A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Nirsevimab, a Monoclonal Antibody With Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm and Term Infants in China

Sponsor Protocol Number:	D5290C00006
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PROTOCOL SYNOPSIS

TITLE

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Nirsevimab, a Monoclonal Antibody With Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm and Term Infants in China

HYPOTHESES

Primary Hypothesis

Compared to placebo, a single intramuscular (IM) nirsevimab dose, 50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg, will be efficacious in reducing medically attended lower respiratory tract infection (LRTI) caused by real-time reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed respiratory syncytial virus (RSV) in healthy preterm and term infants born ≥ 29 weeks 0 days gestational age (GA) and entering their first RSV season, and the safety profile will be acceptable.

Secondary Hypotheses

- There will be a reduction in the incidence of hospitalizations attributable to RT-PCR-confirmed RSV.
- The predicted serum exposures of nirsevimab will be adequate for the duration of the RSV season.
- Antidrug antibody (ADA) to nirsevimab will not impact the serum concentrations or safety of nirsevimab through 150 days post dosing (ie, during a typical 5-month RSV season).

OBJECTIVES AND ASSOCIATED ENDPOINTS

Type	Objective	Endpoint
Primary		
Efficacy	To assess the efficacy of nirsevimab in reducing medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo, when administered as a single fixed IM dose to healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Secondary		
Efficacy	To assess the efficacy of nirsevimab in reducing hospitalizations due to RT-PCR-confirmed RSV, compared to placebo	Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Safety	To evaluate the safety and tolerability of nirsevimab when administered as a single fixed IM dose, compared to placebo	Safety and tolerability of nirsevimab as assessed by the occurrence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs)
Pharmacokinetics (PK)	To evaluate serum concentrations of nirsevimab	Summary of nirsevimab serum concentrations and estimated PK parameters (maximum observed concentration, area under the concentration-time curve, apparent clearance, and terminal-phase half-life), if data permit
ADA	To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum

Type	Objective	Endpoint
Exploratory		
Healthcare resource utilization (HRU)	To assess HRU for nirsevimab recipients compared to placebo recipients	Magnitude of HRU (eg, number of admissions to hospitals and intensive care units and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and type of outpatient visits, eg, emergency room [ER], outpatient clinic; and number of prescription and over-the-counter [OTC] medications and duration of use)
RSV resistance monitoring	To characterize resistance to nirsevimab through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by nirsevimab
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV after Day 151 for nirsevimab recipients compared to placebo	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361

STUDY DESIGN

Study D5290C00006 is a Phase 3, randomized, double-blind, placebo-controlled study to determine if nirsevimab will prevent medically attended RSV-confirmed LRTI in healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season. Approximately 800 subjects will be randomized. Randomization will be stratified by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months), and by GA (< 35 weeks GA, ≥ 35 weeks GA). Enrollment of infants > 6 months of age will be limited to approximately 100. All subjects will be followed through 1 year after dose administration.

Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these respiratory events even those not meeting the protocol-defined endpoint of LRTI. Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower respiratory tract), a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including ER visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a protocol-defined medically attended LRTI. To meet the protocol-defined endpoint of medically attended LRTI, subjects with signs of LRTI must have documented at least one physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/minute; age 2 to 6 months, ≥ 50 breaths/minute; age > 6 months, ≥ 40 breaths/minute), OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous fluid)

A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV. Testing for RSV will be performed centrally in China using an RT-PCR assay.

TARGET SUBJECT POPULATION

Healthy preterm and term infants ≥ 29 weeks 0 days GA entering their first RSV season.

TREATMENT GROUPS AND REGIMENS

Subjects will be randomly assigned in a 2:1 ratio to receive a single IM dose of nirsevimab (N = 530) or placebo (N = 270). The nirsevimab dose level will be stratified by body weight at time of dosing: 50 mg nirsevimab for infants < 5 kg or 100 mg nirsevimab for infants ≥ 5 kg.

STATISTICAL METHODS

General Considerations

There are 2 planned analyses for this study: the primary analysis and the final analysis. The primary analysis will be conducted after all randomized subjects have completed the Day 151 visit, and the final analysis will be conducted when all subjects have completed the last visit of the study (Day 361).

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 Intent-to-treat (ITT) Population is defined as all subjects who are randomized. Subjects will be included in the treatment group corresponding to their randomized treatment. All efficacy and HRU analyses will be performed on the ITT Population unless otherwise specified.

