A Long-Acting Monoclonal Antibody for Seasonal Prevention of Lyme Disease

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Professor of Medicine

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World Vaccine Congress

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Disclosures

Co-Inventor US Patent 10,457,721

Consultant Tonix Pharmaceuticals, Inc

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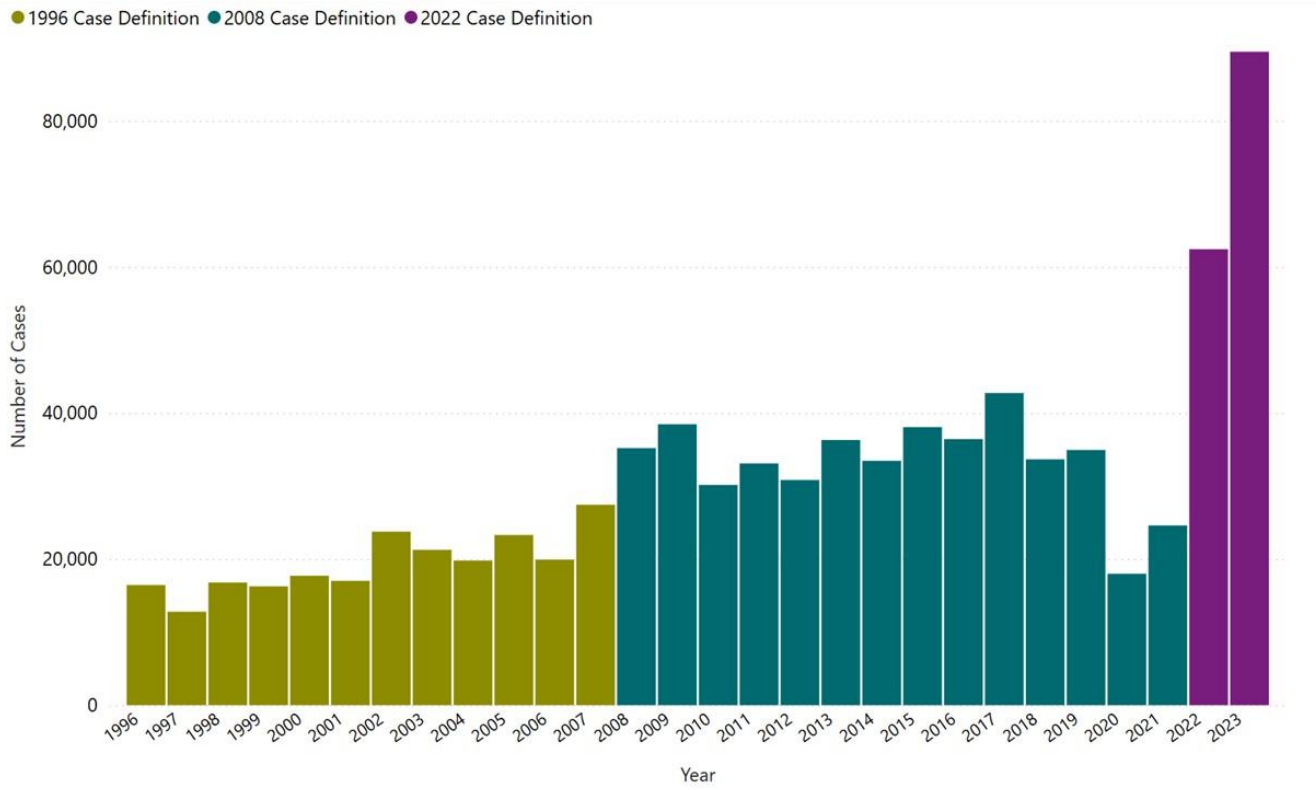
Growing Unmet Need:

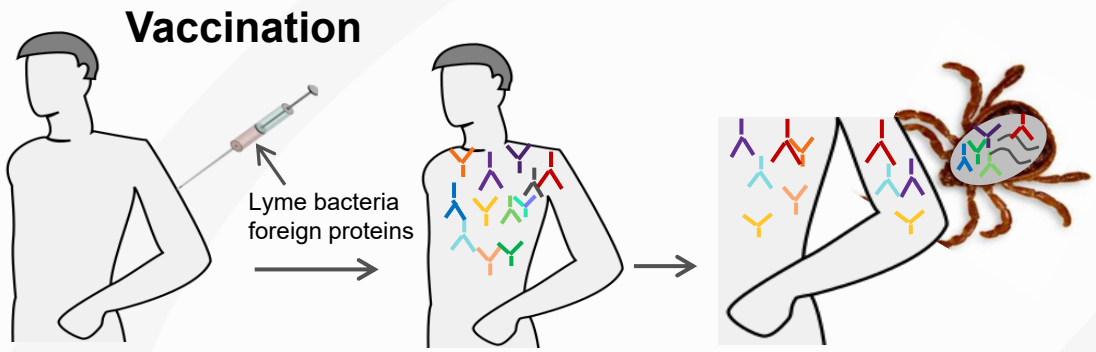
Prevention of Lyme Disease

- Lyme disease is the most common tick-borne illness (80% of all tick-borne diseases) in the Northern hemisphere. The CDC estimates over 450,000 cases annually.
- Global changes in climate is a factor in the expanding habitat range for ticks and other vectors, indicating the problem is likely to worsen in the coming years.
- LYMErix (GSK Vaccine) was FDA approved in 1998 but **withdrawn** due to low sales amid overhyped fears of vaccine-induced side effects including arthritis. LYMErix elicited active immunity (antibody responses) against outer surface protein A (OspA) and demonstrated an efficacy of 78%.
- Vaccine hesitancy, now driven mostly by online misinformation, continues to be a headwind for the uptake of new vaccines.

