# Pharmacokinetic/Pharmacodynamic Analysis of Human Anti-C1s Antibody (TNT009) and Classical Complement Pathway (CP) Activity

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## Introduction

- TNT009 is intended for treatment of the subset of classical pathway (CP)-driven complement-mediated disorders. Such conditions are initiated by antibody binding to a target tissue or organ and this, in turn, activates the CP and inflammatory responses responsible for the clinical manifestations of these disorders (Shi et al, 2014).
- TNT009 is a humanized monoclonal antibody (mAb) directed against human complement factor C1s, which along with C1r is a part of the C1 complex that sits at the apex of the CP.
- By specifically targeting C1s, TNT009 inhibits only the classical complement pathway, leaving the alternative complement pathway (AP) and the lectin complement pathway (LP) available for immune surveillance. Furthermore, by blocking at the level of the C1 complex, TNT009 is expected to prevent generation of all anaphylatoxins and opsonins that drive disease pathology in classical pathway mediated disorders.

## Background

- The objective of this analysis was to assess the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of TNT009 and CP activity.

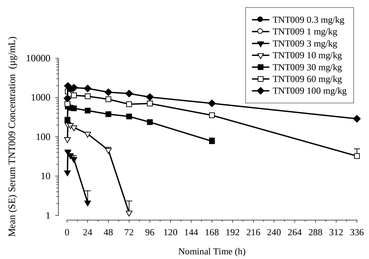
## Methods

- Serum TNT009 concentrations and CP activity were measured following single dose (0.3 to 100 mg/kg, n=36) and multiple once-weekly (QW) doses (30 or 60 mg/kg, n=12) in normal healthy volunteers (NHVs).
- PD samples were timed to coincide with PK draws to characterize the magnitude and duration of inhibition of this pathway and ultimately the PK/PD relationship between TNT009 and CP inhibition.
- PK and PD analyses were conducted using Phoenix NLME (v.7).

## Results

- Mean concentration-time profiles following a single dose of TNT009 (0.3 to 100 mg/kg) in NHVs are presented in **Figure 1**.

**Figure 1: Observed Concentration-Time Profiles Following Single Dose of TNT009 in NHVs**

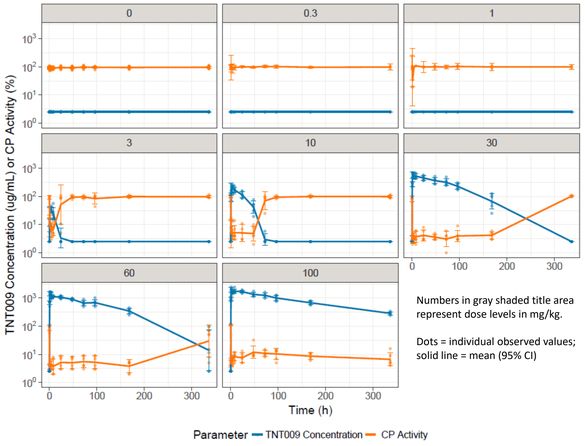



- Following single intravenous (IV) doses of TNT009, mean serum TNT009 concentrations were BLQ over the entire profile for the 0.3 to 1 mg/kg dose levels.
- At the 3 to 10 mg/kg TNT009 dose levels, mean peak serum TNT009 concentrations were observed at 2.5 to 4 h followed by a typical Michaelis-Menten disposition profile at concentrations below 100 µg/mL, whereas mean peak serum TNT009 concentrations after 30 to 100 mg/kg dosing were observed at a median of 1.0 to 2.5 h, followed by a bi-exponential decline with minimal Michaelis-Menten disposition.

## Results

- Mean (SD) concentration-time profiles of TNT009 and CP activity following a single IV administration of TNT009 is presented in **Figure 2**.

**Figure 2: Observed Concentration-Time Profiles of TNT009 and CP Activity Following Single Doses of TNT009 in NHVs**

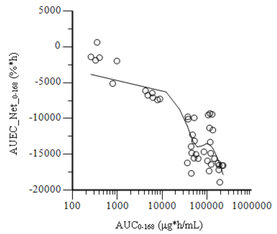



Numbers in gray shaded title area represent dose levels in mg/kg.

Dots = individual observed values; solid line = mean (95% CI)

- A very steep relationship was observed between concentrations of TNT009 and CP activity; there was full inhibition (> 85%) of CP activity when TNT009 concentrations were >100 µg/mL.
- Full inhibition of CP activity was observed at the 30, 60 and 100 mg/kg dose levels.
- Correlations between PK and PD parameters following single IV dosing are presented in **Figure 3.**

**Figure 3: Relationship Between TNT009 Exposure ($AUC_{0\text{-}168}$) and CP Activity ($AUEC\_Net_{\_0\text{-}168}$) Following Single TNT009 Dose**




$AUEC\_Net_{\_0\text{-}168}$ = net area under the effect time curve above and below the baseline effect value; $AUC_{0\text{-}168}$ = area under the TNT009 concentration-time curve

- The $AUC_{0\text{-}168}$ at which half-maximal inhibition of CP activity ($IC_{50}$) occurs is approximately 30000 µg•h/mL, which is intermediate to $AUC_{0\text{-}168}$ values previously observed for TNT009 10 mg/kg and 30 mg/kg doses. This corresponds well with the PD plots (**Figure 2**), where only partial inhibition of CP activity is observed over 168 h at the 10 mg/kg dose level, but nearly complete inhibition is observed at the 30 mg/kg dose level.