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

The PK Population will include all subjects who have received any dose of investigational product, and who 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 performed on the PK Population.

Sample Size

This study will randomize approximately 800 subjects of whom approximately 530 subjects will receive nirsevimab and approximately 270 subjects will receive placebo. Considering 10% attrition, this sample size has at least 90% power to detect 70% relative risk reduction (RRR), assuming a placebo medically attended RSV LRTI incidence of 8%, with a 2-sided $\alpha = 0.05$. The assumption of 8% incidence is supported both by the literature and the observed placebo incidence rate (9.5%) in the Phase 2b Study D5290C00003. The 70% RRR assumption is based on the Phase 2b Study D5290C00003 in which nirsevimab prophylaxis resulted in 70.1% RRR in the incidence of medically attended RSV LRTI (9.5% placebo, 2.6% nirsevimab; $p < 0.0001$) and 78.4% RRR in the incidence of RSV hospitalization (4.1% placebo, 0.8% nirsevimab; $p = 0.0002$).

To evaluate risk, a sample size of 530 subjects exposed to nirsevimab will provide a > 95% probability of observing at least one adverse event (AE) if the true event rate is 0.6%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.6%.

Efficacy Analyses

The primary and secondary efficacy hypotheses will be assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis will be tested at a significance level of 0.05 only if the treatment effect on the primary efficacy endpoint is demonstrated at the significance level of 2-sided 0.05. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose (ie, during a typical 5-month RSV season) for all infants, based on RSV test results (performed centrally using RT-PCR) and objective protocol-defined LRTI criteria, is the primary endpoint and will be presented by treatment groups. For subjects with multiple events, only the first occurrence will be used in the analysis.

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation techniques and will be described in the statistical analysis plan. A Poisson regression model with robust variance, including treatment group and 2 stratification factors (age at randomization and GA group) as covariates, will be used as the primary efficacy analysis model. The RRR, defined as 1-Relative Risk, and its corresponding 2-sided 95% confidence interval, will be estimated from the model. In addition, the 2-sided p value testing null hypothesis that the incidence of medically attended RSV LRTI between nirsevimab and placebo groups are the same, will be obtained from the model. Statistical significance will be achieved if the 2-sided p value is ≤ 0.05.

A Cochran-Mantel-Haenszel approach stratified by the 2 stratification factors will be used to compare the incidence of RSV LRTI through 150 days post dose between treatment groups as a secondary analysis for the primary endpoint.

Additional analyses for the primary efficacy endpoint will be performed to compare the treatment group differences in time-to-first RSV LRTI. Summaries for age at onset of the first RSV LRTI, inpatient/outpatient visit settings, and RSV subtypes associated with the primary endpoint will also be provided. The primary efficacy endpoint will also be examined by prespecified subgroups, including subpopulations (ie, healthy preterm population, healthy late preterm and term population) corresponding to those enrolled in the global Studies D5290C00003 and D5290C00004.

The incidence of RSV hospitalization through 150 days post dose for all infants is the secondary efficacy endpoint and will be presented by treatment group. Similar methods as described above for the primary efficacy endpoint will be used to assess efficacy on RSV hospitalization.

Safety Analyses

AEs will be graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events where applicable for pediatric assessments. AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to investigational product will be summarized. 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.

Pharmacokinetic Analyses

Serum concentrations of nirsevimab at selected time points will be evaluated to confirm that adequate exposures for protection from RSV LRTI are maintained for at least 5 months after dosing. Nirsevimab serum concentration data will be presented in descriptive statistics. PK parameters (eg, maximum observed concentration, area under the concentration-time curve, apparent clearance, and terminal-phase half-life) will be estimated using noncompartmental analysis, if data permit.

Antidrug Antibody Analyses

The incidence of ADA to nirsevimab will be assessed and summarized by number and percentage of subjects who are ADA positive by treatment group. The impact of ADA on PK, efficacy, and association with TEAEs and TESAEs, will be assessed.

Exploratory Analyses

<u>Healthcare Resource Utilization</u>

The magnitude of HRU (eg, number of admissions to hospitals and intensive care units and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, ER, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized overall by treatment group, and for the following subgroups: subjects

with at least one medically attended LRTI caused by RT-PCR-confirmed RSV, subjects with medically attended LRTI not caused by RSV, and subjects with non-protocol-defined LRTIs, which may be further broken down by RSV status.