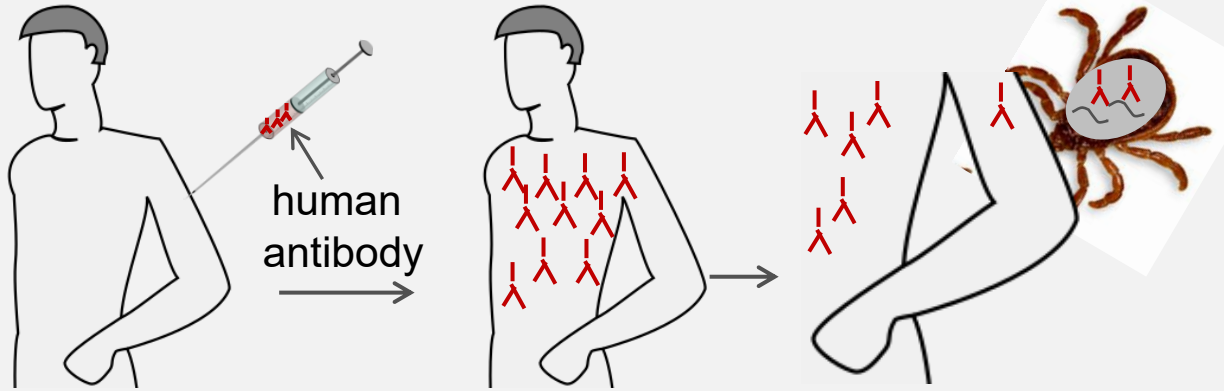
We are developing a monoclonal antibody treatment (not a vaccine) for Lyme Disease prevention. A single shot potentially provides protection 2 days after dosing and lasts approximately 4 months



Preventing Lyme Disease
Vaccine Compared to Antibody Pre-Exposure Prophylaxis



Person receives 3 injections over 6 months of Lyme bacteria proteins and develops many different antibodies. Tick carrying the Lyme disease bacteria bites the vaccinated person, takes in blood containing multiple antibodies including one (red) that prevents transmission.



Person receives 1 injection of a single protective antibody (red) at beginning of tick season. Tick carrying the Lyme disease bacteria bites the person and takes in blood containing the protective antibody preventing transmission.

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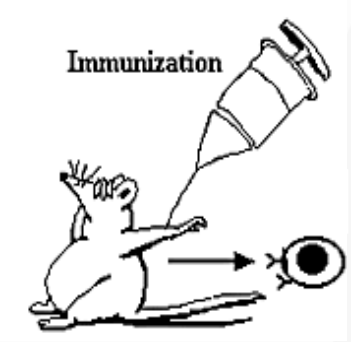
Discovery of mAB 221-7 with Potent Bactericidal Activity and Coverage of Three OspA Serotypes

The Target

Outer surface protein A (OspA) of the Spirochete

- Essential for survival while in tick midgut
- Anti-OspA immunity is effective in both animals and humans

Approach



Immunize mice (HuMab Mice, BMS/Mederex) with recombinant OspA

Immunized transgenic mice with OspA → Fused 12 spleens → Identified hybridomas producing human IgG → Determined whether recognized OspA

589 OspA reactive HuMabs were identified
93 HuMabs had unique CDR3 sequence

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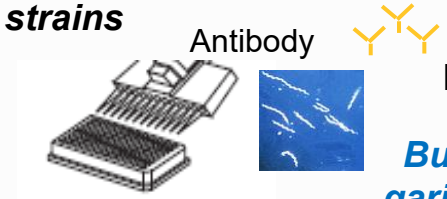
Discovery of mAb 221-7 with Strong Potency and Coverage

In vitro Potency and Coverage

In vitro Borreliacidal assay against three Borrelia strains

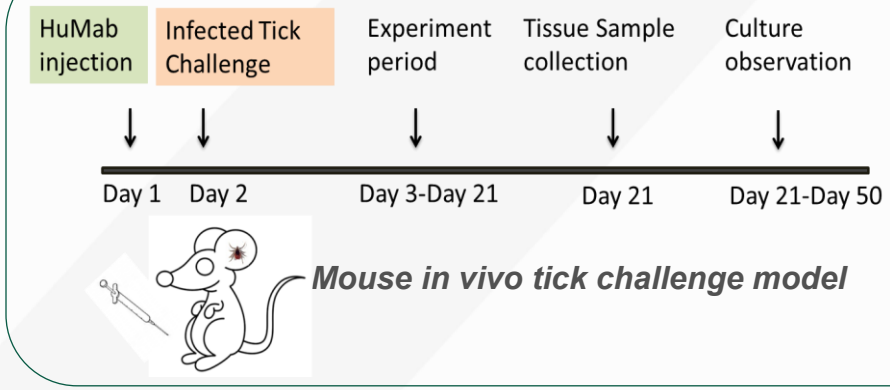


Burgdorferi, afzelii, and garinii

4 leads were selected for animal study

319-44, 221-7, 857-2 and 221-55

In vivo Potency



Mouse in vivo tick challenge model

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Identified Four Lead anti-OspA *Borrelia* Antibodies

Criteria:	319-44	221-7	212-55	857-2
Burgdorferi borreliacidal	YES (<0.4 nM)	**YES (<0.4 nM)**	YES (1.4 nM)	YES (2.0 nM)
Afzelii borreliacidal	YES (4.0 nM)	**YES (0.9 nM)**	NO	YES (2.0 nM)
Garinii borreliacidal	NO	**YES (6.6 nM)**	NO	YES (41.6 nM)
Epitope map (a.a.)	178-273	**71-141**	142-177	106-141
OspA Affinity	328 nM	**0.66 nM (Az 7.8; Gn 1.3)**	0.43 nM	0.65 nM
Protection (10 mg/kg)	100%	**100%**	YES	YES
Protection (5 mg/kg)	100%	**100%**	NA	NA
Protection (1 mg/kg)	40%	**60%**	NA	NA
Half-life in vivo (FcRn mice)	26.9	**23.5**	39	16.2

