Safety, Pharmacokinetics, and Pharmacodynamics of TX000045, a Long-Acting Fc-Relaxin Fusion Protein, After Single Doses in Healthy Volunteers

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BACKGROUND

- Human relaxin-2 is an endogenous hormone that is a pulmonary and systemic vasodilator with lusitropic, anti-fibrotic and anti-inflammatory activity. Relaxin's short half life has limited its use as a therapeutic.
- TX000045 (TX45) is a long-acting Fc-relaxin fusion protein that is a selective agonist for the G protein-coupled relaxin family peptide receptor 1 (RXFP1). TX45 is being developed for Group 2 pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (PH-HFpEF), a disease with no approved therapies and high five-year mortality.
- Preclinical data: In *in vivo* chronic rat models of PH, trough exposure associated with maximal efficacy was 6 μg/mL which corresponded to EC_{70-80} on rat renal plasma flow (RPF). Given 3X potency difference of TX45 rat to human, target EC_{70-80} in human study was predicted at ~2 μg/mL. *In vitro* human cell-based RXFP1 cAMP assays also demonstrated TX45 EC_{70} of 2 μg/mL.
- This first-in-human study evaluated the safety, tolerability, pharmacokinetic and pharmacodynamic profile of TX45 in healthy volunteers after single doses. Repeated measures of renal plasma flow (RPF) post dose in each subject were used to create an exposure-response model, versus a mean cohort dose-response model, for more robust Phase 2 dose selection.

METHODS

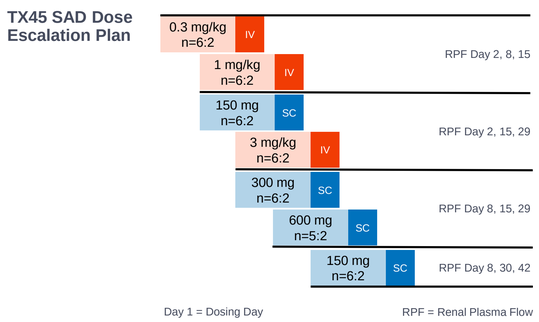
Study Design: This study was a randomized, double-blind, placebo-controlled single ascending dose study. It was performed in seven cohorts of healthy subjects. Each cohort was dosed with TX45 or placebo, 6 subjects to 2, except the 600 mg subcutaneous (SC) dose group which was 5 subjects to 2.

Study Population: Healthy subjects, as defined by protocol.

Primary Outcome Measures: Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), as well as clinically significant changes from baseline in safety laboratory assessments.

Secondary Outcome Measures:
- Plasma concentrations of TX45
- Presence of anti-drug antibodies to TX45
- Change from baseline RPF as determined by analysis of steady-state para-aminohippurate (PAH) blood levels in response to a PAH intravenous (IV) infusion

Figure 1. Design of single ascending dose Phase 1 study



RESULTS

Safety

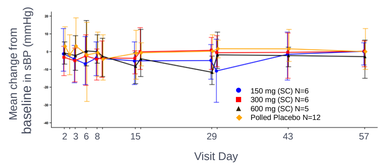
Table 1. Treatment Emergent Adverse Events (TEAEs) occurring in >5% of subjects

