median)	-7% (worsening)
% improvement in VAS Finger Ulcers	19%	35%	-4% (worsening)
% change VAS Raynauds	-17%	-49%	-42%
% change overall SSC Disease Severity	-60% (i.e. improvement)	-63% (i.e. improvement)	67% (i.e. worsening)

Cilnidipine Treats Cold Pressor Response



Change in NE and E in SHR rats with cold exposure(n=10)

Hosono, M., et al.;Japan J Pharm; 69, 119-28, 1995



Change in NE and E in SHR rats after pretreatment with cilnidipine 3 mg/kg

Cilnidipine seems to have a beneficial effect on patient-reported outcomes in Raynaud's and Systemic Sclerosis, compared to placebo

Results

- In 39 patients who received cilnidipine alone in either Part A or Part B of the study, there has been only 1 patient (2.5%) who withdrew due to a possible or likely drug effect, (low BP) who resolved spontaneously without medical treatment. This can be compared to historical use of other calcium blockers for Raynaud's with a reported >30% treatment withdrawal due to drug intolerance. (1)
- Cilnidipine 20 mg (n=3) also improved disability, pain, skin ulcers, Raynaud's, compared to placebo (n=4).

Cold Impacts Performance in Volunteers

Test Parameter	Normal Temp (22C)	5-10°C	-5°C
Pegboard Score	15.1	14.2 (6%)	11.4 (25%)
Typing (WPM)	24.5	20.3 (17%)	18.1 (26%)
Typing Accuracy	95.9	91 (5%)	89.1 (7%)
Grip Strength	92 lbs	77 lbs (16%)	NM

ARCTIC STUDY: Assessment of the Response to Cilnidipine in Temperature-Induced in Capacities

Phase 2 Study	Logistics	COSTS & Monitoring
60 DOD subjects with cold-sensitivity	US or US military sites	$2M total
Prospective, randomized, double-blind, crossover, placebo-controlled	Cold challenge, versus cold location	Monitoring by CRO or Sponsor
Primary Endpoint 1: Cold VAS	0-10 scale	Monitoring/subject/PI: 12K/subject = 720K
Primary Endpoint 2: Dexterity	O'Connor Dexterity test	Stats/Database = 450K
Primary Endpoint 3: Safety	MEDRA recording	Sponsor Costs=500K
>80% power to detect 30% improvement in decrement associated with cold	Based on published efficacy of calcium channel blockers	Clinical Study Material=50K
Two-week trial - 5 weekdays/ rest weekend/5 days	Propose completion within 6 months of study initiation	Regulatory= 80K
Secondary endpoint: Thermography, SF-12	Standardized assessments	Direct study costs=200K

1 Rirash, F.et.al.; Cochrane Syst Rev. 2017 dec 13; 12 (12)

Parameter	Placebo (n=4)	Cilnidipine (20mg) **(n=3)	Rirash 2017 Metanalysis (n=548)
Mean Weekly attacks @ baseline	16.7	12.7	16.4 (n=117 for 2°RP)
Mean % reduction in weekly attacks (1° Endpoint)	18.9*	43.0	24% (n=117 for 2°RP)
Mean Severity @ baseline	3.3	3.7	unknown
Mean % reduction in Severity	-16.2	35.5	10.2 (n = 138 for 2°RP)
Mean Duration of attack @baseline	164.2	19.4	unknown
Mean % reduction in Duration	12.3	20.0	6 (n=138)
Mean Pain level @baseline	2.3	2.3	unknown
Mean % reduction in Pain	-3.9	-11.8	ns
Mean RCS at baseline	2.6	3.5	unknown
Mean % reduction in RCS	5.1	27.9	9 (n=192)

Scleroderma Health Assessment Questionnaire (SHAQ)				
	Mean change (SD)	Mean Change (SD)	Wilcoxon p-value	T-test p-value
VAS - PAIN Change	0.78 (1.23)	-1.1 (0.79)	0.200	0.136
VAS - Raynaud's Change	-0.5 (1.43)	-1.27 (1.06)	0.686	0.436
VAS - Breathing Problems Change	-0.075	-0.83 (1.15)	0.943	0.540
VAS - Overall Disease Severity Change	0.7 (1.31)	-1.63 (0.15)	0.029	0.0115

Conclusions

- **Cilnidipine appears better-tolerated in patients compared with conventional CCBs,** with an overall adverse event rate of 17% in all patients who received any dose of cilnidipine in unblinded data (n=17). Only mild (Grade 1) AE's occurred and no treatment discontinuations for intolerance were reported.
- Preliminary results (n=10) show cilnidipine to be 2x as effective for prevention of Raynaud's attacks than currently available off-label treatments.
- For the primary endpoint, Cilnidipine 20 mg reduced weekly RP attack frequency by 43%, compared to 19% in placebo treated patients. (>25% is considered clinically meaningful).
- While the RECONNOITER study did not assess CIVR response, this can be measured in ARCTIC and may illustrate that cilnidipine augments CIVR, potentially protecting against frostbite and cold related injury. This would be consistent with earlier findings that cilnidipine uniquely inhibits the cold pressor response, compared with other (non dual channel) calcium channel blockers.
- Cilnidipine pre-treatment may be a well-tolerated treatment option for Raynaud's and whose suitability for use to prevent or reduce cold sensitivity, injury, dysfunction could be tested before deployment to cold environments and then utilized to improve performance and safety amongst personnel working in cold temperatures.