STATISTICAL ANALYSIS PLAN	
Study Code	D5290C00007
Edition Number	2.0
Date	20-Dec-2021

A Phase 1, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Nirsevimab in Healthy Chinese Adults

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
ADA	Antidrug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
AUC_{0-150}	Area under the serum concentration-time curve from time zero to 150 days
ATC	Anatomic Therapeutic Chemical
BLQ	Below the limit of quantitation
BMI	Body mass index
C_{max}	Observed maximum serum concentration
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database Lock
ECG	Electrocardiogram
IM	Intramuscular
IP	Investigational Product
IPD	Important Protocol Deviation
NOCD	New Onset Chronic Disease
PDMP	Protocol Deviations Management Plan
PK	Pharmacokinetics
RSV	Respiratory syncytial virus
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T_{max}	Time to maximum observed concentration

AMENDMENT HISTORY

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	12-Apr-2021	Initial approved SAP	N/A	N/A

2.0	20-Dec-2021	Updated the description of the definition of as-treated population in section 3.2 to align with CSP, and clarified ADA analysis will be performed in this population. Added description of decimal places in terms of data presentation in section 3.3. Clarified the baseline definition for blood pressure and heart rate in 3.3.1.2. Added the description for the reporting and presentation of COVID-19 related protocol deviations and issues in sections 3.3.5 and 4.1.3.2. Updated the presentation of subjects screened but not randomized in subject disposition summary in section 4.1.1.2. Clarified algorithm for partial AE start date imputation in appendix. Combined section 4.1.7 with section 4.1.6, for the presentation of medical and surgical history, and updated numbering for subsequent sections. Updated the presentation for allergy history and procedures in section 4.1.7 and 4.1.10. Updated section 4.1.5.2 to remove the presentation of categorical variables since baseline characteristics only include height, weight, and BMI. Updated the analysis of ADA in section 4.2.2.1.4. Removed the summary table for TEAE with outcome fatal; clarified which lab parameters will be graded by CTCAE; removed weight and BMI in the presentation of vital signs in section 4.2.2.4.	Yes, CSP Amendment 1	N/A

1 INTRODUCTION

This is the statistical analysis plan (SAP) for study D5290C00007. The SAP expands on the statistical analyses specified in the Clinical Study Protocol (CSP). Any changes to any specifications in the CSP will be described in Section 2 of this document.

This SAP is based on the CSP Version Amendment 1, dated 04 December2020.

1.1 Study objectives

1.1.1 Primary objective

- The primary objective of this study is:
  - To evaluate serum concentrations of nirsevimab.

1.1.2 Secondary objective

- The secondary objective is:
  - To evaluate the safety and tolerability of nirsevimab when administered as a single fixed IM dose of 300 mg to healthy Chinese adult subjects.
  - To evaluate ADA responses to nirsevimab in serum.

1.2 Study design

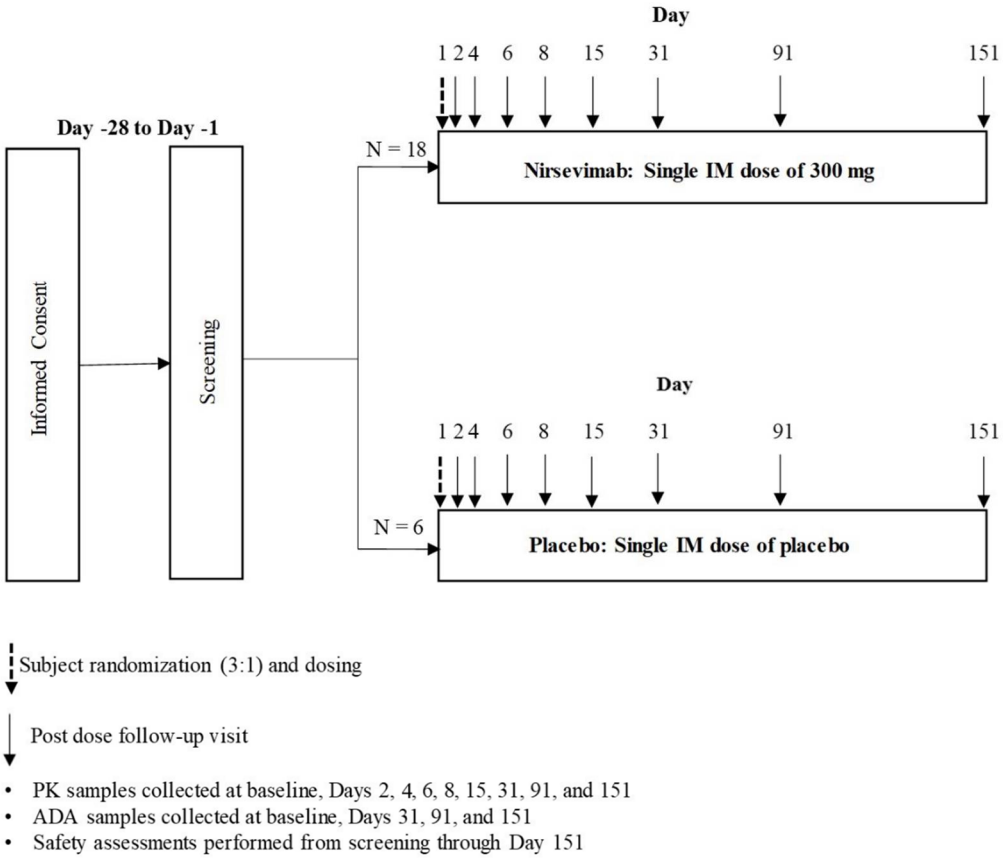
Study D5290C00007 is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetic (PK), safety, and tolerability of nirsevimab compared to placebo when administered as a single fixed IM dose of 300 mg to healthy Chinese adult subjects. Enrollment is planned at a single study center in China.

