

Safety, Tolerability, and Pharmacokinetic After Single Ascending Doses in Healthy Adult Volunteers of TX2100, an Apelin Receptor (APJ) Antagonist

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Authors and Disclosures

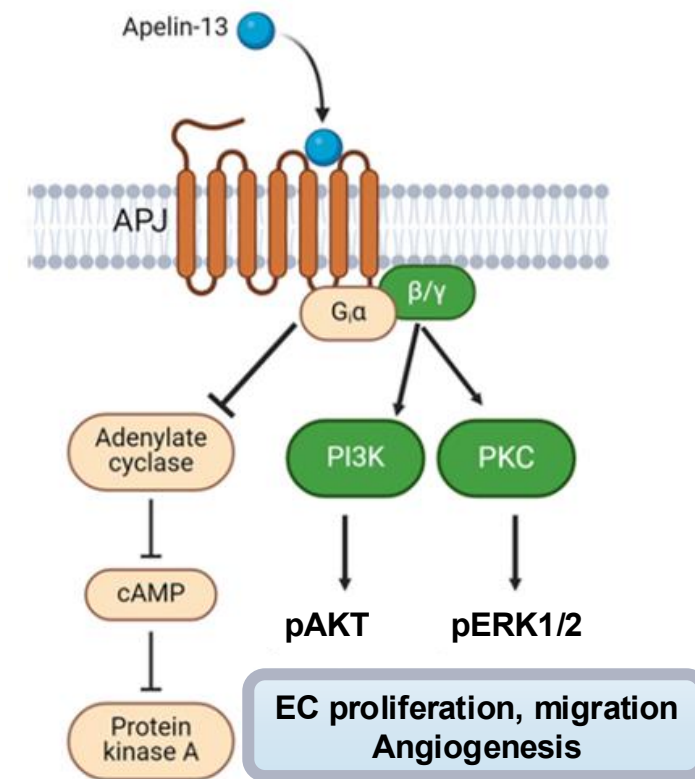
- Avika Dixit (AD), Samuel Wilson (SW), Ali Lacy (AL), Anne Marie Marano (AMM), Mary West (MW), Mark Milton (MM), Anthony J. Muslin (AJM), Marcie Ruddy (MR)
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- This study was funded by Tectonic Therapeutic

TX2100 First-in-Human Clinical Trial: Overview

- Single ascending doses of TX2100, an APJ antagonist, were generally safe and well-tolerated in healthy adult volunteers
- Favorable pharmacokinetic profile, supporting exploration of once weekly and every other week subcutaneous dosing
- Data support continued development of TX2100 for the treatment of HHT

Apelin/APJ Pathway Drives HHT Angiogenesis

- Apelin receptor APJ is enriched in endothelial cells¹
- APJ activation by apelin promotes sprouting angiogenesis²
- Loss-of-function mutations in the BMP9/ENG/ALK1 pathway lead to increased apelin expression, promoting telangiectasia and AVM formation³



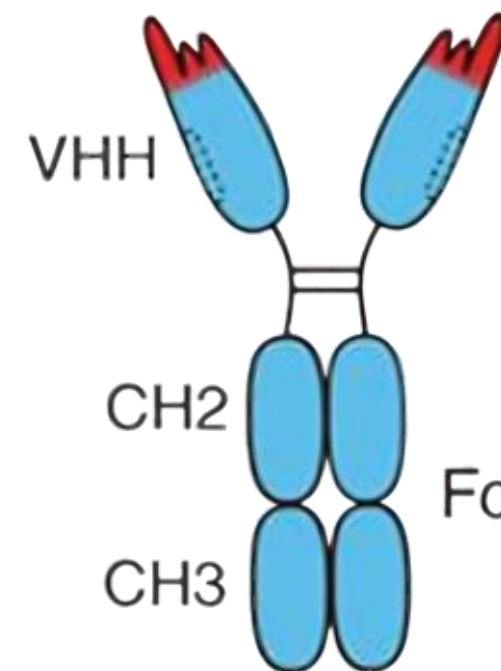
1. Klein MJ, et al. Regul Pept. 2005.
 2. Helker CSM, et al. eLife. 2020.
 3. Darce J. HHT Int Sci Conf. 2026.

