TNX-601 CR*: a Once-Daily Formulation of Tianeptine in Development for the Treatment of Major Depressive Disorder

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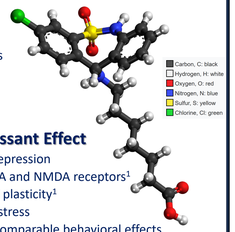
*TNX-601 CR is an investigational drug and has not been approved for any indication

INTRODUCTION

Tianeptine



- Atypical tricyclic antidepressant with a novel mechanism of action
- Marketed for depression in Europe, Asia and Latin America >30 years
- Not commercialized in United States (US) or United Kingdom (UK)
- Comparable efficacy to SSRIs and TCAs; better tolerability
- Prominent anxiolytic effects in depression studies

Mechanism of Tianeptine's Antidepressant Effect

- No affinity for traditionally targeted CNS receptors/transporters in depression
- Has indirect inhibitory modulation of glutamatergic activity, via AMPA and NMDA receptors[1]
  - Demonstrated to promote release of BDNF and adaptive neural plasticity[1]
  - Unique neuroprotective properties opposing effects of chronic stress
- Active primary metabolite MC5 has longer elimination half-life and comparable behavioral effects
- Weak binding to and agonism of human μ-opioid receptor (MOR) make it highly unlikely that it plays a role in antidepressant effect of tianeptine at standard therapeutic dose
  - Weak binding to human MOR - K_i: 383 nM[2]; 768 nM[3]
  - Weak agonist activity[4] ($EC50_{β\text{-arrestin 2}}$: 3262 nM; $EC50_{Mini\text{-}Gi}$: > 1 x 10^4 nM)
  - Yet if high doses are ingested (in range of 8X-80X antidepressant dose), the off-target MOR activity poses a danger for abuse, dependence, and their sequelae

Improved Formulation for US Market Desirable

- Marketed form of tianeptine is amorphous tianeptine sodium 12.5 mg (Stablon®/Coaxil®)
  - Dosing is three-times daily (TID) in depression for total daily dose of 37.5 mg
- Tonix identified a new oxalate crystalline salt of tianeptine (Patent: US 10,946,027 B2, 3/16/2021)
- Tianeptine oxalate has improved pharmaceutical properties suitable for development of a controlled-release once daily (QD) formulation

Phase 1 Formulation Development Pharmacokinetic Studies

- Compared the pharmacokinetics (PK) and safety of immediate-release (IR) tianeptine oxalate 13.1 mg (TNX-601 IR) to tianeptine sodium (Stablon) 12.5 mg (tianeptine base 11.9 mg in both)
- Assessed several novel modified-release (MR) prototype formulations of tianeptine oxalate salt
- Highlighted is the PK in fasted and fed states of TNX-601 MR1 39.4 mg, the selected MR prototype formulation for development as a QD controlled-release (CR) treatment for major depressive disorder (MDD)

Final Formulation, TNX-601 CR, for Testing in Phase 2 Study of MDD

- Due to potential for diversion and abuse of high dosages of tianeptine for its weak MOR activity, naloxone 1 mg is included to mitigate potential for parenteral (intravenous, insufflation) abuse
- Oral naloxone is ≤2% bioavailable; 1 mg is a non-therapeutic ingredient at tianeptine's therapeutic dose
- Final formulation for planned Phase 2 clinical study:

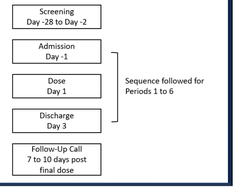
TNX-601 CR (tianeptine oxalate 39.4 mg and naloxone 1 mg controlled-release tablets)

METHODS

Study TNX-TI-P101

- Single center, open-label, 6 sequential period study
- Determined PK and relative bioavailability of TNX-601 IR 13.1 mg compared to Stablon 12.5 mg
- For a QD formulation, 3 MR prototypes tested
- 12 healthy adult male and female subjects received single oral doses of IR and MR formulations in 6 periods
- Each period followed same study design (**Figure 1**)
- Subjects confined to clinical unit evening prior to dosing (Day -1) through 48 hrs post-dosing
- At least 7-day washout between periods