Monitoring RSV Resistance to Nirsevimab

Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using an RT-PCR assay. RSV genotypic analysis will report the sequence changes in the mature F protein from all RSV positive isolates compared to contemporary RSV A and RSV B reference strains. Susceptibility of novel recombinant RSV variants to nirsevimab will be tested and compared to laboratory-adapted RSV A2 or B9320 viruses.

RSV LRTI Occurring From Day 152 to Day 361

The incidence of medically attended RSV LRTI (inpatient and outpatient) from Day 152 to Day 361 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group.

Interim Analyses

No interim analyses are planned.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
aa	amino acid
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration time-curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
CMH	Cochran-Mantel-Haenszel
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
Fc	fragment cystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GA	gestational age
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HRU	healthcare resource utilization
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IM	intramuscular
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
IWRS	interactive web response system
LRTI	lower respiratory tract infection
mAb	monoclonal antibody

Abbreviation or Specialized Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOCD	new onset chronic disease
OTC	over-the-counter
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
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
wGA	weeks gestational age
YTE	M257Y/S259T/T261E triple amino acid substitution

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.

The burden and seriousness of RSV disease has kept RSV a global priority for vaccine development. However, despite many years of attempted vaccine development (Kim et al 1969), there is no safe and effective vaccine, and treatment for patients with RSV illness is limited to supportive care. Internationally, palivizumab (Synagis®) is the only drug approved for prevention of RSV disease. Palivizumab is only indicated for use in high-risk children (ie, preterm infants ≤ 35 weeks gestational age [wGA], children with chronic lung disease [CLD] of prematurity, and children with hemodynamically significant congenital heart disease [CHD]). In China, palivizumab is not licensed and there are currently no options available for the prevention of RSV.

1.2 Nirsevimab Background

Nirsevimab 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) 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 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 study treatment 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 (ITT) 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. 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 nirsevimab global clinical development program includes 2 pivotal studies for infants entering their first RSV season: a completed Phase 2b study (D5290C00003; NCT02878330) and an ongoing Phase 3 study (D5290C00004 [MELODY]; NCT03979313) in healthy late-term and term infants. A Phase 2/3 study (D5290C00005 [MEDLEY]; NCT03959488) is currently being conducted in high-risk palivizumab-eligible population entering their first and second RSV seasons. In addition, this China Phase 3 study is planned to support an indication for a single dose of nirsevimab in healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season. 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 younger infants and in high-risk children, there is an established unmet medical need for the use of nirsevimab as a prophylactic mAb in all infants entering their first RSV season and in high-risk preterm infants and children up to 2 years 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 high-risk children. Infants in this study who receive nirsevimab may potentially benefit by being protected against serious RSV disease.

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 common safety risks 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 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 development through Phase 2b is favorable.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Compared to placebo, a single IM nirsevimab dose, 50 mg if weight < 5 kg or 100 mg if weight ≥ 5 kg, will be efficacious in reducing medically attended LRTI caused by real-time RT-PCR-confirmed RSV in healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season, and the safety profile will be acceptable.

1.7.2 Secondary Hypotheses

- There will be a reduction in the incidence of hospitalizations attributable to RT-PCR-confirmed RSV.
- The predicted serum exposures of nirsevimab will be adequate for the duration of the RSV season.

- ADA to nirsevimab will not impact the serum concentrations or safety of nirsevimab through 150 days post dosing (ie, during a typical 5-month RSV season).

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To assess the efficacy of nirsevimab in reducing medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo, when administered as a single fixed IM dose to healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)

GA = gestational age; IM = intramuscularly; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Efficacy	To assess the efficacy of nirsevimab in reducing hospitalizations due to RT-PCR-confirmed RSV, compared to placebo	Incidence of hospitalizations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Safety	To evaluate the safety and tolerability of nirsevimab when administered as a single fixed IM dose, compared to placebo	Occurrence of TEAEs, TESAEs, AESIs, and NOCDs
PK	To evaluate serum concentrations of nirsevimab	Summary of nirsevimab serum concentrations and estimated PK parameters (C_{max}, AUC, apparent clearance, and terminal-phase $t_{1/2}$) if data permit
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; AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; IM = intramuscular; LRTI = lower respiratory tract infection; NOCD = new onset chronic disease; PK = pharmacokinetics; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