ALK1 = activin receptor-like kinase 1; APJ = apelin receptor; AVM = arteriovenous malformation; BMP9 = bone morphogenetic protein 9; cAMP = cyclic adenosine monophosphate; EC = endothelial cell; ENG = endoglin; HHT = hereditary hemorrhagic telangiectasia; pAKT = phosphorylated protein kinase B; pERK1/2 = phosphorylated extracellular signal-regulated kinase 1/2; PI3K = phosphoinositide 3-kinase; PKC = protein kinase C

TX2100 is a Selective APJ Antagonist

An endothelial enriched and pathology biased anti-angiogenic therapy for HHT

- VHH-Fc antibody that blocks apelin-driven APJ signaling (cAMP, pAKT and pERK)
 - Highly potent and highly selective versus closely related GPCRs
- The clearance of TX2100 is expected to be concentration-dependent due to target-mediated drug disposition which is commonly observed in drugs that bind to cell-surface proteins¹



APJ = apelin receptor; cAMP = cyclic adenosine monophosphate; CH2/CH3 = heavy-chain constant domains 2 and 3; Fc = fragment crystallizable region; GPCR = G protein-coupled receptor; HHT = hereditary hemorrhagic telangiectasia; pAKT = phosphorylated protein kinase B; pERK = phosphorylated extracellular signal-regulated kinase; VHH-Fc = variable heavy-chain domain (VHH) Fc-fusion protein

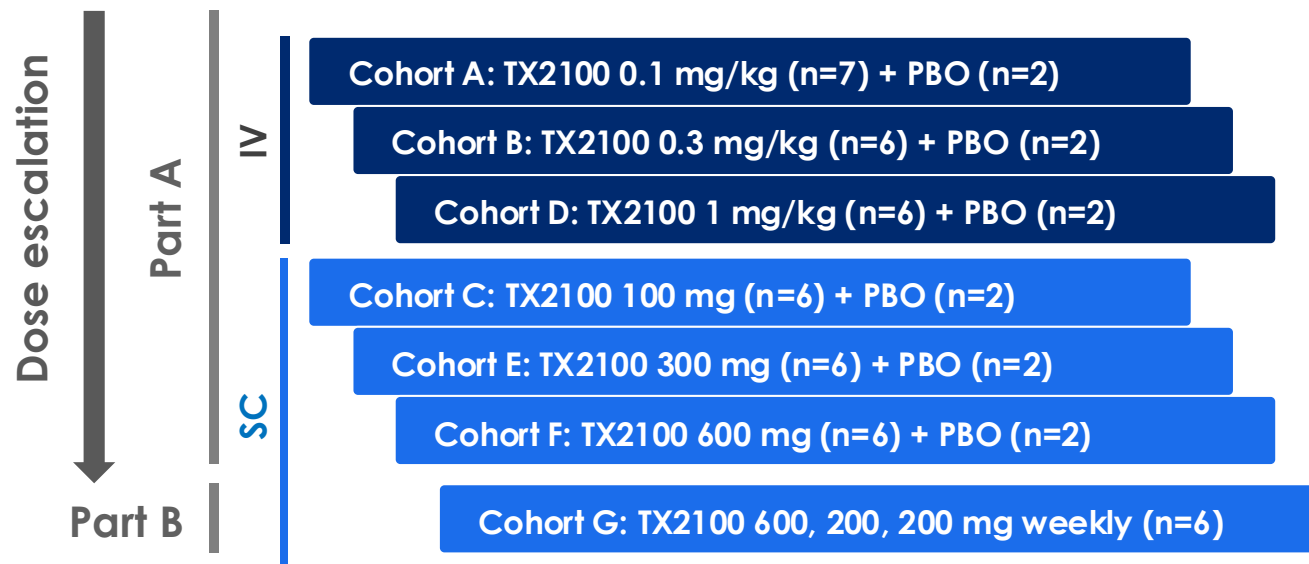
Preclinical Data Support Advancement to FIH Studies

- **Surrogate APJ antagonist efficacious in two mouse models of HHT**
 - Reduced AVMs, bleeding and anemia in the anti-BMP9/10 and iALK1-KO models
- **Toxicology study found no dose-limiting adverse events and TX2100 was generally well-tolerated in nonhuman primates**
 - **NOAEL 100 mg/kg/week IV** and SC in 13-week GLP study
 - Minimal, nonadverse findings, reversible after 12-week recovery
 - **Wide exposure margins** for clinical doses evaluated

APJ = apelin receptor; AVM = arteriovenous malformation; BMP9/10 = bone morphogenetic protein 9/10; FIH = first-in-human; GLP = Good Laboratory Practice; HHT = hereditary hemorrhagic telangiectasia; iALK1-KO = inducible activin receptor-like kinase 1 knockout; IV = intravenous; NOAEL = no-observed-adverse-effect level; SC = subcutaneous

Clinical Trial of TX2100 in Healthy Adult Participants

- Single ascending dose: Double-blind, randomized, placebo-controlled
- Multiple dose: Open-label
- Objectives: safety & tolerability, pharmacokinetics, immunogenicity



