ANC-501: A Novel V1b Receptor Antagonist for Major Depressive Disorder

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Introduction

Stress mediated by the hypothalamus-pituitary-adrenal (HPA) axis has been hypothesized to be a pivotal factor in the pathophysiology of depression. Specifically, both corticotropin-releasing factor and arginine vasopressin, both of which are produced in the paraventricular nucleus of the hypothalamus, are considered primary factors in the regulation of HPA axis activity. Receptor subtypes for these neuropeptides, which may be involved in the regulation of HPA axis activity, have attracted much attention as potential targets for the treatment of depression and anxiety. With chronic stress in the context of the Covid pandemic likely contributing to the dramatic increase in MDD worldwide, correcting disruption in this pathway may be particularly important new way to treat those patients with clearly disrupted HPA axis function.

ANC-501 (formerly TS-121) is an investigational new drug with antagonistic activity of the vasopressin receptor 1b (V1b receptor), which plays a role in the modulation of stress and mood. Based on nonclinical and early clinical studies, ANC-501 appears to be a promising candidate for clinical development with a novel mode of action that may benefit MDD patients. ANC-501 is being developed as an adjunctive therapy for MDD patients who have responded inadequately to standard anti-depressants and clear disruptions in their HPA axis. A phase 2 study of ANC-501 will initiate in 2022.

ANC-501 Mechanism of Action

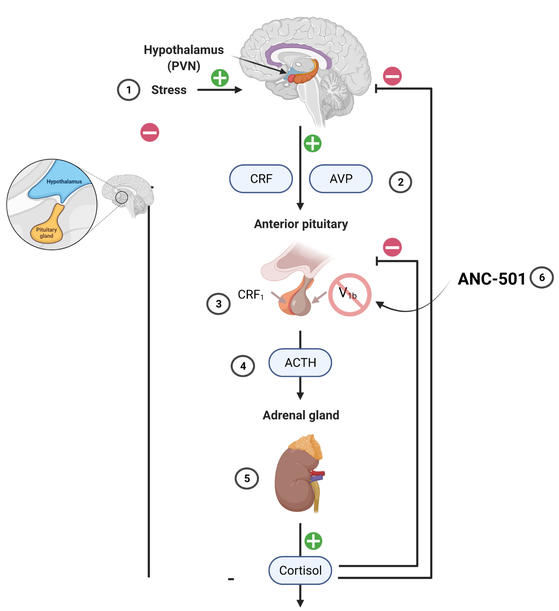
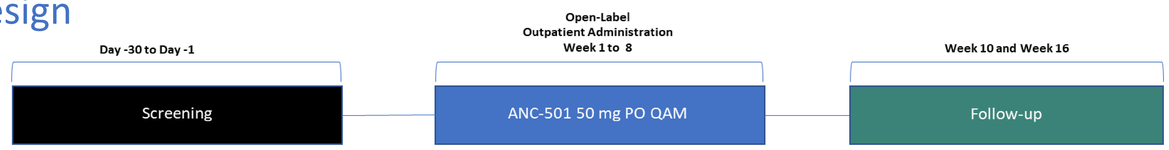


Figure 1. Mechanism of Action of ANC-501. (1) Stress induces Corticotropin releasing factor (CRF) and Arginine Vasopressin (AVP) to be released from the Hypothalamus (2). These together stimulate the CRF1 and V1b receptors (3) in the Anterior Pituitary to release ACTH (4) which stimulates the Adrenals to release Cortisol (5). ANC-501 blocks the V1b receptor, decreasing AVP stimulated Cortisol release (6).

Trial Design



Patients:
- n ≤20 MDD patients
- Age 18-65
- MADRS ≥28
- 12-hour urine Cortisol > 22.7 nmol/L

Primary Endpoint:
- Change from baseline (Day 1) to week 8 in MADRS total score
- Safety (AE reporting, vitals, body weight, ECGs, clinical laboratory test, physical examination, LOCS III, C-SSRS)

Secondary Endpoints:
- MADRS, HAM-A, CGI-I, CGI-S, PGI-I
- Pharmacokinetics/exposure

Exploratory Endpoints
- △Cortisol (14 h urine, plasma and saliva)
- HAMD-6, GAD-7
- Biometric changes (sleep, movement, HRV)
- Serum Biomarkers(optional)

