Statistical Analysis Plan

Protocol title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Controlled Phase III Study to Compare the Efficacy and Safety of Passive Immunization with TNM002 Injection and Human Tetanus Immunoglobulin as Prophylaxis Against Tetanus

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:



Glossary of Abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLQ	Below the lower limit of quantification
CI	Confidence interval
CV	Coefficient of variation
CS	Clinically significant
eCRF	Electronic case report form
ECG	Electrocardiogram
FAS	Full analysis set
GMT	Geometric mean titer
HTIG	Human tetanus immunoglobulin
IAS	Immunogenicity Analysis Set
IB	Investigator's brochure
ICF	Informed consent form
IM	Intramuscular
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
NAb	Neutralizing antibody
NCS	Not clinically significant
PE	Physical Examination
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	International System of Units
SoA	Schedule of Activities
SOC	System organ class
SS	Safety Set
TEAE	Treatment emergent adverse event
VS	Vital Sign

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	16Jun2023	3.0
eCRF	21Feb2023	2.0

2. Background

This Statistical Analysis Plan (SAP) is based on Protocol TNM002-301 “A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Controlled Phase III Study to Compare the Efficacy and Safety of Passive Immunization with TNM002 Injection and Human Tetanus Immunoglobulin (HTIG) as Prophylaxis Against Tetanus”. This SAP provides details of the planned analyses and statistical methods for TNM002-301. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). Any analyses that are beyond those outlined in the protocol are delineated in this document.

3. Protocol Details

3.1. Total Study Design

This is a Phase III, multicenter, randomized, double-blind, parallel-group, active-controlled study to compare the efficacy and safety of TNM002 injection (hereinafter referred to as TNM002) 10 mg and human tetanus immunoglobulin (HTIG) 250 IU as prophylaxis against tetanus in subjects with dirty or contaminated wounds caused by various injury and who require passive immunizing agents against tetanus.

Approximately 675 subjects are planned to be enrolled in this study. These subjects will be randomized and receive a single intramuscular (IM) gluteal injection of TNM002 10 mg (450 subjects) or HTIG 250 IU (225 subjects) in a 2:1 ratio. Randomization will be stratified by with or without concomitant administration of absorbed tetanus vaccine as determined before randomization. The proportion of subjects with concomitant absorbed tetanus vaccine administration will be approximately 10%.

The study personnel responsible for drug preparation and administration will be unblinded due to the apparent difference in the dosing volumes of TNM002 (0.5 mL) and HTIG (2.5 mL). During the study drug administration, measures should be taken to block subject's line of sight, in order to ensure that the subject cannot observe any identifying information of the study drug. The injection time of all study drugs should be controlled within 10 (± 1) seconds. The subjects, investigators, and the other study personnels at the study sites will be blinded throughout the study.

Before and after study drug administration, wound management should be performed in accordance with the clinical standard procedure. Concomitant medicine or other treatment required for injury itself or comorbidities are permitted during the study.

Serum samples for anti-tetanus neutralizing antibody and pharmacokinetic (PK) will be collected from all subjects at pre-dose, 12 hours, and 3, 7, 28 and 90 days after dosing. Serum samples for immunogenicity tests will be collected from all subjects at pre-dose, and 7, 28 and 90 days after dosing. These tests will be performed at a third party bioassay laboratory.

During the visits, subjects will also undergo safety assessments including collection of AEs, physical examinations (PE), vital signs (VS), 12-lead ECGs, and safety laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis), and the tetanus occurrence will also be monitored. The last visit for this study is planned to be performed at 105 days after dosing and will be completed by telephone contact.

As the diagnosis of tetanus is mainly based on clinical symptoms and no reliable objective diagnostic criteria are available, a clinical adjudication committee consisting of clinical

experts in the field of tetanus disease will be established. For subjects with tetanus-related symptoms, the final diagnosis will be made by experts in this committee after discussion.

The primary analysis is planned to be performed after the last enrolled subject has completed the visit at 28 days after dosing, in order to evaluate the efficacy and safety of the study drug. The analysis will be carried out by an independent unblinded team. Sponsor will be responsible for overseeing this team to ensure data analysis is carried out in line with SAP.The Sponsor will clearly document the personnel who are informed of the unblinded analysis result and the measures taken to maintain the double-blind status for the rest of the study. The investigator and, study site staff and all personnels should be kept as blind, and will remain blinded throughout the study.

3.2. Study Objectives

3.2.1. Primary Efficacy Objective(s)

- To compare the efficacy of TNM002 Injection 10 mg with HTIG 250 IU as prophylaxis against tetanus following a single IM injection.

3.2.2. Secondary Efficacy Objective(s)

- To compare the clinical outcomes after administration of TNM002 10 mg with HTIG 250 IU as prophylaxis against tetanus following a single IM injection.

3.2.3. Safety Objective(s)

- To compare the safety profile of TNM002 10 mg with HTIG 250 IU as prophylaxis against tetanus following a single IM injection.

3.2.4. Exploratory Objective(s)

- To compare the protective antibody level of TNM002 10 mg with HTIG 250 IU as prophylaxis against tetanus at different time points following a single IM injection.
- To compare the long-term clinical outcomes after administration of TNM002 10 mg with HTIG 250 IU as prophylaxis against tetanus following a single IM injection.
- To evaluate the PK properties of TNM002 in subjects requiring tetanus passive immunization.
- To evaluate the immunogenicity of TNM002 in subjects requiring tetanus passive immunization.

3.3. Sample Size and Power

Approximately 675 subjects will be randomized such that approximately 540 evaluable subjects will complete the study.

Primary Hypothesis:

The hypothesis is that TNM002 has efficacy that is superior to HTIG as prophylaxis against tetanus. To be more specific, the lower limit of the 95% confidence interval (CI) of the difference (TNM002 group - HTIG group) in the proportion of subjects with Δtiters ≥0.01 IU/mL at 12 hours after the receipt of study drug is >0.

The sample size estimation is based on the above hypothesis and following assumptions: (1) The proportion of subjects with Δ titers ≥0.01 IU/mL at 12 hours after receipt of TNM002 and HTIG based on results of earlier clinical trials; (2) Due to the fact that HTIG is a well-studied product whose efficacy and safety does not need to be evaluated in large amount of subjects in a clinical trial setting, the randomization ratio between TNM002 and HTIG groups is 2:1; (3) One-sided Type I error of 0.025; (4) TNM002 requires adequate exposure during clinical development to fully understand its safety.

