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

Sponsor Protocol Number: D5290C00007

Investigational Product: Nirsevimab (MEDI8897)

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Protocol History, Date: Amendment 1, 04Dec2020
Replacing Original Protocol, 07Jun2020

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	04Dec2020
Original Protocol	07Jun2020

Amendment 1: 26 November 2020

This non-substantial amendment is executed due to Sponsor's decision to adjust operational settings according to the suggestions from study site. The changes are made before study initiation.

Overall Rationale for the Amendment:

Changes are made to adapt to the feasibility of operation at the study site. Additional clarifications regarding procedures are also added to facilitate the operation. The amendment also includes the correction of inconsistencies throughout the document that have been identified since the finalization of the original clinical study protocol.

Protocol D5290C00007 Amendment 1-List of changes:

Section # and Name	Description of Change	Brief Rationale	Substantial (Yes/No)
Section 3.1.1 Overview, Figure 1	To correct days in Figure 1 for PK sampling	To correct days for PK sampling to be consistent with Section 4.2	No
Section 4.1.2 Inclusion Criteria	To add description of "(the day of investigational product administration)" in inclusion criterion No.4	To clarify the inclusion criteria for definition of Day 1	No
Synopsis, Section 4.1.2 Inclusion Criteria	To revise the upper limit of body mass index (BMI) for inclusion from 24 kg/m^2 to 26 kg/m^2 in inclusion criterion No.5, and relative description in the synopsis	To revise the inclusion criteria due to feasibility considerations	No
Section 4.1.2 Inclusion Criteria	To add description of "as judged by the Investigator " in inclusion criterion No.8	To clarify the inclusion criteria for enrollment of subjects according to subjects' ECG readout will be judged by the Investigator	No
Section 4.1.3 Exclusion Criteria	To revise exclusion criterion No.6 to "Receipt of any investigational drug therapy within 120 days prior to investigational product dosing or planned to receive any investigational drug therapy	To clarify that it is the "planned" activity to be prevented	No

Section # and Name	Description of Change	Brief Rationale	Substantial (Yes/No)
	within 150 days after investigational product dosing"		
Section 4.1.3 Exclusion Criteria	To update exclusion criteria No. 16 to "Evidence of infection (ie, positive laboratory test result) with hepatitis A, B, or C virus, syphilis or human immunodeficiency virus."	Revision made to add evidence of syphilis infection as one of the exclusion criteria due to high incidence rate in China	
Section 4.1.3 Exclusion Criteria	To revise the laboratory assessments result limits in exclusion criterion No.17. White blood cell count from $< 4 \times 10^9$/L to $< 3.5 \times 10^9$/L; platelet count from $< 140 \times 10^9$/L to $< 120 \times 10^9$/L	To revise the exclusion criteria according to the actual normal range set by study site	No
Section 4.1.3 Exclusion Criteria	To remove "barbiturates" from exclusion criteria No. 17 e)	Revision made according to commonly used urine drug screen test at site, considering the overall low prevalence of barbiturates abuse in China	
Section 4.1.5 Withdrawal from the study	To delete the statement "Subjects who have not received investigational product, regardless of reason, will not be followed."	Revision made to match the actual operation procedure	No
Section 4.2 Schedule of Study Procedures	To update study procedures on Day -1 and pre-dose on Day 1, added admission/discharge and revised footnotes for Table 4, Table 5 and Table 6 accordingly	Revision made on schedule of study procedures to include 2 overnight stays at study site for easier operation and to obtain better compliance	No
Section 4.2.1 Enrollment/Screening Period and Section 4.3.2 Clinical Laboratory Tests	To revise the assessment of "HIV-1" to "HIV" at screening to clarify both HIV-1 and HIV 2 antibodies will be tested.	Revision made to match the actual operation procedure as both HIV-1 and HIV-2 will be tested	No
Section 4.2.2 Treatment and Follow-up Periods	To add the statement of "Randomization should occur before blood sampling" as footnote b in Table 5	Revision made to clarify the procedure of blood sample collection and randomization	No
Section 4.3.1 Medical History and Physical Examination, Height, Weight, and Vital Signs	To update timing of study procedures described in the section	Revision made to be consistent with updated schedule of study procedures due to added overnight stay	No
Section 4.3.1 Medical History and Physical Examination, Height, Weight, and Vital Signs	To revise the title of Section 4.3.1 from "Medical History and Physical Examination, Height, Weight, and Vital Signs" to "Medical History, Physical	Revision made to match the actual operation procedure	No

Section # and Name	Description of Change	Brief Rationale	Substantial (Yes/No)
	Examination, Height, Weight, Vital Signs and ECG"		
Section 4.3.1 Medical History and Physical Examination, Height, Weight, and Vital Signs	To add the description of "(for any new findings since screening)"	Revision made to clarify the procedure of medical history collection on Day -1	No
Section 4.3.1 Medical History and Physical Examination, Height, Weight, and Vital Signs	Revised the sentence "The physical examination will include assessment of height and/or weight as noted in Table 4 and Table 5" to "The height and/or weight will be assessed as noted in Table 4"	Revision made for clearer instruction	No
Section 4.3.1 Medical History and Physical Examination, Height, Weight, and Vital Signs	To add the following description of ECG procedures: At Screening, 12-lead ECG will be obtained after 5 minutes supine rest and prior to blood draw. Skin must be cleaned, and electrodes should be positioned according to standard 12-lead ECG placement. All 12-lead ECGs will be recorded and evaluated by the Investigator. The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not. The reason for the abnormality will be recorded in the eCRF. These ECGs will be documented in the eCRF by recording date, time, heart rate, overall assessment as normal and abnormal, and whether the abnormality is clinically significant or not. All ECGs will be documented by recording date, time of collection, heart rate, PR, RR, QRS, and QT intervals from the 12-lead ECG. If indicated additional 12-lead ECG assessments can be made at the discretion of the Investigator. These assessments should be entered as an	To add the description of ECG procedures at screening for clear instruction	No

Section # and Name	Description of Change	Brief Rationale	Substantial (Yes/No)
	unscheduled assessment in the appropriate eCRF.		
Section 4.3.2 Clinical Laboratory Test	To update timing of serum pregnancy test to Day -28 to Day -2 and urine pregnancy test to Day -1	Revision made to be consistent with Table 4 and Table 5	No
Section 4.3.2 Clinical Laboratory Test	To delete the sentence "if positive, confirmatory testing will be performed using hepatitis C virus polymerase chain reaction" and "if positive, confirmatory testing will be performed using HIV western blot" To add syphilis test during screening period To remove barbiturates from "other safety tests"	Deletion made to match the actual operation procedure. Any positive test result at screening will meet the exclusion criteria and no confirmatory test will be done. To add syphilis test according to site requirement due to high incidence in China. To remove barbiturates according to commonly used urine drug screen test at site, considering the overall low prevalence of barbiturates abuse in China	No
Section 4.5.1 Identification of Investigational Products	To revise "investigational product" to Nirsevimab" in the description under Table 7.	To clarify Nirsevimab storage requirement and packaging information	
Section 4.5.1.3 Treatment Administration	To revise the administration instruction of investigational product to "Investigational product (nirsevimab or placebo) should be administered IM in the central area and thicker portion of the deltoid" with more detail description	To add the description of treatment administration for clearer instruction	No
Section 4.5.1.3 Treatment Administration	To update to "approximately 1 inch" and add the description of "(2.54 cm)" following the original description of 1 inch	To specify the estimation of distance between injection sites using units (cm) adopted by study site	No
Section 4.7.1 Permitted Concomitant Medications	To revise the description of "Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care." to "Investigators may prescribe concomitant medications or treatments which is considered necessary for the subject's safety and well-being."	Revision made for readability	No
Section 4.4 Study or Study Component Suspension or	To add (version 5.0) to address the version of National Cancer Institute Common Terminology	Clarify version of NCI CTCAE used and keep wording consistent with CTCAE 5.0.	No

Section # and Name	Description of Change	Brief Rationale	Substantial (Yes/No)
Termination and Section 4.8.4.2 Analysis of Clinical Laboratory Parameters Appendix B Additional Safety Guidance	Criteria for Adverse Events (NCI CTCAE) Update CTCAE grading general principles according to CTCAE 5.0.		
Section 5.5.3 Adverse Events Based on Signs and Symptoms	To revise the text "All AEs spontaneously reported by the subject or care provider or reported in response to the open question…" to "All AEs spontaneously reported by the subject or reported in response to the open question…"	Revision made as this is not applicable for the current study which enrolls healthy subjects	No
Section 5.5.4 Adverse Events Based on Examination and Tests	Add screening phase AE reporting clarification wording	Add clarification wording of AE reporting to keep GCP compliance and clinical feasibility	No
Section 6.5 Investigator Coverage	The title is changed to "Investigator Coverage" The text in Section 6.5 is revised to "Each subject will be provided with contact information for the Investigator. When a subject visits a medical facility and requires any medical care (medication or treatment), the treating physician or health care provider should contact the Principal Investigator (or designee Investigator who has knowledge of the investigational product and the clinical study protocol) before any treatment is given to the subject."	Revision made to match the actual operation procedure in China. Subject can either contact the Principle Investigator or designee Investigator.	No
Section 7.3 Informed Consent	To revise the text "Ensure that any incentives for subjects who participate in the study…" to "Ensure that any reimbursement for subjects who participate in the study…"	Revision made for readability	No

PROTOCOL SYNOPSIS

TITLE

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

HYPOTHESES

The primary and secondary research hypotheses are described below. No formal hypothesis is being tested statistically.