	Part A											Part B	
	IV					SC					Pooled		
	TX45 (mg/kg)					TX45 (mg)							
	PBO (N = 6) n (%)	0.3 (N = 6) n (%)	1 (N = 6) n (%)	3 (N = 6) n (%)	Overall (N = 18) n (%)	PBO (N = 6) n (%)	150 (N = 6) n (%)	300 (N = 6) n (%)	600 (N = 5) n (%)	Overall (N = 17) n (%)	PBO (N = 12) n (%)	TX45 (N = 35) n (%)	PBO (n = 2) n (%)	TX45 150 mg SC (N = 6) n (%)
Participants with at least one TEAE	2 (33.3)	4 (66.7)	6 (100.0)	5 (83.3)	15 (83.3)	5 (83.3)	4 (66.7)	4 (66.7)	3 (60.0)	11 (64.7)	7 (58.3)	26 (74.3)	1 (50.0)	4 (66.7)
Tachycardia*	1 (16.7)	-	2 (33.3)	2 (33.3)	4 (22.2)	1 (16.7)	2 (33.3)	1 (16.7)	1 (20.0)	4 (23.5)	2 (16.7)	8 (22.9)	1 (50.0)	3 (50.0)
Dizziness	-	-	1 (16.7)	1 (16.7)	2 (11.1)	-	-	-	1 (20.0)	1 (5.9)	-	3 (8.6)	-	-
Palpitations	-	-	1 (16.7)	-	1 (5.6)	-	1 (16.7)	-	1 (20.0)	2 (11.8)	-	3 (8.6)	-	-
Diarrhea	-	1 (16.7)	1 (16.7)	-	2 (11.1)	1 (16.7)	-	-	-	-	1 (8.3)	2 (5.7)	-	-
Vessel puncture site bruise	-	-	-	-	-	1 (16.7)	1 (16.7)	1 (16.7)	-	2 (11.8)	1 (8.3)	2 (5.7)	-	-
Abdominal pain	-	-	1 (16.7)	-	1 (5.6)	-	-	-	1 (20.0)	1 (5.9)	-	2 (5.7)	-	-
Headache	-	-	-	1 (16.7)	1 (5.6)	-	-	1 (16.7)	-	1 (5.9)	-	2 (5.7)	-	-
Nausea	-	-	1 (16.7)	1 (16.7)	2 (11.1)	-	-	-	-	-	-	2 (5.7)	-	1 (16.7)
Presyncope	-	1 (16.7)	1 (16.7)	-	2 (11.1)	-	-	-	-	-	-	2 (5.7)	-	-
COVID-19	-	-	-	1 (16.7)	1 (5.6)	1 (16.7)	-	-	-	-	1 (8.3)	1 (2.9)	-	1 (16.7)
Dermatitis contact	-	-	1 (16.7)	-	1 (5.6)	1 (16.7)	-	-	-	-	1 (8.3)	1 (2.9)	-	-
Arthralgia	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-
Chronic sinusitis	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-
Contusion	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-
Dizziness postural	1 (16.7)	-	-	-	-	-	-	-	-	-	1 (8.3)	-	-	-
Infusion site warmth	1 (16.7)	-	-	-	-	-	-	-	-	-	1 (8.3)	-	-	-
Injection site bruising	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-
Injection site pain	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-
Post-traumatic neck syndrome	1 (16.7)	-	-	-	-	-	-	-	-	-	1 (8.3)	-	-	-
Somnolence	-	-	-	-	-	1 (16.7)	-	-	-	-	1 (8.3)	-	-	-

Note: Two SAEs not treatment related: 150 mg SC cohort from part A: appendicitis at day 24 post dose; 150 mg SC cohort from part B: Nephrolithiasis day 64 post dose.
* Tachycardia was predominantly orthostatic tachycardia on day 1 of dosing.

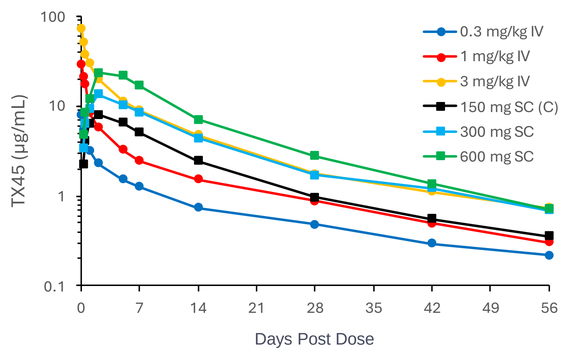
- No discontinuations, infusion reactions or injection site reactions were observed, and no antidrug antibodies (ADAs) were detected. No treatment-related SAEs were observed.
- TEAEs of tachycardia, palpitations, dizziness, and presyncope were transient, not associated with changes in blood pressure, and mild, with the exception of one patient who had moderate orthostatic tachycardia without symptoms.
- No clinically meaningful changes in vital signs, laboratory values (including hematocrit) or ECG intervals.