Approximately 24 healthy Chinese subjects will be randomly assigned in a 3:1 ratio to receive nirsevimab (n = 18) or placebo (n = 6). All subjects will be followed for approximately 150 days after dosing to assess safety, pharmacokinetics (PK), and antidrug antibody (ADA) response. Serum concentration of nirsevimab at selected time points will be evaluated as the primary endpoint to confirm that adequate serum exposures are maintained at least 5 months after dosing (ie, through Day 151; over a RSV season).

ADA will be measured at selected time points throughout the study up to Day 151.

Safety endpoints include TEAEs, TESAEs, AESIs (defined as hypersensitivity including anaphylaxis, immune complex disease, and thrombocytopenia), NOCDs, clinical laboratory assessments and vital signs.

Figure 1 Study Flow Diagram



ADA = antidrug antibody; IM = intramuscular; PK = pharmacokinetics.

1.3 Number of subjects

This study will randomize approximately 24 subjects of whom approximately 18 will receive nirsevimab and approximately 6 will receive placebo. Because all analyses will be descriptive in nature and no hypothesis is being tested statistically, no formal sample size calculation was performed. Current sample size and sampling scheme are selected to facilitate estimation and numerical comparison of C_{max}, time to maximum observed concentration (T_{max}), and area under the concentration-time curve from time 0 to 150 days (AUC_{0-150}) between Chinese and non-Chinese adult subjects.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

There will be no interim analysis for this study. A final analysis will be conducted when all subjects have completed the last visit of the study (Day 151).

The final analysis will be performed by IQVIA Biostatistics and PK Biostatistics teams following sponsor authorization of this SAP, database lock and sponsor authorization of analysis sets.

3.2 Analysis Populations

Two analysis sets will be considered in this study:

PK Population
The PK population will include all subjects who have received any dose of investigational product (IP), and have at least one measurable postdose serum PK observation and for whom PK blood samples are assumed not to be affected by factors such as important protocol deviations (to be determined prior to unblinding). Pharmacokinetic analyses will be based on the PK population. Subjects who receive placebo will not be part of the PK population.

As-treated Population
All subjects who are randomized into the study and who received any amount of IP will be included in the as-treated population. All safety and ADA summaries will be based on this analysis set and all subjects will be analyzed according to the actual treatment received.

3.3 General Considerations

Statistical summaries and analyses will be performed by IQVIA under the direction of the Biostatistics Group, AstraZeneca using SAS® Version 9.4 or higher and, where appropriate, additional validated software.

No statistical tests will be conducted in this study. For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g. Q1 and Q3) will be mentioned in the relevant section. Frequencies and percentages will be displayed for categorical data. The denominators for all percentages will be defined as the number of non-missing values for each variable within the analysis set. Percentages will be presented with 1 decimal place. If the original data has N decimal places (if original data has more than 2 decimal places, then N= 2), then the summary statistics except for PK variables should have the following decimal places:

- Minimum and maximum: N
- Mean, median: N + 1
- SD: N + 2

Summaries will be presented within either PK population or as-treated population depending on the endpoint, unless specifically stated otherwise.

Nirsevimab serum concentrations and serum PK parameters will be summarized using descriptive statistics (e.g., n, arithmetic mean, SD, geometric mean, geometric SD, geometric coefficient of variation (CV%) minimum, median, and maximum).

The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The geometric CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. For T_{max} only n, median, minimum, and maximum will be reported.

Individual PK concentration versus actual time plots will be presented on linear and semi-log scales. Mean PK concentration versus scheduled sampling time plots will also be presented on linear and semi-log scales.

- All serum concentration data will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes both in the summary tables and by-subject listings. For the calculation of descriptive statistics and the statistical analysis, rounded PK parameter values as presented in the data listings will be used. For derived PK parameters, C_{max} will be reported and analyzed with the same precision as the source data, others will be reported and analyzed with 2 decimal places.

Reporting of mean, SD, minimum, median, and maximum will follow the rounding convention of the individual PK variables. Coefficient of variation will always be reported to 1 decimal place.

3.3.1 General Study Level Definitions

3.3.1.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date (Day 1) is defined as the day on which the study medication is administered, and will appear in every listing where an assessment date or event date appears. There is no day 0 in this study.

- If the date of the assessment/event is on or after the reference start date then:

Study Day = (date of assessment/event – reference start date) + 1.

- If the date of the assessment/event is prior to the reference start date then:

Study Day = (date of assessment/event – reference start date).