Primary Hypothesis

The pharmacokinetic (PK) profile of nirsevimab assessed up to 150 days after dose administration in Chinese subjects will be similar to subjects with different racial and ethnic backgrounds.

Secondary Hypothesis

A single dose of nirsevimab will be well tolerated in healthy Chinese adult subjects, with an acceptable safety profile. The incidence of antidrug antibody (ADA) to nirsevimab will be acceptable.

OBJECTIVES AND ASSOCIATED ENDPOINTS

Type	Objective	Endpoint
Primary		
PK	To evaluate serum concentrations of nirsevimab	Summary of nirsevimab serum concentrations and estimated PK parameters (maximum observed concentration [C_{max}], time to C_{max} [T_{max}], area under the concentration-time curve from time 0 to 150 days [AUC_{0-150}], and others if data permit)
Secondary		
Safety	To evaluate the safety and tolerability of nirsevimab when administered as a single fixed intramuscular (IM) dose of 300 mg to healthy Chinese adult subjects	• 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	To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum

STUDY DESIGN

Study D5290C00007 is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the PK, safety and tolerability, and ADA 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 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, PK, and ADA response.

TARGET SUBJECT POPULATION

Healthy male and female adult subjects aged 18 through 45 years with weight ≥ 45 kg and ≤ 110 kg and body mass index of 19 to 26 kg/m^2 at the time of screening.

TREATMENT GROUPS AND REGIMENS

Subjects will be randomly assigned to receive a single fixed IM dose of nirsevimab 300 mg (n = 18) or placebo (n = 6) on Day 1.

STATISTICAL METHODS

General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The PK Population will include all subjects who have received any dose of investigational product, and have at least one measurable post-dose 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). PK analyses will be based on the PK Population.

The As-treated Population will include all subjects who are randomized into the study and who receive any amount of investigational product. Subjects will be included in the treatment group corresponding to the treatment actually received. Safety and ADA analyses will be based on the As-treated Population.

Sample Size

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}, T_{max}, and $AUC_{0\text{-}150}$ between Chinese and non-Chinese adult subjects.

Pharmacokinetic Analyses

Serum concentrations of nirsevimab at selected time points will be evaluated to confirm that adequate exposures are maintained after dosing. Nirsevimab serum concentration data will be presented in descriptive statistics. Serum PK parameters such as C_{max}, T_{max}, and $AUC_{0\text{-}150}$ will be estimated using noncompartmental analysis and summarized with descriptive statistics. The estimated PK parameters from the adult Chinese subjects from this study will be compared for similarity with those obtained from non-Chinese adult subjects from the global Phase 1a Study D5290C00001. Notably, regression-dependent PK parameters such as $t_{1/2}$ and apparent systemic clearance will not be estimated due to the limited sampling up to 150 days which would require at least 40% extrapolation of the total area under the concentration-time curve from time 0 to infinity. Nonetheless, the predictability and consistency of the PK properties of nirsevimab, as demonstrated in 102 adults in the Phase 1a Study D5290C00001 and 984 infants in the Phase 1b/2a Study D5290C00002 and Phase 2b Study D5290C00003, support the hypothesis that the apparent clearance and other regression-dependent PK parameters should be similar if the C_{max}, T_{max}, and $AUC_{0\text{-}150}$ are shown to be similar.

Safety Analyses

All TEAEs will be summarized overall and by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, severity, and relationship to investigational product. In addition, summaries of deaths and TESAEs will be provided. Other safety assessments will include the occurrence of AESIs defined as adverse events of anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), or thrombocytopenia following investigational product administration, and the occurrence of NOCDs following investigational product administration.

Safety of nirsevimab will also be assessed and measured by the summary of clinical laboratory measurements (ie, serum chemistry, hematology, and urinalysis) through 150 days postdose.

Antidrug Antibody Analyses

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.

Interim Analyses

No interim analyses are planned.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{0-150}	area under the concentration-time curve from time 0 to 150 days
βhCG	beta human chorionic gonadotropin
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
C_{max}	maximum observed concentration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
GA	gestational age
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular(ly)
IRB	Institutional Review Board
IV	intravenous(ly)
IWRS	interactive web response system
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody

Abbreviation or Specialized Term	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOCD	new onset chronic disease
PK	pharmacokinetic(s)
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SID	subject identification
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
wGA	weeks gestational age
YTE	M257Y/S259T/T261E

1 INTRODUCTION

1.1 Disease Background

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) among infants and young children, resulting in annual epidemics worldwide (Jain et al 2015, PERCH 2019, Shi et al 2017). All children, including healthy term infants, are at risk for severe RSV lower respiratory illness with primary RSV infection during infancy. Ninety percent of children are infected with RSV in the first 2 years of life and up to 40% of those will have LRTI (Greenough et al 2001, Meissner 2003, Parrott et al 1973). RSV LRTI, characterized predominantly as bronchiolitis or pneumonia, represents a serious illness with acute and perhaps long-term consequences to the developing lungs in these young children (Blanken et al 2013). It is estimated that RSV causes up to 90% of childhood bronchiolitis and up to 40% of pediatric pneumonias (Hall 2001). In 2015, an estimated 33.1 million (uncertainty range, 21.6 to 50.3 million) new episodes of RSV-associated LRTI occurred worldwide in children < 5 years of age (28% of LRTI episodes), with approximately 3.2 million (range, 2.7 to 3.8 million) episodes necessitating hospitalizations, leading to 59,600 (range, 48,000 to 74,500) in-hospital deaths (Shi et al 2017).

Infants with severe LRTI may present with apnea, tachypnea, tachycardia, cyanosis, diminished breath sounds, wheezing, cough, nasal flaring, retraction, and listlessness. Poor gas exchange sets off a downward spiral in the infant's condition, including hypoxia, increased respiratory effort, decreased ability to maintain adequate oral intake, and dehydration (Coffmann 2009). In the United States (US), RSV bronchiolitis was the leading cause of hospital admissions for infants < 1 year of age for any reason between 1997 and 1999 (Leader and Kohlhase 2002). Most children hospitalized with RSV infection, including those with severe illness and requiring intensive care, were previously healthy term infants and without comorbid conditions, making it difficult to identify specific subgroups to target for RSV prophylaxis (Hall 2012).

As noted above, hospitalization is well recognized as an important consequence of RSV illness. Additionally, a large percentage of the healthcare burden from RSV occurs outside the hospital (Carroll et al 2008, Hall et al 2009, Hall 2012, Paramore et al 2010) such that office visits and emergency department visits are more frequent than subsequent hospitalization, especially in healthy infants. The general severity of RSV infection observed among infants in outpatient settings is almost as severe as those observed in hospitalized infants, with symptoms including labored breathing requiring supplemental oxygen, wheezing, and fever (Hall 2012). While 95% of children hospitalized with RSV had labored respirations, similar percentages of outpatients were also observed to have labored respirations (85% of children cared for in emergency departments, and 73% of children treated in private practice settings) (Hall et al 2009). The outpatient burden and severity of disease accounts for a significant portion of the morbidity associated with RSV in all infants.

In China, RSV has been identified in 23% to 38% of children diagnosed with LRTI in ambulatory and hospital settings (Tang et al 2008, Yu et al 2019, Zhang et al 2009, Zhang et al 2013b). Studies of severe acute respiratory infections in Harbin (northeastern China), Suzhou (eastern coastal China), Lanzhou (northwestern China), and Hong Kong reported that RSV infection is responsible for approximately one-quarter of hospital admissions among children < 5 years of age with acute respiratory illness (Hon et al 2012, Jin et al 2012, Zhang et al 2009, Zhang et al 2013a). RSV is the leading viral pathogen identified in children < 2 years of age hospitalized for LRTI in China, and is associated with significant morbidity, with mortality rates as high as 3.5% in children who develop severe disease (Feng et al 2014, Zhang et al 2013b). A study conducted from December 2011 to November 2012 among hospitalized children in Lanzhou identified RSV as the most common virus detected in children with pneumonia or bronchiolitis (Zhang et al 2014). In addition, direct medical costs have been found to be a source of economic burden to families of children with RSV-related hospitalization. Severe LRTI rates were 17.1% in RSV single infections and 11.1% in RSV associated with other viruses (Yan et al 2017). Given the substantial disease burden in the large China pediatric population (Zhang et al 2015), an effective RSV prevention strategy has the potential to provide an important public health benefit.

Prevention of RSV illness in all infants is a major public health priority. However, despite many years of attempted vaccine development (Kim et al 1969), there is no safe and effective vaccine for these children. The medical management for these patients with RSV illness is supportive care. Palivizumab (Synagis®) is the only approved agent for RSV prophylaxis, and its use is limited internationally to high-risk children (preterm infants ≤ 35 weeks gestational age [wGA], children with chronic lung disease [CLD] of prematurity [also known as bronchopulmonary dysplasia], and children with hemodynamically significant congenital heart disease [CHD]). In China, palivizumab is not licensed and there are currently no available options for RSV prophylaxis.

1.2 Nirsevimab Background

Nirsevimab (MEDI8897) is briefly described below. Refer to the current Investigator's Brochure for details.