Taken together, the estimated sample size is approximately 540 subjects, i.e., 360 in the TNM002 group and 180 in the HTIG group. This will provide a power of >99% to evaluate the above efficacy hypothesis. The dropout rate is expected to be 20% in this study. Therefore, the planned enrollment will be 675 subjects, i.e., 450 in the TNM002 group and 225 in the HTIG group.

Secondary Hypothesis:

The tetanus protection rate is assumed to be 99.99% at 28 days post-dose in the HTIG group and 99.999% at 28 days post-dose in the TNM002 group. The current sample size will not provide sufficient power to test a formal statistical hypothesis in terms of tetanus protection rate between TNM002 and HTIG.

Safety Hypothesis:

Table 1 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 1%, there is a 95.1% probability of observing at least 1 AE in 300 subjects.

Table 1: Probability of Observing at Least One Adverse Event at Different Sample Sizes and Different True Incidences of Adverse Events

Assumed True Incidence of AEs	Probability of observing at least one AE at different sample sizes			
	N=200	N=300	N=500	N=600
0.10%	18.0%	25.9%	39.4%	45.2%
0.50%	63.3%	77.8%	91.8%	95.1%
1.00%	86.6%	95.1%	>99.0%	>99.0%
2.00%	98.2%	>99.0%	>99.0%	>99.0%
3.00%	>99.0%	>99.0%	>99.0%	>99.0%

Assumed True Incidence of AEs	Probability of observing at least one AE at different sample sizes			
	N=200	N=300	N=500	N=600
4.00%	>99.0%	>99.0%	>99.0%	>99.0%
5.00%	>99.0%	>99.0%	>99.0%	>99.0%
6.00%	>99.0%	>99.0%	>99.0%	>99.0%
7.00%	>99.0%	>99.0%	>99.0%	>99.0%
8.00%	>99.0%	>99.0%	>99.0%	>99.0%
9.00%	>99.0%	>99.0%	>99.0%	>99.0%
10.00%	>99.0%	>99.0%	>99.0%	>99.0%

4. Endpoints

4.1. Primary Efficacy Endpoint

- The increase of anti-tetanus neutralizing antibody titers from baseline at 12 hours after receipt of study drug

4.2. Secondary Efficacy Endpoint

- Tetanus protection rate within 28 days after receipt of study drug

Tetanus protection rate is defined as 1 - tetanus incidence within 28 days after receipt of study drug.

4.3. Other Efficacy Endpoints

- The increase of anti-tetanus neutralizing antibody titers from baseline at 3, 7, 28 and 90 days after receipt of study drug
- Tetanus protection rate within 90 and 105 Days after receipt of study drug

4.4. Safety Endpoints

- AEs
- SAEs
- Laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs)

4.5. Immunogenicity Endpoints

- Anti-drug antibodies (ADA) in subjects following TNM002 administration

4.6. Pharmacokinetic Endpoints

- Serum TNM002 concentrations in subjects following TNM002 administration.

5. Estimands

The ICH E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of subjects targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

5.1. Estimand(s) for Primary Endpoint

The primary estimand is the difference in proportions between TNM002 10 mg and HTIG 250 IU with an increase in anti-tetanus neutralizing antibody titers from baseline (Δ titers) ≥0.01 IU/mL at 12 hours after receipt of study drug, in subjects as defined by the enrollment criteria.

The main estimand is defined through the following five attributes:

5.1.1. Treatment Condition of Interest

The primary treatment condition of interest is a single IM gluteal injection of TNM002 10 mg; compared against the alternative treatment condition of HTIG 250 IU.

5.1.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol 3.0. It will be analyzed in all randomized subjects who received study drug.

5.1.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variable to address the clinical question is a binary response variable of an increase of anti-tetanus neutralizing antibody titers (Δ titers) ≥0.01 IU/mL from baseline at 12 hours after receipt of study drug.

5.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 2 Handling of Intercurrent Events for the Primary Estimand

Intercurrent event	Data collection and analysis
AE leading to discontinuation from study prior to the 12 hours after dosing	The event will be integrated into the non-response variable (Δ titers <0.01 IU/mL) in line with a composite strategy.
Important protocol deviations that affect neutralizing antibody titers prior to the 12 hours after dosing	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.
Receiving additional passive immunizing agents for tetanus due to reasons unrelated to the original wound prior to the 12 hours after dosing	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.
Receiving additional passive immunizing agents for tetanus due to reasons related to the original wound prior to the 12 hours after dosing	The event will be integrated into the non-response variable (Δ titers <0.01 IU/mL) in line with a composite strategy.

5.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by evaluating the differenceof proportions of subjects with an increase in anti-tetanus neutralizing antibody titers (Δ titers) ≥0.01 IU/mL from baseline at 12 hours after receipt of TNM002 and HTIG.

5.1.6. Sensitivity Analysis for Primary Estimand

The sensitivity analysis for primary estimand of the difference in the proportions between the TNM002 and HTIG groups and its two-sided 95% CI will be performed by stratified Newcombe Wilson method instead of the main analysis of stratified Miettinen-Nurminen method.

5.1.7. Supplementary Analyses for Primary Estimand

The following table describes how intercurrent events will be handled within the primary supplementary analysis.

Table 3 Handling of Intercurrent Events for the Supplementary Analyses for Primary Estimand

Intercurrent event	Data collection and analysis
AE leading to discontinuation of study prior to the 12 hours after dosing	While on treatment strategy, exclude values after discontinuation of study.
Important protocol deviations that affect neutralizing antibody titers prior to the 12 hours after dosing	While on treatment strategy, exclude values after the important protocol deviation occurred.
Receiving additional passive immunizing agents for tetanus due to reasons unrelated to the original wound prior to the 12 hours after dosing	While on treatment strategy, exclude values after additional passive immunizing agents for tetanus received.
Receiving additional passive immunizing agents for tetanus due to reasons related to the original wound prior to the 12 hours after dosing	While on treatment strategy, exclude values after additional passive immunizing agents for tetanus received.