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the mock-up tables, figures, and listings document. For example, where day or month is missing from the date recorded, but is required in the calculation of time to first dose, e.g. from first diagnosis or clinical laboratory tests, day and/or month will be imputed as 01 i.e. 1st of the month or 1st January. Otherwise no imputations will be made for any missing data, unless agreed by the study team. In the situation where the event date is partial or missing, the Study Day and any corresponding durations will appear partial or missing in the listings. If a date is partial, no imputation will be done except for adverse events (AEs).

3.3.1.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the administration of study treatment (including unscheduled assessments).

Additionally, baseline measurements of systolic, diastolic blood pressure and heart rate should come from the same assessment, and the average of two readings within schedule prior to dosing will be taken as a baseline.

Change from baseline will be defined as the post-baseline value minus the baseline value.

3.3.2 Analysis Visit Window

For the visit-based summaries for PK, ADA, vital signs, and clinical laboratory data, the summaries will be based on the scheduled days with adjusted analysis visit windows. The analysis visit windows will be based on the collection schedule listed in the protocol and summaries will be windowed to the closest scheduled visit for those data. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. However, all data will be included in the listings. If multiple readings are recorded within a single analysis visit window, the following rules will apply:

- If there are 2 or more valid, non-missing observations within the same visit window, and
    - if they are on different days, then the non-missing one which is closest to the scheduled visit day will be used in the analysis.

- if 2 or more valid observations are on different days but equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.

- if 2 or more valid, non-missing observations are on the same day which is closest to the scheduled visit day, and have a different assessment time, then the earlier one will be used in the analysis.

- For the visit-based summaries for ADA, if both ADA positive and negative samples are available within a subject's visit, ADA positive will be reported.

- If a visit window does not contain any observations, then the data will remain missing.

The detailed analysis visit windows are summarized between table 1 to table 4 as below:

Table 1. The detailed analysis visit windows for PK:

Scheduled Study Day	Scheduled time relative to dosing	Analysis Windows
Day 1 (pre-dose)	Pre-dose	Any time prior to dosing
Day 2	24 h (1 day)	±2h
Day 4	72h (3 days)	±4h
Day 6	120 h (5 days)	±6h
Day 8	168 h (7 days)	±8h
Day 15	14 days	±1d
Day 31	30 days	±2d
Day 91	90 days	±5d
Day 151	150 days	±10d

Table 2. The detailed analysis visit windows for vital signs:

Scheduled Study Day	Analysis Windows
Day 1 (post-dose)	Study Day = 1
Day 2	2 ≤ Study Day ≤ 3
Day 6	4 ≤ Study Day ≤ 10
Day 15	11 ≤ Study Day ≤ 22
Day 31	23 ≤ Study Day ≤ 60
Day 91	61 ≤ Study Day ≤ 120
Day 151	121 ≤ Study Day

Table 3. The detailed analysis visit windows for ADA:

Scheduled Study Day	Analysis Windows
Day 1 (pre-dose)	Study Day = 1
Day 31	2 ≤ Study Day ≤ 60
Day 91	61 ≤ Study Day ≤ 120
Day 151	121 ≤ Study Day

Table 4. The detailed analysis visit windows for clinical lab assessment:

Scheduled Study Day	Analysis Windows
Day 6	2 ≤ Study Day ≤ 10
Day 15	11 ≤ Study Day ≤ 22
Day 31	23 ≤ Study Day ≤ 60
Day 91	61 ≤ Study Day

3.3.3 Handling of Unscheduled Visits, Retest and Early Discontinuation Data

Any data collected at unscheduled visits, retest or early discontinuation assessments will be listed, and will be included in any definitions of maximum value, minimum value or last value within the relevant study period.

Measurements collected from unscheduled visits, retest or early discontinuation assessments may also be considered in the analysis visit window. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or retest assessment within the same visit window, the non-missing value at the unscheduled/retest assessment will be used.

3.3.4 Multiplicity/Multiple Comparisons

No adjustment for multiplicity will be performed.

3.3.5 Handling of Protocol Deviations in Study Analysis

Important protocol deviations (IPDs) will be listed and tabulated in the Clinical Study Report (CSR). IPDs are defined as deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. They may include but not be limited to:

- Subjects who do not meet the inclusion criteria
- Subjects who meet any of the exclusion criteria
- Subjects who use one or more disallowed medication (for any reason, unless otherwise specified) during the treatment period
- Subjects who received the incorrect IP or study dose

IPD in this study will include, please refer to Protocol Deviations Management Plan (PDMP) table 2: list of potential protocol deviations. All important protocol deviations will be identified and documented prior to unblinding of the data.

In addition, COVID-19 related protocol deviations and issues will be captured for reporting.

3.3.6 Handling of missing data

No imputations will be made for any missing data. In the case where prior or concomitant medication start/end dates are partial, but are required in the calculation of administration time of the study medication, temporary imputed variable(s) will be set to the earliest/latest possible date for medication start/end dates respectively. Partial dates handling rules of AEs are described in Appendix 1. All available dates without imputation will be listed.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history (including surgical history), prior and concomitant medication, and study drug exposure.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

All subjects who were screened will be used for reporting of disposition. The number of subjects screened, screen failures with justifications will be summarized using all subjects enrolled; the number and percentage of subjects randomized, subjects who received treatment, subjects who completed the study, and subjects who discontinued from the study will also be summarized by treatment group.