Part A Participant Follow-up

- **Cohorts A–C, E, F:** follow-up through 56 days complete (n=40)
- **Cohort D** follow-up ongoing as of data cut – through 28 days complete (n=8)
- **1 discontinuation** (Cohort A participant withdrew on day 20 due to family issue)

Demographics and Baseline Characteristics

Characteristic		Value (n = 49)
Age	Age, years (mean $\pm$ SD)	33.2 $\pm$ 9.9
	Age, years (range)	20–55
Gender	Male, n (%)	43 (87.8)
Race	White, n (%)	30 (61.2)
	Asian, n (%)	11 (22.4)
Ethnicity	Hispanic or Latino, n (%)	10 (20.4)
Body Measurements	Weight, kg (mean $\pm$ SD)	81.5 $\pm$ 11.2
	BMI, kg/m ² (mean $\pm$ SD)	26.2 $\pm$ 2.9

TX2100 Was Generally Safe & Well-Tolerated

No emerging safety issues observed

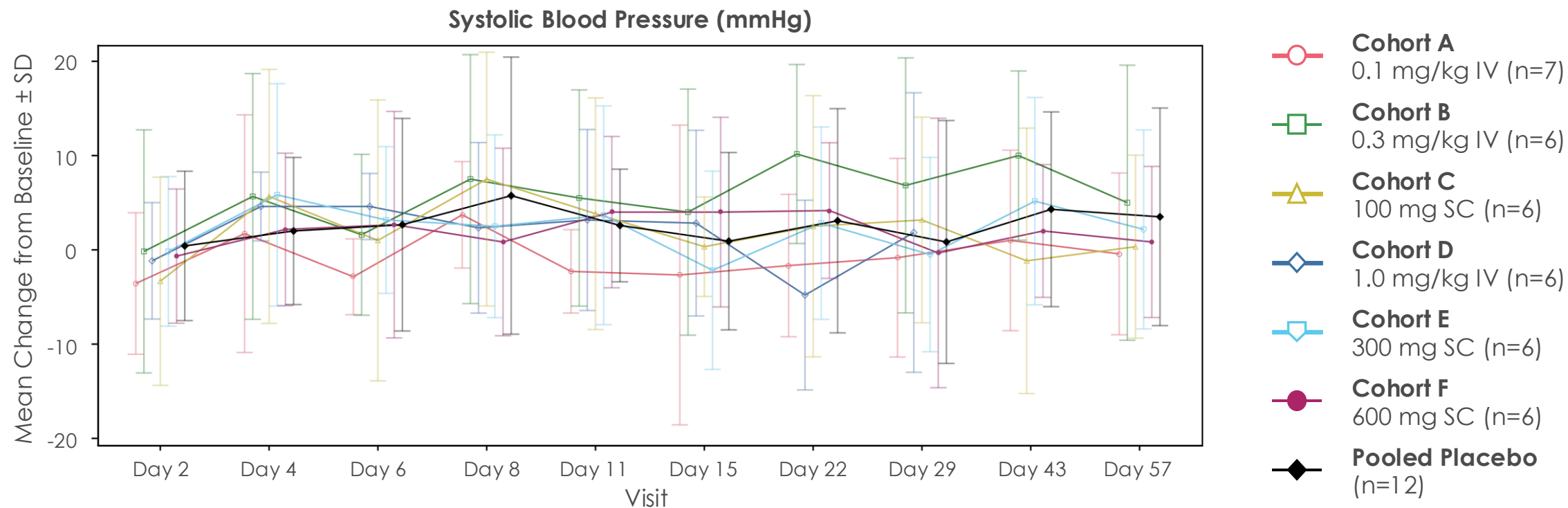
- TEAEs were mild to moderate in intensity and transient
- Moderate TEAEs (n=2): Myalgia, Food poisoning
 - Considered not related to study drug by investigator
- No serious TEAEs, no severe (Grade ≥ 3) TEAEs
- No fatal TEAEs, no TEAEs led to study discontinuation

