TNX-4800: A Monoclonal Antibody (mAb) to Protect Against Lyme Disease

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Abstract

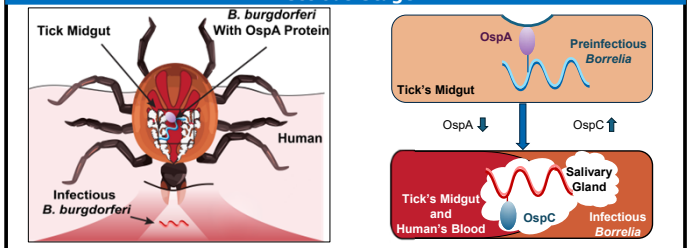
- *Borrelia burgdorferi* causes 99.9% of Lyme disease cases in the US
- There are currently no marketed US Food and Drug Administration (FDA)-approved vaccines or prophylactics to protect against Lyme disease
- TNX-4800 is a long-acting borreliacidal, human monoclonal antibody (mAb) with an engineered crystallizable fragment (Fc) domain for an extended half-life that targets outer surface protein A (OspA) of *Borrelia burgdorferi*
- TNX-4800 was studied in a phase 1, randomized, double-blind, sequential dose-escalation study (NCT04863287) that evaluated safety, tolerability, pharmacokinetics (PK), and immunogenicity of TNX-4800 in healthy adults
- The phase 1 data support a planned adaptive phase 2 field study, pending FDA agreement, to evaluate the safety and efficacy of TNX-4800 in preventing primary Lyme disease in volunteers from Lyme-endemic areas
- TNX-4800 is being developed as a prophylactic to be administered subcutaneously in the spring with a booster after 2 months, which is expected to provide protection within 2 days for at least 6 months to people in endemic areas during the US tick season

Introduction

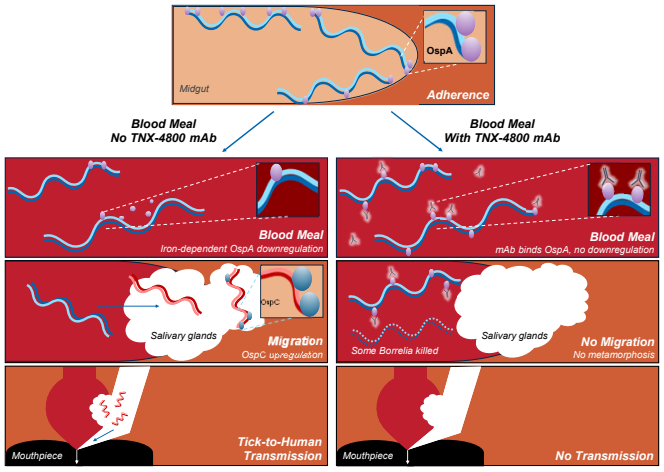
- TNX-4800 acts inside the tick to kill *Borrelia* and block the differentiation and transmission of *Borrelia*

OspA Is an Outer Membrane Protein on *Borrelia* That Facilitates Bacterial Adherence to the Tick Midgut[1-3]

Blood Induces Metamorphosis of *Borrelia* From the Preinfectious to Infectious Stage[4,5]

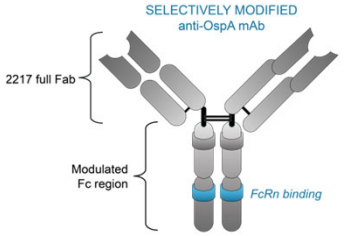


Anti-OspA mAb TNX-4800 Blocks Differentiation of *Borrelia* From the Preinfectious to Infectious Stage, Migration to Salivary Glands, and Transmission[6]



Methodology

TNX-4800 Long-Acting Anti-OspA Monoclonal Antibody Design



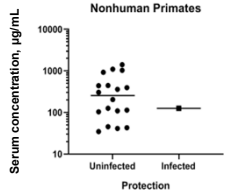
LS substitutions maintain C1q binding and function and augment FcRn binding for extended half-life

- TNX-4800 (formerly 2217LS) is a long-acting borreliacidal, human mAb with an engineered Fc domain for an extended half-life that targets OspA of *Borrelia burgdorferi*[7,8]

Multiple Approaches Informing Protective Exposure

Three methods:

- **Serum ~5 µg/mL – in vitro bactericidal activity**
  - TNX-4800 showed EC_{50} ≈ 0.56 µg/mL in vitro[1]
  - MEC ~ 10 times EC_{50}[8]
- **Serum <10 µg/mL – in vitro tick feeding experiment**
  - TNX-4800 showed killing ≥10 µg/mL[9]
- **Serum <21 µg/mL – in vivo primate challenge model (upper benchmark)**
  - TNX-4800 serum levels >21 µg/mL were 95% protective and represent an empirically observed upper correlate of protection (ceiling), not a minimum required concentration[7]



