UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): May 27, 2026

TONIX PHARMACEUTICALS HOLDING CORP.
(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

200 Connell Drive, Suite 3100, Berkeley Heights, New Jersey 07922
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 799-8599

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On May 27, 2026, Tonix Pharmaceuticals Holding Corp. (the "Company") announced the publication of a paper, "First-in-Human, Phase 1, Randomized, Double-Blind, Placebo-Controlled Study of TNX-1500, an Fc-Modified anti-CD154 Monoclonal Antibody, Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single-Ascending Doses in Healthy Adults," in the peer-reviewed Journal of Clinical Immunology (the "Manuscript"). A copy of the press release that discussed this matter is attached hereto as Exhibit 99.01. A copy of the Manuscript is attached hereto as Exhibit 99.02.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01 and 99.02 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On May 27, 2026, the Company announced the publication of the Manuscript, which reports findings from a single-center, first-in-human, Phase 1, randomized, double-blind, placebo-controlled, single-ascending dose escalation study in 26 healthy adult volunteers of the Company's TNX-1500 product candidate, a monoclonal antibody in development for the prevention of organ transplant rejection and the treatment of autoimmune diseases. Participants were enrolled across three ascending dose cohorts (3, 10, and 30 mg/kg) or placebo and received a single intravenous infusion of TNX-1500 or placebo, followed by intramuscular injections of keyhole limpet hemocyanin ("KLH") on days 2 and 29 to assess the primary and secondary T cell-dependent antibody responses ("TDAR"), and monitored over a 120-day follow-up period. TNX-1500 blocked the primary TDAR to KLH at all doses, blocked the secondary response at the 10 and 30 mg/kg doses, and reduced peak secondary response to KLH by approximately 70% relative to placebo at the 3 mg/kg dose.

Forward-Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release, date May 27, 2026
99.02	First-in-Human, Phase 1, Randomized, Double-Blind, Placebo-Controlled Study of TNX-1500, an Fc-Modified anti-CD154 Monoclonal Antibody, Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single-Ascending Doses in Healthy Adults
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: May 27, 2026

By: */s/ Bradley Saenger*
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Tonix Pharmaceuticals Announces Publication of Phase 1 Clinical Data of TNX-1500, an Fc-Modified anti-CD40L (CD154) Monoclonal Antibody, in the Peer-Reviewed *Journal of Clinical Immunology*

Phase 1 data support TNX-1500 as a potentially first-in-class, best-in-class, third-generation anti-CD40L monoclonal antibody for the prevention of kidney transplant rejection

Phase 2 investigator-initiated study in adult kidney transplant at Massachusetts General Hospital (MGH) expected to initiate in the 2nd half of 2026 pending U.S. Food and Drug Administration (FDA) clearance of MGH's Investigational New Drug (IND) application

BERKELEY HEIGHTS, N.J., May 27, 2026 (GLOBE NEWSWIRE) — Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) ("Tonix" or the "Company"), a fully integrated, commercial-stage biotechnology company, today announced the publication of a paper, "First-in-Human, Phase 1, Randomized, Double-Blind, Placebo-Controlled Study of TNX-1500, an Fc-Modified anti-CD154 Monoclonal Antibody, Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single-Ascending Doses in Healthy Adults," in the peer-reviewed *Journal of Clinical Immunology*. TNX-1500 is an investigational, third-generation Fc-modified IgG4 anti-CD40L (also known as CD154) monoclonal antibody (mAb) in development for the prevention of organ transplant rejection and the treatment of autoimmune diseases. The manuscript can be accessed at https://pubmed.ncbi.nlm.nih.gov/42053701/.

"The CD40L is a validated target for preventing organ rejection in transplant and treating autoimmune disease, yet no anti-CD40L mAb has been approved for any indication," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "TNX-1500 is a Phase 2 ready humanized mAb engineered to improve safety and tolerability relative to first-generation anti-CD40L mAbs, while preserving the durable half-life and certain effector functions associated with the Fc or crystallizable fragment. We believe the Phase 1 results show that these design objectives were achieved in TNX-1500."

Dr. Gregory Sullivan, M.D., Chief Medical Officer of Tonix Pharmaceuticals added, "The Phase 1 study evaluated TNX-1500's safety, tolerability, pharmacokinetics, and pharmacodynamics. TNX-1500 was generally well tolerated, demonstrated a favorable safety profile, suppressed the primary and secondary T cell-dependent antibody responses (TDARs) to keyhole limpet hemocyanin (KLH) antigen, and showed a half-life which supports monthly intravenous dosing. We expect a Phase 2, investigator-initiated study of TNX-1500 in the prevention of kidney allograft rejection at MGH to begin in the 2nd half of 2026 pending clearance of the IND by the FDA."

The publication reports findings from a single-center, first-in-human, Phase 1, randomized, double-blind, placebo-controlled, single-ascending dose escalation study in 26 healthy adult volunteers. Participants were enrolled across three ascending dose cohorts (3, 10, and 30 mg/kg) or placebo and received a single intravenous infusion of TNX-1500 or placebo, followed by intramuscular injections of KLH on days 2 and 29 to assess the TDAR, and monitored over a 120-day follow-up period. TNX-1500 blocked the primary T cell–dependent antibody response to KLH at all doses, blocked the secondary response at the 10 and 30 mg/kg doses, and reduced peak secondary response to KLH by ~70% relative to placebo at the 3 mg/kg dose.

