Sponsor: Sanofi **Drug substance(s):** TNT009	**Study code:** TNT009-02

Title of the study:

The Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of Multiple-dose TNT009 in Normal Human Volunteers: A Phase 1 Dose Confirmation Study

Study period:

30 January 2017 (date of first informed consent) to 31 May 2017 (date of final poststudy observation)

Study Status: Completed

Phase of development: 1

Objectives:

The primary objective of this study was:

・To evaluate the safety and tolerability of multi-dose TNT009 in healthy adults.

Secondary objectives of this study were:

・To evaluate the pharmacokinetics (PK) of the newly optimized dose regimen of TNT009

・To evaluate the pharmacodynamics (PD) of the newly optimized dose regimen TNT009 with respect to complement classical pathway function.

Methodology:

Study TNT009-02 was a prospective, double-blind, randomized, placebo-controlled study of multi-dose TNT009 in healthy subjects. A single cohort with a total of approximately 24 healthy adult subjects was randomized to TNT009 or placebo at a ratio of 3:1. During the screening period, that began as early as Day -28, subjects were evaluated for enrollment and vaccinated at least 14 days prior to randomization and administration of the first dose of study drug on Day 1. Subjects were dosed again on Days 8, 22, and 36.

Intensive PK/PD/exploratory complement sampling was performed over the first 96 hours following the first (Day 1) and final (Day 36) doses of study drug with an additional sample taken for analysis at 168 hours after the final dose (Day 36). Safety observation and PK/PD/exploratory complement system sampling continued to the End of Study Visit on Day 50, and follow-up PK/PD/exploratory complement system samples were obtained on Day 64 and Day 92 (optional visit).

This single-cohort study was divided into 2 groups, with each group being dosed approximately 3 days apart. The first group was comprised of 4 subjects, 3 of whom received TNT009 and the other received placebo. The second group was comprised of the remaining 20 subjects, where 15 subjects received TNT009 and 5 subjects received placebo. Continuation to dose the second group was at the Investigator's discretion.

Number of participants:

It was planned to study a total of approximately 24 subjects in 2 groups. Twenty-four subjects entered and 20 subjects completed the study. Data for 24 subjects entered into the study were included in the PD, PK/PD, and Safety Populations and 18 subjects, who received TNT009, were included in the PK Population.

Diagnosis and criteria for inclusion:

Subjects were healthy males or females between 18 to 50 years of age, inclusive, with a body mass index between 18 and 32 kg/m^2, inclusive.

Study products

Investigational medicinal product(s):

Subjects received either TNT009 or matching placebo infused intravenously (IV) by a suitable infusion pump over a period of approximately 60 minutes.

Duration of treatment:

Screening Period: ≤ 4 weeks

Treatment Period: approximately 5 weeks

Post-treatment Observation Period: 2 weeks

Remote PK/PD/Exploratory Complement Assays Blood Sample Collection: 2 to 6 weeks

Planned Study Conduct Duration (first subject screened to last subject Follow-up Visit): approximately 17 weeks

Criteria for evaluation:

Pharmacokinetics:
The following PK parameters were calculated where possible: area under the concentration-time curve (AUC) from time zero to 24 h post-dose (AUC_{0-24}), AUC over 168 hours (AUC_{0-168}), AUC over the dosing interval tau (AUC_{0-tau}), AUC from time zero to the time of the last quantifiable concentration (tlast) postdose (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), maximum observed concentration (C_{max}), concentration at the end of the dosing interval tau (C_{trough}), time of maximum observed concentration (t_{max}), apparent terminal phase half-life ($t_{1/2}$), clearance (CL), volume of distribution at steady state (V_{ss}), accumulation ratio (based on AUC; AR_{AUC}), and accumulation ratio (based on C_{max}; AR_{Cmax}).

Pharmacodynamics:
The following PD parameters were calculated where possible: Baseline effect value (B), net area of the response curve above and below the baseline effect value ($AUEC\_Net_{\_0-168}$), net area of the response curve above and below the baseline effect value ($AUEC\_Net_{\_0-336}$), maximum observed effect value over the dosing interval (336 h; E_{max}), maximum change from baseline effect value over the dosing interval (336 h; BE_{max}), time of maximum observed effect over the dosing interval (336 h; t_{Emax}), minimum observed effect value over the dosing interval (336 h; E_{min}), minimum change from baseline effect value over the dosing interval (336 h; BE_{min}), and time of minimum observed effect over the dosing interval (336 h; tE_{min}).

Safety:
Adverse events (AEs), clinical laboratory evaluations, systemic lupus erythematosus panel, vital signs measurements, electrocardiograms (ECGs), and physical examination findings.