Nirsevimab is a recombinant human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against the prefusion conformation of the RSV F protein. The antibody has been engineered with a triple amino acid substitution (YTE; M257Y/S259T/T261E [M252Y/S254T/T256E, according to the EU numbering system]) in the fragment crystallizable (Fc) region to prolong the terminal half-life ($t_{1/2}$), which is expected to provide protection from serious RSV disease for the duration of the RSV season. Nirsevimab neutralizes RSV by binding the prefusion conformation of the RSV F protein at a site distinct from that bound by palivizumab. In nonclinical studies, nirsevimab was > 150-fold more potent than palivizumab in vitro and approximately 9-fold more potent than palivizumab in

vivo in the cotton rat model (Zhu et al 2017). Nirsevimab is currently under development by AstraZeneca (hereafter, the Sponsor) as a mAb for the passive immunization of all infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season for the prevention of LRTI caused by RSV. Nirsevimab may provide a cost-effective opportunity to protect all infants from RSV disease based on an improvement in potency and the extended $t_{1/2}$ that is expected to support once-per-RSV-season dosing.

1.3 Summary of Nonclinical Experience

The potential clinical utility of nirsevimab and dose predictions of the antibody were evaluated in the cotton rat model of RSV infection. The pharmacokinetics (PK) of 1G7, the non-YTE version of nirsevimab, was evaluated in cotton rats following a single intramuscular (IM) dose of 0.25 to 3.0 mg/kg. Serum concentrations increased dose proportionally across the entire dose range with a terminal-phase elimination $t_{1/2}$ of approximately 1 day. In cotton rats, a serum concentration of 6.8 μg/mL resulted in a 3-log reduction in lung RSV titers and for Phase 2b was identified as the target serum concentration to maintain in children to provide antiviral activity against RSV over a typical 5-month RSV season.

The YTE amino acid substitutions introduced into nirsevimab do not impact RSV neutralizing activity when compared to the parental mAb, 1G7. Nirsevimab/1G7 showed potent antiviral activity in vitro against RSV A and B laboratory strains, clinical isolates, as well as palivizumab-resistant viruses. Nirsevimab/1G7 was > 150-fold more potent than palivizumab in vitro against the laboratory strains and > 50-fold more potent than palivizumab against clinical isolates based on the median half-maximal inhibitory concentration (Zhu et al 2017).

Toxicity, toxicokinetics, and immunogenicity of nirsevimab were evaluated in a Good Laboratory Practice-compliant repeat-dose intravenous (IV) and IM toxicology study conducted in cynomolgus monkeys. Cynomolgus monkeys represent a pharmacologically relevant model for nonclinical safety assessment based on similar binding of nirsevimab to cynomolgus monkey neonatal Fc receptor (FcRn) compared to human FcRn. Toxicology studies in cynomolgus monkeys indicate that there is no evidence of nirsevimab toxicity in these animal models. Once weekly IV or IM administration (5 doses total) of nirsevimab to monkeys, up to and including 300 mg/kg IV or 300 mg IM dose levels, was not associated with any treatment-related adverse effects locally or systemically. The no-observed-adverse-effect-level was considered to be 300 mg/kg IV and 300 mg IM. No antidrug antibody (ADA) was detected in any of the monkeys during the treatment phase. During the recovery phase, 4 of 12 animals treated with nirsevimab and 0 of 6 control animals were ADA positive with variable impact on toxicokinetics. In addition, tissue cross-reactivity against cryosections of a full panel of adult and a selected panel of juvenile, neonatal, and fetal human tissues showed no staining of any tissues, as expected, given the target for nirsevimab is a non-endogenous

viral-specific target. Overall, data from nonclinical studies do not reveal any nirsevimab-related safety concerns.

Details of these studies are included in the current Investigator's Brochure.

1.4 Summary of Clinical Experience

Nirsevimab has been investigated in 3 completed clinical studies (see the current Investigator's Brochure for additional detail on nirsevimab clinical development).

1.4.1 Phase 1a Study D5290C00001

Study D5290C00001 was a first-time-in-human Phase 1a, randomized, double-blind, placebo-controlled, dose-escalation study conducted to evaluate the safety, tolerability, PK, and ADA of nirsevimab compared to placebo in healthy adult volunteers (Griffin et al 2017). This study was completed in June 2015. A total of 136 subjects were randomized and received a single fixed dose of nirsevimab (6 subjects each at doses of 300 mg IV, 1000 mg IV, 3000 mg IV, 100 mg IM, and 78 subjects at 300 mg IM) or placebo (34 subjects). All subjects were followed for approximately 360 days after dosing.

Safety

The safety profile of nirsevimab was favorable, with similar proportions of treatment-emergent adverse events (TEAEs) reported in the placebo (61.8%) group and the nirsevimab (62.7%) total group. Two treatment-emergent serious adverse events (TESAEs; gunshot wound and appendicitis) were reported in 2 nirsevimab subjects. TEAEs judged to be related to investigational product were reported in 29.4% of subjects in the placebo group, and 17.6% of subjects in the nirsevimab total group. The most frequent TEAEs in the nirsevimab total group included upper respiratory tract infection (URTI; 18.6%); headache (8.8%); urinary tract infection (5.9%); and dermatitis contact, musculoskeletal pain, nausea, and vomiting (4.9% each). The most frequently occurring TEAEs in the placebo group were headache (17.6%); URTI (8.8%); and nausea, increased blood creatine phosphokinase level, and paresthesia (5.9% each). There were no adverse events of special interest (AESIs) or new onset chronic diseases (NOCDs). There were no deaths. No safety signals in this healthy adult population were observed. These results demonstrated an acceptable safety profile for nirsevimab, including no observed hypersensitivity reactions, and supported further clinical studies of IM administration of 1 dose of nirsevimab in the target population of infants to provide protection for the duration of the RSV season.

Pharmacokinetics

A 2-compartment PK model adequately described the PK profile following both IV and IM administrations. Body weight was determined to be a significant covariate on systemic clearance and volume of distribution with allometric exponents. The mean population

clearance and volume of distribution were 42.3 mL/day and 2.8 L, respectively. The mean $t_{1/2}$ of nirsevimab ranged from 85 to 117 days across dose groups, and bioavailability after IM administration was 77%. The predicted 3- to 4-fold increase in the $t_{1/2}$ of nirsevimab compared to a standard IgG antibody was confirmed.

Antidrug Antibody

Post-baseline ADA was detected in 13.7% of subjects in the nirsevimab total group and 15.2% of subjects in the placebo group, with a maximum titer of 1:800 and 1:400, respectively. On Day 361, ADA was detected in 5.3% of nirsevimab subjects and 10.7% of placebo subjects. The highest titer at Day 361 was 1:200 for both the nirsevimab and placebo groups. The presence and titer of ADA had no effect on the PK or safety profiles.

1.4.2 Phase 1b/2a Study D5290C00002

Study D5290C00002 was a Phase 1b/2a, randomized, double-blind, placebo-controlled, single ascending-dose study to evaluate safety, PK, and ADA of nirsevimab in healthy preterm infants (Domachowske et al 2018). The population enrolled was healthy preterm infants born between 32 weeks 0 days and 34 weeks 6 days gestation who would not receive RSV prophylaxis based on the American Academy of Pediatrics or other national or local guidelines. These subjects would not be receiving palivizumab, allowing for a placebo comparator group. A total of 89 infants from sites in the US, Chile, and South Africa were randomized and received a single IM dose of nirsevimab (10, 25, or 50 mg; 8, 31, and 32 subjects, respectively) or placebo (18 subjects) and were followed for approximately 360 days after dosing.

Safety

A total of 66 subjects (93.0%) in the nirsevimab group and 17 subjects (94.4%) in the placebo group reported at least 1 TEAE. No safety signals were observed with ascending dose levels. The majority of the events were mild or moderate in severity; only 2 TEAEs were assessed as ≥ Grade 3 severity, and neither was considered to be related to investigational product by the Investigator. There were no deaths, AESIs, or NOCDs in any dose group.

Three nirsevimab subjects (4.2%) had a total of 5 TESAEs, none of which were considered related to investigational product by the Investigator; no subjects in the placebo group had a TESAE. One infant who received 25 mg of nirsevimab was hospitalized for LRTI. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing from the central laboratory was negative for RSV (but positive for human metapneumovirus [hMPV]); the illness resolved. The same infant was again hospitalized for LRTI, and subsequent RT-PCR testing was positive for RSV B; the event resolved. One infant who received 50 mg of nirsevimab was hospitalized for febrile convulsion; the infant recovered. A second infant who received

50 mg of nirsevimab was hospitalized for febrile convulsion and a concurrent LRTI. Testing for RSV was not performed, and the infant recovered from both events.

The most frequently reported TEAEs for the nirsevimab group were URTI (69.0%), gastroenteritis (29.6%), cough (25.4%), pyrexia (22.5%), and otitis media (21.1%). There were no trends by dose of nirsevimab for these events. The most frequently reported TEAEs in the placebo group were URTI (66.7%), anemia (33.3%), and gastroenteritis, cough, and otitis media (22.2% each). Skin rashes (defined as adverse events [AEs] that coded to the Medical Dictionary for Regulatory Activities [MedDRA] preferred terms of dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, dermatitis diaper, dry skin, eczema, rash, and rash papular) were reported for 38.9% of subjects in the placebo group and 47.9% of subjects in the nirsevimab group. No skin events were consistent with hypersensitivity.

Pharmacokinetics

Nirsevimab exhibited a less-than-dose-proportional exposure increase between the 10- and 25-mg doses; however, exposure increase was dose proportional between 25- and 50-mg doses. Following a single IM dose of 10, 25, or 50 mg, the estimated $t_{1/2}$ of nirsevimab ranged from 62.5 to 72.9 days. On Day 151, 87% of the nirsevimab serum concentrations following the 50 mg IM dose were above the 90% effective concentration threshold of 6.8 μg/mL.