TNX-1500 was generally well tolerated, with no serious adverse events, and no discontinuations due to adverse events. The only treatment-emergent adverse event (TEAE) deemed possibly related to study drug was aphthous ulcer, which occurred in 1 participant in each of the three TNX-1500 groups; all TEAEs were rated as mild and resolved in 2-10 days. No TEAEs were determined to be related to KLH administration. There were no administration or injection site reactions (one of the prespecified TEAEs of special interest). Pharmacokinetic analyses suggested approximately dose-proportional exposure across the 3 to 30 mg/kg range, with mean terminal elimination half-lives of 37.8 and 33.8 days at the 10 and 30 mg/kg dose levels, respectively. TNX-1500 at 10 and 30 mg/kg blocked the primary and secondary anti-KLH TDAR through day 120, and at 3 mg/kg reduced the peak secondary response by approximately 70% relative to placebo. Across all dose cohorts, TNX-1500 was associated with a rapid (less than one-hour post-dose) and sustained reduction in soluble CD40L (sCD154) over the 120-day study period.

About TNX-1500

TNX-1500 (Fc-modified humanized anti-CD40L mAb) is a Phase 2 ready, humanized monoclonal antibody that interacts with the CD40-ligand (CD40L), also known as CD154. TNX-1500 is being developed for the prevention of kidney transplant rejection and the treatment of autoimmune diseases. Anti-CD40L has multiple potential indications in addition to solid organ and bone marrow transplantation including autoimmune diseases. Collaborations are ongoing with MGH on allo-heart and -kidney transplantation in nonhuman primates, as well as prevention of xenograft rejection, preclinical studies, and prevention of allograft rejection in sensitized patients. The Phase 2 investigator-initiated study by MGH is expected to initiate enrollment in the 2nd half of 2026, pending FDA clearance of the IND, to evaluate TNX-1500 in five kidney transplant recipients. The study is designed to assess the safety, tolerability, and activity of TNX-1500 in preventing kidney transplant rejection while decreasing the exposure to conventional immunosuppressive drugs, which are associated with infection, cancer, cardiovascular side effects, and various metabolic derangements with long term use.

Tonix Pharmaceuticals Holding Corp.

Tonix Pharmaceuticals* is a fully integrated, commercial-stage biotechnology company focused on central nervous system (CNS) disorders, infectious diseases, immunology conditions, and rare diseases where there exists high unmet medical need. TONMYA® (cyclobenzaprine HCl sublingual tablets 2.8mg), the Company's flagship internally conceived and developed medicine, is the first new treatment for fibromyalgia in more than 15 years. Tonix's CNS commercial infrastructure supports its marketed products, including its acute migraine products, Zembrace® SymTouch® (sumatriptan injection 3 mg) and Tosymra® (sumatriptan nasal spray 10 mg). Tonix is extending the science behind TONMYA in Phase 2 clinical studies to evaluate its potential in major depressive disorder and acute stress disorder/acute stress reaction. Tonix is also advancing a pipeline of infectious disease programs, including monoclonal antibody TNX-4800 (anti-OspA mAb) for Lyme disease prevention in the U.S. and TNX-801 (horsepox, live virus vaccine), a vaccine in development for the prevention of mpox and smallpox. Within immunology, Tonix is developing TNX-1500 (anti-CD40L mAb), a third-generation CD40 ligand inhibitor for the prevention of kidney transplant rejection. Finally, the Company's rare disease portfolio includes TNX-2900, which is Phase 2 ready for the treatment of Prader-Willi syndrome. To learn more, visit www.tonixpharma.com.

**Tonix's product development candidates are investigational new drugs or biologics; their efficacy and safety have not been established and have not been approved for any indication.*

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995 including those relating to the completion of the offering, the satisfaction of customary closing conditions, the intended use of proceeds from the offering and other statements that are predictive in nature. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to successfully launch and commercialize TONMYA® and any of our approved products; risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set in the Company's Annual Report on Form 10-K for the year ended December 31, 2025, as filed with the SEC on March 12, 2026, and periodic reports filed with the SEC on or after the date thereof. Tonix does not undertake an obligation to update or revise any forward-looking statement. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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First-in-Human, Phase 1, Randomized, Double-Blind, Placebo-Controlled Study of TNX-1500, an Fc-Modified anti-CD154 Monoclonal Antibody, Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single-Ascending Doses in Healthy Adults

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Abstract

Blocking CD154 (CD40L) has the potential to prolong transplanted solid organ graft survival and treat autoimmune diseases. However, first-generation anti-CD154 IgG1 monoclonal antibodies (mAbs) were associated with an increased risk of thrombosis linked to Fc binding to FcγRIIa (CD32A). Here, we describe a first-in-human, phase 1 clinical trial of TNX-1500, a novel Fc-modified IgG4 anti-CD154 mAb designed to decrease binding to FcγRIIa. Healthy volunteers (N=26) were enrolled into single-ascending dose (3, 10, and 30 mg/kg) cohorts and received TNX-1500 intravenously. TNX-1500 was generally well tolerated. Among participants receiving TNX-1500 3, 10, and 30 mg/kg, 1 (25%), 3 (38%), and 3 (38%) participants, respectively, reported ≥1 treatment-emergent adverse event; all were mild or moderate in severity, and none resulted in study discontinuation. There were no thromboembolic events. Pharmacokinetic analyses of TNX-1500 demonstrated a mean half-life of 37.8 and 33.8 days for 10 and 30 mg/kg, respectively, supportive of monthly dosing; dose-proportional exposure was suggested over the 3 to 30 mg/kg range. TNX-1500 blocked the primary T cell–dependent antibody response to keyhole limpet hemocyanin (KLH) at all doses and blocked the secondary response at the 10 and 30 mg/kg doses. At 3 mg/kg, TNX-1500 reduced peak secondary response to KLH by ~70% relative to placebo. TNX-1500 administration was associated with immediate and sustained reduction in soluble CD154. Overall, TNX-1500 demonstrated a safety profile and

pharmacologic properties that support further development as an agent with potential for prevention of organ transplant rejection and treatment for autoimmune conditions.