4.1.1.2 Presentation

A summary table will be presented specifying respectively:

- Number of subjects screened
- Number of subject screened but not randomized
    - Reasons for screened but not randomized
        - Did not meet inclusion/exclusion criteria

  - Lost to follow-up
  - Withdrawal of consent
  - Other (Include withdrawal due to limited number of subjects for randomized)

- Number of subjects randomized
- Number of subjects who received study treatment
- Number of subjects randomized but not received study treatment
- Number of subjects who completed the study
- Number of subjects who discontinued from the study
  - Reasons for discontinuation from the study
    - Death
    - Lost to follow-up
    - Withdrawal by Subject
    - Pregnancy
    - Adverse event
    - Sponsor decision
    - Other
    - Due to COVID-19 pandemic

4.1.2 Analysis Sets

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the database lock (DBL).

4.1.2.1 Definitions and Derivations

Analysis sets will be summarized by treatment group for participants randomized. The number of participants included or excluded (and reason) from an analysis set within each treatment group will be presented.

4.1.2.2 Presentation

Summary of analysis populations will be provided. Participants excluded from any analysis population will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Protocol deviations will be reviewed on a case-by-case basis by the medical advisors and statisticians prior to unblinding. The Statistical Analysis Plan may be revised due to these reviews.

4.1.3.2 Presentation

The numbers and the percentages of subjects with each important protocol deviations will be presented for as-treated population. Only subject level protocol deviations will be listed for as-treated population. In addition, issues reported due to COVID-19 pandemic, regardless of whether the type of issue is considered a protocol deviation or not, will be listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic data will be summarized for as-treated population. No statistical testing will be carried out for demographic or other baseline characteristics.

Following demographic will be reported for this study:

- Age (years) - calculated relative to date of consent
  - Age (years) = (Date informed consent signed– Date of Birth)/365.25.
- Sex:
  - Male
  - Female
- Ethnicity:
  - Not Hispanic or Latino
  - Hispanic or Latino
- Race
  - Asian
  - Other

4.1.4.2 Presentation

Continuous data will be summarized using number of observations (n), mean, SD, median, minimum, maximum for non-missing observations; categorical data will be summarized using frequency counts and percentages for non-missing observations.

Listings of subjects' demographic will be provided.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics will be summarized for as-treated population.

Following baseline characteristics will be reported for this study:

- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)
  - BMI (kg/m2) = weight (kg)/ (height (m))^2

4.1.5.2 Presentation

Continuous data will be summarized using number of observations (n), mean, SD, median, minimum, maximum for non-missing observations.

Listings of subjects' baseline characteristics will be provided.

4.1.6 Medical and Surgical History

4.1.6.1 Definitions and Derivations

Medical History and Surgical History information are collected in "Medical history" and "Surgical History" CRF page and will be summarized and listed for as-treated population.

Medical history and Surgical history will be summarized by using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.1 or higher codes of System Organ Class (SOC) and Preferred Term (PT).

4.1.6.2 Presentation

Numbers and percentages of subjects will be presented by treatment group for each System Organ Class (SOC) and Preferred Term (PT). If a medical history or surgical history condition occurs more than once for a subjects per level of summarization the subjects is only counted once per MedDRA SOC or PT. SOCs are to be sorted by total decreasing frequency. PTs are to be sorted by total decreasing frequency within each SOC. If SOCs or PTs have the same total frequency they are to be sorted alphabetically.

4.1.7 Allergy History

4.1.7.1 Definitions and Derivations

Allergy History information are collected in “Allergy History” CRF page.

4.1.7.2 Presentation

Subjects will be listed for as-treated population.

4.1.8 Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior and concomitant medication data will be captured from “Concomitant Medications” page on CRF. Medications will be coded using the World Health Organization (WHO) Drug Dictionary Global September 2020 B3 or higher. The number and percentage of subjects with prior and concomitant medications will be tabulated by Anatomic Therapeutic Chemical (ATC) level 4 and Drug Preferred Name by treatment arm. Any disallowed concomitant medications taken during study treatment will also be tabulated.

Prior medications are defined as medications which started and stopped prior to the administration of study treatment. Concomitant medications are defined as medications which are taken on or after the administration of study treatment (reference start date).

Subjects taking the same medication multiple times in a given study period will only be counted once for each term in the drug dictionary hierarchy being presented.

4.1.8.2 Presentation

The number and percentage of subjects experiencing each prior and concomitant medication will be presented by ATC/PT by treatment for the as-treated population. ATC terms are to be sorted by total decreasing frequency. PTs are to be sorted by total decreasing frequency within each ATC. If ATCs or PTs have the same total frequency they are to be sorted alphabetically.

4.1.9 Study Drug Exposure and Compliance

4.1.9.1 Definitions and Derivations

Extent of exposure to IP is defined as the number of days between the start and the end dates of study drug. As there is only a single dose for nirsevimab, extent of exposure will be presented as Yes/No.

Exposure

- The answer for the question "Treatment" as entered into the “Dose” eCRF page will be used to identify extent of exposure.