5.2. Estimand(s) for Secondary Endpoint

The secondary estimand is the difference between TNM002 10 mg and HTIG 250 IU in tetanus protection rate within 28 days after receipt of study drug, in subjects as defined by the enrollment criteria.

5.2.1. Treatment Condition of Interest

The secondary treatment condition of interest is a single IM gluteal injection of TNM002 10 mg; compared against the alternative treatment condition of HTIG 250 IU.

5.2.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol 3.0.

5.2.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variable to address the clinical question is a binary response variable of without tetanus occurrence within 28 days after receipt of study drug.

5.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following table describes how intercurrent events will be handled within the analysis.

Table 4 Handling of Intercurrent Events for the Secondary Estimand

Intercurrent event	Data collection and analysis
AE leading to discontinuation of study prior to 28 days after receipt of study drug	Discontinuation of study will be ignored (treat as missing data) in line with a treatment-policy strategy.
Important protocol deviations that affect tetanus occurrence prior to 28 days after receipt of study drug	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.
Receiving additional passive immunizing agents for tetanus due to reasons unrelated to the original wound prior to 28 days after receipt of study drug	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.
Receiving additional passive immunizing agents for tetanus due to reasons related to the original wound prior to 28 days after receipt of study drug	Subjects will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.

5.2.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by evaluating thetetanus protection rate difference within 28 days after receipt of TNM002 and HTIG,where, tetanus protection rate = 1 - tetanus incidence.

5.2.6. Sensitivity Analysis for Secondary Estimand

The sensitivity analysis for secondary estimand of the difference in tetanus protection rate between the TNM002 and HTIG groups and its two-sided 95% CI will be performed by stratified Newcombe Wilson method instead of the main analysis of stratified Miettinen-Nurminen method.

5.2.7. Supplementary Analyses for the Secondary Estimand

Supplementary analyses are not considered for secondary estimand.

6. Analysis Populations

6.1. All-Screened Set

The All-Screened Set will include every subject who has signed the informed consent form. The All-Screened Set will be used for summaries of disposition and the associated listing.

6.2. Intention-To-Treat (ITT) Population

All subjects randomized will be included in the ITT Population. ITT Population are analyzed according to their randomized treatment.

6.3. Full Analysis Set (FAS)

All randomized subjects who received the study drug. FAS subjects are analyzed according to their randomized treatment.

6.4. Per Protocol Set (PPS)

The PPS will consist of all subjects in the FAS who do not have any important protocol deviations considered to have a major effect on primary efficacy leading to exclusion from the PPS. PPS subjects are analyzed according to their randomized treatment.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 6.4.1 details the deviations.

6.4.1. Important Protocol Deviations Leading to Exclusion from the PPS

Deviations from the protocol, as defined in the protocol and / or protocol deviation plan, will e documented by the study monitors and project management throughout the study period.

Only those important protocol deviations considered to have a major effect on primary efficacy will lead to complete exclusion of the subject from the PPS.

Criteria which require medical and/or clinical pharmacological interpretation will be reviewed prior to interim database lock for primary analysis and final database lock for final analysis. All important protocol deviations leading to exclusion from the PPS occurring during the study will be reviewed and approved by Sponsor prior to interim and final database lock.

6.5. Safety Set (SS)

All randomized subjects who received the study drug with at least one post-dose safety evaluation. SS subjects are analyzed according to the actual treatment they received.

6.6. Immunogenicity Analysis Set (IAS)

All randomized subjects who received TMN002 with at least one post-dose immunogenicity data. If the immunogenicity results are affected by protocol deviations, all or partial immunogenicity data of corresponding subjects will not be included in the IAS.

6.7. Pharmacokinetic Set (PKS)

All randomized subjects who received TNM002 with at least one post-dose evaluable PK concentration. If the PK concentration results are affected by important protocol deviations, all or partial PK data of corresponding subjects will not be included in the PKS. All important protocol deviations leading to exclusion from the PKS occurring during the study will be reviewed and approved by Investigators and Sponsor prior to interim and final database lock.

7. Data Handling

7.1. Time Points and Visit Windows

7.1.1. General Definitions

All assessment days will be related to the first day of treatment.

Day 1 is defined as the date of dosing of study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the dosing of study drug for each subject will be taken from the Study Drug Administration eCRF page.

7.1.2. Baseline

For all subjects, the baseline is defined as the period from informed consent to the dosing of study drug.

The baseline value will be defined as last scheduled or unscheduled value collected prior to the dosing of study drug. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.1.3. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis.

7.2. Calculation of Δ titers

Unless specified otherwise, Δ Titers in TNM002 group will be calculated by post-dose antibody titers - pre-dose antibody titers, both measured by TNM002 PD bioanalysis method; Δ Titers in HTIG group will be calculated by post-dose antibody titers - pre-dose antibody titers, both measured by HTIG PD bioanalysis method.

7.3. Handling of Dropouts, Missing Data, and Outliers

7.3.1. Handling of Missing Efficacy Data

Subjects with missing data for the primary efficacy endpoint of the increase of anti-tetanus neutralizing antibody titers from baseline at 12 hours after receipt of study drug will be treated as non-responders if missing data caused by AE leading to discontinuation of study prior to the 12 hours after dosing for the primary analysis. Additionally, subjects who receive additional passive immunizing agents for tetanus due to reasons related to the original wound prior to the 12 hours after dosing will also be deemed non-responders, regardless of any subsequent response recorded for the primary efficacy endpoint. Besides, subjects whose data is missing at some time points but without discontinuation from the study will be excluded from the analysis for the missing time points.

In addition, NR (Not Reported) will be reported for subjects in TNM002 group if the baseline antibody level over a certain value, and will exclude these subjects from analysis.

Subjects with missing data for the endpoint of tetanus protection rate at certain time point after receipt of study drug will be treated as without tetanus occurrence if the subject stayed in the study and continued to be tetanus free at later time points.

7.3.2. Handling of Missing Safety Data

In general, summary statistics will be reported for observed data only. Missing data will not be imputed in this study such as missing clinical laboratory data, vital signs data, ECG data and efficacy data. Adverse event imputations for missing severity or relationship are given in Section 8.7.1.2. Unknown or partial dates of medication and surgeries/procedures imputations are given below and to be used only for the assessment of prior/concomitant status for medications, surgeries/procedures.