Keywords: allograft transplant, immunosuppression, monoclonal antibodies, anti-CD154, anti-CD40L, clinical trials

Introduction

CD154 (CD40L) is the molecular basis for T cell–helper activity for humoral and cell-mediated immunity [1-9] and, consequently, plays a critical role in immune responses. Blocking the CD154 pathway with anti-CD154 monoclonal antibodies (mAbs) has been shown to modulate T cell–dependent humoral immune responses, treat autoimmunity, and prevent allograft and xenograft rejection [10-23]. First-generation immunoglobulin G1 (IgG1) anti-CD154 mAb therapies were effective at treating autoimmunity and improving graft survival and function, but were also associated with an increased risk of thrombosis [24]. Subsequent studies showed that thrombosis risk was related to the interaction of the crystallizable fragment (Fc)–domain of IgG1 anti-CD154 mAbs with the Fc gamma receptor IIa (FcγRIIa, CD32A) [25,26].

The knowledge gained from first-generation therapies led to the development of anti-CD154 mAbs that either lacked an Fc domain or contained a silenced aglycosyl Fc domain [17,18,27-29]. These second-generation anti-CD154 mAbs successfully addressed the thrombosis risk but were limited to modulating humoral immunity but not cellular immunity. For example, treatment with an aglycosyl anti-CD154 construct modulated the humoral immune response in nonhuman primates but was largely ineffective at preventing renal allograft rejection [27]. These findings suggested that certain Fc-domain functions of anti-CD154 mAbs may be

necessary for modulating cellular immunity and for successful long-term organ transplant survival and function.

Most recently, third generation Fc-modified anti-CD154 mAbs were designed to limit the risk of thrombosis, without sacrificing the immunomodulatory activity of first-generation anti-CD154 mAbs. Frexalimab (SAR441344, INX 021) is an Fc-modified IgG1 anti-CD154 mAb that has shown promise in treating multiple sclerosis [23]. Tegoprubart (AT-1501) is an Fc-modified, non–disulfide-linked IgG1 anti-CD154 mAb that has shown promise in preventing allograft rejection [22].

TNX-1500 is an Fc-modified IgG4 anti-CD154 mAb that is being developed as a potential treatment for autoimmune conditions and to prevent organ transplant rejection. TNX-1500 contains the antigen-binding fragment (Fab) region of hu5c8 (ruplizumab) [21], which has been extensively characterized [30]. TNX-1500 was engineered with a modified Fc domain (S228P, L235A) [31-33] to decrease FcγRIIa binding [20,21]. Preclinical *in vitro* studies demonstrated that TNX-1500 modulates immune function [20]. Moreover, TNX-1500 treatment of nonhuman primate kidney or heart allo-transplant recipients (approximately 20-30 mg/kg) prolonged allograft survival and was well tolerated with no evidence of thromboembolic events [20,21]. These results supported the development of TNX-1500 as a candidate to potentially prevent transplant organ rejection and treat autoimmunity. Here, we report a first-in-human study designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of TNX-

1500, administered intravenously as single-ascending doses in healthy participants.

Methods

Study Design

This was a single-center, first-in-human, phase 1, randomized, double-blind, placebo-controlled, single-ascending dose escalation study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of TNX-1500 in healthy adult volunteers. The study included a 28-day screening period followed by a 1-day check-in period (day –1), a 2-day treatment and observation period (days 1 and 2), and a 118-day follow-up period (days 3-120). Participants were enrolled into 3 ascending dose cohorts (3, 10, and 30 mg/kg) and within each cohort were randomly assigned to receive a single dose of TNX-1500 or placebo (3-mg/kg cohort, 2:1; 10- and 30-mg/kg cohorts, 4:1). Following enrollment and dosing of 2 participants into the lowest dose level (randomized 1:1 to receive TNX-1500 or placebo), a safety review committee reviewed safety and relevant data before proceeding with the remaining participants in the lowest dose cohort. Dose escalation only proceeded if there were no signs of cytokine release syndrome, infusion-related reactions, or significant adverse events (AEs) within 48 hours postdose.

Participants received the study drug on day 1, infused intravenously over a period of 1 hour. All relevant information obtained from preclinical studies

and the estimated half-life of TNX-1500 [20,21] was used to model a human equivalent dose, as well as the time points for pharmacokinetic and pharmacodynamics sample collections. Following study drug administration, participants remained in the clinic for ≥24 hours to complete safety and laboratory assessments and were monitored for signs and symptoms of AEs. On day 2, participants received an intramuscular injection of keyhole limpet hemocyanin (KLH; Immucothel®) 1 mg, an immunogenic T cell–dependent antigen used to assess a T cell–dependent antibody response (TDAR). All subsequent safety assessments and blood draws for pharmacokinetic and pharmacodynamic analyses during the follow-up period were performed at the study site; on day 29, all participants were to receive a second injection of KLH 1 mg. Screening of approximately 76 volunteers was planned, with a goal of approximately 26 participants enrolled with evaluable data.

The study protocol, associated documents, and informed consent forms were reviewed and approved by an institutional review board (Advarra; IRB registration number, 00000971). The study was conducted in accordance with the Declaration of Helsinki, the ethical principles of Good Clinical Practice guidelines established by the International Council for Harmonisation, and all other applicable local regulatory requirements. Written informed consent was obtained from each participant prior to initiation of study procedures.