Serum anti-RSV neutralizing antibody (NAb) titers increased dose-dependently following administration of nirsevimab and were higher than placebo by Day 8 and through Day 151. Serum nirsevimab concentrations were correlated with serum anti-RSV NAb across all the dose levels, confirming anti-RSV activity of nirsevimab.

Antidrug Antibody

ADA was not detected in any subject at Day 151. Post-baseline ADA was detected at Day 361 only in 18/68 (26.5%) subjects, and there were 2 subjects with transient ADA-positive titers at Day 50 only who were ADA negative at Day 361. Overall, post-baseline ADA was detected in 20/71 subjects (28.2%) in the nirsevimab group and 0/17 subjects (0%) in the placebo group. None of the post-baseline nirsevimab ADA-positive subjects were ADA positive at baseline; only one subject (in the placebo group) was ADA-positive at baseline. The highest titer detected was 1:25,600 (observed in 2 subjects [2.8%]). The 20 subjects in the nirsevimab group who had ADA detected were positive for the presence of ADA targeting the YTE domain and 4 of the 20 subjects with samples available had neutralizing ADA antibody.

There was no impact of the presence of ADA on safety. ADAs did not appear to impact PK for 150 days after dosing, but there may have been an impact between Day 151 and Day 361.

1.4.3 Phase 2b Study D5290C00003

Study D5290C00003 was a Phase 2b global, randomized, double-blind, placebo-controlled, single-dose study to evaluate the efficacy, safety, PK, and ADA of nirsevimab in healthy preterm infants, born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA), entering their first RSV season. Subjects were not eligible for RSV prophylaxis with palivizumab based on the Joint Committee on Vaccination and Immunisation, American Academy of Pediatrics, or other local or national guidelines, allowing for a placebo comparator group. Overall, 1,453 subjects were randomized 2:1 to receive a single dose of 50 mg IM nirsevimab or placebo. A total of 1,447 subjects were dosed, including 968 subjects in the nirsevimab group and 479 subjects in the placebo group. Subjects were followed for 360 days after dosing.

Efficacy

Based on the analysis in the Intent-to-treat Population, a single dose of 50 mg IM nirsevimab resulted in a 70.1% (95% confidence interval [CI]: 52.3%, 81.2%; $p < 0.0001$) relative risk reduction (RRR) in the incidence of medically attended RSV-confirmed LRTI through Day 151 when compared to placebo. Additionally, a 78.4% (95% CI: 51.9%, 90.3%; $p = 0.0002$) RRR in the incidence of RSV LRTI hospitalization through Day 151 was seen in the nirsevimab recipients when compared to placebo.

Safety

The safety profile of nirsevimab was comparable to that of placebo, with no identified risks. Overall, 86.2% of subjects in the nirsevimab group and 86.8% of subjects in the placebo group had at least 1 TEAE. TEAEs ≤ 1 day post dose occurred in 2.5% of subjects in both groups. In comparison to the placebo group, the nirsevimab group had a lower incidence of TEAEs occurring ≤ 7 days post dose (nirsevimab 12.5%, placebo 15.2%), TEAEs ≥ Grade 3 in severity (nirsevimab 8.0%, placebo 12.5%), or TESAEs (nirsevimab 11.2%, placebo 16.9%). The majority of the TEAEs were mild or moderate in severity. The most common TESAEs, based on the nirsevimab group, were bronchiolitis (2.1% nirsevimab, 4.4% placebo), LRTI (1.4% nirsevimab, 2.7% placebo), bronchitis (1.4% nirsevimab, 2.3% placebo), and pneumonia (1.3% nirsevimab, 2.1% placebo). None of the TESAEs were considered related to investigational product by the Investigator. Five deaths were reported during the study through Day 361, including 2 subjects (0.2%) in the nirsevimab group and 3 subjects (0.6%) in the placebo group. None of the deaths were related to investigational product according to the Investigator.

Overall, the incidence of treatment-related TEAEs (nirsevimab 2.3%, placebo 2.1%); AESIs, including hypersensitivity, immune complex disease, and thrombocytopenia (nirsevimab 0.5%, placebo 0.6%); and NOCDs (nirsevimab 0.4%, placebo 0.8%) was low and generally comparable between the placebo and nirsevimab groups. AESIs were reported in 5 subjects

(4 subjects with rash or rash macular and 1 subject with petechiae) in the nirsevimab and 3 subjects (rash or rash papular) in the placebo group. All events were Grade 1 in severity. The TEAE of petechiae that was reported as an AESI was 1 day in duration and was reported by the Site Investigator based on description by the parent. There were no laboratory assessments for the petechiae.

TEAEs that involved the skin and subcutaneous tissues (including diaper rash) were collected as skin reactions, with a few exceptions for skin reactions that could be definitively diagnosed such as impetigo, varicella, and scabies. Skin reactions were reported in a similar percentage of subjects in both treatment groups (nirsevimab 32.9%, placebo 30.9%).

Pharmacokinetics

Following a single fixed 50-mg IM dose of nirsevimab, 97.8% of measurable Day 151 serum concentrations were above the nonclinical 90% effective concentration target of 6.8 µg/mL. The mean (% coefficient of variation) area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) and estimated apparent $t_{1/2}$ were 5176.3 (35.0) day·µg/mL and 59.3 (9.6) days, respectively.

Antidrug Antibody

Overall, the rate and titers of ADA were low, and in post-baseline ADA-positive subjects there was no effect on PK, efficacy, or safety. Of the subjects who had serum samples available for testing, ADA was detected post baseline in 5.6% (52/929) of subjects in the nirsevimab group and 3.8% (18/469) of subjects in the placebo group. ADA titers ranged from 1:50 to 1:6,400 in the nirsevimab group and from 1:50 to 1:400 in the placebo group. Of the nirsevimab subjects who were post-baseline ADA positive, ADA targeting the YTE domain was observed in 4/17 subjects (23.5%) on Day 151 and 23/30 subjects (76.7%) on Day 361. Three nirsevimab subjects had neutralizing ADA on Day 361.

1.5 Rationale for Conducting the Study

Prevention of RSV illnesses in all infants is a major public health priority (Giersing et al 2019); however, despite almost 50 years of attempted vaccine development (Kim et al 1969, Mazur et al 2018), there are no licenced vaccines. While RSV prevention exists in the form of a specific RSV IgG (palivizumab) requiring 5 once monthly injections, it is not licensed for use in China. The mAb, nirsevimab, is being developed as a cost-effective opportunity to protect all infants from RSV disease based on improved potency and an extended $t_{1/2}$, which is expected to support once per-RSV-season dosing.

The purpose of this study is to evaluate the PK, safety, tolerability, and immunogenicity of nirsevimab in healthy adult Chinese subjects. The results from this study will support drug registration in China.

1.6 Benefit-Risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

To evaluate the clinical benefit-risk balance for nirsevimab, nonclinical and clinical data have been taken into consideration. Based on the risk of serious RSV disease in infants and high-risk children, there is an established unmet medical need for the use of nirsevimab for prophylaxis in all infants entering their first RSV season and in high-risk- preterm infants and children ≤ 24 months of age with CLD or CHD. Benefits for nirsevimab over placebo include a clinically meaningful reduction in medically attended LRTI due to RSV in infants and expected similar benefit for high-risk children. Nirsevimab is not expected to offer benefit to the healthy Chinese adult subjects in this study. The PK, ADA, and safety results of this study will support the registration of nirsevimab in China.

Nirsevimab has no endogenous targets, and no safety concerns have been identified in nonclinical or clinical studies to date. The potential risks are based primarily on safety risks that may be observed with any immunoglobulin, including mAbs such as palivizumab. These potential risks include, but are not limited to, hypersensitivity (including anaphylaxis), immune complex disease, thrombocytopenia, and injection site reactions. To date, there have been no observed events of anaphylaxis, significant hypersensitivity reactions, immune complex disease, or thrombocytopenia attributable to nirsevimab in the clinical studies. Nonetheless, subjects in nirsevimab clinical studies will continue to be monitored for important potential risks, and routine pharmacovigilance and risk minimization activities will be performed accordingly.

The benefit-risk assessment for nirsevimab in prevention of RSV disease based on the development through Phase 2b is favorable.

1.7 Research Hypotheses

The primary and secondary research hypotheses are described below. No formal hypothesis is being tested statistically.

1.7.1 Primary Hypothesis

The PK profile of nirsevimab assessed up to 150 days after dose administration in Chinese subjects will be similar to subjects with different racial and ethnic backgrounds.

1.7.2 Secondary Hypotheses

A single dose of nirsevimab will be well tolerated in healthy Chinese adult subjects, with an acceptable safety profile. The incidence of ADA to nirsevimab will be acceptable.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
PK	To evaluate serum concentrations of nirsevimab	Summary of nirsevimab serum concentrations and estimated PK parameters (C_{max}, T_{max}, AUC_{0-150}, and others if data permit)

AUC_{0-150} = area under the concentration-time curve from time 0 to 150 days; C_{max} = maximum observed concentration; PK = pharmacokinetics; T_{max} = time to maximum observed concentration.

