A New Dawn for Social Anxiety Treatment: Clinical Advancement of the Novel V1aR Antagonist, NTX-1472

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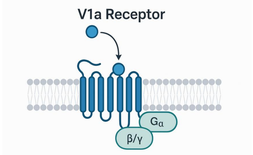
SOAR: SOcial Anxiety Reduction Study

Background

NTX-1472
V1a Antagonist

Highly selective for V1a receptor, predominantly expressed in the lateral septum and amygdala



Key Attributes

Mechanism: Targets V1a receptor
- ✓Vasopressin (AVP) is a neuropeptide that plays a major role in response to social threat and chronic stress[1]
- ✓V1a receptor antagonism has been shown to decrease anxious behavior in pre-clinical anxiety models[2]

NTX-1472: Selective & de-risked
- ✓High-affinity binding & functional activity in preclinical models
- ✓Molecularly and clinically-informed by development of related molecule (Balovaptan)

Methods

Completed: Study BP41695

Single Ascending Dose (n=48) NTX-1472 orally administered 5 to 360mg, including fed condition

Multiple Ascending Dose (n=24) NTX-1472 orally administered 45 to 210mg for 10 days

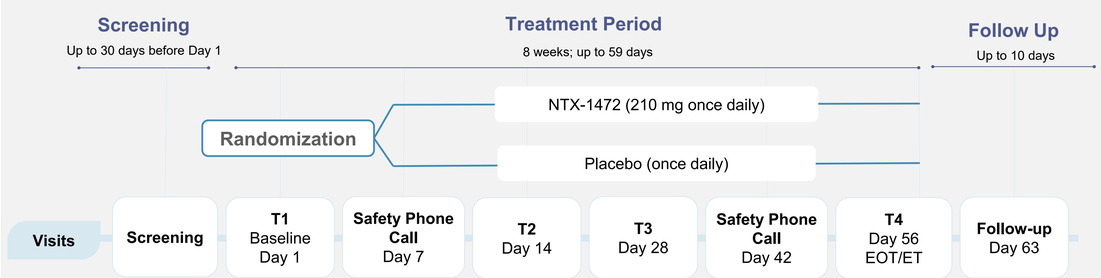
Drug-drug Interaction (n=16)
- Midazolam (CYP3A4 substrate) intravenously administered on days 1 & 13 (100µg), orally on days 2 & 14 (300µg)
- NTX-1472 orally administered 210 mg for 12 days

Completed: Study 2 BP42393

Period 1 (n=16) NTX-1472 orally administered 45mg under fed conditions

Period 2 (n=16)
- Itraconazole (CYP3A4 inhibitor) orally administered 200mg twice daily (BID) on day 1, 200mg daily (QD) on days 2-10
- NTX-1472 orally administered 45mg on day 4

In Progress: Phase 2 Proof-of-Concept Study (SOAR) to assess NTX-1472 in participants with Social Anxiety Disorder (SAD)



Sample Size: N=100; 50 per group, 1:1 stratified by sex
Screening: Characterization of depressive symptoms, trait anxiety, childhood trauma, adult attachment/avoidance

Primary Objective: To assess the safety and tolerability of NTX-1472 in participants with SAD
Secondary Objective: To investigate the efficacy of NTX-1472 (LSAS) during 8 weeks of treatment in participants with SAD

Results

- NTX-1472 administered to a total of **86 healthy participants across Phase 1 studies**
- **Rapid Absorption**: T_{max} achieved at 1-3 hours (h) post-dose; cerebral spinal fluid concentrations equal to unbound fraction in plasma
- **Elimination**: No accumulation observed; half-life ~5-7 h
- **Food effect**: Food increased C_{max} of NTX-1472, delayed T_{max} by 2 h, slightly shortened half-life. No effect on area under the curve (AUC).
- **DDI**:
  - Daily NTX-1472 had no effect on the pharmacokinetics (PK) of midazolam, a CYP3A4 substrate.
  - Daily intraconazole, a strong CYP3A4 inhibitor, increased the AUC_{inf} of NTX-1472 by 2.5-fold.
- NTX-1472 **well tolerated**, all adverse events non-serious and non-dose-limiting

Adverse Events (MAD)	NTX-1472			Placebo
	45mg (n=6)	140mg (n=6)	210mg (n=6)	(n=6)
Headache	2 (33.3%)	3 (50%)	2 (33.3%)	1 (16.7%)
Puncture site pain	2 (33.3%)	2 (33.3%)	1 (16.7%)	0
Procedural headache	1 (16.7%)	2 (33.3%)	0	1 (16.7%)
Total number of subjects w/ at least 1 AE	4 (66.7)	6 (100%)	4 (66.7%)	2 (33.3)
Total number of events	7	21	6	9

Conclusions

- In humans, **V1aR antagonists** have been shown to decrease amygdala activation to threatening social cues[3] and to reduce anxiety-potentiated startle, a biomarker associated with treatment response in SAD[4].
- NTX-1472 is a novel V1aR antagonist **currently in development for SAD** (generalized subtype, distinguished below):

Generalized / Overall	• Marked fear or anxiety about social situations which the individual is exposed to possible scrutiny of others • Social situations are avoided or endured with intense fear or anxiety
Performance - only	• Fear restricted to speaking or performing in public • Tends to have greater autonomic nervous system response to performance than SAD generalized[5]
Comorbidities	• Panic disorder, specific phobia, generalized anxiety disorder • Any personality disorder (severe SAD may meet criteria for avoidant personality disorder) • Alcohol use disorder (SAD primary)

- Phase 1 data informed study design and dose selection of current Phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study (SOAR), **currently enrolling** across 11 sites in the United States

Acknowledgements & Disclosures

- The authors would like to acknowledge the work of Silke Simon (Roche) and Mary Morrison (Roche), and to thank them for their review and collaboration on this poster. The completed studies were sponsored by Roche, Basel, Switzerland. The ongoing Phase 2 study is sponsored by Newleos Therapeutics, Inc., Boston, MA, USA.
- TL, MG, AS, SS, FB are employees and owners of equity securities of Newleos Therapeutics, Inc. SD is a consultant of Newleos Therapeutics, Inc.

References
1. Shalev et al, 2011
2. Bayerl et. al., 2015, Bleickardt et. al., 2009, Wigger et. al., 2004
3. Lee et. al., 2013
4. Hoge et al., 2024, Lago et. al., 2021
5. Stein & Stein, 2008