Participants

Eligible participants were healthy adults (18-65 years) with a body mass index (BMI) between 18.5 and 34.9 kg/m^2, who were nonsmokers (no use of tobacco products ≤3 months before screening). All participants must have had proof of receiving the COVID-19 vaccine (either Pfizer-BioNTech [COMIRNATY®] or Moderna [SPIKEVAX™]) ≥14 days prior to consent. Female participants of childbearing potential must have been using nonhormonal contraceptive methods for ≥3 months prior to dosing and agreed to continue use throughout the study; male participants had to agree to the use of protocol-approved contraception with female partners unless the partner was surgically sterile or ≥2 years postmenopausal.

Participants were excluded from the study if they met any of the following criteria: history of allergic reaction to parenteral administration of contrast agents, human or murine proteins, or mAbs or allergy to any of the TNX-1500 inactive components; history of shellfish allergy; history of protein C or protein S deficiency disorders and/or abnormality in protein C and protein S levels at screening; required treatment with antiplatelet and/or antithrombotic drugs; previous exposure to KLH; negative for Epstein–Barr virus viral capsid or nuclear antigen IgG; positive serologic test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, or human immunodeficiency virus; or history of positive tuberculin (TB) test or positive QuantiFERON TB Gold at screening. Participants were also excluded if they exhibited increased risk for thromboembolic events or

history of confirmed venous thromboembolism, arterial thrombosis, coagulopathy, or known platelet disorders; history of diabetes; history of clinically significant and currently relevant cardiovascular, pulmonary, hepatic, or kidney diseases; use of hormonal replacement therapy or hormonal contraception; or history of drug or alcohol use disorder or positive urine drug test at the time of screening.

Study Objectives

The primary objective was to assess the safety and tolerability of single-ascending doses of TNX-1500, administered intravenously. The secondary objectives were to evaluate the pharmacokinetic parameters of TNX-1500, the effect of TNX-1500 on KLH antigen challenge, and the effect of TNX-1500 on coagulation and platelet activation parameters. The key exploratory objectives were to evaluate the effect of TNX-1500 on lymphocyte subsets, inflammatory markers, and soluble CD154 (sCD154).

Safety and Tolerability

Safety assessments included AE reporting, clinical laboratory testing, vital signs, electrocardiogram (ECG) parameters, and physical examination. Monitoring of safety parameters and reporting of AEs occurred throughout screening, from predose to 24 hours postdose, and continued throughout the study. AEs of special interest were defined as any thromboembolic events and incidences of infection, administration or injection site reactions,

or cytokine release syndrome considered Common Terminology Criteria for AEs (CTCAE) grade 2 in severity.

Pharmacokinetic Analysis

Blood samples were collected for pharmacokinetic analyses predose (ie, baseline) and at 0.5, 1, 1.5, 2, 3, 4, and 8 hours postdose on day 1; subsequent blood samples were collected on days 2, 3, 5, 8, 15, 22, 29, 36, 50, 64, 78, and 120 (or at early termination). The following pharmacokinetic parameters of TNX-1500 were calculated: maximum measured serum concentration (C_{max}), time to C_{max} (T_{max}), area under the serum concentration-versus-time curve (AUC) from time 0 to the time of the last measurable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$), dose normalized maximum serum concentration (C_{max}/Dose), AUC from time of dosing to the time of last measurable concentration (AUC_{0-t}/Dose), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$/Dose), apparent first-order terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), total clearance (CL), and terminal volume of distribution (V_z).

Pharmacodynamics and Exploratory Biomarkers

The following pharmacodynamic parameters were measured: mean and change in anti-KLH antibody levels, coagulation markers (prothrombin time, partial prothrombin time, international normalized ration [INR], D-dimer, and fibrinogen), lymphocyte subsets (natural killer cells; monocytes; $CD19^+$ B cells; and $CD3^+$, $CD4^+$, and $CD8^+$ T cells and subtypes), proinflammatory

cytokines (interferon [IFN]-γ, interleukin [IL]-1β, IL-2, IL-6, and tumor necrosis factor [TNF]-α), and inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, and homocysteine). Blood collection to assess anti-KLH antibodies occurred predose and on days 8, 15, 29, 36, 50, 64, 78, and 120. Coagulation panels were performed at screening; check-in; and on days 2, 3, 5, 8, 15, 22, 29, 36, 50, 64, 78, and 120. Blood samples for inflammatory markers were taken at screening; predose; and on days 2, 3, 5, 8, 15, 29, 50, 78, and 120. A key exploratory pharmacodynamic parameter was the change from baseline in sCD154 in serum. Blood samples for lymphocyte subsets and sCD154 were taken predose and at 1, 2, 3, 4, and 8 hours postdose on day 1; subsequent samples were collected on days 2, 3, 8, 29, 50, and 120.

Statistical Analysis

Safety was assessed in the safety population, defined as all participants who received study drug (TNX-1500 or placebo). Pharmacokinetic parameters were assessed in the pharmacokinetic population, which included all participants who received the study drug and for whom the pharmacokinetic profile could be adequately characterized. Pharmacodynamic analyses were assessed in the modified intent-to-treat (mITT) population, which consisted of all randomized participants who received the study drug. Outcomes were assessed by dose and cohort using descriptive statistics. Categorical variables are presented with the number

of observations and percentage in each category; geometric mean and coefficient of variation were calculated for pharmacokinetic analyses.