4.1.9.2 Presentation

The number (%) of subjects will be summarised across all subjects by treatment with the following variables for as-treated population.

- Number (%) of subjects who take complete dose.
- Number (%) of subjects who take incomplete dose.
- Overdose Occurrence
- Medication Error Occurrence

4.1.10 Procedures

4.1.10.1 Definitions and Derivations

Procedures data will be captured from "Procedures" page on CRF.

4.1.10.2 Presentation

Subjects will be listedforas-treated population.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary and secondary analyses.

Table 5. Objectives and Endpoints:

Statistical category	Endpoint	Population	Details in section
To evaluate serum concentrations of nirsevimab	Summary of nirsevimab serum concentrations	PK population	4.2.1
	Estimated PK parameters (Cmax, Tmax, AUC0-150, and others if data permit)	PK population	4.2.1
To evaluate the safety and tolerability of nirsevimab when administered as a single fixed IM dose of 300 mg to healthy Chinese adult subjects	Occurrence of all TEAEs, TESAEs, AESIs, and NOCDs	As-treated Population	4.2.2
	Clinical laboratory assessments	As-treated Population	4.2.2
	Vital signs	As-treated Population	4.2.2
To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum	As-treated Population	4.2.2

4.2.1 Primary Endpoint

4.2.1.1 Definition

This section covers details related to pharmacokinetics endpoints and analyses.

Pharmacokinetic analysis of the serum concentration data for nirsevimab will be performed at IQVIA, Overland Park, Kansas, United States. Pharmacokinetic parameters will be derived using standard noncompartmental methods using Phoenix WinNonlin® 8.1 or higher (Pharsight Corp., Certara Company, Princeton, New Jersey, United States); and/or SAS® Version 9.4 or higher. Graphics will be prepared with SAS® Version 9.4, or higher. Actual elapsed sampling times, if available, will be used for the final PK parameter calculations.

The PK concentration, collection time and collection time deviation will be presented in one listing. Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will not be included in the summary tables, but will be included in subject listings.

Concentration-time data will be summarized by scheduled time.

Samples that are collected outside the analysis visit windows will be flagged for identification in the listing. They will not be included in the concentration summary.

Figures of arithmetic mean (±SD) serum concentrations versus nominal time will be prepared on linear and semi-logarithmic scales. Figures of individual serum concentrations versus actual time will be presented by subject on linear and semi-logarithmic scales.

Calculation or derivation of pharmacokinetic variables

The PK analysis will be performed using the PK population.

Where possible, the following serum PK parameters will be determined for nirsevimab using the serum concentration data.

C_{max}	Observed maximum serum concentration (µg/mL), taken directly from the individual concentration-time curve
T_{max}	Time to reach maximum serum concentration (day), taken directly from the individual concentration-time curve
$AUC_{0\text{-}150}$	Area under the serum concentration-curve from time zero to 150 days, calculated by linear up/log down trapezoidal summation

Additional calculations may be performed at the discretion of the PK scientist as appropriate.

4.2.1.2 Presentation

Pharmacokinetic parameters will be summarized using descriptive statistics as described in Section 3.3. A subject listing of individual PK parameters will also be provided.

4.2.1.3 Handling of BLQ and Missing Values

Individual concentrations which are BLQ will be reported as not quantifiable (NQ) with the lower limit of quantitation (LLOQ) defined in the listings, tables, and figures as appropriate. Any missing values reported as no sample (NS) will be excluded from the summary tables and corresponding figures.

For descriptive statistics:

- if, at a given time point, 50% or less of the plasma concentrations are NQ, the Gmean, CV, Geometric SD, Gmean ± gSD, arithmetic mean and SD are calculated by substituting the LLOQ for values which are NQ
- if more than 50%, but not all, of the concentrations are NQ, the Gmean, CV, Geometric SD, Gmean ± gSD, arithmetic mean, and SD are reported as not calculable (NC). The max value will be reported from the individual data, and the min and median will be set as NQ
- if all the concentrations are NQ, no descriptive statistics will be calculated for that time point. The Gmean, arithmetic mean, median, minimum, and maximum are reported as NQ and the CV, Geometric SD, Gmean ± gSD, and SD as NC
- The number of values below LLOQ are reported for each time point along with the total number of collected values

Three observations ≥LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC.

For graphical presentation, postdose BLQ values will be set to ½ of LLOQ values for individual plots. For mean plots, BLQ values will be handled as described for concentration descriptive statistics.

For PK analysis, predose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of PK parameters. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed, listed, and included in all summaries if the anomalous value is not greater than 5% of C_{max}. If the anomalous value is greater than 5% of C_{max}, PK parameters will be calculated and listed, but affected profiles

will be excluded from summaries for both the observed concentrations and derived PK parameters. Handling of affected profiles will be documented in the PK analysis review form with a description of how the value was treated for the computation, and in the clinical study report.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing. If BLQ values occur at the end of the collection interval (after the last quantifiable concentration), these will be set to missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

No imputations will be made for any dropouts and missing data.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

4.2.2.1.1 Adverse events

Adverse Events

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. AEs will be collected from the time of signature of informed consent through Day 151.

Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) will be defined as an AE with the start date on or after the administration date, and up to Day 151.

Serious Adverse Events

AEs and SAEs will be collected from the time of signature of informed consent through Day 151.

Treatment-Emergent Serious Adverse Events

A treatment-emergent serious adverse event (TESAE) will be defined as a SAE with the start date and time on or after the administration date and time, and up to Day 151.

Adverse Events of Special Interest

The occurrence of AESIs defined as AEs of anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), or thrombocytopenia following investigational product administration. The SMQ broad and narrow for anaphylaxis, SMQ narrow for hypersensitivity and PT for thrombocytopenia and immune complex disease will be used to extract AESI terms.

New Onset Chronic Disease

An NOCD is a newly diagnosed medical condition that is of a chronic, ongoing nature. It is observed after receiving the investigational product and is assessed by the Investigator as medically significant. Examples of NOCDs include, but are not limited to diabetes, autoimmune disease (eg, lupus, rheumatoid arthritis), and neurological disease (eg, epilepsy). Events that would not be considered as NOCDs are mild eczema, diagnosis of a congenital anomaly present at study entry, or acute illness (eg, upper respiratory infection, otitis media, bronchitis).

4.2.2.1.2 Clinical Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP, and will be assessed in local lab. The parameters outlined in Section 4.3.2 of the CSP, will be collected. Laboratory data will be reported in SI units.

4.2.2.1.3 Vital Signs

Vital signs (temperature, blood pressure, respiration rate, and heart rate measurements) will be collected at screening visit (Day -28 to Day -2), Day -1 and on Day 1 as defined in Table 4 and Table 5 of the CSP. Refer to Table 6 of the CSP for the timings of assessments during the follow-up period.

4.2.2.1.4 ADA

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in the CSP (Section 4.2.2). ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. The impact of ADA on PK, and association with TEAEs and TESAEs will be assessed, if data permit. The number of patients in the as-treated population (defined in Section 3.2) who fulfil the following the criteria will be determined. The percentage of ADA-positive patients in each of the category will be calculated, using the number of patients in the as-treated population of the treatment group as the denominator. A patient is defined as being ADA positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative.

- ADA positive at any visit; the percentage of ADA-positive patients is known as ADA

prevalence.
- The sum of both treatment-induced and treatment-boosted ADA; the percentage of patients fulfilling this criterion is known as ADA incidence.
- ADA positive post-baseline and positive at baseline.
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA).
- ADA not detected post-baseline and positive at baseline.
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration.
- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or an ADA positive result at the last available assessment. The category includes patients meeting these criteria who are ADA negative at baseline.
- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The category includes patients meeting these criteria who are ADA negative at baseline.
- nAb prevalence, defined as the proportion of nAb positive at any point in time, baseline or post-baseline (remove if not needed)
- anti-YTE prevalence, defined as the proportion of anti-YTE positive at any point in time, baseline or post-baseline (remove if not needed)
- nAb incidence, defined as the proportion of nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visits (remove if not needed)
- anti-YTE incidence, defined as the proportion of anti-YTE negative at baseline (or ADA negative at baseline) and anti-YTE positive at any post-baseline visits (remove if not needed)

4.2.2.2 Derivations
Not applicable.

4.2.2.3 Handling of Dropouts and Missing Data
No imputations will be made for any dropouts and missing data.

The imputation for partial start dates of AEs detail, please refer to the Appendix 1.

4.2.2.4 Primary Analysis of Secondary Endpoint
Safety endpoints include:

- Occurrence of all treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs).

- Clinical laboratory assessments, vital signs.

ADA endpoints will be summarized as incidence of ADA to nirsevimab in serum.

The primary analysis of secondary endpoints will be summarized by number and percentage for qualitative variables, using the as-treated population. Quantitative variables will be summarized by subjects (n), mean, SD, median, minimum and maximum. Those variables details are described below:

Adverse Events
All AEs will be coded using MedDRA version 23.1 or higher by system organ class and preferred term. Specific AEs will be counted once for each subject for calculating rates but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. AEs will be captured on CRF page "Adverse Event".

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarized descriptively by count (n) and percentage (%) for each treatment group. The current MedDRA dictionary will be used for coding. The majority of the AE summaries, unless stated otherwise, will be based on TEAEs. Any AE occurring before study treatment (i.e. before the administration of the first dose on Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first dose on Study Day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the majority of summary tables.

Treatment-Emergent Adverse Events
All TEAEs will be summarized overall and by MedDRA system organ class and preferred term, severity, and relationship to investigational product.

Severity is classed according to NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, grade 1-5. Severity will be presented as Grade 1 to 5 (increasing severity), which corresponds to the 5 classes. TEAEs of each severity grade will be summarized by SOC/PT.
If a subject reports the same TEAE more than once within that SOC/ PT, the TEAE with the worst case severity and causally related to the product will be used in the corresponding severity and causally related to the product summaries.

Serious Adverse Events
Serious adverse events (SAEs) are recorded in the "Adverse Events" CRF page with answer "Yes" to question "Serious" and Serious Adverse Event Report page. A summary of SAEs by SOC and PT will be prepared.