Safety Endpoint of Special Interest LOCSIII

Preliminary Data

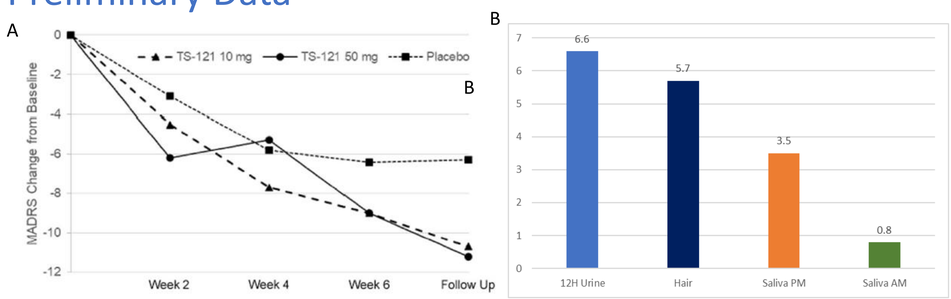


Figure 2. Panel A Both 10 mg and 50 mg ANC 501 (TS-121) PO QD reduced MDRS symptoms in adults with MDD when dosed for 6 weeks when compared with placebo. (p This study was stopped for prior to completion of the trial. (p-n.s). **Panel B**. Post hoc analysis of patients demonstrate that difference from placebo for individuals dosed with 50mg and high levels of baseline cortisol as measured in 12 urine, hair, saliva AM sample, saliva PM. High groups were determined using a median split among samples collected during this preliminary trial. Patients with elevations in the urine showed the largest changes in MADRS vs. Placebo (6.6) at the end of dosing (data from Kamiya et al, 2020).

Preferred Term	Treatment Emergent Adverse Events N (%)		
Group	Placebo	10mg	50mg
N	18	16	16
Lenticular Opacities	0	0	2 (12.5)
UTI	0	0	2 (12.5)
Medication Error	0	1 (6.3)	1 (6.3)
Headaches	0	1 (6.3)	1 (6.3)

Table 1. Treatment emergent adverse events in Preliminary Phase 2 trial of ANC-501 (TS-121) ordered by frequency in the ANC-501 group. All adverse events were mild or moderate, there were no reported severe, or Serious Adverse Events (SAE) (Kamiya et al 2020).

References

Kamiya et al. 2020 Efficacy and safety of TS-121, a novel vasopressin V1B receptor antagonist, as adjunctive treatment for patients with major depressive disorder: a randomized, double-blind, placebo-controlled study J. Psych Res 128 43-51.

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Meynen G, Unmehopa UA, van Heerikhuize JJ, Hofman MA, Swaab DF, Hoogendijk WJG. Increased arginine vasopressin mRNA expression in the human hypothalamus in depression: A preliminary report. *Biol Psychiatry*. 2006; 60(8): 892–895.

Discussion

Arginine vasopressin AVP, a cyclic nonapeptide, together with CRF, are principal factors in the regulation of ACTH release from the anterior pituitary and have been reported to play an important role in mood regulation. Clinically, the plasma AVP levels and cortisol are elevated in patients with major depression, compared with healthy controls particularly in subjects with melancholic-type or anxious-retarded depression. Importantly, these effect are seen most dramatically in individuals who have experienced 1 or more adverse childhood experiences (ACES) and/or trauma and are associated with high rates of depression, substance abuse along with increased risk for obesity, heart disease, asthma and other adverse health outcomes.

ANC-501 is a potent and selective antagonist of V1b receptor in both in vitro and in vivo studies and has been shown to possess antidepressant activity in several animal models of depression. During in vivo rat studies, the immobility time in the forced swimming test and the hyperemotionality in a rat olfactory bulbectomy model, both of which are indicative of depressive states, were each significantly reduced by treatment with ANC-501. In the olfactory bulbectomy model, ANC-501 exhibited efficacy following chronic treatment for 14 days, as did fluvoxamine. In addition, ANC-501 significantly improved depressive-like behavior induced by repeated corticosterone injection, a depression model which has been reported to be resistant to fluvoxamine and imipramine indicating that ANC-501 may be effective for patients with severely impaired HPA axis function. In an anxiety model (social interaction behavior in rats), ANC-501 demonstrated anxiolytic activity as well. This preclinical and clinical evidence suggests that ANC-501 may be useful in the treatment of MDD in patient who are poorly responsive to standard therapy, and who have clearly demonstrated disruption in the HPA axis. This would be an important step in the development of a specific personalized treatment in MDD.

The next step after completion of this trial will be a double-blind placebo controlled trial in adult MDD patients.