Results

Participants

Of the 144 healthy volunteers screened, 26 were enrolled and received the study drug in 3 cohorts (3 mg/kg, n=4; 10 mg/kg, n=8; and 30 mg/kg, n=8) or placebo (n=2 per cohort). In total, 24 (92%) participants completed the study, and 2 discontinued (n=1 placebo, lost to follow-up after study day 22; n=1 TNX-1500 30 mg/kg, withdrew consent after study day 29). Baseline demographics and clinical characteristics are presented in **Table 1**. Mean (SD) age was 47.5 years, and most participants (73%) were male, including all participants randomized to placebo.

Table 1. Participant Demographics and Baseline Characteristics (Safety Population)

Characteristic	TNX-1500			Placebo (n=6)
	3 mg/kg (n=4)	10 mg/kg (n=8)	30 mg/kg (n=8)	
Age, mean (range) years	39.8 (33-46)	44.0 (21-62)	47.9 (31-62)	57.0 (47-63)
Sex, n (%)[a]				
Female	3 (75)	1 (13)	3 (38)	0

Male	1 (25)	7 (88)	5 (63)	6 (100)
Ethnicity, n (%)[a]				
Hispanic or Latino	0	0	1 (13)	0
Not Hispanic or Latino	4 (100)	8 (100)	7 (88)	6 (100)
Race, n (%)[a]				
Asian	0	1 (13)	0	0
Black	3 (75)	2 (25)	2 (25)	3 (50)
White	1 (25)	5 (63)	6 (75)	3 (50)
BMI, mean (SD) kg/m^2	30.1 (4.3)	29.8 (2.6)	27.9 (3.1)	28.2 (5.4)

BMI, body mass index.
[a]Percentages may not sum to 100 due to rounding.

Safety

Overall, 9 participants (35%) reported ≥1 treatment-emergent AE (TEAE; n=27 events) during the study. There were no deaths or serious AEs (**Table 2**; **Table S1**). All TEAEs were considered mild or moderate in severity, and none led to study discontinuation. There were no TEAEs of special interest, and no TEAEs were assessed as related to KLH administration. The only TEAE occurring in >2 participants among all TNX-1500 groups was aphthous ulcer, which occurred in 1 participant in each of the TNX-1500 cohorts; all cases were considered mild in severity and resolved in 2 to 10 days. Of these 3 participants, 2 had reported a medical history of aphthous

ulcers. TNX-1500 administration was not associated with any clinically meaningful changes in laboratory testing, vital signs, or ECG, and physical examination revealed no other abnormal findings. There were no dose-limiting or dose-related safety findings.

Table 2. Summary of Safety (Safety Population)

Participants with TEAE, n (%)	TNX-1500			Placebo (n=6)
	3 mg/kg (n=4)	10 mg/kg (n=8)	30 mg/kg (n=8)	
≥1 TEAE	1 (25)	3 (38)	3 (38)	2 (33)
≥1 study drug–related TEAE	1 (25)	1 (13)	1 (13)	0
KLH-challenge related TEAE	0	0	0	0
Discontinuations due to a TEAE	0	0	0	0
Deaths	0	0	0	0
TEAEs occurring in ≥2 participants overall				
Aphthous ulcer	1 (25)	1 (13)	1 (13)	0
Oropharyngeal pain	1 (25)	1 (13)	0	1 (17)
Diarrhea	0	0	2 (25)	0
Headache	1 (25)	0	1 (13)	0
Nasal congestion	0	1 (13)	0	1 (17)

Nasopharyngitis	0	0	1 (13)	1 (17)

KLH, keyhole limpet hemocyanin; TEAE, treatment-emergent adverse event.

Pharmacokinetic Parameters

A summary of the pharmacokinetic parameters of TNX-1500 in serum is provided in Table 3. TNX-1500 concentrations increased rapidly after infusion and declined in a monoexponential manner. Following single-dose administration of TNX-1500 at 3, 10, or 30 mg/kg, mean C_{max} ranged from 110 to 945 µg/mL, and median T_{max} ranged from 2.00 to 2.50 h. Mean AUC_{0-t} and $AUC_{0-\infty}$ ranged from 46,700 to 463,000 h*µg/mL and 48,100 to 532,000 h*µg/mL, respectively. Mean λz ranged from 0.001 to 0.002 h, and mean CL ranged from 4.77 to 5.34 mL/h. Mean V_z ranged from 3.36 to 6.08 L. The mean (SD) half-life of TNX-1500 was 19.6 (9.3) days for 3 mg/kg, 37.8 (5.5) days for 10 mg/kg, and 33.8 (4.9) days for 30 mg/kg. An assessment of dose proportionality suggested that exposure was approximately dose-proportional over the tested dose range of 3 to 30 mg/kg (Figure 1).

Table 3. Pharmacokinetic Parameters for TNX-1500 (Pharmacokinetic Population)

Parameter, mean (SD)	**TNX-1500 3 mg/kg (n=4)**	**TNX-1500 10 mg/kg (n=8)**	**TNX-1500 30 mg/kg (n=8)**

C_{max}, µg/mL	110 (6.8)	373 (52.2)	945 (203)
T_{max}, h[a]	2.50 (1.05, 4.00)	2.00 (1.50, 4.00)	2.50 (1.00, 8.00)
AUC_{0-t}, h*µg/mL	46,700 (5800)	174,000 (21,100)	463,000 (101,000)
$AUC_{0-\infty}$, h*µg/mL	48,100 (7180)	195,000 (29,400)	532,000 (66,900)
λ_z, 1/h	0.002 (0.001)	0.001 (0.0001)	0.001 (0.0001)
$t_{1/2}$, h	471 (223)	907 (131)	810 (117)
CL, mL/h	5.34 (1.34)	4.77 (1.01)	4.83 (0.88)
V_z, L	3.36 (1.20)	6.08 (0.53)	5.56 (1.28)

AUC, area under the serum concentration-versus-time curve; AUC_{0-t}, AUC from time 0 to last measurable concentration; $AUC_{0-\infty}$, AUC from time 0 extrapolated to infinity; C_{max}, maximum measured serum concentration; CL, clearance; λ_z, apparent first-order terminal elimination constant; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; V_z, terminal volume of distribution.