7.3.3. Handling of Partial and Missing Dates for Prior / Concomitant Medications and Surgeries/Procedures

<u>Missing or Partial Prior / Concomitant Medication and Surgeries/Procedures Start Dates</u>

Missing and / or incomplete dates for medications, surgeries/procedures are imputed in a manner resulting in the earliest onset or the longest duration after the start of treatment, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication is “Ongoing”. Technically, this will be done as follows:

For a missing / incomplete start date / time the earliest date / time of the following will be imputed:

- The later date of: the earliest possible start date / time, and the date / time of first dose of treatment.
- The latest possible start date / time.
- The latest possible stop date / time.

For a missing / incomplete stop date / time the later date / time of the following will be imputed:

- The earlier date / time of the latest possible stop date / time and the date / time of last dose of treatment.
- The earliest possible stop date / time.
- The earliest possible start date / time.

Here, the earliest possible date / time is defined as:

- The date / time of the first day of the month at 00:00hrs, if month and year are available but the day / time is missing.
- The date / time of the first day of the year at 00:00hrs, if year is available but day / time and month are missing.
- 00:00hrs on the day of informed consent, if the date / time is completely missing.

The latest possible date / time is defined as:

- The date / time of the last day of the month at 23:59hrs, if month and year are available but the day / time is missing.
- The date / time of the last day of the year at 23:59hrs, if year is available but day / time and month are missing.
- 23:59hrs on the date of last known date on the study for the subject plus one year, if the date / time is completely missing.

7.3.4. Handling of Serum Concentrations that are Below the Lower Limit of Quantification(BLQ)

7.3.4.1. Pharmacokinetic Analysis

Serum concentrations that are below the lower limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV) % of geometric mean will be reported as not calculated (NC).

7.3.4.2. Anti-tetanus Neutralizing Antibody Titers Analysis

Anti-tetanus neutralizing antibody titers that are below the lower limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Titers that are BLQ will be set to 0 for the calculation of summary statistics.
- Values of Δ titers ≤0 will be set to 0 for the calculation of summary statistics. Descriptive statistics of geometric mean and geometric CV% will be reported as not calculated (NC) when the treatment group contains 0.

8. Statistical Methods

8.1. General Principles

All data processing, summarization and analyses will be performed using [redacted]SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for continuous variables will be the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max)，for those subjects with data, unless stated otherwise.

For categorical variables, the number (n) and percentage (%) of subjects with non-missing observations per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

All statistical comparisons will be made using two sided tests at the p=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided including calculating 95% CI. Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study.

8.2. Subject Disposition and Data Sets Analyzed

Subject disposition will be summarized by treatment group and overall, where appropriate, for the All-Screened Set, unless stated otherwise.

The following information will be reported:

- Number of subjects for the following categories:
  - Screened
- Number and percentage of subjects for the following categories:
  - Screen Failure,
  - Reason for screen failure,
  - Randomized,
  - Treated,
  - Not Treated,
  - Completed the study,
  - Discontinued the Study,
  - Reasons for study discontinuation.
- Number and percentage of subjects included in, and excluded from, each study population together with the reasons for exclusion from the analysis set;

- Number and percentage of subjects who met / did not meet all eligibility criteria, together with the criteria not met.
- Number and percentage of subjects by stratification factors. Each stratification variable will be presented by the stratum collected in IXRS. This will be repeated in the two subgroups by age group (≤65 vs >65).

The following subject data listings will be prepared as below:
A listing of all subjects with their study completion status, including the reasons for study discontinuation will be presented for the All-Screened Set.

A listing of all screen failed subjects with their reasons for screen failure will be presented for the All-Screened Set. A separate listing of subjects who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for the All-Screened Set.

A listing of all randomized subjects with their randomization details, including dosing date and time, and actual treatment received will be presented for the ITT Population.

A listing of subject unblinding information will be presented for the ITT Population.

A listing of all subjects excluded from at least one analysis set will be presented for the ITT Population.

8.3. Protocol Deviations

All important protocol deviations will be summarized for the ITT Population by treatment group and overall as described below:

- The number of unique subjects with at least one important protocol deviation as well as the number of subjects in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all subjects with one or more important / non important protocol deviations will be presented for the ITT Population.

8.4. Demographic and Other Baseline Characteristics

8.4.1. Demographic and Baseline Characteristics

Demographic characteristics will be summarized for the FAS by treatment group separately and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm)
- Weight(kg)
- Body mass index (kg/m^2) [calculated as (body weight / height^2) where weight is in kg and height is in m] and presented to one decimal precision
- Anti-tetanus antibody titer at baseline (by HTIG PD bioanalysis method)

Anti-tetanus antibody titers will use the summary statistics including n, arithmetic mean, arithmetic SD, arithmetic CV%, median, min, max, GMT (geometric mean titer), geometric SD, geometric CV% , 95% CI of GMT, and proportion of BLQ subjects. If the GMT and geometric CV% could not be calculated due to subjects with values of anti-tetanus antibody titer containing BLQ (i.e., set to 0), the below sensitivity analysis will be performed as follow:

- LLOQ/2 of the corresponding detection method will be added to all values in the treatment group, and then the GMT and geometric CV% will be calculated. The final GMT and 95% CI of GMT will be calculated by subtracting LLOQ/2 of the corresponding detection method.

For the following category variables, the total counts and percentage will be provided.

- Age group (years):
    - ≤65
    - >65 to ≤75
    - >75
- Gender
    - Male
    - Female
- Is the subject of childbearing potential? (female only)
    - Yes
    - No
- Ethnicity
    - Han Nationality
    - Other
- Race
    - Asian
    - Other
- Classification of anti-tetanus antibody titer at baseline
    - < 0.01 IU/mL

- ≥ 0.01 IU/mL

Besides, demographic characteristics will be repeated by two subgroups based on the use of tetanus vaccine as determined before randomization, and by two subgroups based on age group (≤65 vs >65).

Demographic characteristics will be listed for the FAS.

8.4.2. Medical History

Medical history refers to the information of prior or concomitant diseases that exist prior to dosing, including history of infectious diseases, surgery, injury and allergy.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)[version 25.1 or later] and will be presented by System Organ Class (SOC) and Preferred Term (PT). The SOCs and PTs are to be sorted by descending order of incidence in TNM002 group.