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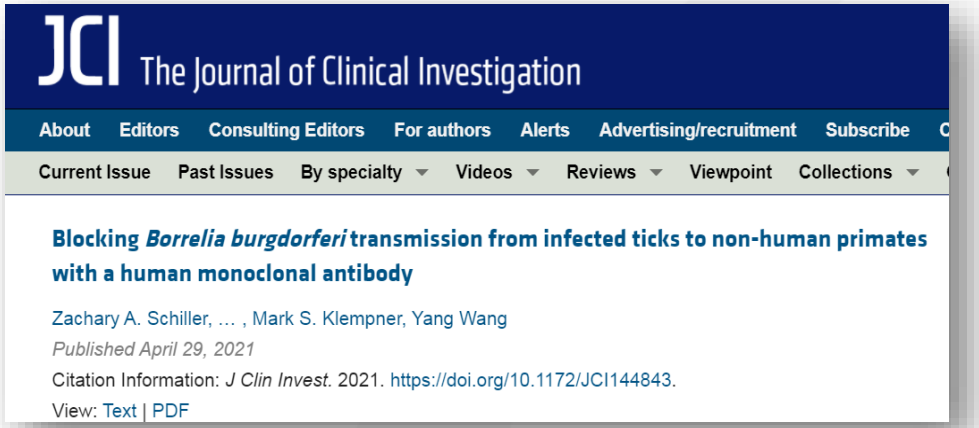
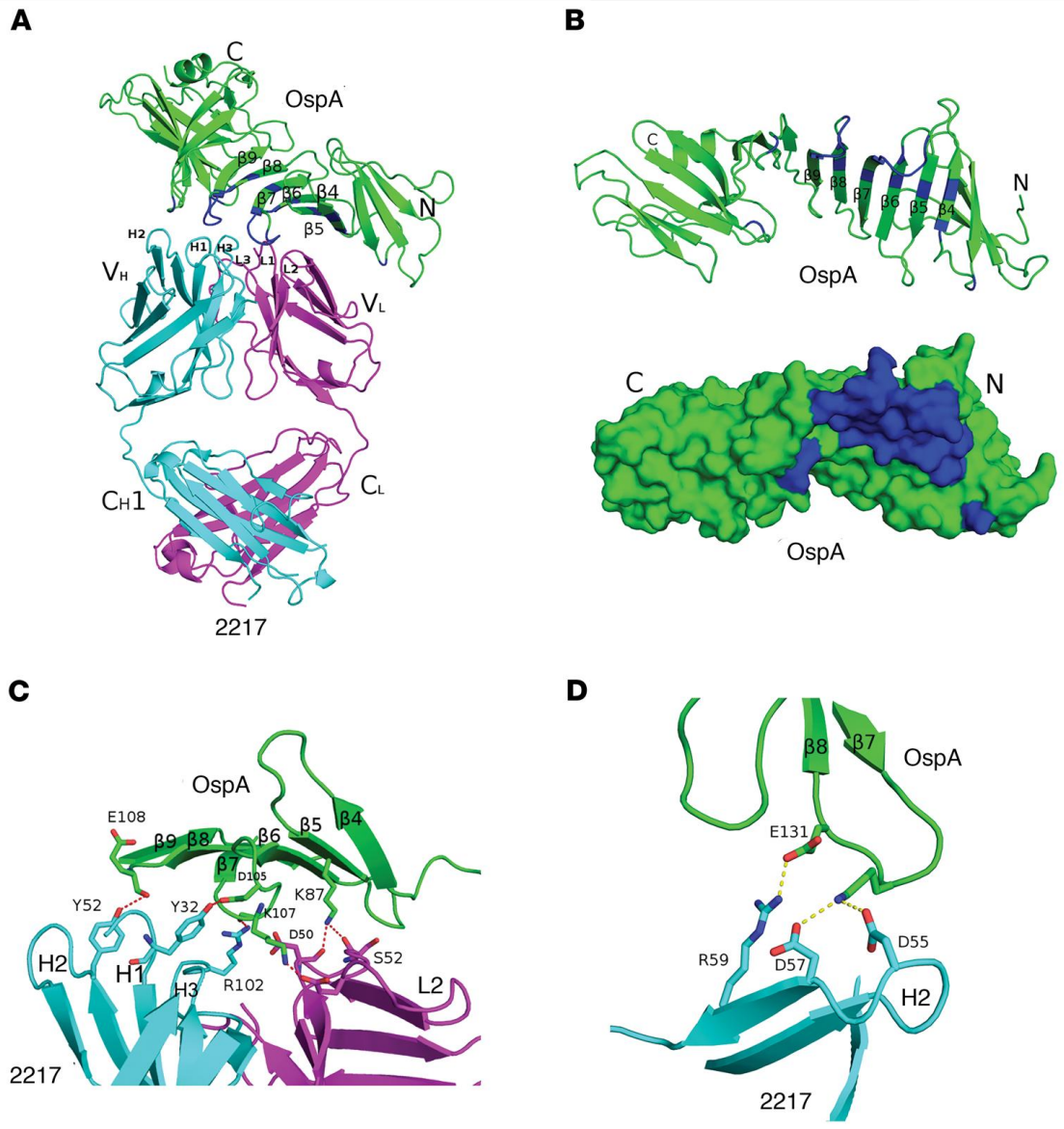
mAb 221-7 Epitope Resolved by Crystallization