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	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 • Clinical laboratory assessments, vital signs
ADA	To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum

ADA = antidrug antibody; AESI = adverse event of special interest; IM = intramuscular; NOCD = new onset chronic disease; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

3 STUDY DESIGN

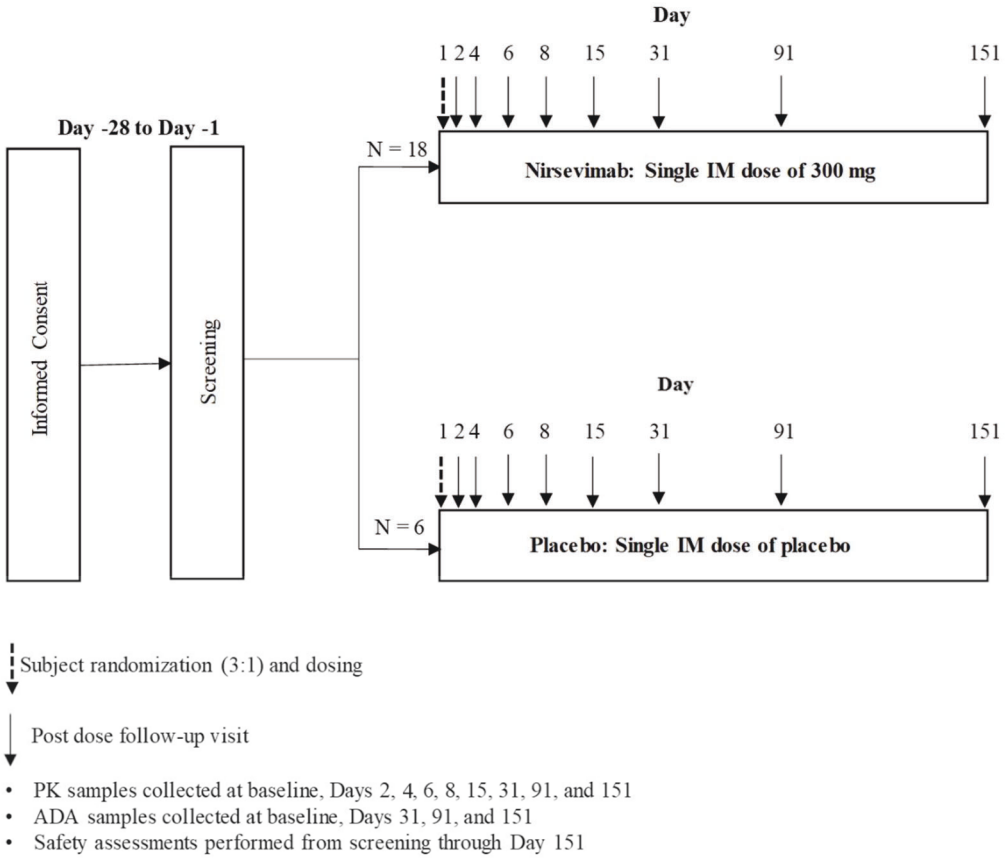
3.1 Description of the Study

3.1.1 Overview

Study D5290C00007 is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the 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 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, PK, and ADA response.

Figure 1 Study Flow Diagram



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

3.1.2 Treatment Regimen

Subjects will be randomly assigned to receive a single fixed IM dose of nirsevimab 300 mg (n = 18) or placebo (n = 6) on Day 1.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

Nirsevimab is supplied as a liquid product intended for IM administration. Nirsevimab is formulated at 100 mg/mL and is supplied as a sterile solution in a glass vial at nominal fill volume of 0.5 mL. Each vial contains 50 mg of nirsevimab. The proposed pediatric dosing regimen for nirsevimab is a single fixed IM dose of 50 mg for infants < 5 kg or 100 mg for infants ≥ 5 kg body weight entering their first RSV season, and a single fixed IM dose of 200 mg for high-risk children with CLD or CHD entering their second RSV season.

In the Phase 1a first-time-in-human Study D5290C00001, a total of 136 healthy adult subjects were randomized and received a single dose of nirsevimab (6 subjects each at doses of 300 mg

IV, 1000 mg IV, 3000 mg IV, and 100 mg IM; 78 subjects at 300 mg IM) or placebo (34 subjects). The IM dose was limited to 300 mg because this dose required 3 simultaneous 1 mL IM injections, and more injections per dose were not considered practical. Higher doses to ensure safety exposure coverage were tested with IV administration (Table 3). Data demonstrated a favorable safety profile similar to placebo at all doses tested. A 2-compartment PK model adequately described the PK profile following both IV and IM administrations. The mean $t_{1/2}$ of nirsevimab ranged from 85 to 117 days across the dose groups, and bioavailability after IM administration was 77%. The predicted 3- to 4-fold increase in the $t_{1/2}$ of nirsevimab compared to a standard IgG antibody was confirmed. A single 300-mg IM dose of nirsevimab will be administered in this Phase 1 study in Chinese adult subjects to confirm a similar PK profile in the Chinese population. Higher doses to provide safety exposure coverage were tested in Study D5290C00001 but will not be necessary in this Phase 1 study in China.

In addition, the highest anticipated maximum observed concentration (C_{max}) and $AUC_{0-\infty}$ among all infants to be dosed with nirsevimab at 50 or 100 mg in the first season are predicted to be covered by exposures observed to date in the Phase 2b Study D5290C00003 population (> 29 to < 35 wGA), in cynomolgus monkey, or in human adults, and were demonstrated to be safe and well tolerated (Table 3).

Table 3 Exposure Comparison in Cynomolgus Monkey, and Human Adult and Pediatric Populations

Population	Nirsevimab Dose	C_{max} (µg/mL) Median (max)	$AUC_{0-\infty}$ (µg·day/mL) Median (max)
Cynomolgus monkey Observed PK	300 mg IM	4,982 (6,080)[a]	90,560 (113,000)[b]
	300 mg/kg IV	13,440 (19,000)[a]	193,300 (298,000)[b]
Adult Observed PK from Phase 1a Study D5290C00001	300 mg IM	45.8 (78.4)	4,917 (9,956)
	3000 mg IV	1,199 (1,465)	61,792 (71,918)
Pediatric (1st season) Observed PK from Phase 1b/2a Study D5290C00002	50 mg IM	69.5 (109)	7,120 (11,300)
Pediatric (1st season) Observed PK from Phase 2b Study D5290C00003	50 mg IM	66.2 (201)	14,220 (20,910)

$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; $AUC_{day1-31}$ = area under the concentration-time curve from Day 1 to 31; C_{max} = maximum observed concentration; IM = intramuscular; IV = intravenous; max = maximum; PK = pharmacokinetics.

Data are reported as median and maximum observed.

C_{max} after repeat dosing.

Based on $AUC_{day1-31}$.

3.2.2 Rationale for Study Population

Nirsevimab has the potential to address a serious unmet medical need by protecting all infants from RSV disease with once-per-season dosing. Palivizumab is not licensed in China and currently there are no other options available for the prevention of RSV disease. This Phase 1 adult study is designed to assess the PK, ADA, safety, and tolerability of a single IM dose of nirsevimab in healthy Chinese adult subjects to support the registration of nirsevimab in China. The PK profile of nirsevimab assessed after dose administration in Chinese adult subjects will be compared to global adult subjects with different racial and ethnic backgrounds.

3.2.3 Rationale for Endpoints

Serum concentration of nirsevimab at selected time points will be evaluated as the primary endpoint to confirm that adequate serum exposures are maintain ed at least 5 months after dosing (ie, through Day 151; duration of a typical RSV season). The estimated PK parameters from the adult Chinese subjects in this study will be compared for similarity with those obtained from non-Chinese adult subjects from the global Phase 1a Study D5290C00001.

Nirsevimab being a mAb with a half-life extending YTE modification has a predictable linear PK profile across a range of doses studied both in adults and infants. Also, it does not have any internal targets; thus, it does not go through any target-mediated clearances to have the potential to alter the PK profile past the 150 days from the injection. Therefore, the 150-day PK profile comparison based on only C_{max}, t_{max}, and AUC_{0-150} assures the similarity of efficacious exposures as well as provides the opportunity to confirm the safety.

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), and NOCDs.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of approximately 24 subjects will be randomized to receive a single IM dose of either nirsevimab (n = 18) or placebo (n = 6).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Age 18 to 45 years, inclusive, at the time of screening.

2 Written informed consent and any locally required authorization obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3 Females of childbearing potential who are sexually active with a nonsterilized male partner must have used at least 1 highly effective method of contraception (see Appendix A for definition of females of childbearing potential and for a description of highly effective methods of contraception) from screening and must agree to continue using such precautions for 150 days after receipt of the dose of investigational product. It is strongly recommended for the male partner of a female subject to also use a male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

   (a) Females not of childbearing potential who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or postmenopausal. Women < 50 years of age will be considered postmenopausal if they have been amenorrheic for ≥ 12 months prior to the planned date of randomization without an alternative medical cause and have follicle-stimulating hormone levels in the postmenopausal range.

4 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from Day 1 (the day of investigational product administration) through 150 days after receipt of the dose of investigational product. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as described in Appendix A. In addition, male subjects must refrain from sperm donation while on study and for 150 days after the final dose of investigational product.

5 Weight ≥ 45 kg and ≤ 110 kg and body mass index of 19 to 26 kg/m^2 at screening.

6 Healthy Chinese subjects (both male and female) based on medical history, physical examination, vital signs, and laboratory tests, as determined by the Investigator.