Medical history records will be summarized for the FAS by treatment group and overall as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using descending order of numerical counts in TNM002 group first and then HTIG group for both SOC and PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-subject and within-subject by medical history start date for the FAS.

8.4.3. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version Sep 2022 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior and concomitant medications are defined as follows:

- Prior medications are defined as medications that stopped before the date of dosing of study medication.
- Concomitant medications are defined as any medications taken on or after the dosing of study medication until the end of the study.

See Section 7.3.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the FAS by treatment group and overall as follows:

- The number and percentage of subjects with at least one prior / concomitant medication will be presented.
- The number and percentage of subjects with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the TNM002 group first and then HTIG group. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the FAS. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the dosing date and time of treatment and will be presented for those subjects who received at least one dose of treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, additional passive immunizing agents for tetanus and adsorbed tetanus vaccine administration will be coded using the WHO Drug Global Dictionary, Format B3 [Version Sep 2022 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes as well, and will be summarized separately for the FAS by treatment group and overall, similar to the analysis of prior and concomitant medications.

Tetanus vaccination history will be summarized using standard descriptive statistics for the FAS by treatment group separately and overall as well.

8.4.4. Prior and Concomitant Surgeries/Procedures

All surgeries/procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)[version 25.1 or later], System Organ Class (SOC) and Preferred Term (PT).

Prior and concomitant surgeries/procedures are defined as follows:

- Prior surgeries/procedures are defined as surgeries/procedures that stopped before the date of dosing of study medication.
- Concomitant surgeries/procedures are defined as any surgeries/procedures taken on or after the dosing of study medication until the end of the study.

See Section 7.3.3 for imputation of missing or partial dates for surgeries/procedures.

Prior and concomitant surgeries/procedures will be summarized separately for the FAS by treatment group and overall as follows:

- The number and percentage of subjects with at least one prior / concomitant surgeries/procedures will be presented.
  The number and percentage of subjects with at least one prior / concomitant surgeries/procedures within each primary SOC and PT will be presented. The summary will be sorted using numerical counts in the TNM002 group first and then HTIG group by descending order for SOC and PT. Where groups or terms tie these will be sorted alphabetically.

Prior surgeries/procedures and concomitant surgeries/procedures will be listed separately for the FAS. In the listings the relative start and stop day of prior / concomitant surgeries/procedures will be calculated relative to the dosing date and time of treatment and will be presented for those subjects who received at least one dose of treatment. If the concomitant surgery/procedure is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

8.5. Measurements of Treatment Compliance

Not applicable for this study.

8.6. Efficacy

Efficacy analysis will be performed on the FAS.

8.6.1. Primary Efficacy Analysis

The primary efficacy variable is defined as binary response of increase of anti-tetanus neutralizing antibody titers (Δ titers) ≥ 0.01 IU/mL from baseline at 12 hours after receipt of study drug.

Subjects with missing data for the primary efficacy endpoint will be treated as non-responders if missing data caused by AE leading to discontinuation of study prior to the 12 hours after dosing for the primary analysis. Additionally, subjects who receive additional passive immunizing agents for tetanus due to reasons related to the original wound prior to the 12 hours after dosing will also be deemed non-responders, regardless of any subsequent response recorded for the primary efficacy endpoint. Besides, subjects whose data is missing at some time points but without discontinuation from the study will be excluded from the analysis for the missing time points.

The primary efficacy analysis can be summarized as follows:

1. Summarizing the proportion of subjects with an increase of anti-tetanus neutralizing antibody titers (Δ titers) ≥ 0.01 IU/mL from baseline at 12 hours after receipt of study drug and its two-sided 95% CI from FAS.

Clopper-Pearson method, which is an alternative to calculating binomial CI using normal approximation, will be used to calculate the 95% CI for each of the two treatment groups.

2. Calculating the difference of the proportion of subjects with an increase of anti-tetanus neutralizing antibody titers (Δ titers) ≥0.01 IU/mL from baseline at 12 hours after receipt of study drug and the corresponding 95% CI stratified by with or without concomitant administration of tetanus vaccine as determined before randomization.

   Stratified Miettinen-Nurminen method, will be used for constructing CI of the difference in binomial proportions between the TNM002 and HTIG groups from those stratified 2×2 samples.

Subjects who are diagnosed with tetanus or receive additional passive immunizing agents for tetanus due to reasons related to the original wound within 12 hours after receipt of study drug will be considered to have Δ titers < 0.01 IU/mL.

The above analysis will be repeated in subjects from FAS whose baseline antibody titers <0.01 IU/mL. If appropriate, the above analysis will be repeated in the two subgroups by age group (≤ 65 vs > 65).

8.6.2. Sensitivity for the Primary Efficacy Analyses

To assess the sensitivity of the results to the primary analysis, the difference in the proportions between the TNM002 and HTIG groups and its two-sided 95% CI (by Newcombe Wilson method stratified by with or without concomitant administration of tetanus vaccine as determined before randomization) will also be performed. The handling manner of intercurrent events is same as the primary estimand.

8.6.3. Supplementary for Primary Efficacy Analyses

8.6.3.1. Supplementary Analysis I

The handling manner of intercurrent events is same as the supplementary analyses for primary estimand in Table 3.

The analysis method is same as the primary analysis.

8.6.3.2. Supplementary Analysis II

To assess the robustness of the results to the primary analysis, the supplementary analysis will be performed using the PPS with observed data only.

8.6.4. Secondary Efficacy Analysis

8.6.4.1. Tetanus protection rate within 28 days after receipt of study drug

The secondary efficacy variable is defined as a binary response variable of without tetanus occurrence within 28 days after receipt of study drug.

Secondary efficacy analysis can be summarized as follows:

1. The tetanus protection rate at 28 days after receipt of study drug and its two-sided 95% CI in FAS will be calculated for each treatment group. The protection rate defined as 1− tetanus incidence.

   Clopper-Pearson method will be used to construct the 95% CI for each of those two treatment groups.

2. The difference in tetanus protection rate between the TNM002 and HTIG groups and its two-sided 95% CI will be calculated as well. The difference of 95% CI will be stratified by the use of tetanus vaccine as determined before randomization.