TEAEs Reported in ≥ 2 Participants: No Dose-Limiting AEs

	IV				SC			
	Placebo (n=6)	0.1 mg/kg (n=7)	0.3 mg/kg (n=6)	1.0 mg/kg (n=6)	Placebo (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Any TEAE	3 (50.0)	1 (14.3)	3 (50.0)	5 (83.3)	3 (50.0)	4 (66.7)	3 (50.0)	6 (100.0)
Treatment-related	1 (16.7)	1 (14.3)	1 (16.7)	2 (33.3)	3 (50.0)	2 (33.3)	1 (16.7)	3 (50.0)
Preferred Term (≥ 2 Participants)								
Infusion site bruising	1 (16.7)	0	0	1 (16.7)	NA	NA	NA	NA
Infusion site pain	0	0	1 (16.7)	1 (16.7)	NA	NA	NA	NA
Injection site reaction	NA	NA	NA	NA	2 (33.3)	1 (16.7)	1 (16.7)	0
Headache	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0
Myalgia	0	0	0	0	0	1 (16.7)	1 (16.7)	0
Viral Infection	0	0	0	2 (33.3)	0	0	0	0
Viral URI	0	0	1 (16.7)	0	0	0	0	1 (16.7)
Vessel puncture site bruise	1 (16.7)	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	0
Contusion	1 (16.7)	0	0	0	0	0	0	1 (16.7)

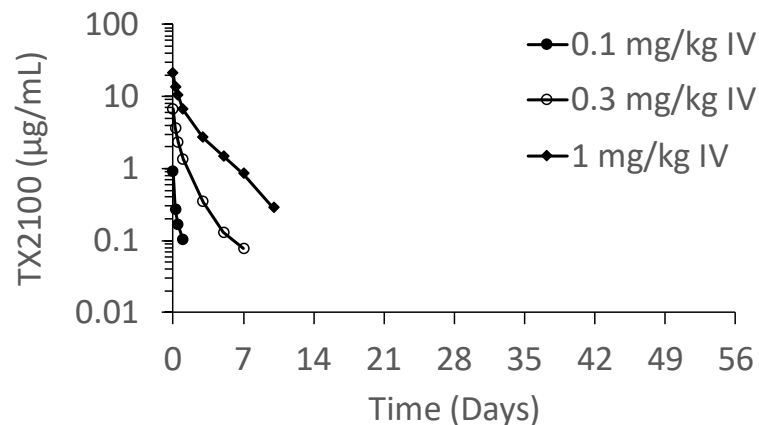
Safety Assessments: No Clinically Significant Changes

- No clinically significant or dose-related changes in vital signs, laboratory assessments, and ECG parameters as compared to baseline
 - No blood pressure increases (as are associated with anti-VEGF agents)



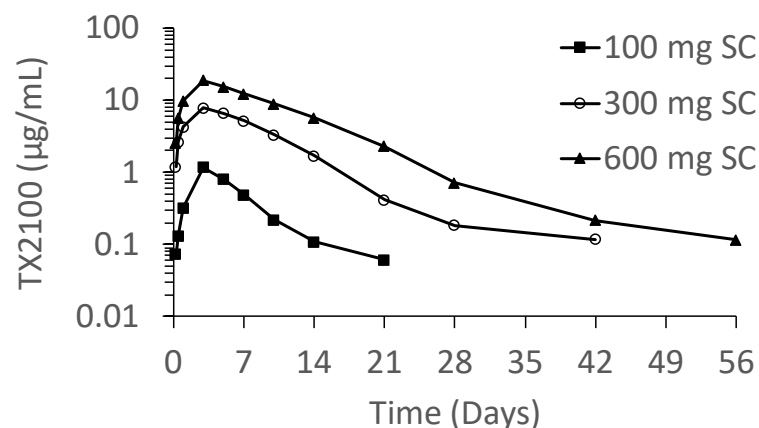
PK Supports Exploring Weekly and Every Other Week SC Dosing

IV Administration



- Peak concentration ~3 days after SC administration
- Target-mediated drug disposition (TMDD) was observed at low concentrations of TX2100
 - Corroborating high affinity and potent binding to APJ
 - Half-life was dose-dependent consistent with TMDD

SC Administration



- No anti-drug antibodies were detected

TX2100 First-in-Human Trial: Conclusions

Single ascending doses of TX2100, an APJ antagonist, were generally safe, well-tolerated, and pharmacokinetically favorable in healthy volunteers

Safety & tolerability

- Most TEAEs were mild and transient
- No deaths, serious, or severe adverse events observed
- No clinically significant changes in vital signs, laboratory values, and ECG parameters

Pharmacokinetics

- Target-mediated drug disposition consistent with potent target engagement
- PK profile supports exploration of once weekly and every other week SC dosing
- No anti-drug antibodies were detected

Path forward

- Findings support continued development of TX2100 for HHT
- Phase 1b open-label in hematologic-support dependent HHT expected by year-end 2026
- Phase 2 placebo-controlled in moderate to severe HHT expected to initiate in early 2027

Thank You



- Study Participants
- Investigators
- CureHHT
- Study Team