7 Normotensive (defined as systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg).

8 Normal electrocardiogram (ECG) as judged by the Investigator at screening (within 28 days prior to Day 1).

9 Ability to complete the follow-up period of 150 days following administration of investigational product as required by the protocol.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1 Acute illness at study entry (pre-dose on Day 1). If, in the opinion of the Investigator, the illness is transient and of no medical importance, it would be permissible to reassess the subject for study and dosing eligibility after resolution as long as it is within the overall 28-day study screening period.

2 Fever ≥ 99.5°F (37.5°C) on day of dosing.

3 Any drug therapy within 14 days prior to Day 1 (except contraceptives). If, in the opinion of the Investigator, the medication was taken for a transient illness that has resolved, it would be permissible to reassess the subject for study and dosing eligibility after resolution as long as it is within the overall 28-day study screening period.

4 Blood donation or in any other way had a loss of blood in excess of 400 mL within 6 months prior to study entry.

5 Receipt of immunoglobulin or blood products within 6 months prior to study entry.

6 Receipt of any investigational drug therapy within 120 days prior to investigational product dosing or planned to receive any investigational drug therapy within 150 days after investigational product dosing.

7 Receipt of any live vaccine within 30 days and other vaccines within 14 days prior to investigational product dosing.

8 Previous receipt of any marketed or investigational mAb.

9 Previous vaccination against RSV.

10 History of immunodeficiency or receipt of immunosuppressive medications during the prior year.

11 History of allergic disease or reactions likely to be exacerbated by any component of the investigational product or a history of drug or other allergy that, in the opinion of the investigator, contraindicates their participation.

12 History of asthma.

13 History of autoimmune disorder.

14 Previous medical history or evidence of an intercurrent illness that, in the Investigator's opinion, may compromise the safety of the subject in the study.

15 Evidence of any systemic disease on physical examination.

16 Evidence of infection (ie, positive laboratory test result) with hepatitis A, B, or C virus, syphilis, or human immunodeficiency virus.

17 Any of the following laboratory assessments at screening (must be within 28 days before study entry):

(a) Hemoglobin < 120 g/L for males and < 110 g/L for females

(b) White blood cell count $< 3.5 \times 10^9$/L

(c) Platelet count $< 120 \times 10^9$/L

(d) Aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, serum creatinine > upper limit of normal (ULN)

(e) Urine Class A drug screen positive for amphetamines, opiates, or cocaine

(f) Other abnormal laboratory values in the screening panel, which in the opinion of the Investigator, are judged to be clinically significant; other abnormal laboratory values in the screening panel which, in the opinion of the Investigator, are judged to potentially confound analysis of study results

18 Pregnant or nursing mother. All female subjects will be screened to rule out pregnancy prior to enrollment using serum beta human chorionic gonadotropin (βhCG) testing.

19 Active alcohol or drug abuse or history of alcohol or drug abuse that, in the opinion of the Investigator, might compromise subject safety, study safety assessments, or ability of the subject to comply with study requirements.
20 Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.
21 Concurrent enrollment in another interventional study.
22 Employees of the Sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive web response system [IWRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized (if applicable) or receive investigational product. Rescreening is not permitted.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the Investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place. The reason for withdrawal must be recorded in the eCRF.

Subjects who have received investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation or the subject is lost to follow-up (Section 4.1.7).

4.1.6 Discontinuation of Investigational Product

Not applicable as each subject will receive a single dose of investigational product.

4.1.7 Lost to Follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

To prevent the subject from being lost to follow-up, it is recommended that the study sites maintain up-to-date contact details for subjects, including next of kin or other emergency contacts (if allowed by national regulation).

The Investigator should educate the subject on the importance of maintaining contact with the Investigator/study site throughout the study.

The following actions must be taken if a subject fails to return to the site for required study visits:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Repeated attempts must be made to regain contact with the subject or next of kin/emergency contact by repeat telephone calls, emails, and/or certified letter. These contact attempts should be documented in the subject's medical record.

Efforts to reach the subject should continue until the end of the study.

The subject will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study, despite all above listed efforts.

4.1.8 Replacement of Subjects

Subjects will not be replaced.

4.1.9 Withdrawal of Informed Consent for Data and Biological Samples

The Sponsor ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent for further study participation, any samples collected prior to that time may still be given to and used by the Sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to the Sponsor.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.
- Ensures that the subject and the Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4 shows all procedures to be conducted at the screening visit. Assessments should be performed in the order shown in the table.

Table 4 Schedule of Screening Procedures

Study Period	Screening	
Procedure / Study Day or Week	**Day -28 to Day -2**	**Day -1**
Written informed consent/ assignment of SID number	X	
Medical history	X	X[a]
Physical examination (complete)	X	X[a]
Height, weight	X	
Electrocardiogram (ECG)	X	X
Vital signs	X	X
Serum chemistry[b]	X	X
Hematology[b]	X	X
Urinalysis[b]	X	X
Pregnancy test[c]	X	X
FSH[d]	X	
Hepatitis A, B, C; HIV; Syphilis	X	
Urine Class A drug screen[b]	X	X
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X
Verify eligibility criteria	X	X

Table 4 Schedule of Screening Procedures

Study Period	Screening	
Procedure / Study Day or Week	**Day -28 to Day -2**	**Day -1**
Admission		X

ADA = antidrug antibody; AE = adverse event; βhCG = beta human chorionic gonadotropin; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; PK = pharmacokinetics; SAE = serious adverse event; SID = subject identification.

[a] Update screening medical history and complete physical examination (any new findings since screening).

[b] Screening serum chemistry and hematology assessments reviewed and found to be within normal limits by the Site Investigator. Serum chemistry assessments should be collected under fasting conditions (fasting starts 8 hours before sample collection). If serum chemistry, hematology, urinalysis and urine class A drug screen assessments at screening visit (Day -28 to Day -2) are performed within 7 days of randomization, the assessments at Day -1 can be omitted.

[c] Female subjects only. Serum pregnancy test will be performed at screening visit (Day -28 to Day -2). Urine pregnancy test will be performed on Day -1 to confirm eligibility. Pregnancy test must be negative prior to dosing.

[d] FSH will be tested only in women < 50 years of age who have been amenorrheic for ≥ 12 months.

4.2.2 Treatment and Follow-up Periods

Investigational product is administered on Day 1. Table 5 and Table 6 show all procedures to be conducted on Day 1 and during the post-dose follow-up period, respectively.

Table 5 Schedule of Treatment Period Procedures

Procedure	Investigational Product Administration: Day 1			
	Pre-dose	Dosing	Post-dose	
			30 min post (± 5 min)	60 min post (± 5 min)
Abbreviated Physical examination	X			
Vital signs[a]	X		X	X
Blood sample for PK, ADA	X			
Assessment of AEs/SAEs	X	X	X	X
Assessment of AESIs and NOCDs		X	X	X
Concomitant medications	X			
Randomization[b]	X			
Investigational product administration		X		

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; IM = intramuscular; NOCD = new onset chronic disease; PK = pharmacokinetic; SAE = serious adverse event.

[a] Vital signs will be monitored before and after IM administration of investigational product. Two pre-dose (within 60 minutes prior to dosing) blood pressure and heart rate readings should be obtained 5 minutes apart. Vital signs should be monitored within 60 minutes prior to dosing, and 30 and 60 (± 5 minutes) minutes after the administration of the investigational product.

[b] Randomization should occur before blood sampling.

Table 6 Schedule of Follow-up Period Procedures

Procedure	Post-dose Follow-up: Day (± Assessment Window [day])							
	2	4	6	8	15 (± 1d)	31 (± 2d)	91 (± 5d)	151 (± 10d)
Physical examination[a]	X		X		X	X	X	X
Vital signs	X		X		X	X	X	X
Serum chemistry			X		X	X	X	
Hematology			X		X	X	X	
Urinalysis			X		X	X	X	
PK blood sample	X (± 2h)	X (± 3h)	X (± 3h)	X (± 3h)	X	X	X	X
ADA blood sample						X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X
Assessment of AESIs and NOCDs	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Discharge	X							

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; d = day; h = hour; NOCD = new onset chronic disease; PK = pharmacokinetic; SAE = serious adverse event.

[a] Abbreviated physical examinations will be performed at Day 2, Day 6, Day 15, Day 31 and Day 91. A complete physical examination should be performed on Day 151.

4.3 Description of Study Procedures

4.3.1 Medical History, Physical Examination, Height, Weight, Vital Signs and Electrocardiogram

A complete medical history will be obtained at screening and a medical history update (for any new findings since screening) will be obtained on Day -1.

A complete physical examination will be performed at screening visit (Day -28 to Day -2), Day -1 (updated with any new findings since screening), and Day 151, and it will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. An abbreviated physical examination will be performed at all other study visits, and it will include an assessment of general appearance, abdomen, cardiovascular, and respiratory systems. The height and/or weight will be performed as noted in Table 4.

Vital signs (temperature, blood pressure, respiratory 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. Refer to Table 6 for the timings of assessments during the follow-up period.

At Screening, 12-lead ECG will be obtained after 5 minutes supine rest and prior to blood draw. Skin must be cleaned, and electrodes should be positioned according to standard 12-lead ECG placement. All 12-lead ECGs will be recorded and evaluated by the Investigator. The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not. The reason for the abnormality will be recorded in the eCRF. These ECGs will be documented in the eCRF by recording date, time, heart rate, overall assessment as normal and abnormal, and whether the abnormality is clinically significant or not.

All ECGs will be documented by recording date, time of collection, heart rate, PR, RR, QRS, and QT intervals from the 12-lead ECG.