   Stratified Miettinen-Nurminen method, will be used for constructing CI of the difference in binomial proportions between the TNM002 and HTIG groups from those stratified 2×2 samples.

If appropriate, subjects will be divided into two subgroups based on the use of tetanus vaccine as determined before randomization, as well as in the two subgroups by age group (≤65 vs >65). The tetanus protection rate at 28 days after receipt of study drug and its two-sided 95% CI in FAS will be presented by treatment group and subgroup. Clopper-Pearson method will be used to construct the 95% CI for each treatment groups.

8.6.4.2. Sensitivity Analyses for the Secondary Efficacy Analysis

To assess the sensitivity of the results to the secondary analysis, the difference in tetanus protection rate between the TNM002 and HTIG groups and its two-sided 95% CI by Newcombe Wilson method stratified by with or without concomitant administration of tetanus vaccine as determined before randomization will also be performed.

8.6.5. Other Efficacy Analyses

The other efficacy endpoints will be analyzed using the FAS with observed data only.

8.6.5.1. Anti-tetanus neutralizing antibody titers at 3, 7, 28 and 90 days after receipt of study drug

The anti-tetanus neutralizing antibody titer analysis at 3, 7, 28 and 90 days after receipt of study drug will be performed in subjects from FAS that didn't receive tetanus vaccine up to the respective time point.

Subjects who were diagnosed with tetanus or receive additional passive immunizing agents for tetanus due to reasons related to the original wound before the respective time point are considered to have a titer = LLOQ/2 and a Δ titer <0.01 IU/mL at that time point.

8.6.5.1.1. Proportion of subjects with Δ titers ≥0.01 IU/mL from baseline at 3, 7, 28 and 90 days after receipt of study drug, respectively

Using the same methods described in Section 8.6.1, the proportion of subjects with Δ titers ≥0.01 IU/mL from baseline at 3, 7, 28 and 90 days after receipt of study drug and its two-sided 95% CI will be calculated for each treatment group. The difference in those proportions between the TNM002 and HTIG groups and its two-sided 95% CI will also be calculated. Miettinen-Nurminen method will be used for constructing CI of the difference of proportions between the TNM002 and HTIG groups.

If appropriate, the above analysis will be repeated in the two subgroups by age group (≤65 vs >65).

8.6.5.1.2. Geometric mean of Δ titers from baseline at 12 hours, 3, 7, 28 and 90 days after receipt of study drug, respectively

The anti-tetanus neutralizing antibody titers and Δ Titers will be summarized by treatment group at each scheduled time point using the summary statistics including n, arithmetic mean, arithmetic SD, arithmetic CV%, median, min, max, geometric mean, geometric SD, geometric CV% and 95% CI of geometric mean.

The analysis will be performed in subjects from FAS that haven't received tetanus vaccine up to the respective time point.

Individual and mean (including geometric and arithmetic) TNM002 titers - time profiles and Δ titers - time profiles will also be presented graphically, nominal collection time will be used in mean profile and actual collection time will be used in individual profile.

If the GMT and geometric CV% could not be calculated due to subjects with anti-tetanus antibody titer of BLQ (i.e., set to 0), the below sensitivity analysis will be performed:

- LLOQ/2 of the corresponding detection method will be added to all values in the treatment group , and then the GMT and geometric CV% will be calculated. The final GMT and 95% CI of geometric mean will be calculated by subtracting LLOQ/2 of the corresponding detection method.

If the geometric mean and geometric CV% could not be calculated due to the large number of visit contain values of Δ titers ≤0 (i.e., set to 0), two sensitivity analyses will be performed as follow:

- The geometric mean and geometric CV% will be calculated by setting 0 to LLOQ/4 of the corresponding detection method.
- LLOQ/2 of the corresponding detection method will be added to all values in the treatment group , and then the geometric mean and geometric CV% will be calculated. The final geometric mean and 95% CI of geometric mean will be calculated by subtracting LLOQ/2 of the corresponding detection method.

In addition, Δ titers at each scheduled time point after dosing will be compared and analyzed between treatment groups based on the mixed-effect model for repeated measures (MMRM) method. The MMRM model will use the log-transformed Δ titers at each scheduled time point as the dependent variable, the treatment group, time point, and treatment group-time point interaction as the independent variables, the the log-transformed baseline anti-tetanus neutralizing antibody titer as the covariate. Baseline anti-tetanus neutralizing antibody titers that are BLQ will be treated as LLOQ/2 for the purpose of log-transformation. The intra-subject variance-covariance structure will be the unstructured (UN). The difference in Δ titers and 95% CI of the difference between different treatment groups will be calculated and then antilog-transformed to obtain the ratio of GMT and CI of ratio. If the model does not converge when the covariance structure is UN, other possible covariance structures, such as Toelitz, autoregression (1) (AR (1)), etc., can be selected, and the covariance structure with the smallest final AIC value will be the standard to select the best for the final model.

The above analysis will be repeated in for subjects in TNM002 group by subgroups of ADA status. No statistical comparisons will be performed.

If appropriate, the above analysis will be repeated in the two subgroups by age group (≤65 vs >65). No statistical comparisons will be performed.

8.6.5.1.3. Antibody titers in the subgroup of subjects who received Tetanus vaccine as determined before randomization

In randomized subjects who received study drug and tetanus vaccine as determined before randomization, the proportion of subjects with Δ titers ≥0.01 IU/mL from baseline at 3, 7, 28 and 90 days after receipt of study drug and its two-sided 95% CI will be calculated for each treatment group using method described in section 8.6.1.

Antibody titers and Δ titers from baseline at 12 hours, 3, 7, 28 and 90 days after receipt of study drug will be summarized in the subgroup of FAS consisting of subjects who received tetanus vaccine as determined before randomization. Baseline and post-dose antibody titers by HTIG bioanalysis PD method will be used for HTIG group. Baseline and post-dose antibody titers by both TNM002 and HTIG bioanalysis PD method will be

presented for TNM002 group. Antibody titers and Δ titers will be summarized by treatment group and detection method at each scheduled time point using the summary statistics including n, arithmetic mean, arithmetic SD, arithmetic CV%, median, min, max, geometric mean, geometric SD, geometric CV% , 95% CI of geometric mean, the proportion of subjects with Δ titers ≥0.1 IU/mL and the proportion of subjects with antibody titers ≥0.1 IU/mL. Data handling rules, statistical methods and appropriate sensitivity analysis from previous sections will apply.