Figure 1. Study Sequence



MR Tablet Formulation Prototypes

- A 2-D design space for matrix prototypes was used with flexibility to modify release rate via changing polymer content/composition and drug dose in response to emerging clinical PK data
- Relative bioavailability of TNX-601 IR formulation was compared to Stablon
- Food effects determined for selected TNX-601 MR1 prototype on plasma PK (tianeptine & MC5)
- Quotient Sciences, Nottingham, UK responsible for manufacture of TNX-601 IR and three prototype MR formulations according to GMP; Quotient Sciences' MHRA-licensed facility
- Reference product Stablon acquisitioned by Quotient
- Plasma concentrations of tianeptine & MC5 determined using validated methods at LGC Ltd, Fordham, Cambridgeshire, UK. LLQ: 2 ng/mL for tianeptine; 1 ng/mL for MC5
- MHRA approval granted for the Clinical Trial Authorisation (CTA) application for study

Statistical Analyses

- Formal analyses performed on PK parameters C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ for tianeptine and MC5, analyzed using mixed modelling techniques after natural logarithmic transformation. **Tables 1** & **2** show the geometric means and for results of pairwise comparisons, adjusted geometric mean ratios and 90% confidence intervals (CIs) are presented with p-values
- For plasma PK concentrations in **Figures 2** & **3**, arithmetic means and standard deviations are shown
- Safety Population: all subjects who received ≥1 dose IP. Safety assessed by adverse events (AEs), Columbia Suicide Severity Rating Scale (C-SSRS), physical exams, vital signs, ECG and labs

RESULTS

Pharmacokinetic Results: PK results for plasma tianeptine and metabolite MC5 are presented for TNX-601 IR 13.1 mg in comparison with Stablon 12.5 mg in **Table 1** (below) and **Figure 2** (top of third column), both in a fasted state. For $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$, TNX-601 IR 13.1 mg had greater relative bioavailability than Stablon by 7% for tianeptine and 14-15% for MC5 (**Table 1**). Inter-subject variability for exposure (AUC & C_{max}) was moderate and unaffected by salt form (Stablon 31.9-34.2%; TNX-601 IR 28.2-34.5%).

Table 1. PK Parameters of Plasma Tianeptine & MC5 with Stablon and TNX-601 IR

	Stablon 12.5 mg N=11	TNX-601 IR 13.1 mg N=12	Stablon 12.5 mg N=11	TNX-601 IR 13.1 mg N=12
Parameter (Mean)	Tianeptine		Metabolite MC5	
$AUC_{0\text{-}24}$ (ng.h/mL)	884	943	490	556
$AUC_{0\text{-}last}$ (ng.h/mL)	872	934	580	664
F_{rel} $AUC_{0\text{-}last}$ (%)	105.18 [101.47, 109.02], p=0.029		112.08 [106.98, 117.43], p=0.001	
$AUC_{0\text{-}inf}$ (ng.h/mL)	890	955	604	695
F_{rel} $AUC_{0\text{-}inf}$ (%)	105.36 [101.46, 109.42], p=0.031		112.98 [107.87, 118.34], p<0.001	
C_{max} (ng/mL)	229	237	51.4	55.0
F_{rel} C_{max} (%)	102.07 [95.05, 109.61], p=0.61		104.67 [97.16, 112.77], p=0.29	
AUC_{extrap} (%)	1.808	1.919	3.592	3.954
T_{max} (h)[a]	1.500	1.025	3.000	3.000
$T_{1/2}$ (h)	3.140	3.525	9.309	9.893
CL/F (mL/min)	223	208	*ND	*ND
Vz/F (L)	60.6	63.4	*ND	*ND

[a]median; *ND = not done

The following PK parameters are displayed for tianeptine and active metabolite MC5 in **Tables 1 & 2**:

$AUC_{0\text{-}24}$: Area under the curve from time 0 to 24 h post-dose for plasma concentration

$AUC_{0\text{-}inf}$: Area under the curve from time 0 extrapolated to infinity for plasma concentration

C_{max}: Maximum observed concentration

AUC_{extrap}: Percentage of $AUC_{0\text{-}inf}$ extrapolated beyond last measurable concentration