Treatment-Emergent Serious Adverse Events

A summary of TESAEs by SOC and PT will be provided.

Presentation
All reported AEs will be listed along with SAE or not indicator, action taken, and outcome of AE, AE start date (study day), AE stop date (study day), duration and investigator's assessment of severity and relationship to study drug.

The following summary tables will be presented:

- any TEAE,
- any IP related (assessed by the investigator) TEAE,

The answer for the question "Relationship, investigational product" as entered into the CRF will be used to identify any IP related TEAE.

In the case that a subject report multiple TEAEs within the same PT, the TEAE with strongest relationship will be used in the corresponding summaries.

- any TEAE with CTCAE grade 3 or higher,

The answer for the question 'AE Severity grade' as entered into the eCRF will be used to identify TEAE of CTCAE grade 3 or higher.

- any IP related TEAE of CTCAE grade 3 or higher,
- any IP related TEAE,

The answer for the question 'Outcome of AE' as entered into the eCRF will be used to identify outcome of TEAE.

- any TESAE,
- any TESAE with outcome fatal,
- any IP related TESAE,

The answer 'Yes' for the question 'Serious' as entered into the eCRF will be used to identify TESAE.

- any TEAE of special interest based on investigator assessment.

Summary information (the number and percent of subjects by system organ class and preferred term separated by treatment group) will be tabulated. If a TEAE condition occurs more than once for a subjects per level of summarization the subjects is only counted once

per MedDRA SOC or PT. SOCs are to be sorted by total decreasing frequency. PTs are to be sorted by total decreasing frequency within each SOC. If SOCs or PTs have the same total frequency they are to be sorted alphabetically.

- Summary of number (%) of subjects who had at least 1 TEAE by PT.
- Summary of number (%) of subjects who had at least 1 TEAE by PT, arranged by SOC.
- Summary of number (%) of subjects who had at least 1 TEAE by PT presented by maximum reported CTCAE grade.
- Summary of number (%) of subjects who had at least 1 TEAE with CTCAE grade 3 or higher by SOC and PT.
- Summary of number (%) of subjects who had at least 1 IP related TEAE by SOC and PT.
- Summary of number (%) of subjects with TESAEs by PT, arranged by SOC. In addition, a data listing of key information for TESAEs will be presented.
- Summary of number (%) of subjects who had at least 1 IP related TESAE by SOC and PT.

Adverse Events of Special Interest

AESIs will be collected from the time of dosing through Day 151 and will be recorded on the "Adverse Events" CRF page with the answer "Yes" to the question "Adverse Events of Special Interest".

A summary of number (%) of subjects with an AESI will be produced.

- Summary of number (%) of subjects who had at least 1 AESI by PT, arranged by SOC.

New Onset Chronic Disease

NOCDs will be collected from the time of dosing through Day 151 and will be recorded on the "Adverse Events" CRF page with the answer "Yes" to the question "Is this New Onset Chronic Disease?" and the "New Onset Chronic Disease" page.

A summary of number (%) of subjects with an adverse event of NOCD will be produced.

- Summary of number (%) of subjects who had at least 1 NOCD by PT, arranged by SOC.

Skin Reaction

Skin reactions will be collected from the time of dosing through Day 151 and will be recorded on the "Adverse Events" CRF page with the answer "Yes" to the question "Is this Skin Reaction?" and the "Skin Reactions" page.

A summary of number (%) of subjects with skin reaction will be produced.

- Summary of number (%) of subjects who had at least 1 skin reaction by PT, arranged by SOC.

Deaths

If any subjects die during the study, relevant information will be captured on "Serious Adverse Event Report", "End of Study" and "Statement of Death" CRF pages. All death results will be listed.

Clinical Laboratory, Blood Sample

Frequencies of worst observed Grade 3-4 toxicity, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), will be presented for each laboratory parameter by treatment group. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline as well as descriptively over time. Safety of nirsevimab will also be assessed and measured by the summary of serum chemistry and hematology through 150 days postdose.

All laboratory safety data, incorporating serum chemistry and hematology data will be listed for each subject and summarized where appropriate. Serum chemistry and hematology values outside the standard reference ranges will be highlighted in the listings.

Numerical laboratory data (absolute and change from baseline) will be summarised by scheduled study day using standard summary statistics (mean, SD, minimum, Q1, median, Q3, maximum, and number of subjects).

Shift tables for laboratory values by CTCAE 2-grade or greater will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- For Haematology, Hemoglobin, Platelets Count, Neutrophils, Lymphocytes and Leukocytes with CTCAE grading will be provided. Eosinophils, Basophils, Monocytes and Hematocrit will not have CTCAE grading.

- For Chemistry, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatas, Creatinine, Total bilirubin, Sodium, Potassium Gamma-Glutamyltransferase, and Glucose with CTCAE grading will be provided. Calcium, Urea will not have CTCAE grading.

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on-treatment will be provided.

Clinical Laboratory, Urinalysis

Results from the laboratory will be included in the reporting of this study for urinalysis. A list of laboratory assessments included in the outputs can be found in the protocol section 4.3.2.

Frequencies of worst observed Grade 3-4 toxicity, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), will be presented for each laboratory parameter by treatment group. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline as well as descriptively over time. Safety of nirsevimab will also be assessed and measured by the summary of urinalysis through 150 days postdose.