8.6.5.2. Tetanus protection rate within 90 and 105 Days after receipt of study drug

The tetanus protection rate within 90 and 105 days will be calculated in FAS for each treatment group respectively.

The protection rate differences at those two respective timepoints will be compared between TNM002 and HTIG groups stratified by the use of tetanus vaccine before randomization, same as the secondary analysis method.

Subjects will be divided into two subgroups based on the use of tetanus vaccine before randomization. Clopper-Pearson method will be used to construct the 95% CI for each treatment group. The difference in tetanus protection rate between the TNM002 and HTIG groups will be calculated and its two-sided 95% CI will be performed by Miettinen-Nurminen method. If appropriate, the above analysis will also be repeated in the two subgroups by age group (≤65 vs >65).

8.7. Safety

Safety analysis will be summarized for SS according to the study drug they actually received. Subjects will be divided into two subgroups based on the actual administration of tetanus vaccine and all the safety assessments will be repeated, except AEs leading to death or discontinuation of study and physical examination.

8.7.1. Adverse Events

If appropriate, the analysis described in this section will be repeated in the two subgroups by age group (≤65 vs >65).

8.7.1.1. Injection Site Assessment

An injection site reaction assessment should be performed 30 (± 5) minutes, 12 hours (± 30 mins) and 3 days (± 4 hours) after IM injection of the study drug. The number and percentage of injection site assessed and injection site reaction symptom will be summarized using default descriptive statistics by treatment group separately and overall at scheduled time points for the SS.

The injection site reaction assessment will be listed.

8.7.1.2. Other Adverse Events

All AEs recorded on the eCRF are TEAEs with start date and time after the start of treatment, and will be coded using the MedDRA dictionary [version 25.1 or higher].

- Treatment Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious Event= "Yes".
- The relationship between a TEAE and treatment is assessed as related, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator or sponsor as related to treatment or with missing relationship to treatment.
- Assessment of AE severity will be based on the following guidelines:
    - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated;
    - Moderate: requiring small, local or noninvasive treatment; restricted in age-appropriate instrumental activities of daily living (ADLs) (ADLs refer to cooking, shopping for clothing, using the telephone, managing money, etc.);
    - Severe: serious or medically significant but not immediately life-threatening; requiring hospitalization or prolongation of hospitalization; disabling; restricted in self-care ADLs (ADLs refer to bathing, dressing, undressing, eating, toileting, taking medications, etc., rather than bedridden).

In addition to the afore mentioned AE types, hypersensitivity reactions will be identified as TEAEs of special interest .

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the SS by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:
    - Any TEAE
        - Leading to death
        - Leading to discontinuation of study
        - Mild
        - Moderate
        - Severe
    - Any study treatment related TEAE
        - Mild
        - Moderate
        - Severe
    - Any serious TEAE
    - Any serious study treatment related TEAE
    - TEAEs of Special Interest
- The number and percentage of subjects reporting each TEAE will be summarized by SOC and PT for the following types of TEAEs:

- TEAEs
- TEAEs of Special Interest
- TEAEs Leading to Death
- TEAEs Leading to Discontinuation of Study
- TEAEs by Maximum Severity
- TEAEs by Relationship to Treatment
- TEAEs by Relationship and Severity
- Study Treatment related TEAEs
- Serious TEAEs
- Study Treatment Related Serious TEAEs

- The number and percentage of subjects who died will be summarized by the primary reason of death

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT, respectively.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included (as Severe) in the overall count of subjects with TEAEs, and will be included in the counts of subjects with TEAEs within a SOC or PT as well.

Summaries by SOCs and PTs will be sorted by SOCs and PTs within SOC by descending order of incidence in TNM002 group first and then HTIG group. Where SOCs or preferred terms tie will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed will be presented. The listing will present the relative start and stop day of the AE calculated relative to the dosing of study drug and will be presented for those subjects who received study treatment. If the AE is “Ongoing” it will be indicated as such in the listing and the relative stop day will not be calculated.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of TEAEs Leading to Discontinuation of Study
- Listing of Serious TEAEs
- Listing of TEAEs of Special Interest
- Listing of Treatment Related TEAEs
- Listing of Treatment Related Serious TEAEs

8.7.2. Laboratory Evaluations

Data for the following clinical chemistry, hematology, coagulation, urinalysis and pregnancy tests are required by the protocol as below:

Table 5 Laboratory Tests

Chemistry	Hematology	Urinalysis

• Total protein • Albumin • Sodium • Potassium • Chloride • Calcium • Glucose • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Total bilirubin • Direct bilirubin • Urea (blood urea nitrogen) • Creatinine	• Red blood cell count • Hemoglobin • Platelet count • White blood cell count • Absolute neutrophil count • Neutrophil percentage • Absolute lymphocyte count • Lymphocytes percentage • Absolute monocyte count • Hematocrit	• Protein • Glucose • Urobilinogen • Urine occult blood • Red blood cell • White blood cell
	• **Coagulation**	**Others**
	• Prothrombin time • Activated partial thromboplastin time	• Serum pregnancy test (β-hCG)

All laboratory data will be reported in SI units. Normal, abnormal (including clinically significant (CS) and not clinically significant (NCS)) will be used to evaluate the laboratory data. All quantitative laboratory test values at each assessed timepoints will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the SS by treatment group and overall as follows:

- Observed values and percentage change from baseline at each assessed timepoint for each standard continuous laboratory parameter;
- Shifts from baseline (normal vs. abnormal, NCS vs. abnormal, CS) to each post-baseline timepoint for each laboratory parameter.

Listings of all clinical laboratory data including derived percentage change from baseline will be provided for the SS. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low for applicable laboratory assessments.

8.7.3. Vital Signs

Vital signs data will be summarized descriptively by scheduled time point at SoA defined in

the Protocol. The following vital sign parameters will be assessed:

- Systolic blood pressure (mmHg)

- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breaths / min)
- Body temperature (ear,°C)

Normal, abnormal(including CS and NCS) will be used to evaluate the vital sign measurements.