T_{max}: Time of maximum observed concentration

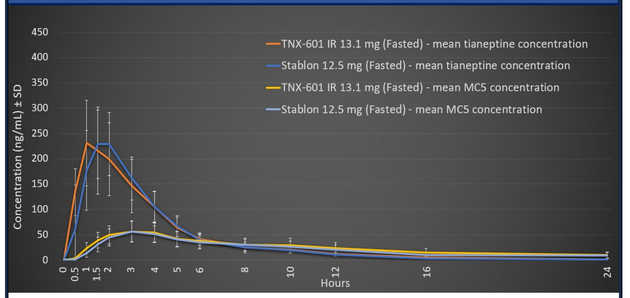
$T_{1/2}$: Apparent elimination half-life

CL/F (for plasma tianeptine only): Apparent total body clearance calculated after a single (non-IV) administration where F (fraction of dose bioavailable) is unknown

Vz/F (for plasma tianeptine only): Apparent volume of distribution based on terminal phase calculated after single (non-IV) administration where F (fraction of dose absorbed) is unknown

F_{rel}: Relative bioavailability based on C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ in the two sets of group comparisons

Figure 2. Mean Tianeptine and MC5 Concentrations for Stablon and TNX-601 IR



PK results for plasma tianeptine and MC5 are presented for selected prototype TNX-601 MR1 39.4 mg in fasted and fed states in **Table 2** (below) and **Figure 3** (top of 4th column). The C_{max} was significantly *greater* in the fed state for both tianeptine and MC5, by 40% and 34%, respectively. Whereas, $AUC_{0\text{-}last}$ was *lower* by 10% in the fed state for tianeptine only. The $T_{1/2}$ for TNX-601 MR1 39.4 mg was numerically reduced in fed state for tianeptine (not statistically compared). **Figure 3** shows the extended elevations of plasma tianeptine and MC5 from TNX-601 MR1 over daytime hours compared with TNX-601 IR in **Figure 2**.

Comparing PK of TNX-601 MR1 39.4 mg and predicted Stablon 12.5 mg TID dosing (data not shown), plasma tianeptine $AUC_{0\text{-}24}$ was 20% lower, C_{max} was not significantly different, and neither differed for MC5.

Table 2. PK Parameters of Plasma Tianeptine & MC5 with TNX-601 MR1 in Fasted and Fed States

	TNX-601 MR1 39.4 mg (fasted) N=12	TNX-601 MR1 39.4 mg (fed) N=12	TNX-601 MR1 39.4 mg (fasted) N=12	TNX-601 MR1 39.4 mg (fed) N=12
Parameter (Mean)	Tianeptine		Metabolite MC5	
$AUC_{0\text{-}24}$ (ng.h/mL)	2040	1990	1220	1270
$AUC_{0\text{-}last}$ (ng.h/mL)	2300	2060	1750	1700
F_{rel} $AUC_{0\text{-}last}$ (%)	89.22 [81.59, 97.56], p=0.043		97.02 [90.55, 103.96], p=0.45	
$AUC_{0\text{-}inf}$ (ng.h/mL)	2360	2230	2030	1830
F_{rel} $AUC_{0\text{-}inf}$ (%)	92.81 [84.63, 101.77], p=0.17		93.57 [86.25, 101.51], p=0.17	
C_{max} (ng/mL)	230	321	76.3	102
F_{rel} C_{max} (%)	139.70 [114.19, 170.91], p=0.013		134.19 [117.30, 153.51], p=0.002	
AUC_{extrap} (%)	1.944	1.691	6.821	6.198
T_{max} (h)[a]	3.500	5.000	8.042	8.000
$T_{1/2}$ (h)	6.874	5.050	11.306	11.175
CL/F (mL/min)	252	266	*ND	*ND
Vz/F (L)	150	116	*ND	*ND