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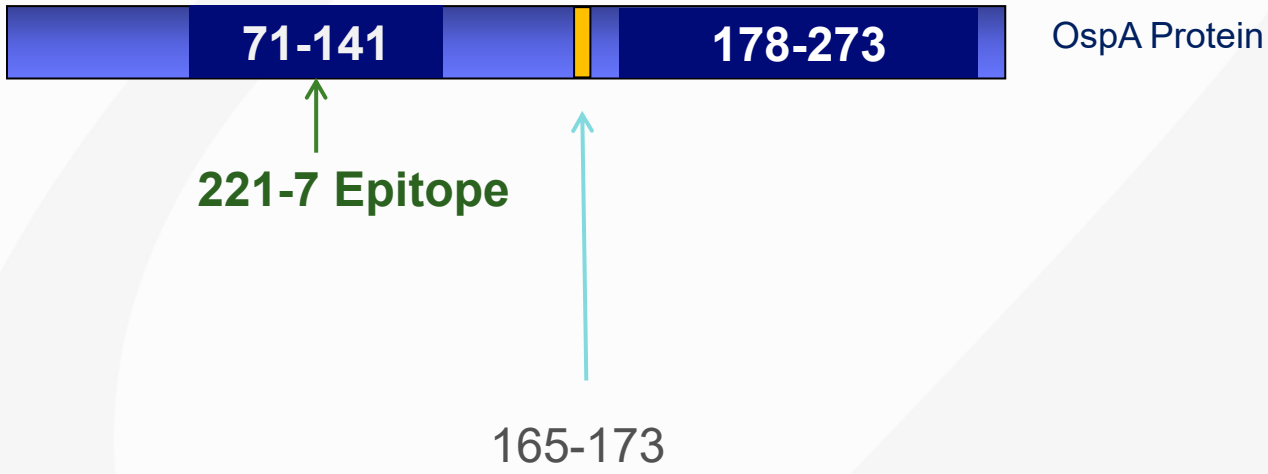
mAb 221-7 Does not Recognize the Putative Arthritogenic T-cell Epitope



Putative arthritogenic T-cell epitope (YVLEGTLTA),
mimicking human leukocyte function-associated antigen-1 (hLFA-1)

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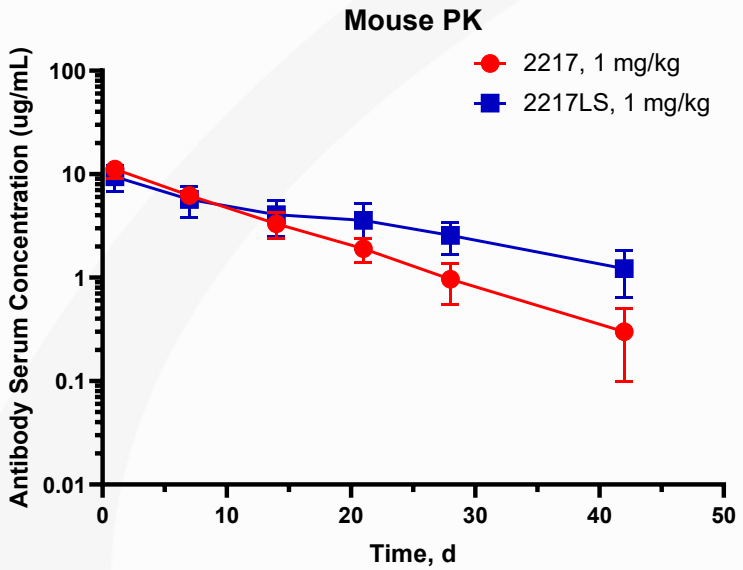
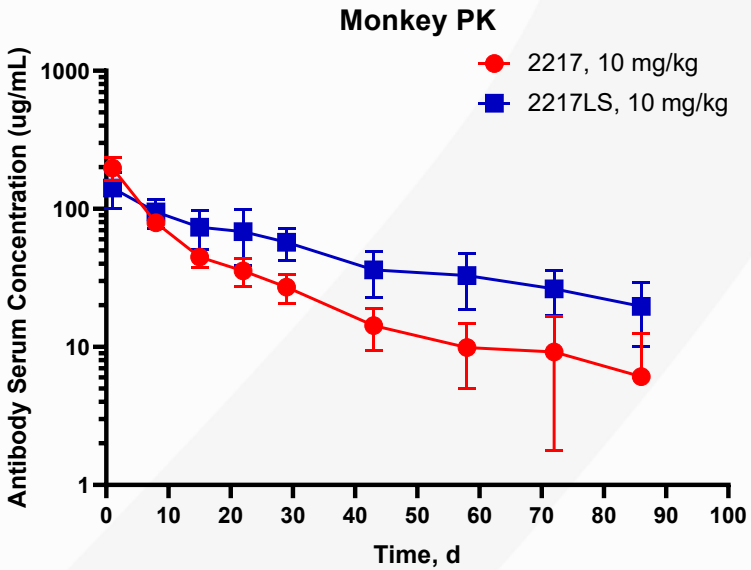
Half-Life Extension in FcRn Mice and NHP: TNX-4800 (2217LS)





Species	Average Human Ab half-life	2217WT	2217LS	Fold Change to WT
FcRN Mice	6-8 days	8.0 ± 0.4 days	16.0 ± 1.1 days	2.0
Nonhuman Primates	10.2 ± 3.3 days	15.41 ± 7.5 days	31.8 ± 2.5 days	2.1

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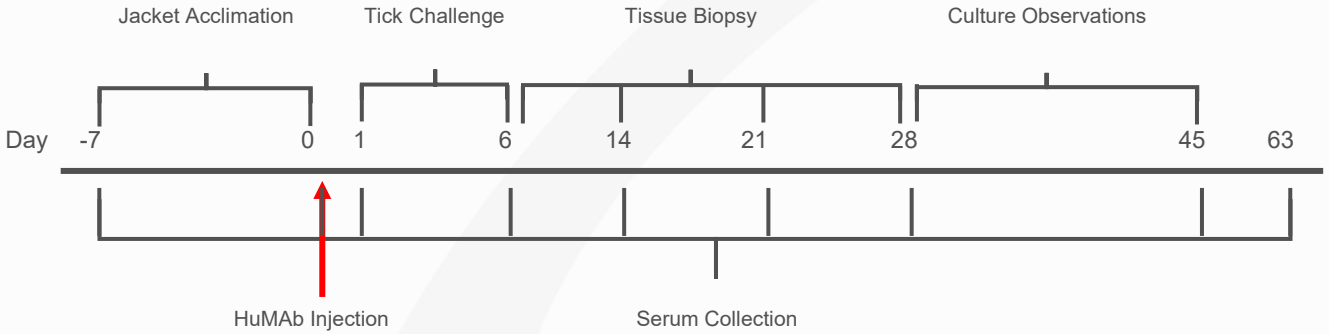
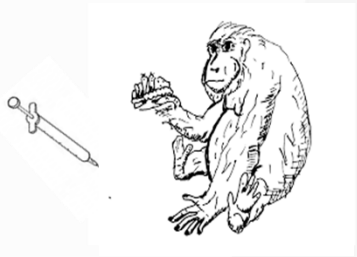
NHP= non-human primate