[a]Presented as median (min, max).

Figure 1

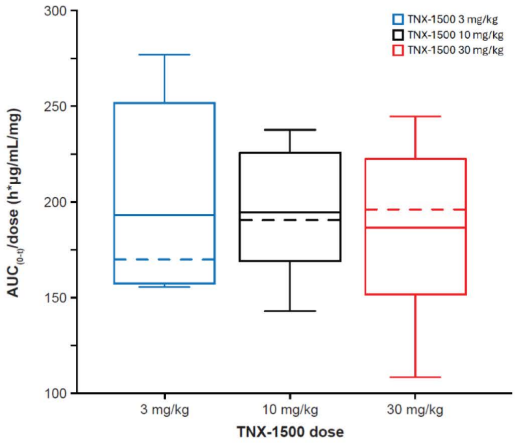

Figure 1. Dose-normalized $AUC_{0\text{-}t}$ by TNX-1500 dose level (pharmacokinetic population). $AUC_{0\text{-}t}$, area under the serum concentration-versus-time curve from time 0 to last measurable concentration. Note: dashed line = median; solid line = mean.

Pharmacodynamic Profile of TNX-1500 and Key Exploratory Endpoints

KLH Antigen Challenge

TNX-1500 administration had an inhibitory effect on the TDAR to KLH challenge; the magnitude and duration of the inhibition varied by dose. TNX-1500 10 and 30 mg/kg blocked the primary and secondary anti-KLH TDAR to the test antigen, evidenced by the mean antibody level at all sampled time points (through day 120) being below the lower limit of quantitation (400 µg/L) (**Figure 2**). TNX-1500 3 mg/kg caused a nearly complete block of the primary response to KLH and reduced the peak secondary response to KLH day 29 challenge by 69% relative to the peak response to placebo. The peak secondary response to KLH day 29 challenge was observed at day 50 in the placebo cohort (mean [SD] anti-KLH Ab levels, 12,040 [15,485] µg/L) and the TNX-1500 3 mg/kg cohort (3732 [4131] µg/L).

Figure 2

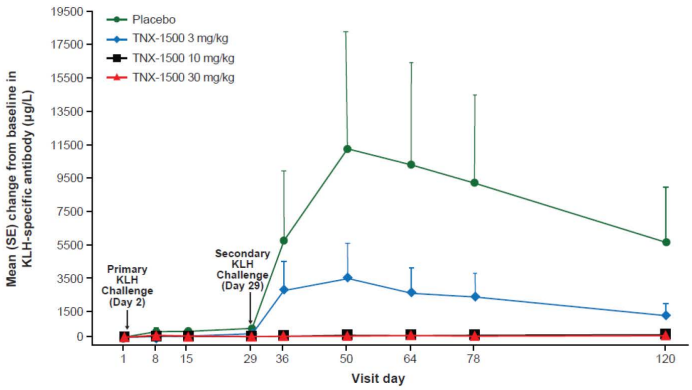

Fig. 2 Mean (SE) change from baseline in KLH-specific TDAR by drug cohort (mITT population). Participants received a primary KLH challenge on day 1 and a secondary KLH challenge on day 29. KLH, keyhole limpet hemocyanin; mITT, modified intent-to-treat; TDAR, T cell–dependent antibody response.

Lymphocyte Subsets and Total Lymphocyte and Neutrophil Counts

There were no clinically meaningful changes or dose-dependent effects in any lymphocyte subset following TNX-1500 administration. No events of neutropenia or lymphopenia were reported.

Proinflammatory Cytokines

No clinically meaningful trends were noted across treatment groups in mean change from baseline in levels of IFN-γ, IL-1β, IL-6, or TNF-α. While the mean (SD) IFN-γ concentration at baseline was notably higher in the TNX-1500 10 mg/kg dose group (21.00 [43.553] ng/mL) than in the overall population (10.94 [24.295]), this was mostly driven by a single subject with a reported baseline concentration of 128.46 ng/mL compared to the baseline median of 5.78 ng/mL in the mITT population. However, trends in

change from baseline in the TNX-1500 10 mg/kg group did not differ from the other TNX-1500 groups or placebo. IL-2 concentrations were below the lower limit of quantification for all subjects at all time points.

Coagulation and Inflammatory Markers

Measures of all coagulation markers (prothrombin, fibrinogen, and D-dimer levels) remained within the normal range following administration of TNX-1500 at all doses. There were also no meaningful observed trends with TNX-1500 on any of the assessed inflammatory markers (C-reactive protein, homocysteine levels, and erythrocyte sedimentation rate). Mean C-reactive protein levels remained within the normal range for all treatment groups with no dose-dependent effects. Similarly, there were no meaningful changes in homocysteine levels in response to TNX-1500. There was a mean increase from baseline of ≥1.0 mm/h in the erythrocyte sedimentation rate for TNX-1500 10 and 30 mg/kg at all measured timepoints except for day 2. Across all treatment groups, the greatest mean increase from baseline was for TNX-1500 10 mg/kg at day 3 (6.0 mm/h), but overall, no meaningful trends were observed.

sCD154

Across all dose cohorts, TNX-1500 was associated with an immediate and sustained decrease in sCD154 over the initial 8 hours postdose (**Figure 3; Figure S1**). sCD154 levels remained reduced in all TNX-1500 dose cohorts relative to baseline and to the cohort that received placebo. At each

successive study visit, mean sCD154 levels increased toward predose levels for all TNX-1500 dose cohorts, but all remained lower compared with baseline measurements and the placebo cohort at day 120.