Statistical methods:

Pharmacokinetic:

Plasma concentrations and derived PK parameters for TNT009 were listed and summarized using descriptive statistics. Individual and mean plasma concentrations of TNT009 figures were presented.

Pharmacodynamic and exploratory:

The PD parameters and exploratory endpoints were listed and summarized using descriptive statistics, as appropriate.

Safety:

No formal statistical analyses were planned or performed for the safety data.

Summary Results:

Safety results:

Multiple doses of 75 mg/kg TNT009 were safe and well tolerated when administered to healthy subjects. Overall, 6 subjects (25.0%) experienced a total of 10 treatment-emergent AEs (TEAEs). All TEAEs reported were considered Grade 1/mild in severity and resolved spontaneously by the end of the study. There were no severe AEs or serious AEs during the study; however, 1 subject receiving TNT009 discontinued the study due to a TEAE of first-degree atrioventricular (AV) block (preferred term Atrioventricular block first degree) assessed by the Investigator as not related to study treatment. No TEAEs were assessed as probably related to study treatment. Two of 24 subjects (8.3%) experienced a total of 3 Grade 1/mild TEAEs assessed as possibly related to study treatment by the Investigator, 2 of which occurred in a subject receiving placebo. There were no treatment-related trends in the incidence of TEAEs. No concomitant medications were administered in this study.

There were no apparent treatment-related trends in vital signs measurements or ECG and clinical laboratory parameters during the study. Additionally, there were no abnormal physical examination findings. There was 1 instance of alanine aminotransferase increased recorded as a TEAE. As a result, that subject did not receive the final dose of TNT009 on Day 36, but remained on study. One subject receiving TNT009 experienced elevated PR values and was discontinued from the study due to a clinically significant first-degree AV block reported as a Grade 1/mild TEAE. Outside of these 2 TEAEs, there were no other vital signs measurements or ECG and clinical laboratory parameters considered by the Investigator to be clinically significant. Overall, the safety risk of the dose regimen utilized in this study appeared to be low.

Pharmacokinetic results:

The PK of plasma TNT009 and PD of various biomarkers following single and multiple 60-minute IV infusions of TNT009 at 75 mg/kg were evaluated in normal healthy subjects. Following a single 75-mg/kg dose, plasma C_{max} was 1872 µg/mL. This value was increased by approximately 46% after multiple doses every other week to 2724 µg/mL. The $AUC_{0\text{-}168}$ was increased 1.8 times from single to multiple doses.

Clearance was 14.2 mL/h at steady state. The V_{ss} was approximately 3 to 4 L, corresponding roughly to the plasma volume in a typical adult.

Non-linearities in the terminal slope were observed after the last dose. However, the $t_{1/2}$ when the target-mediated disposition process is saturated (ie, during the every other week interval) was approximately 7 days. It was expected that dosing within that interval would result in accumulation, as confirmed in this study by comparing Day 1 (first dose) and Day 8 (second dose), where the second dose was given after 7 days. A dose regimen where administration is greater than 1 week would result in minimal accumulation in the average subject. This was confirmed via visual assessment of the trough concentrations over time. In summary, single and multiple doses of 75 mg/kg TNT009 once weekly and every other week after the second dose provided predictable and typical PK and PD profiles after single dose and steady state. Dosing of the drug at greater than 2-week intervals demonstrated that the non-linear process would be observed should levels drop below 100 µg/mL since a Michaelis-Menten disposition was observed at concentrations below the 100 to 300 µg/mL range. The C1s knockdown was important and sustained, with an almost complete knockdown of C1s and related total complement (CH50) activity whenever TNT009 was present in the plasma. Effects appear reversible.

Pharmacodynamic results:

Following a single dose of 75 mg/kg of TNT009, close to full inhibition of Complement System Classical Pathway (CCP), CH50, C1s, and C1s-C1INH was shown at the first sampling timepoint (0.5 hours postdose). The > 90% inhibitions were observed throughout the treatment period, and were maintained up to 2 weeks after the final dose on Day 36. In line with the mechanism of action of TNT009, there was no discernible effect of TNT009 on Complement System Alternative Pathway (CAP) activity or the concentration levels of C1q. In addition, the administration of TNT009 in healthy subjects did not impact the concentration levels of total C4. The TNT009 concentration at which half-maximal inhibition of C1s activity (EC50) occurred was approximately 250 to 300 µg/mL and levels appear consistently suppressed when TNT009 was above 500 to 700 µg/mL. The C1s inhibition was important and sustained, with an almost complete inhibition of C1s and related CH50 activity whenever TNT009 was present in the plasma.

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