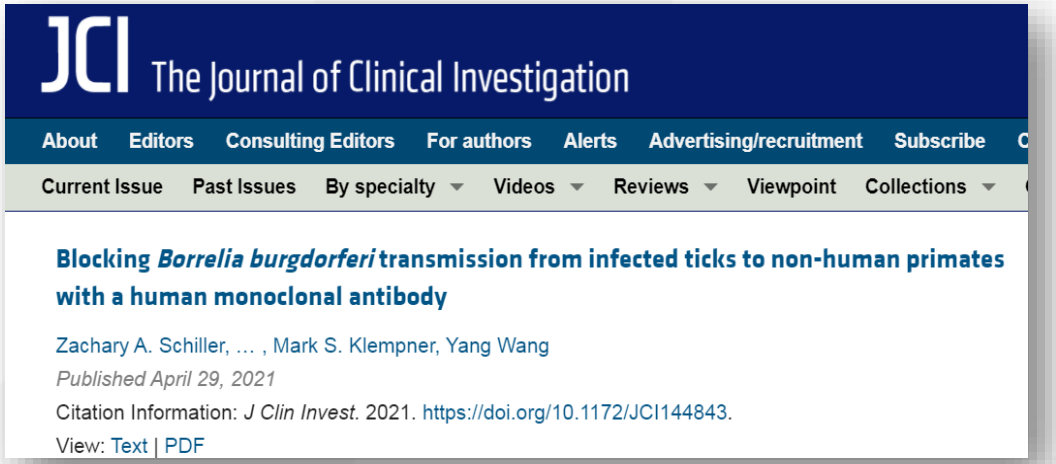
Blocking *Borrelia burgdorferi* Transmission from Infected Ticks to Non-Human Primates with TNX-4800 (2217-LS)





4-6 animals each dose group

Monoclonal Antibody	Dose (mg/kg)	Protection (%)	P value
2217LS	90	100%	<0.001
2217LS	30	100%	<0.001
2217LS	10	83%	<0.001
2217LS	3	100%	<0.001
Irrelevant IgG	10	0%	N/A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Blocking *Borrelia burgdorferi* transmission from infected ticks to non-human primates with a human monoclonal antibody

Zachary A. Schiller, … , Mark S. Klempner, Yang Wang

Published April 29, 2021

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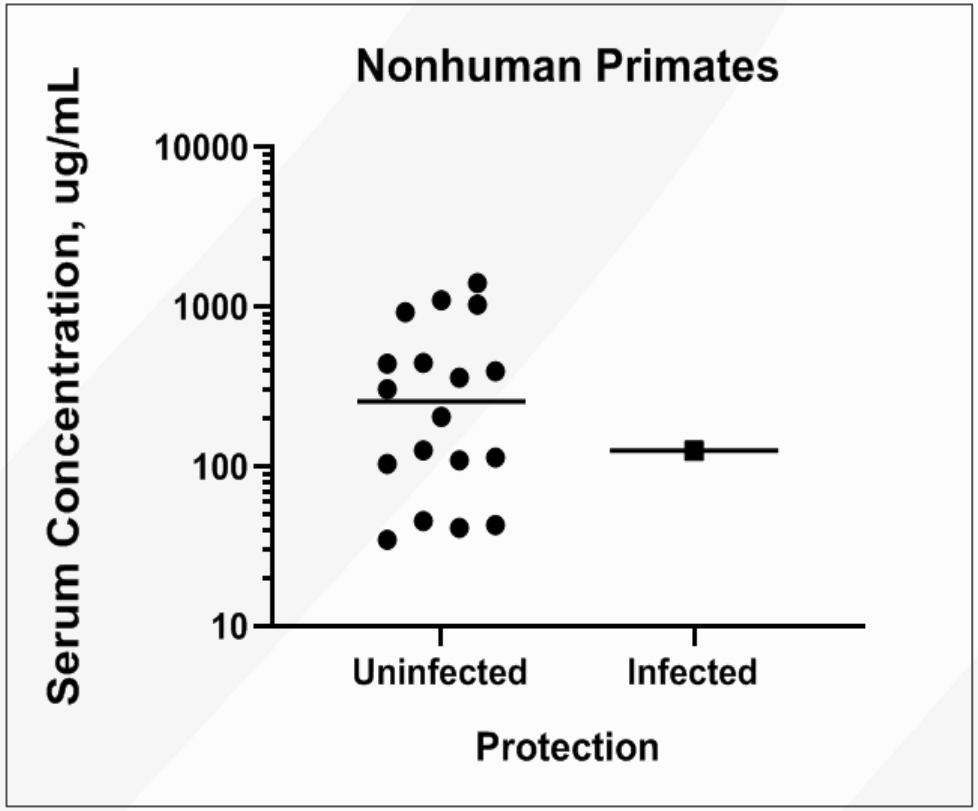
Estimating Minimum Effective Concentration of TNX-4800 (2217-LS) in Non-Human Primates

Serum levels above 21 µg/mL were ~95% protective.



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Minimum Effective Concentration (MEC) TNX-4800 (2217-LS)

- **~5 µg/mL – *in vitro* bactericidal activity**
  - TNX-4800 showed EC_{50} ≈ 0.56 µg/mL *in vitro*[1]
  - MEC ~ 10X EC_{50}
- **<10 µg/mL – *in vitro* tick feeding experiment**
  - TNX-4800 showed bactericidal activity ≥10 µg/ml
- **<21 µg/mL – *in vivo* primate challenge models**[1,2]
  - TNX-4800 serum levels >21 µg/ml were 95% protective

[1]Wang Y, et al. J Infect Dis. 2016 Jul 15;214(2):205-11.
[2]Schiller ZA, et al. *J Clin Invest*. 2021;131(11):e144843.