Figure 3

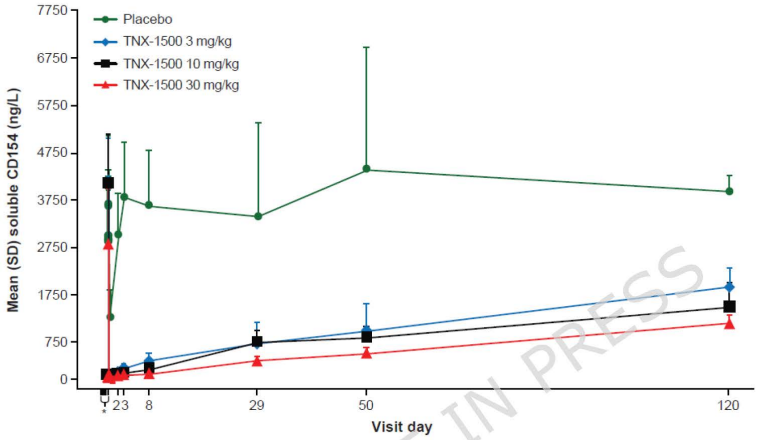

Fig. 3 Mean (SD) change from baseline in soluble CD154 by drug cohort (mITT population). mITT, modified intent-to-treat. *See Fig. S1 for first 8 h.

Discussion

In this first-in-human, phase 1, randomized, double-blind, placebo-controlled, single-ascending dose escalation study, TNX-1500 was generally well tolerated in healthy adults at doses of 3 to 30 mg/kg with no evidence of thromboembolic complications. TNX-1500 exposure was approximately dose-proportional across the tested range of 3 to 30 mg/kg and had a calculated half-life of 38 and 34 days in the 10- and 30-mg/kg cohorts,

respectively. Moreover, TNX-1500 was associated with the inhibition of the primary and secondary anti-KLH TDAR, as well as reductions in sCD154 levels.

Results of the KLH challenge show robust inhibition of T cell–mediated antibody production with the 10- and 30-mg/kg doses of TNX-1500. Even a low dose (3 mg/kg) of TNX-1500 reduced the peak secondary response to KLH challenge by ~70% relative to placebo. These data demonstrate that TNX-1500, compared with placebo, modulates the T cell–dependent humoral immune response. There were no notable effects of TNX-1500 on specific populations or subpopulations of lymphocytes measured, and additional pharmacodynamic assessments suggested that there were no concerning changes in markers related to coagulation or inflammation. Additionally, single-dose TNX-1500 administration was associated with a substantial decrease in sCD154 levels across all doses. The decrease in sCD154 levels was rapid (≤1 h postdose) and sustained over the course of the 120-day study. The discordant effects of 3 mg/kg of TNX-1500 on sCD154 levels (substantial decrease) and the secondary response to KLH (only partial inhibition) are consistent with the interpretation that cell-associated CD154 is more intimately associated with T cell helper function than sCD154 [34]. Together, these analyses indicate that TNX-1500 has a favorable safety profile and that Fc modifications that decreased binding to FcγRIIa achieved the design objectives [20].

TNX-1500 was generally safe across the tested doses, with no serious TEAEs, or discontinuations due to AEs. The proportion of participants reporting TEAEs was similar across all TNX-1500 dose cohorts. In this trial, the only AE that occurred in >2 participants across all TNX-1500 groups was aphthous ulcer, and in all cases, symptoms were mild in severity and resolved within 2 to 10 days. Additionally, 2 of the 3 participants had reported aphthous ulcers in their medical history.

First-generation IgG1 anti-CD154 therapies were associated with an increased risk of thrombosis, related to Fc interactions with FcγRIIa [24-26]. Second-generation anti-CD154 antibodies were engineered with either a silenced or excised Fc region [17,18,27-29], which addressed the potential for thromboembolic complications but may limit the utility of these constructs to modulating T cell–dependent humoral immunity and not cell-mediated immunity [27]. While Fab-based anti-CD154 mAbs have potential applications in treating systemic lupus erythematosus (SLE) [18,29], we reasoned that restoring some Fc functionality may equip a next-generation of anti-CD154 agents to also modulate cell-mediated immunity [27].

TNX-1500 is a third-generation anti-CD154 antibody, designed with a modified Fc domain (S228P, L235A) [31-33], to reduce FcγRIIa binding, while maintaining the desirable immunomodulatory properties and pharmacokinetics of first-generation anti-CD154 mAbs [20,21]. Previous in vitro analysis of TNX-1500 revealed a 14-fold decrease in affinity to FcγRIIa [20]. Indeed, subsequent in vivo studies in nonhuman primates revealed

that TNX-1500 was well tolerated without evidence of thromboembolic events and maintained the ability to prolong kidney and cardiac allograft survival and function [20,21]. Importantly, participants receiving TNX-1500 in the current study had no incidents of thromboembolic events, nor activity on assessed coagulation and platelet activation parameters. Together, these data indicate a favorable safety and tolerability profile of TNX-1500.

