Poster 1176

FORMULATION MATTERS!

Variability in Drug Physicochemical Properties and Plasma Concentration May Obscure Drug Effects: Impact on the RECONNOITER-1 Trial of AISA-021 in Systemic Sclerosis-Associated Raynaud's

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Key finding: Current tablets give highly variable cilnidipine levels, but patients with higher drug levels had greater improvement in Raynaud's burden, with no increase in side effects.

Background

- Raynaud's (RP) affects ~95% of SSc patients and is their most burdensome symptom
- No approved therapy; off-label CCBs and PDE-5 inhibitors have limited efficacy and tolerability
- Cilnidipine (AISA-021), a CCB with N-type channel blockade, nearly halved defined attacks vs placebo in this trial
- Current tablet: poor solubility, high first-pass metabolism → >10-fold variation in plasma levels
- Initial RECONNOITER-1 analysis on all patient-reported color changes: reduced attacks vs placebo but missed significance (p=0.10)

Methods

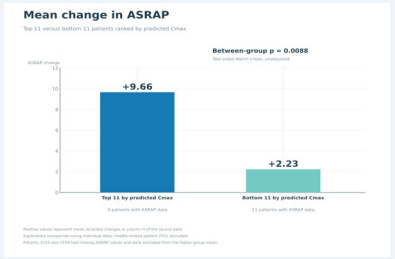
- One plasma sample (25 of 32 patients), mostly 2–3 h post-dose (≈ Tmax); validated LC-MS/MS
- Individual Cmax modeled from measured level, time since dose and published PK analysis[1]
- Higher vs lower Cmax patients compared for efficacy and safety (exploratory)

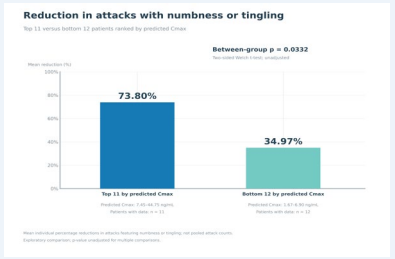
Results

27×
range in modeled Cmax (1.67–44.75 ng/mL)

8 of 11
higher-Cmax patients had clinically meaningful ASRAP gain (vs 1 of 11)

0
serious AEs or AE withdrawals; no rise in AEs at higher levels





Endpoint (higher vs lower Cmax)	Higher	Lower	p
ASRAP improvement (points)	**+9.66**	**+2.23**	**0.009**
Attacks with numbness/tingling (reduction)	**73.8%**	**35.0%**	**0.033**
Attack-free days per week*	+2.00	+1.25	0.43
Raynaud's pain (improvement)	38.8%	35.0%	0.89
Attack severity (improvement)	14.7%	18.2%	0.88
Weekly symptomatic attacks (reduction)	26.9%	33.0%	0.85

*Exploratory analysis; two-sided Welch t-tests, unadjusted for multiplicity. *Grouped by measured plasma level.*

Conclusions

- A fixed dose of the current tablet gives widely variable cilnidipine levels in SSc-RP, as previously seen in hypertension
- Higher exposure was well tolerated, with no increase in adverse events
- Higher Cmax tracked with greater ASRAP improvement (Spearman p = 0.009), a response the initial analysis missed
- Higher Cmax was also linked to fewer digital ischemic attacks (color change with numbness, tingling or pain)(p=0.033).

Next step

A new formulation designed for uniform, higher exposure will be tested in a planned Phase 3 trial.

Disclosure: The RECONNOITER study was supported by AISA Pharma.

1. Lee J, et.al.; Drug Des Devel Ther.; 2014 Oct 8;8:1781-8.