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Nonclinical Safety Data TNX-4800

- cGLP Tissue Cross Reactivity study in rat and human tissues
  - No significant cross-reactivity
- Non-GLP pharmacokinetic and tick challenge studies in monkeys
  - Did not reveal a safety signal
- cGLP 5 week multiple dose study with 4 week recovery in rats and a cGLP single dose local tolerance study in rats
  - Observed abnormalities were mild to moderate and all findings were judged non aversive (hematologic and ALT, AST ALP and APTT increases (notably without bilirubin changes), injection site inflammation, liver and spleen organ weight increases, liver histopathology, primarily in males. All findings were reversible).
- Exposure in Phase 1 was multiples relative to NOAEL in rats
  - Starting dose: 63 to 242 –fold lower
  - Highest dose: 3 to 12 –fold lower

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NOAEL = No-observed-adverse-effect level

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TNX-4800 Phase 1 Study Overview

Primary Objective:

- Evaluate safety and tolerability of a SC injection of TNX-4800 (2217LS) when administered to healthy subjects

Secondary Objective:

- Evaluate pharmacokinetics (PK) of a SC dose of TNX-4800 (2217LS) when administered to healthy subjects

Study Population:

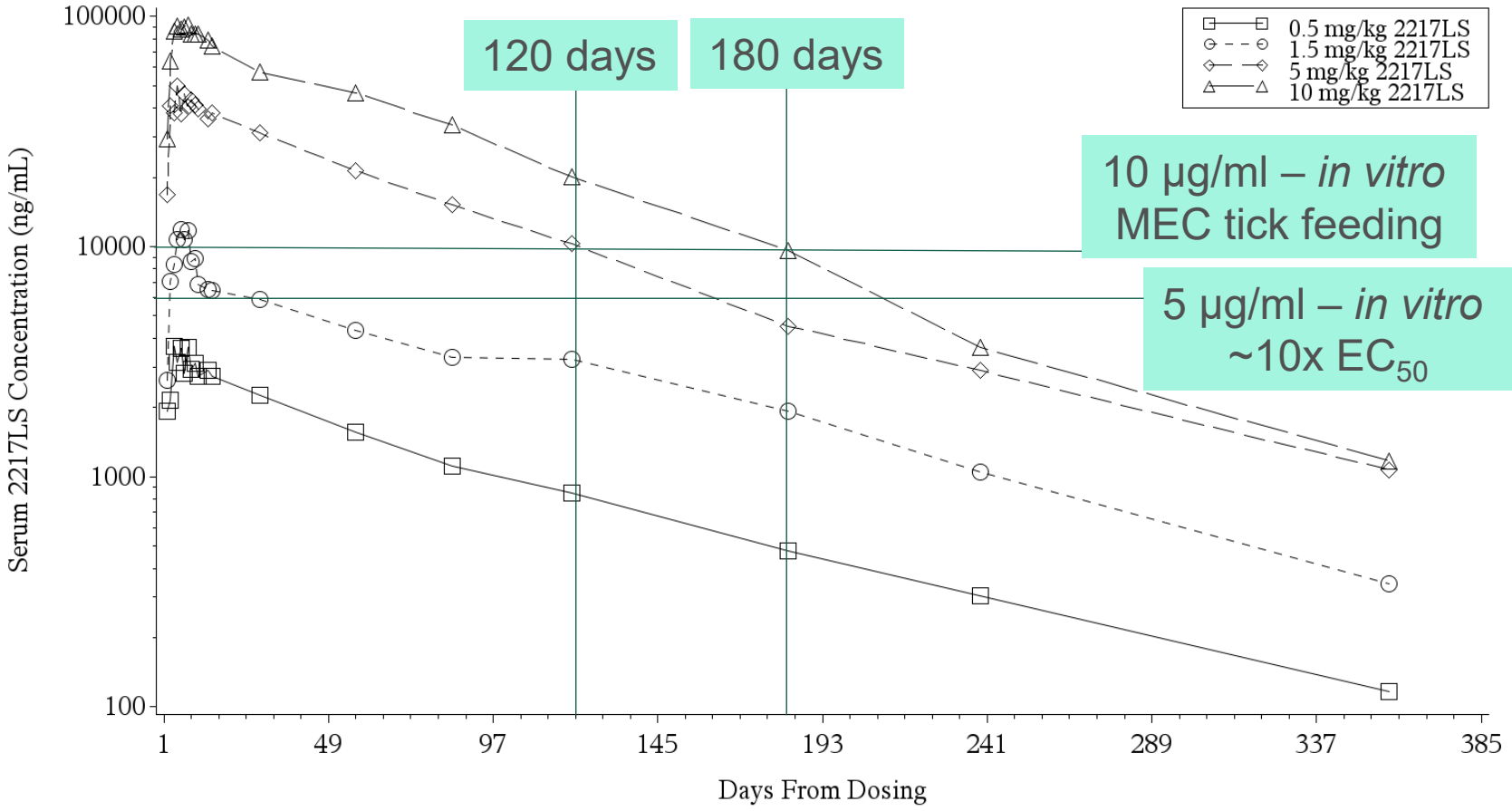
- Healthy male and female subjects, age 19 to 65 years, inclusive. 44 volunteers enrolled, 41 completed.