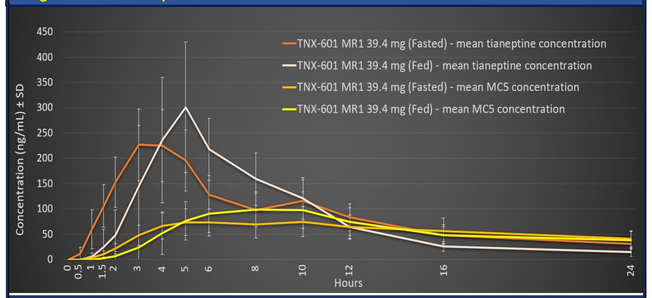
[a]median; *ND = not done

Safety Results: Single doses of Stablon 12.5 mg fasted (reference), TNX-601 IR 13.1 mg fasted, prototype TNX-601 MR1 39.4 mg fasted and fed, prototype TNX-601 MR2 39.4 mg fasted, prototype TNX-601 MR3 50 mg fed[#] and TNX-601 MR3 50 mg fasted[#] were well tolerated in 12 healthy male (7) and female (5) subjects. Two subjects reported treatment emergent adverse events (TEAEs) deemed possibly related to study drug, namely somnolence (on TNX-601 IR 13.1 mg fasted) and headache (on TNX-601 MR1 39.4 mg fed), while all other TEAEs were deemed not related to study drug.

All TEAEs were mild in severity, and all resolved by end of the study. There were no significant laboratory, vital signs, ECG, C-SSRS or physical examination findings. The two possibly related TEAEs, headache and somnolence, are both described in the Stablon Summary of Product Characteristics (v. 27 May 2016) as common (defined ≥1/100, <1/10).

[#]Group sizes for groups marked with hashmark were N=6 each; all other groups were N=12

Figure 3. Mean Tianeptine and MC5 Concentrations for TNX-601 MR1 in Fasted and Fed States



Upcoming Phase 2 Trial of TNX-601 CR in MDD

- Tonix is sponsoring an upcoming US trial, TNX-TI-M201, of TNX-601 CR (tianeptine oxalate 39.4 mg and naloxone 1 mg controlled-release tablets) for once daily treatment of MDD, currently in IND preparation
- Design is a Phase 2, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of TNX-601 CR monotherapy versus placebo in MDD
- Treatment duration is 6 weeks, preceded by up to 5 weeks of screening and followed by a 2-week safety follow-up period (total up to 13 weeks of participation)
- Approximately 260 individuals with MDD will be randomized 1:1 to two arms of 130 each at approximately 25-30 US sites
- Primary efficacy endpoint will be the change from Baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) score
- Enrollment is estimated to start by April 2022

CONCLUSIONS

- Following single oral administration of TNX-601 IR 13.1 mg, there was greater relative bioavailability of tianeptine and MC5 compared to single dose of Stablon 12.5 mg. Yet the PK curves were notably similar, and differences were not clinically relevant given TNX-601 IR 13.1 mg in tianeptine relative bioavailability ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) at only 7% over Stablon, no difference in C_{max} for tianeptine and MC5, and ~15% increase in relative bioavailability of MC5. Inter-subject variability in plasma tianeptine and MC5 exposure was unaffected by salt form, sodium versus oxalate.
- Single dose of TNX-601 MR1 39.4 mg compared with predicted PK for Stablon 12.5 mg TID dosing showed a similar tianeptine C_{max} (within ~11% of each other) and an $AUC_{0\text{-}24}$ which was ~20% less than that predicted; while exposure to MC5 was similar to that predicted, C_{max} (w/i 9%) and $AUC_{0\text{-}24}$ (w/i 1%).
- Administration of TNX-601 MR1 39.4 mg tablet with a high fat breakfast demonstrated a delay in absorption and an increase in C_{max} for tianeptine and MC5 of 40% and 34%, respectively, compared to fasted. Whereas by $AUC_{0\text{-}last}$ in fed state, there was a reduction by 10% in in tianeptine exposure, and no significant difference in $AUC_{0\text{-}inf}$ for tianeptine, or for either $AUC_{0\text{-}last}$ or $AUC_{0\text{-}inf}$ for MC5. Thus, despite higher peak exposure in fed state (C_{max}), overall exposure by AUC was similar or minimally reduced.
- The PK profile of TNX-601 MR1 39.4 mg tablet in **Figure 3** is suitable for once-daily dosing, providing a similar profile for tianeptine and MC5 as that resulting from Stablon 12.5 mg when dosed TID in daytime.
- As a result of this work, a QD controlled-release formulation, TNX-601 CR, was subsequently developed which contains 39.4 mg of tianeptine oxalate and 1 mg of naloxone (included to mitigate high dose parenteral abuse). This formulation will be advanced to clinical testing in an upcoming US Phase 2 trial.

CITATIONS

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3. PDSP Certified Data. https://pdsp.unc.edu/pdspweb/

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