If indicated additional 12-lead ECG assessments can be made at the discretion of the Investigator. These assessments should be entered as an unscheduled assessment in the appropriate eCRF.

4.3.2 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed at a local laboratory at or near the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Abnormal laboratory results after randomization should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 4, Table 5, and Table 6):

Serum Chemistry

- AST
- ALT
- Alkaline phosphatase (ALP)
- Calcium
- Chloride
- Creatinine
- Gamma-glutamyltransferase
- Glucose
- Potassium
- Sodium
- Total bilirubin (TBL)
- Urea

Note for serum chemistries: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy (including WBC/HPF, RBC/HPF)

Pregnancy Test (All Females of Childbearing Potential Only)

- Serum beta human chorionic gonadotropin (βhCG; Day -28 to Day -2)
- Urine hCG (on Day -1)

Other Safety Tests

- Hepatitis A immunoglobulin M antibody, and hepatitis B surface antigen
- Hepatitis C antibody screen
- Human immunodeficiency virus (HIV) antibody screen, syphilis test
- Urine Class A drug screen for amphetamines, opiates, and cocaine
- Follicle-stimulating hormone (only for women < 50 years of age who have been amenorrheic for ≥ 12 months at screening)

4.3.3 Pharmacokinetic Evaluation

Blood samples to evaluate the PK of nirsevimab in serum will be collected according to the scheduled time points (see Section 4.2). The concentration of nirsevimab in serum will be measured using validated assays.

4.3.4 Antidrug Antibody Evaluation

Blood samples to evaluate ADA responses to nirsevimab in serum will be collected according to the scheduled time points (see Section 4.2). ADA samples may also be further tested for characterization of the ADA response. Evaluations will be performed using validated immunoassays.

4.4 Study or Study Component Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1 Death in any subject in which the cause of death is assessed as related to investigational product
2 Anaphylactic reaction that is related to investigational product (see Appendix C for a definition of anaphylaxis)
3 Grade 3 and/or 4 hypersensitivity AEs based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 5.0) grading scale that are assessed as related to nirsevimab in 2 or more subjects. Refer to Appendix B for events not covered in NCI CTCAE.
4 Two SAEs of the same type that are assessed as related to nirsevimab
5 Subject enrollment is unsatisfactory
6 Sponsor decision to terminate development

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will discuss the reasons for taking such action with the Investigator (or head of the medical institution, where applicable). When feasible, the Sponsor will provide advance notice to all participating Investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator, head of the medical institution (where applicable), and/or institution conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs, when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

The Sponsor will provide the Investigator(s) with investigational product (Table 7) using designated distribution centers.

Table 7 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Nirsevimab	MedImmune	Supplied as 50 mg (nominal) per vial solution. The solution contains 100 mg/mL nirsevimab, CCI histidine/histidine-HCl, CCI arginine-HCl, CCI sucrose, CCI polysorbate 80, pH 6.0. The nominal fill volume is 0.5 mL.
Placebo	To be provided by study sites	Commercially available 0.9% (w/v) saline (sterile for human use)

HCl = hydrochloride; w/v = weight/volume.

Nirsevimab should be stored at 2°C to 8°C.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines.

Nirsevimab will be supplied to the site in open-labelled kits. Each kit has a unique number printed on all labels within the kit (ie, the outer carton label and the label of each vial).

Refer to Section 4.6.2 for information on coding of the container for blinding purposes.

See the Pharmacy Manual, which is prepared by the Sponsor, for additional information.

4.5.1.1 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. Refer to Table 7 for identification of investigational product.

If there are any defects noted with the investigational product, the Investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.5) for further instructions.

4.5.1.2 Dose Preparation Steps

No incompatibilities between nirsevimab and polycarbonate or polypropylene syringes have been observed.

Nirsevimab does not contain preservatives and any unused portion must be discarded. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used.

The dose administration steps are as follows:

1 The required volume of nirsevimab (3 mL) will be obtained by withdrawing the contents of 6 investigational product vials into 3 appropriately sized syringes (ie, 2 vials per syringe). Normal saline placebo will be provided by the study sites and the required volume (3 mL) divided into 3 appropriately sized syringes. The maximum volume for each injection is 1 mL. Syringes used must be polycarbonate or polypropylene syringes. For ease of preparation, a 1.5 inch 19 gauge withdrawal needle should be used.
2 Switch the needle prior to administration.
3 Administer investigational product using the appropriate size needle ranging from 22 to 25 gauge and 5/8 to 1.5 inches based on subject weight, as per standard of care.

4.5.1.3 Treatment Administration

The first day of dosing is considered Day 1.

Investigational product (nirsevimab or placebo) will be supplied by an unblinded investigational product manager. Blinding will be performed at the site level to ensure that nirsevimab and placebo are indistinguishable in appearance and are not labelled to reveal treatment identity.

Investigational product (nirsevimab or placebo) should be administered IM in the central area and thicker portion of the deltoid (ie, above the level of the armpit and below the acromion) according to standard practice procedures for IM injections. The injection should be given using standard aseptic technique. The IM dose of nirsevimab or placebo should be given as 3 separate 1 mL injections. Two injections given in the same deltoid muscle must be separated by approximately 1 inch (2.54 cm). The third injection will be given in the other deltoid muscle.

4.5.1.4 Monitoring of Dose Administration

Subjects will be monitored before and after investigational product administration through assessment of vital signs (temperature, blood pressure, heart rate, and respiratory rate). All vital signs should be obtained within 60 minutes prior to dosing, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post dose.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

4.5.1.5 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the Sponsor's Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to the Sponsor and investigated further with the Product

Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

Sponsor's contact information for reporting product complaints:

Email: PPD

Phone: PPD

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at 2°C to 8°C.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The Investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the Sponsor. All unused investigational product will be returned to a Sponsor-authorized depot or disposed of upon authorization by the Sponsor.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when

the Investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized using a 3:1 ratio to receive either nirsevimab (n = 18) or placebo (n = 6).

The procedure for using IWRS is as follows:

- The Investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- Placebo (provided by site) or a vial from a nirsevimab kit will be assigned to the subject
- Confirmation of this information is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log

Investigational product (nirsevimab or placebo) must be administered the same day the investigational product is assigned. Total in-use storage time from needle puncture of the investigational product vial to administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new vial should be used. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the unblinded investigational product manager must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a double-blind study in which the site is using commercially available saline as the placebo. Nirsevimab and placebo are visually indistinguishable once in syringes. Neither the subject nor the Investigator or any of the site staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9). In the event that treatment allocation for a subject becomes known to the Investigator or other blinded study staff involved in the management of study subjects, the Sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the Investigator must notify the Sponsor *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product preparation and administration used to maintain the blind.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the Investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. In general, unblinding

should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded. In the event there is unblinding, the Investigator should promptly document and explain to the Sponsor the reason for any premature unblinding.

The Sponsor retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the electronic case report form (eCRF).

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments which is considered necessary for the subject's safety and well-being. Specifically, subjects may receive contraceptives during the study.

4.7.2 Prohibited Concomitant Medications

Other than contraceptives, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc from Day 1 through Day 15 post dose is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The PK Population will include all subjects who have received any dose of investigational product, and have at least one measurable post-dose 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). PK analyses will be based on the PK Population.

The As-treated Population will include all subjects who are randomized into the study and who receive any amount of investigational product. Subjects will be included in the treatment group corresponding to the treatment actually received. Safety and ADA analyses will be based on the As-treated Population.

4.8.2 Sample Size

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.

4.8.3 Analysis of Pharmacokinetics

Serum concentrations of nirsevimab at selected time points will be evaluated to confirm that adequate exposures are maintained after dosing. Nirsevimab serum concentration data will be presented in descriptive statistics. Serum PK parameters such as C_{max}, T_{max}, and AUC_{0-150} will be estimated using noncompartmental analysis and summarized with descriptive statistics. The estimated PK parameters from the adult Chinese subjects from this study will be compared for similarity with those obtained from non-Chinese adult subjects from the global Phase 1a Study D5290C00001. This PK comparison will be presented separately from the clinical study report. Notably, regression-dependent PK parameters such as $t_{1/2}$ and apparent systemic clearance will not be estimated due to the limited sampling up to 150 days which would require at least 40% extrapolation of the total $AUC_{0-\infty}$. Nonetheless, the predictability and consistency of the PK properties of nirsevimab as demonstrated in 102 adults in the Phase 1a Study D5290C00001 and 984 infants in the Phase 1b/2a Study D5290C00002 and Phase 2b Study D5290C00003 support the hypothesis that the apparent clearance and other regression-dependent PK parameters should be similar if the C_{max}, T_{max}, and AUC_{0-150} are shown to be similar.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

All AEs will be coded using MedDRA 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. All TEAEs will be summarized overall and by MedDRA system organ class and preferred term, severity, and relationship to investigational product. In addition, summaries of deaths and TESAEs will be provided. Other safety assessments will include 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, and the occurrence of NOCDs following investigational product administration.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. 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 clinical laboratory measurements (ie, serum chemistry, hematology, and urinalysis) through 150 days postdose.

4.8.5 Analysis of Antidrug Antibody

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.

4.8.6 Interim Analysis

No interim analysis is planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no investigational product has been administered.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical

event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

5.3.1 Anaphylaxis and Other Serious Hypersensitivity Reactions Including Immune Complex Disease

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, that occurs during or after dosing. Anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. It is potentially a fatal, systemic allergic reaction that is distinct from simple allergic reactions (eg, rash, pruritus) because of the simultaneous involvement of several organ systems (Sampson et al 2006). A full definition of anaphylaxis is provided in Appendix C. See Section 5.5 for recording AEs. A hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during or after administration of investigational product (but does not meet the definition of anaphylaxis) (Pichler 2019).