Urinalysis data will be listed for each subject and summarized where appropriate. Urinalysis values outside the standard reference ranges will be highlighted in the listings.

Numerical laboratory data (absolute and change from baseline) will be summarised by scheduled study day using standard summary statistics (mean, SD, minimum, Q1, median, Q3, maximum, and number of subjects).

Shift tables for laboratory values by CTCAE 2-grade or greater will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Protein with CTCAE grading will be provided. pH, Bilirubin, Blood, Specific Gravity, Ketone Bodies (Urine), Color (Urine), Appearance (Urine), RBC/HPF and WBS/HPF will not have CTCAE grading.

Other Laboratory Evaluations

Results from the laboratory will be included in the reporting of this study for pregnancy test and other safety tests. A list of laboratory assessments included in the outputs can be found in the protocol section 4.3.2.

For clinical laboratory assessments, changes in haematology and clinical chemistry variables between baseline and each subsequent on-treatment assessment will be calculated.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). Two shift tables will be presented:

- Baseline to highest value post-baseline

- Baseline to lowest value post-baseline

For laboratory values which fall below the lower limit of quantification such that the result is of the form "<xx", the value will be imputed to be "xx" for the purpose of calculating descriptive statistics in the tables. The original value of "<xx" will still be presented in the listings.

The pregnancy test will be listed subjects whose result is negative or positive.

Vital Signs
The following vital signs measurements will be reported for this study:

Vitals:
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (BPM)
- Respiratory Rate (resp/min)
- Temperature (ºC)
- Temperature location
  - Oral
  - Tympanic
  - Rectal
  - Axillary
  - Temporal

Vital signs data obtained up until the 151 day safety follow-up visit will be included in the summary tables. Vital sign values and change from baseline (applicable to post baseline measurements) will be summarized by each scheduled time-point. All observed vital signs results will be listed. Worst post-baseline increase is defined as maximum increase compared to baseline, and worst post-baseline decrease is defined as maximum decrease compared to baseline. Both worst changes will be listed as well.

The denominator in vital signs data should include only those subjects with recorded data.

Vital Signs will be presented by treatment group. Systolic and diastolic BP, pulse rate, respiratory rate and temperature will be listed by subject and summarised using standard summary statistics (mean, SD, minimum, Q1, median, Q3, maximum, and number of subjects) for the observed value and change from baseline at each scheduled study visit.

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Parameter	Unit	Lower limit	Upper limit
Diastolic blood pressure	mmHg	60	90
Systolic blood pressure	mmHg	90	140
Pulse rate	Beats/min	50	100
Body temperature	Celsius	36.0	37.5
Respiratory rate	Breaths /min	8	20

Pregnancy

Pregnancy information are collected in "Pregnancy Test Urine" and "Pregnancy Report" CRF page and will be listed for as-treated population.

Increased Liver Biochemistry and Evaluation of Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin (TBL) ≥ 2 × ULN may need to be reported as SAEs.

A potential Hy's Law (PHL) case is defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

A Hy's Law (HL) case is defined as AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For potential Hy's Law and Hy's Law, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur. Liver biochemistry data are collected in "Liver Diagnostic Investigations", "Liver Signs and Symptoms" and "Liver Risk Factors/Life Style Events" CRF page.

Hy's Law data are collected in "Local Lab Hy's law" CRF page.

Liver related information and Potential Hy's Law and Hy's Law will be listed by subjects for as-treated population.

ADA

The incidence of ADA to nirsevimab will be assessed and summarized by number and percentage of subjects who are ADA positive. The impact of ADA on PK, and association with TEAEs and TESAEs will be assessed, if data permit. For ADA summarization details, please refer to 4.2.2.1.4 section.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 REFERENCES

CTCAE v5.0 2017
Common Terminology Criteria for Adverse Events Version 5.0 2017. Available from URL: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

7 APPENDIX

Partial Date Convention

The detail imputation for partial start dates of AEs as below:

- Partial AE start dates where only the year is known:
  - If year is different from the year of dose date, assume January 1:
  - If year is same as the year of dose date:
    - Assume (dose date + 1 day) if AE started ≤ 7 days after dosing
    - Assume (dose date + 7 days) if AE started 8 to 14 days after dosing
    - Assume (dose date + 14 days) if AE started > 14 days after dosing
    - Assume (dose date + 1 day) if range of days started after dosing was not selected
- Partial AE start dates where only the month and year are known:
  - If year and/or month are different from the year and/or month of dose date, assume first day of the month
  - If year and month are the same as the year and month of dose date:
    - Assume (dose date + 1 day) if AE started ≤ 7 days after dosing

  - Assume (dose date + 7 days) if AE started 8 to 14 days after dosing
  - Assume (dose date + 14 days) if AE started > 14 days after dosing
  - Assume (dose date + 1 day) if range of days started after dosing was not selected

- If AE stop date is partially missing, assume December 31 if only the year is known; assume end of the month if only the year and the month are known.

If AE onset date is completely missing, then it will be counted as treatment-emergent AE (TEAE).

Imputed dates will NOT be presented in the listings.

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