Figure 2. Systolic blood pressure unaffected in subjects after single dose of SC TX45



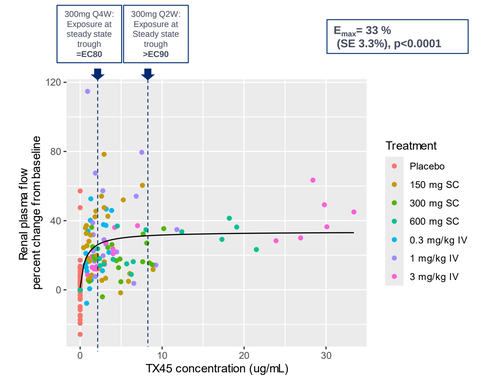
Pharmacokinetics/ Pharmacodynamics

Figure 3. Single dose TX45 exposure over time demonstrates extended half-life in subjects



- PK was dose proportional with SC bioavailability of ~50%.
- No evidence of immune mediated clearance.
- Terminal elimination half-life ranged from 14-20 days.
- Modeled accumulation at steady state after multiple doses is predicted to be 1.5X for 300 mg SC every 4 weeks (Q4W) and 2X for 300 mg SC every 2 weeks (Q2W).

Figure 4. Robust human exposure-response model allows for Phase 2 dose selection



- Mean increases in RPF by dose cohorts ranged from 11% (0.3 mg/kg IV on Day 15, [TX45] = 0.73 μg/mL) to 42% (3 mg/kg IV on Day 2, [TX45] = 29 μg/mL).
- A nonlinear, mixed-effects Emax model was developed to explore the relationship of TX45 exposure on RPF.
- Incorporation of all exposure-response data across all doses and time points post dose resulted in a modeled E_{max} = 33% (SE 3.3%, p<0.0001).

Table 2: Comparison of preclinical studies and human study

Experimental Model	[TX45]
Rat potency-adjusted trough concentration associated with maximal efficacy in rat PH model[1]	2 μg/mL
Rat potency-adjusted trough concentration achieving EC_{70} in rat model of RBF[1]	2 μg/mL
In vitro human cell-based RXFP1 cAMP assays, EC_{70}	2 μg/mL
TX 45 300 mg SC Q4W steady-state trough concentration achieving EC_{80} in human model of RPF	2.6 μg/mL

[1] TX45 is 3X more potent on human versus rat RXFP1

Doses selected for the Phase 2 study

- **300 mg SC Q4W:** Steady state trough exposure is predicted to be 2.6 μg/mL consistent with near maximal (EC_{80}) effect on RPF in the human exposure/response model. This exposure is slightly higher than the preclinical *in vivo* and *in vitro* pharmacology results, as shown in Table 2.
- **300 mg SC Q2W:** Steady state trough exposure is predicted to be 8.7 μg/mL (>EC_{90}) on RPF. This higher dose allows evaluation of whether increased exposure would translate into more efficacy in human trials.

SUMMARY

Data from this Phase 1a study support further evaluation of TX45 in patients with Group 2 pulmonary hypertension associated with HFpEF:

- TX45 was well-tolerated in healthy volunteers with no clinically meaningful change in systolic BP or laboratory values, and no anti-drug antibodies were detected.
- TX45 demonstrated dose proportional PK with a terminal half-life of 14-20 days.
- TX45 is an active drug molecule with effects on renal blood flow consistent with other relaxin molecules.[1,2]
- Selection of 300 mg SC Q4W and Q2W dosing arms in the ongoing Phase 2 study is based upon doses projected to provide exposures resulting in near-maximal and maximal PD effects, respectively, on human RPF at trough which were associated with maximal efficacy in rat chronic pulmonary hypertension models.

[1]Voors et al., 2014, Circ Heart Failure 7:994-1002. [2]Tham et al., 2024, Neph Dial Transplant. 10.1093/ndt/gfae112