The following will be presented for SS:

- Observed values and change from baseline at each scheduled timepoint for each standard vital sign parameter using default summary statistics for continuous variables.
- Shifts from baseline of vital sign (normal vs. abnormal, NCS vs. abnormal, CS) to each post-baseline timepoint.

A listing of all vital signs data including derived percentage change from baseline will be provided for the SS.

8.7.4. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, NCS / abnormal, CS
- Heart rate (bpm)
- PR interval (msec)
- QT interval (msec)
- QTc interval (msec)
- QRS interval(ms)

The maximum post-baseline QTc values will be classified in accordance with the ICH E14[1], Boundaries as presented in Table 6.

Table 6 QTcF / QTcB Interval ICH E14 Boundaries

QTc Interval	Criteria (msec)
Observed QTc interval	≤450 msec >450 to ≤480 msec >480 to ≤500 msec >500 msec
Change from baseline in QTc interval	≤30 >30 to ≤60 msec >60 msec

The ECG findings will be summarized by treatment group and overall for the SS as follows:

- Observed values and change from baseline at each scheduled timepoint for each standard ECG parameter using default summary statistics for continuous variables.
- Shifts from baseline of overall ECG assessment (normal vs. abnormal, NCS vs. abnormal, CS) to each post-baseline timepoint.
- A categorical summary of QTc classification according to ICH E14 boundaries will be provided using counts and percentages for baseline and maximum post-baseline value.

A listing of all ECG data including derived percentage change from baseline will be provided for the SS.

8.7.5. Physical Examination

Physical examinations will be performed according to SoA. The physical examination generally includes skin, lymph nodes, eyes, head and neck, chest, abdomen, spine, extremities, neurological, etc.

The physical examination data will be summarized descriptively at scheduled time points by treatment group separately and overall for the SS as follows.

- Shifts from baseline of physical examinations (normal vs. abnormal, NCS vs. abnormal, CS) to each post-baseline timepoint.

Physical examination findings (normal / abnormal) and details of abnormalities will be listed for each subject at each assessed timepoint.

8.7.6. Primary Analysis and Data Monitoring Committee (DMC)

The primary analysis will be performed after the last enrolled subject has completed the Day 28 visit. This analysis includes the final analysis of the primary and secondary efficacy endpoints and the interim analysis of the safety and other endpoints. The Sponsor is responsible for overseeing the whole process and ensuring that it is in line with the SAP. The Sponsor will clearly document the personnel who are informed of the unblinded

analysis result and the measures taken to maintain the double-blind status for the rest of the study. The investigators, study site staff and all personnels should be kept as blind will remain blinded throughout the study.

Data Monitoring Committee is not applicable for this study.

8.8. Pharmacokinetics Analysis

Pharmacokinetic analyses will be performed on the PKS. If appropriate, the analysis will be repeated in subgroups based on whether or not subjects received Tetanus vaccine as determined before randomization as well as in the two subgroups by age group (≤65 vs >65).

Samples collected for measurement of serum concentrations of investigational product will be sent to a third party bioassay laboratory and analyzed using a validated analytical method in compliance with applicable SOPs. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Drug concentration-time relationship will be summarized by nominal collection time points for serum samples using descriptive statistics. Individual and mean (including arithmetic and geometric) TNM002 concentration-time profiles will also be presented graphically, nominal collection time will be used in mean profile and actual collection time will be used in individual profile.

8.8.1. Presentation of Pharmacokinetic Concentration Data

- Descriptive statistics of number of subjects (n), arithmetic mean, arithmetic SD and arithmetic CV%, geometric mean, geometric SD and geometric CV%, median, minimum and maximum will be calculated in summaries.
- For the calculation of summary statistics, the BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentrationtime profile, this value will be excluded from the summary statistics.
- Where there is no result (NR), these will be set to missing.
- If there are less than three values in the data series, only the n, min and max will be presented. The other summary statistics will be denoted as not calculated (NC).
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean, geometric SD and geometric CV% as well as the arithmetic CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean,

geometric SD and geometric CV% as well as the arithmetic CV% will be denoted as NC.

- Out-of-window blood samples will be excluded from calculation of descriptive statistics.

8.9. Immunogenicity Analysis

Serum samples for immunogenicity tests will be collected from all subjects at pre-dose, and 7, 28 and 90 days after dosing.

Immunogenicity analysis will evaluate the result of titers and rate of ADA positivity in the subject. If confirming ADA positive, Neutralizing antibodies (NAbs) will be tested further. Meanwhile the effect of ADA on the PK and PD profile of the study drug will be evaluated if the data allow as well.

Based on the analysis results ADA positive rate (and the incidence of NAb, if applicable) at baseline and at different post-baseline timepoints will be summarized for the IAS. The number and percentage of NAb will also be further calculated for those positive subjects if data permit.

Descriptive statistics of number of subjects (n), arithmetic mean, arithmetic SD and arithmetic CV%, geometric mean, geometric SD and geometric CV%, median, minimum and maximum will be calculated for titers of ADA.

Immunogenicity data analysis will be performed on the IAS.

9. Changes in the Conduct of the Study or Planned Analysis

When defining the Immunogenicity Set (IAS), if the immunogenicity results are affected by protocol deviations, all or partial immunogenicity data of corresponding subjects will not be included in the IAS.

10. References

[1]Wang, Hongbo,Liu Si,Liu Cheng,Li Xueying,Xiong Hui,Wang, Chuanlin. *Meta-analysis on tetanus- antibody protection rate of healthy population born after 1978 in China*[C]//. Compilation of papers of the 2019 China Animal Injury Treatment Summit Forum,2019:86.DOI:10.26914/c.cnkihy.2019.014966.

[2]ICH. *Addendum on Estimands and Sensitivity Analysis in Clinical Trials*, Guideline E9(R1). Available at

https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[3] Brown H and Prescott R. *Applied Mixed Models in Medicine*. John Wiley & sons (Chichester), 1999.

[4] ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 12 May 2005. Available at

https://database.ich.org/sites/default/files/E14_Guideline.pdf

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Final, 09JUL2023	Final version
Version 2.0, Final, 30AUG2023	Updated wording based on protocol 3.0 (16Jun2023). No planned analysis was changed from Version 1.0 to Version 2.0.