At least 2 other Fc-modified anti-CD154 mAbs are in clinical development. Each of these was engineered in different ways to address the risk of thrombosis associated with first-generation anti-CD154 mAbs. Frexalimab, an Fc-modified IgG1 anti-CD154 mAb, has an Fc region modified to reduce FcRγ and C1q binding [35,36], and has shown promise in treating multiple sclerosis [23]. The Fab region of frexalimab is a modified version of IDEC-131, [37] which has changes in framework amino acids in the combining region to increase avidity to CD154 [35,36]. The affinity of IDEC-131 for CD154 was lower than that of chimeric 5c8 which may have resulted in reduced activity in preventing allograft rejection in animals [38].

Tegoprubart (AT-1501) is an Fc-modified, non–disulfide-linked IgG1 anti-CD154 mAb that has shown promise in preventing allograft rejection [22]. The Fab's of both TNX-1500 and tegoprubart are derived from ruplizumab (humanized 5c8, Antova, BG9588) [20,30]. The unique characteristics of ruplizumab's Fab binding with CD154 have been analyzed at the atomic level [30]. Tegoprubart lacks disulfide bonds between either the heavy chains or the heavy and light chains [39,40]. The Fc regions of tegoprubart

are based on those of the CTLA-4 fusion proteins abatacept (Orencia®) and belatacept (Nulojix®). In contrast to tegoprubart, both abatacept and belatacept are disulfide-linked homodimers because the CTLA-4 domain preserves the disulfide linkage of CTLA-4. In a dose-ranging pharmacokinetics study of sequential ascending doses of tegoprubart (0.5 to 8 mg/kg), the mean half-life in healthy volunteers ranged from 18 to 26 days. In an ongoing phase 2 trial in transplant patients, tegoprubart is being dosed every 3 weeks.

Anti-CD154 mAbs have shown potential across a variety of immune-mediated disorders owing to the broad actions of the CD40-CD154 costimulatory pathway. The use of anti-CD154 mAbs has been explored in autoimmune disease models such as SLE [13,18], rheumatoid arthritis [16], and multiple sclerosis [23]. For example, pegylated Fab anti-CD40L (dapirolizumab pegol) has shown positive results in a phase 2 [18] and a phase 3 study of SLE [41]. However, this pegylated Fab inhibited the humoral immune response in nonhuman primates but was largely ineffective at preventing renal allograft rejection [27], suggesting that certain Fc-domain functionality of anti-CD154 mAbs is necessary for successful long-term organ transplants. The modified, yet pharmacologically active Fc domain of TNX-1500 supports its potential utility for treating autoimmune diseases associated with cell-mediated autoimmunity, in addition to its use in solid organ transplantations.

The biological activity of anti-CD154 mAbs is largely attributed to the blockade of CD154:CD40 interaction [2,5,6,8]. However, functional interactions of CD154 and CD11b on antigen-presenting cells appear to play roles in organ transplant rejection. Indeed, blocking the interaction of CD154 with the integrin molecule CD11b on activated antigen-presenting cells inhibits the infiltration of T cells and innate immune cells into recipient allografts, thus contributing to the prolongation of their survival [42]. Consequently, anti-CD40 mAbs have shown comparably less ability than anti-CD154 mAbs to prolong organ transplant survival and function [38,43].

There are several limitations of this study inherent to phase 1 clinical trials. The number of planned participants for each dose cohort was consistent with studies of similar design (ie, first-in-human studies assessing the safety, tolerability, pharmacokinetics, and pharmacodynamics of an investigational product in healthy adults) [44]. However, the relatively small sample size (26 participants enrolled and 24 completed) limits the ability to detect less frequently occurring AEs. Moreover, 73% of participants were male, including all individuals randomized to receive placebo, which limits the ability to observe sex-specific trends in pharmacokinetics or pharmacodynamics in response to TNX-1500. As with most phase 1 trials, the relatively short duration (120 days) and the use of healthy volunteers prevent the assessment of TNX-1500 effects in the intended target populations, and therefore, the results may yield an incomplete safety profile. Finally, as this was a single-dose study, the effects of cumulative

dosing, long-term exposure, or drug–drug interactions were not evaluated, all of which are important considerations for future clinical trials.

The results of this first-in-human, phase 1 trial support the conclusions of previous preclinical studies, revealing a favorable safety profile and showing for the first time that TNX-1500 was generally well tolerated in healthy adults and showed no evidence of increased risk of thrombosis. The clinically efficacious dosing regimen is yet to be determined; however, the calculated half-life of TNX-1500 in the 10- and 30-mg/kg cohorts (38 and 34 days, respectively) is comparable with another Fc-modified anti-CD154 mAb in development (frexamilab) [23] and suggests monthly intravenous dosing in the clinic may maintain stable blood levels. Combined with the absence of serious safety concerns, these data provide strong justification for the continued development of TNX-1500 as a potential therapeutic to prevent rejection in solid organ transplant recipients and to treat autoimmune disorders.

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Statements and Declarations

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Competing Interests

SL, BLD, and GMS are employees of Tonix Pharmaceuticals and own stock and/or have options in the company. NH is a consultant to Tonix Pharmaceuticals.

Author Contributions

All authors made substantial contributions to the study conception and design and were involved in the acquisition, analysis, and interpretation of the data. All authors were involved in drafting and critically revising the manuscript for important intellectual content, read and approved the final version for submission, and agree to be accountable for all aspects of the work.

Ethics Approval

The study protocol, associated documents, and informed consent forms were reviewed and approved by an institutional review board (Advarra). The study was conducted in accordance with the Declaration of Helsinki, the ethical principles of Good Clinical Practice Guidelines established by the International Council for Harmonisation, and all other applicable local regulatory requirements. Written informed consent was obtained from each participant prior to initiation of study procedures.

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