Cohort	N[1]	Treatment	2217LS Dose (mg/kg)	Route
1	12	2 subjects: placebo 10 subjects: 2217LS	0.5	SC
2	10	2 subjects: placebo 8 subjects: 2217LS	1.5	SC
3	10	2 subjects: placebo 8 subjects: 2217LS	5	SC
4	10	2 subjects: placebo 8 subjects: 2217LS	10	SC

TNX-4800 Phase 1 Study Results

- No significant clinical or laboratory safety signals
- The mean exposure, based on AUC-inf and C_{max} for Cohort 4 (10mg/kg), was less than 17% of the highest exposures in the rat toxicology study
- Serum TNX-4800 (2217LS) was measurable at the earliest sampling time of 24 hours indicating rapid absorption.
- For all cohorts C_{max} was observed at 10-13 days followed by a prolonged elimination phase.
- Apparent terminal $T_{½}$ after 10 mg/kg dose was 64 days
- Max $T_{½}$ ranged from 81-104 days: (**10mg/kg - 97 days, 5mg/kg - 87 days, 1.5mg/kg - 104 days, 0.5mg/kg - 81 days)**
- **Cohort 3 (5mg/kg) serum concentrations:**
  - **10 µg/ml at 4 months (~ *in vitro* tick-feeding MEC and >*in vitro* MEC or ~10x EC_{50})**

Observed Phase 1 Pharmacokinetics



Each point represents a mean for the cohort at that timepoint and dose

Next Steps: Phase 2 Field Study

- Licensed to Tonix Pharmaceuticals - 2025 now TNX-4800
- Proposed Phase 2 field study – 2027 pending FDA clearance

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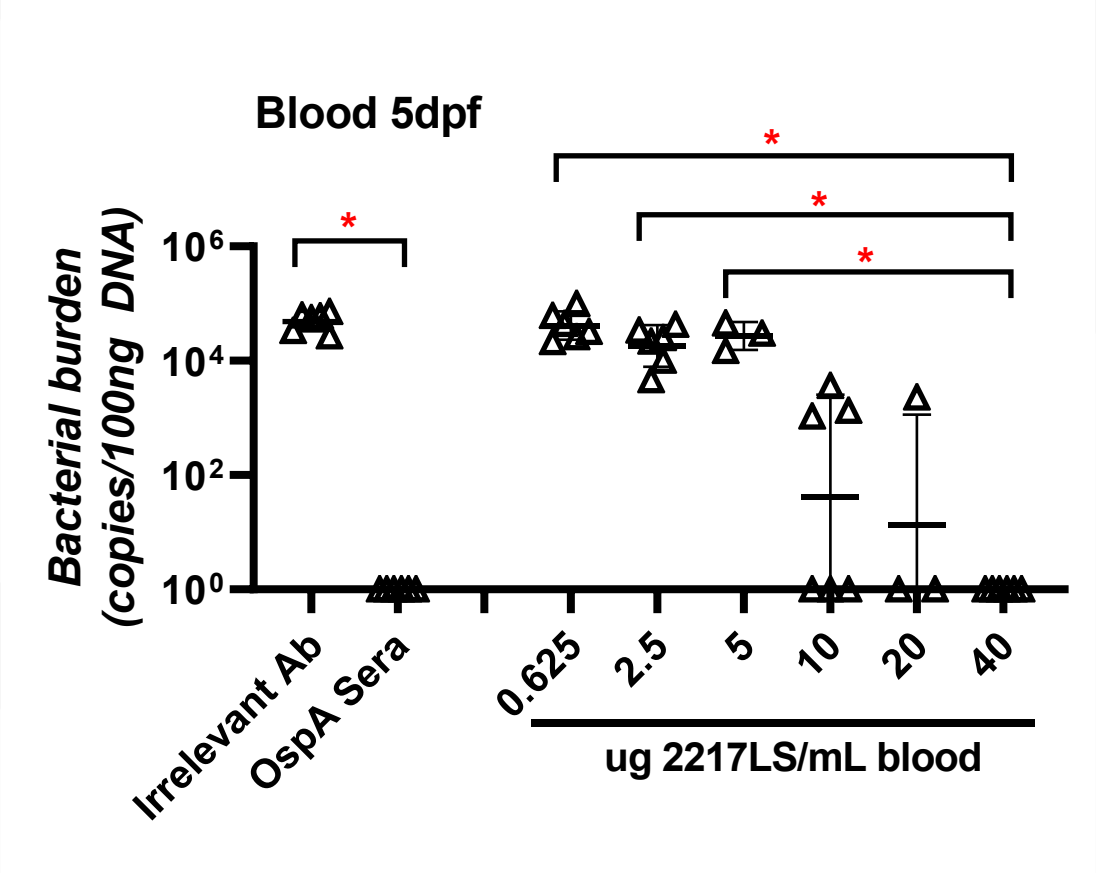
Supplemental Slides

Minimum Effective Concentration of TNX-4800 is < 10µg/ml in the Infected Tick

The monoclonal OspA antibody TNX-4800 (2217LS) inhibits tick-to-blood transmission of *B. burgdorferi* B31-5A4 in a dose-dependent manner in an artificial membrane feeding system.