## Results (Cont'd)

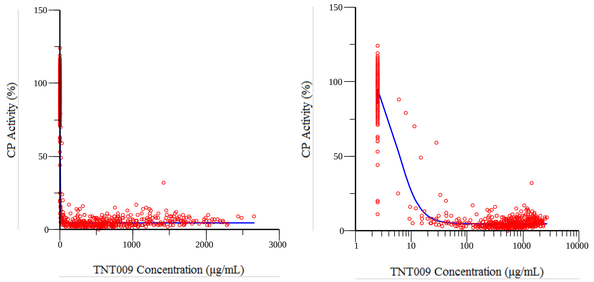
- An inhibitory $E_{max}$ model was used to describe the relationship between TNT009 exposure and CP activity inhibition in NHVs.

$$E = E_0 - \frac{I_{max} \times C^H}{C^H + IC_{50}{}^H}$$

Where $E_0$ is the effect at baseline, Imax is the maximum inhibition, C is the concentration of TNT009, $IC_{50}$ is the concentration associated to 50% of the maximum effect and H is the Hill factor (also referred as gamma, a parameter used to describe sigmoidicity).

- The relationship between serum TNT009 concentrations and CP activity are presented in **Figure 4**.

**Figure 4: Relationship Between TNT009 Concentrations and CP Activity**




- PK/PD parameters derived with the inhibitory $E_{max}$ model are presented in **Table 1**.

**Table 1: $E_{max}$ Model Parameters for TNT009 and CP Activity**

| Parameter | Estimate (RSE) |
|---|---|
| $I_{max}$ (%) | 90.2 (1.1) |
| $IC_{50}$ (µg/mL) | 6.2 (25.7) |
| $E_0$ (%) | 94.8 (1.1) |
| H | 2.4 (19.9) |

Imax = maximum inhibition, $E_0$ = effect at baseline, $IC_{50}$ = concentration associated to 50% of the maximum effect, H = Hill factor, RSE= relative standard error

- The maximum percent inhibition ($I_{max}$) of TNT009 on CP activity was 90.2%, with a 90% reduction of CP activity ($IC_{90}$) predicted at a TNT009 concentration (C) of 15.5 µg/mL, a value similar to the $IC_{90}$ observed in monkeys.
- The very low $IC_{90}$, combined with a Hill factor (H) of 2.4, suggests a very steep concentration-effect relationship .
- This corresponds well with the preceding PK and PD analyses, which suggested that a TNT009 concentration above 100 µg/mL would be sufficient to maintain near-maximal CP activity knockdown inhibition while avoiding nonlinear PK behavior.

## Results

- Simulations were performed in order to estimate the maximum and minimum TNT009 and CP activity exposures at steady state at doses of 30 mg/kg weekly, 60 mg/kg weekly and a new dose to be tested 75 mg/kg (given on Day 0, Day 7 and then every other week).
- Median (90%CI) values of key parameters derived from the simulations are presented in **Table 2**.

**Table 2: Predicted Exposures at Steady State**

| Parameters | Median (90% CI) | | |
|---|---|---|---|
| | 30 mg/kg (QW) | 60 mg/kg (QW) | 75 mg/kg (QW;Q2W*) |
| $C_{max,ss}$ (µg/mL) | 881 (449 – 2034) | 3396 (1892 – 6382) | 2036 (1175-3853) |
| $C_{min,ss}$ (µg/mL) | 309 (12.2 – 1301) | 2267 (925 – 4988) | 600 (49.7- 2011) |
| $AUC_{ss}$ (µg•h/mL) | 91920 (32691 – 269740) | 459915 (223945 – 934200) | 376085 (158060 – 902085) |

Cmax,ss = maximum predicted concentration at steady state; Cmin, ss = minimum predicted concentration at steady state; QW = once-weekly; Q2W: once every two weeks. BW range = 50 – 98 kg. Descriptive statistics are performed on 100 replicates of 500 subjects.

- For the 75 mg/kg (QW; Q2W) regimen, peak and trough plasma TNT009 concentrations are much lower relative to the 60 mg/kg (QW) regimen.
- However, steady-state exposure remains nearly the same in both cases, which will ensure that near-maximal CP inhibition is maintained.

## Conclusions

- In the 60 mg/kg QW TNT009 group, complete inhibition of serum CP was observed in all subjects over the entire dosing period and up to at least 14 days beyond the last dose of TNT009.
- A single 75 mg/kg induction dose followed one week later by maintenance doses of 75 mg/kg Q2W are expected to result in concentrations of TNT009 above the $IC_{90}$ and optimal suppression of CP activity.

## References

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