Derived from Schiller et al.[7]

- **Primate challenge model**
  - Tick-mediated transmission
  - Stringent test (prolonged exposure to 20 infected ticks over 6 days)

Results

Phase 1 Study Design

Primary Objective:
- Evaluate safety and tolerability of a SC injection of TNX-4800 when administered to healthy volunteers

Secondary Objective:
- Evaluate PK of a SC dose of TNX-4800 when administered to healthy volunteers

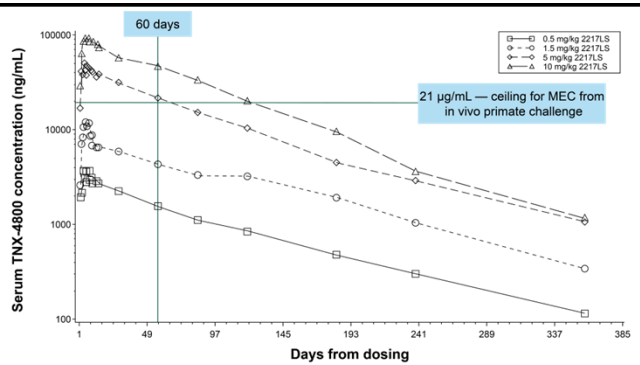
Study Population:
- Healthy male and female subjects, aged 19 to 65 years, inclusive. 44 volunteers enrolled; 41 completed

Cohort	No. of participants	TX-4800 dose (mg/kg)
1	10 TNX-4800 2 placebo	0.5
2	8 TNX-4800 2 placebo	1.5
3	8 TNX-4800 2 placebo	5
4	8 TNX-4800 2 placebo	10

Participants received either placebo or TNX-4800 by subcutaneous (SC) injection

Observed Phase 1 Pharmacodynamics

- Drug exposure increased by approximately 25 times for a 20-times increase in dose
- Serum TNX-4800 was measurable at the earliest sampling time of 2 days, indicating rapid systemic absorption
- TNX-4800 concentrations remained quantifiable for >200 days in 80% of volunteers at the lowest dose and for up to 350 days in the majority of volunteers at higher doses (ie, ≥1.5 mg/kg)
- Mean half-life ranged from 62 to 69 days across groups. Serum concentrations remained quantifiable for up to 12 months in most volunteers. Mean exposure for the 10 mg/kg cohort was less than 17% of the highest exposures in a rat toxicology study
- Transient low levels of antidrug antibodies were detected in <10% of treated volunteers, with no impact on PK
- All drug-related adverse events (AEs) were mild or moderate: injection site AEs 14%, headache 12%, COVID-19 and fatigue 9%, with rest reported in 2 of fewer cases (≤6%)



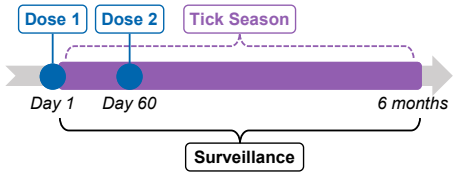
Each point represents a mean for the cohort at the time point and dose

Summary

- TNX-4800 acts inside the tick to kill *Borrelia* and block the differentiation and transmission of *Borrelia*
- Estimates of MEC indicate that serum levels of 21 µg/mL in nonhuman primates are a ceiling but that lower serum levels can be protective
- Phase 1 study of TNX-4800, a long-acting, human mAb, showed no significant clinical or laboratory safety signals
- Serum TNX-4800 was measurable at the earliest sampling time of 48 hours, indicating rapid absorption
- TNX-4800 was found to be safe when administered to healthy volunteers
- The PK of TNX-4800 were typical of a human IgG1 with an Fc domain mutation that extends half-life

Design of Planned Phase 2 Study

2027 Planned TNX-4800 Adaptive Phase 2 Field Study Design



Study participants randomized 1:1 to receive TNX-4800 or placebo

- An adaptive phase 2 field study of TNX-4800 is planned for 2027
- Dosing regimen: day 1 initial dose (fixed dose with ~5 mg/kg exposure) will be followed by a booster at 2 months
- Primary endpoint will be decrease in Lyme disease at 6 months in TNX-4800 arm

Conclusions

- TNX-4800 is being developed as a prophylactic to be administered subcutaneously in the spring with a booster after 2 months, which is expected to provide protection within 2 days for at least 6 months to people in endemic areas during the US tick season
- TNX-4800 avoids the onerous immunization regimens of over 6 to 12 months for protection required by OspA vaccines in development
- TNX-4800 is a mAb measured by µg/mL in serum, which is different from the polyclonal antibody responses to vaccines that are measured in "titers"
- TNX-4800 serum concentration enables direct PK-driven exposure targeting

References

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