5.3.2 Thrombocytopenia

Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150,000 to 450,000 platelets per µL. The 3 major causes of low platelet counts include: 1) insufficient platelet synthesis in the bone marrow; 2) increased breakdown of platelets in the bloodstream; and 3) increased breakdown of platelets in the spleen or liver. General symptoms of thrombocytopenia include bleeding in the mouth and gums, bruising, nosebleeds, and petechiae (pinpoint red spots/rash). Severe bleeding is the major complication, which may occur in the brain or gastrointestinal tract. Drug-induced thrombocytopenia is a reversible form of thrombocytopenia that should be suspected in a subject who presents with new onset thrombocytopenia or recurrent episodes of acute thrombocytopenia, without an obvious alternative etiology. It is commonly induced by drug-dependent antibodies that cause platelet destruction or clearance by the reticuloendothelial system (drug-induced immune thrombocytopenia), and less commonly by drug-induced bone marrow suppression or autoimmune thrombocytopenia that is initiated by exposure to the offending drug but persists in its absence. The initial approach to the subject with suspected drug-induced thrombocytopenia involves confirming thrombocytopenia, establishing a temporal relationship to a drug, and eliminating other causes of thrombocytopenia. The diagnosis is made clinically by documenting prompt resolution of thrombocytopenia after discontinuation of the suspected drug (typically within 1 week). Most subjects with drug-induced thrombocytopenia require no specific treatment, as their platelet counts will recover promptly following withdrawal of the causative agent. See Section 5.5 for recording AEs.

5.4 Definition of 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). See Section 5.5 for recording AEs.

5.5 Recording of Adverse Events

AEs, including SAEs, AESIs, and NOCDs, will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. These events will be assessed by the Investigator for severity, relationship to the investigational product and study procedure(s), possible etiologies, and whether the event meets criteria of an SAE (see Section 5.2 and 5.6), or is an AESI or NOCD (see Section 5.3, 5.4 and 5.7) and therefore requires immediate notification to the Sponsor. See Appendix B for guidelines for assessment of severity and relationship to investigational product.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the AE form in the eCRF as an SAE.

5.5.1 Time Period for Collection of Adverse Events

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

AESIs and NOCDs will be collected from the time of dosing through Day 151.

5.5.2 Follow-up of Unresolved Adverse Events

Any AE that is unresolved at the subject's last visit will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.5.3 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question ("Have you had any health problems since the previous visit/since you were last asked?") from study site staff or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.5.4 Adverse Events Based on Examination and Tests

Abnormal results of examination and tests at screening (e.g. hematology, clinical chemistry, urinalysis, ECG, physical examination, vital signs, etc.) are regarded as existing conditions before ICF and will not be recorded as AE. Relevant clinically significant abnormality during screening can be recorded as medical history according to investigator's medical judgement.

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report. An abnormal laboratory finding that requires medical intervention by the Investigator, or a finding judged by the Investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia vs low hemoglobin value). In the

absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

5.5.5 Potential Hy's Law and 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. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.6 Reporting of Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and/or will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel must inform the appropriate Sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor's Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated Sponsor representative(s).

If the EDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate Sponsor representative by telephone. The Sponsor representative will advise the Investigator/study site personnel how to proceed.

5.7 Other Events Requiring Immediate Reporting

5.7.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of the assigned dosage in the study, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a Sponsor investigational product occurs during the study, then the Investigator or other site personnel should inform appropriate Sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.6. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.7.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor except for:

- A pregnancy that is discovered before the study subject has received any investigational product.

5.7.2.1 Maternal Exposure

If a subject is pregnant, investigational product should not be administered.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel will inform the appropriate Sponsor representatives within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.6) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.7.2.2 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of dosing until 150 days after the last dose and as indicated by previous studies (preclinical and clinical) should, if possible, be followed up and documented.

5.7.3 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for a Sponsor investigational product that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred

- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IWRS errors)
- Wrong drug administered to subject (excluding IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IWRS including those which lead to one of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.6) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

5.7.4 Adverse Events of Special Interest

5.7.4.1 Anaphylaxis and Other Serious Hypersensitivity Reactions Including Immune Complex Disease

Events of hypersensitivity, including anaphylaxis (as defined in Appendix C), require that the Investigator or other site personnel inform appropriate Sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. The designated Sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered in EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

Signs of hypersensitivity include urticaria, pruritus, angioedema, skin rash, difficulty breathing, and wheezing. Subjects will be provided a card with this information to aid in prompt identification and reporting of these signs. Subjects will be instructed to immediately report the occurrence of any of these findings to the site Investigator who should then report the events to appropriate Sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. Events of immune complex disease (as defined in Section 5.3.1) require that the Investigator or other site personnel inform appropriate Sponsor study representatives immediately, or no later than 24 hours of when he or she becomes aware of the event. The designated Sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

5.7.4.2 Thrombocytopenia

Events of thrombocytopenia (platelet count < 120,000 per µL) require that the Investigator or other site personnel inform appropriate Sponsor study representatives immediately, or **no later than 24 hours** of when he or she becomes aware of the event. The designated Sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

5.7.5 New Onset Chronic Disease

If a case of NOCD occurs in the course of this study, the Investigator or other site personnel must inform appropriate Sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. The designated Sponsor study representative works with the Investigator to ensure that all relevant information is provided and entered into EDC. If the event is considered serious it must be reported as an SAE (see Section 5.6).

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a Sponsor representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a Sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The Sponsor representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at the site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between the Sponsor and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

6.4 Data Management

Data management will be performed by the Sponsor's Data Management staff or other party according to the Data Management Plan.

An EDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Investigator Coverage

Each subject will be provided with contact information for the Investigator. When a subject visits a medical facility and requires any medical care (medication or treatment), the treating physician or health care provider should contact the Principal Investigator (or designee Investigator who has knowledge of the investigational product and the clinical study protocol) before any treatment is given to the subject.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the study, eg, demographic information, physical or mental health condition, laboratory test results, etc will only be collected with the subject's informed consent. The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for the site must review and approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The Investigator is responsible for submitting these documents to the applicable IRB/IEC and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The Investigator must provide a copy of the written approval to the Sponsor before enrollment of any subject into the study.

The Sponsor should approve any substantive modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, the Sponsor will ensure that the national regulatory authority in China has been notified and their approval has been obtained, as required. The Sponsor will provide safety updates/reports according to local requirements, including SUSARs where relevant, to regulatory authorities, IRB/IEC, and Principal Investigators.

The Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. The Sponsor will provide this information to the Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. The Sponsor will develop a core informed consent form for use by all Investigators in the clinical study. The Sponsor must approve any modifications to the informed consent form that are needed to meet local requirements.

The Principal Investigator(s) at the site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any reimbursement for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Investigators and the Sponsor. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, the Sponsor will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by the IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the site.

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Appendix A Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table A1.
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 150 days after the final dose of investigational product.

Table A1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS)[a] • Bilateral tubal occlusion • Vasectomized partner[b] • Sexual abstinence[c]	Combined (estrogen and progestogen containing hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation[d] ° Injectable ° Implantable ° Intravaginal

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

Appendix B Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from adverse event (AE) as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Assessment of Severity

Assessment of severity is one of the responsibilities of the Investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the Investigator based upon medical judgment and the grading scales in NCI CTCAE version 5.0 for all events with an

assigned CTCAE grading. For those events without assigned CTCAE grades, the following general guideline from CTCAE should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Instrumental activities of daily living refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care activities of daily living. Self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates ‘or’ within the description of the grade.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

A guide to Interpreting the Causality Question

The Investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology)

or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? The Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The Investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix C National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Disease (NAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient/subject (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that patient/subject (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including all local laboratory evaluations even if collected outside of the study visits.

The Investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The Investigator participates, together with the Sponsor's clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the investigational product.

The Investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting AEs and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

D 2.1 Potential Hy's Law

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).

D 2.2 Hy's Law

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.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor study representative
- Determine whether the subject meets PHL criteria (see Section D 3 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

D 4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the Investigator will:

- Notify the Sponsor study representative who will then inform the study team
- Within 1 day of potential Hy's Law criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the relevant CRF Modules as information becomes available.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician will contact the Investigator to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug-induced liver injury (DILI) caused by the investigational product. This will ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. The Study Physician and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Send the updated SAE (report term 'Hy's Law') according to the Sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law (report term now 'Hy's Law case'), ensuring causality assessment is related to the investigational product and seriousness criteria are medically important, according to the clinical study protocol process for SAE reporting
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are met. Update the previously submitted potential Hy's Law SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets potential Hy's Law criteria on investigational product and has already met potential Hy's Law criteria at a previous on investigational product visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's Law is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of potential Hy's Law criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease?

If **No**: follow the process described in Section D 4.2 for reporting potential Hy's Law as an SAE.

If **Yes**: Determine if there has been a significant change in the subject's condition compared with when potential Hy's Law criteria were previously met:

- If there is no significant change no action is required

- If there is a significant change, follow the process described in Section D 4.2 for reporting potential Hy's Law as an SAE

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

D 7 Laboratory Tests

To evaluate the underlying etiology of potential Hy's Law cases, relevant laboratory tests may be performed as clinically indicated.

D 8 References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: premarketing clinical evaluation'

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