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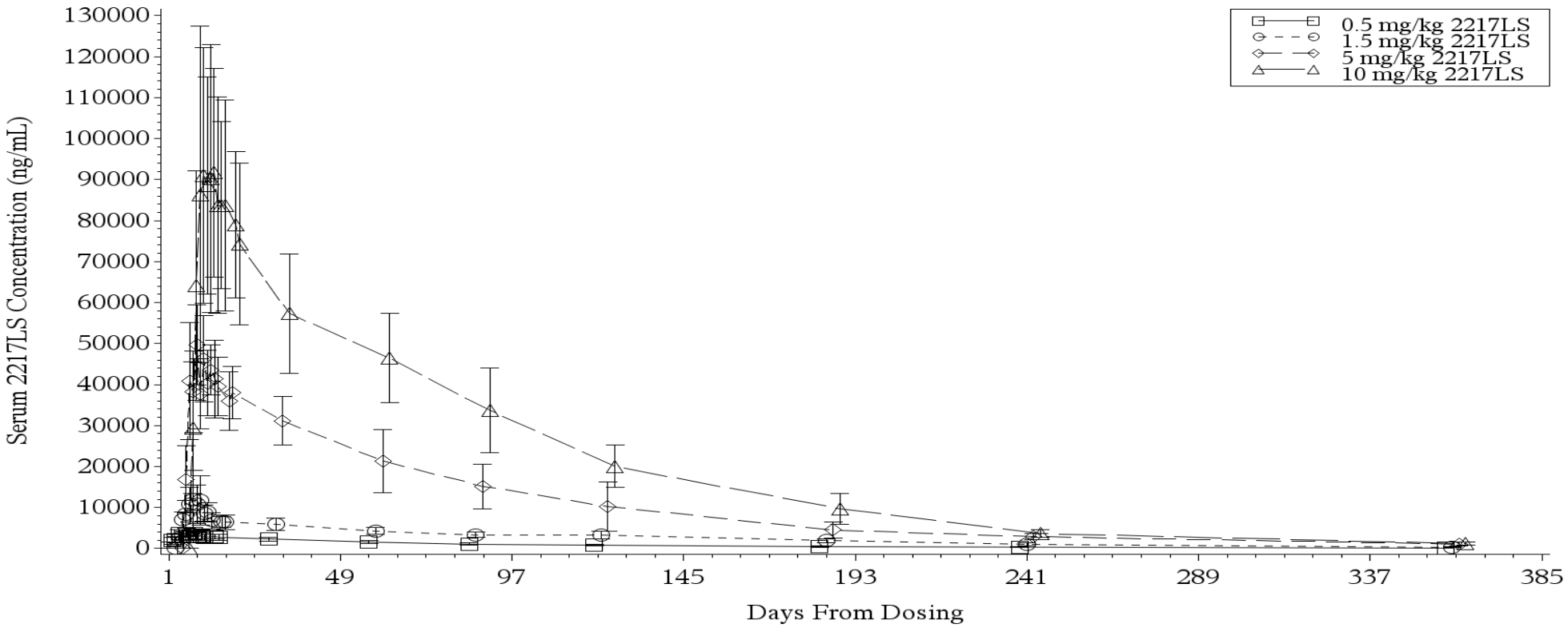
Variability of serum concentrations at sampling time points among subjects in each dosing cohort



The profiles for 1.5 mg/kg 2217LS, 5 mg/kg 2217LS, and 10 mg/kg 2217LS are shifted to the right for ease of reading.
Source: ADaM.ADPC
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Pharmacokinetic Parameters

Pharmacokinetic Parameters	0.5 mg/kg 2217LS	1.5 mg/kg 2217LS	5 mg/kg 2217LS	10 mg/kg 2217LS
AUC0-t (ng*hr/mL)	6271000 (26.0) [n=10]	20610000 (23.7) [n=8]	79760000 (36.5) [n=8]	165500000 (26.0) [n=8]
AUC0-inf (ng*hr/mL)	6812000 (25.3) [n=10]	21490000 (23.5) [n=8]	82070000 (37.2) [n=8]	168100000 (25.9) [n=8]
AUC%ext (%)	7.832 ± 4.8735 [n=10]	4.103 ± 1.6271 [n=8]	2.805 ± 1.3920 [n=8]	1.494 ± 0.49258 [n=8]
Cmax (ng/mL)	3397 (31.4) [n=10]	10880 (41.3) [n=8]	45650 (22.0) [n=8]	84560 (37.5) [n=8]
Tmax (hr)	96.075 (72.00, 335.91) [n=10]	144.019 (95.95, 215.95) [n=8]	108.319 (71.98, 216.06) [n=8]	108.050 (48.00, 167.78) [n=8]
Kel (1/hr)	0.0004984 ± 0.00025308 [n=10]	0.0004258 ± 0.000060386 [n=8]	0.0005851 ± 0.00037231 [n=8]	0.0004751 ± 0.000072023 [n=8]
t½ (hr)	1614 ± 533.84 [n=10]	1658 ± 243.26 [n=8]	1516 ± 655.84 [n=8]	1491 ± 244.47 [n=8]
CL/F (mL/hr/kg)	0.07557 ± 0.020144 [n=10]	0.07151 ± 0.017398 [n=8]	0.06474 ± 0.025934 [n=8]	0.06121 ± 0.015541 [n=8]
Vd/F (mL/kg)	171.2 ± 61.264 [n=10]	170.1 ± 47.286 [n=8]	123.7 ± 29.838 [n=8]	133.0 ± 44.405 [n=8]

0.5 mg/kg 2217LS: A single subcutaneous injection of 0.5 mg/kg 2217LS, Cohort 1
1.5 mg/kg 2217LS: A single subcutaneous injection of 1.5 mg/kg 2217LS, Cohort 2
5 mg/kg 2217LS: A single subcutaneous injection of 5 mg/kg 2217LS, Cohort 3
10 mg/kg 2217LS: A single subcutaneous injection of 10 mg/kg 2217LS, Cohort 4
AUCs and Cmax are presented as geometric mean (geometric CV%).
Tmax values are presented as median (min, max).
Other parameters are presented as arithmetic mean ± SD.
Source: Tables 14.2.1.5 through 14.2.1.8
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CDC Study Makes a Strong case for Antibody vs Vaccine

Lyme Disease Vaccine Intentions Among Parents of 5–18 Year Olds in U.S. States with High or Emerging Incidence

(CDC-sponsored study presented at 2023 Pediatric Academic Societies (PAS) Conference)

Methods

- Conducted online survey (N=1,351) of parents of children aged 5–18 years in states with high or emerging Lyme Disease (LD) incidence.
- Primary outcome was willingness (definitely / probably would vs unsure or definitely / probably would not) for their child to receive an LD vaccine.
- Secondary outcome was preference for annual monoclonal antibody injections vs. a 3-dose vaccine series with boosters every few years.

Outcome

- Two-thirds of parents were willing to vaccinate their child against LD (68.0% definitely/probably would, 18.4% unsure, 13.7% definitely/probably would not)
- Parental willingness to be vaccinated against LD was highly correlated with willingness for their child in.
- Vaccine safety concerns were among the top reasons for LD vaccine hesitancy
- More parents preferred pre-formed antibody (42.4%) over 3-dose vaccine series (36.2%)
- Significant predictors of preference for monoclonal antibody included prior awareness of LD, living in a rural area, and positive attitude towards vaccines

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CDC = U.S. Centers for Disease Control