2.3 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
HRU	To assess HRU for nirsevimab recipients compared to placebo recipients	Magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and type of outpatient visits, eg, ER, outpatient clinic; and number of prescription and over-the-counter medications and duration of use)
RSV resistance monitoring	To characterize resistance to nirsevimab through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralization by nirsevimab
RSV LRTI after Day 151	To assess the incidence of medically attended LRTI due to RT-PCR-confirmed RSV after Day 151 for nirsevimab recipients compared to placebo	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361

ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

Study D5290C00006 is a Phase 3, randomized, double-blind, placebo-controlled study to determine if nirsevimab will prevent medically attended RSV-confirmed LRTI in healthy preterm and term infants born ≥ 29 weeks 0 days GA entering their first RSV season (Figure 1). Approximately 800 subjects will be randomized. Randomization will be stratified by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months), and by GA (< 35 wGA, ≥ 35 wGA). Enrollment of infants > 6 months of age will be limited to approximately 100. Subjects will be followed through 1 year after dose administration.

Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these respiratory events even those not meeting the protocol-defined endpoint of LRTI. Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower respiratory tract), a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including emergency room [ER] visits) for a lower

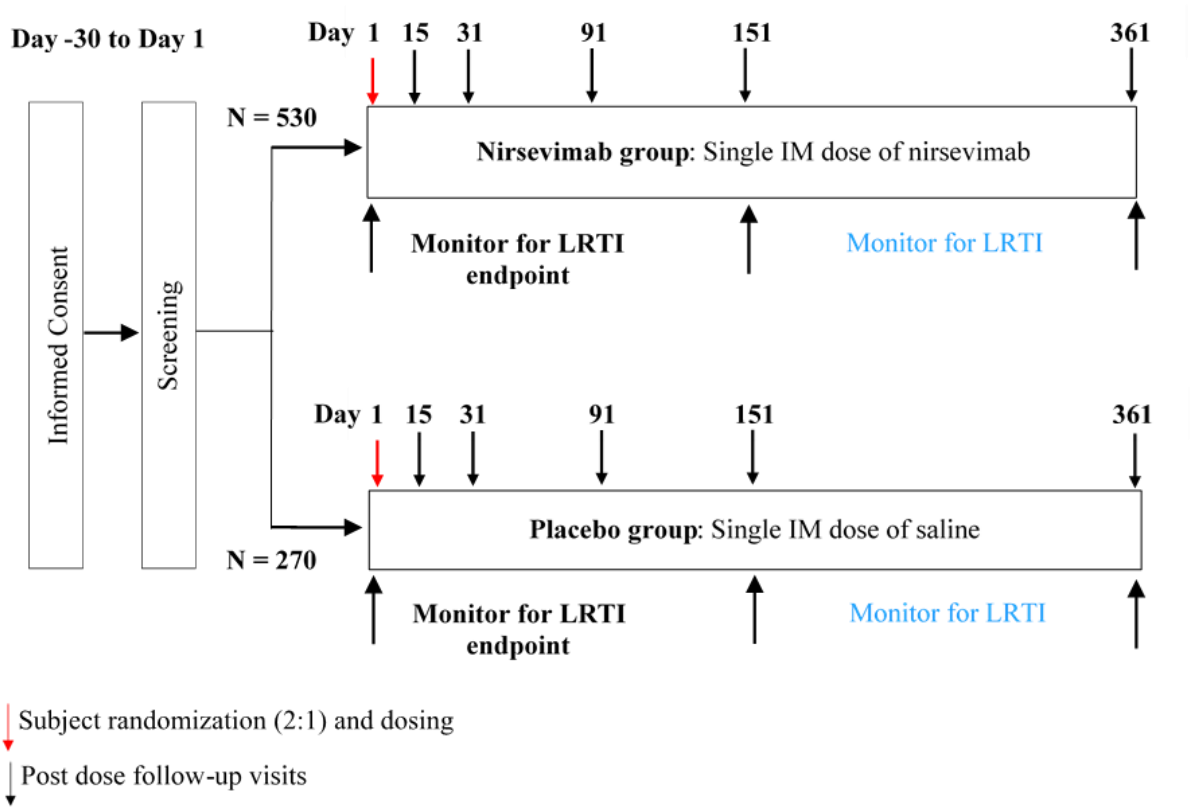
respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of a protocol-defined medically attended LRTI. To meet the protocol-defined endpoint of medically attended LRTI, subjects with signs of LRTI must have documented at least one physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/minute; age 2 to 6 months, ≥ 50 breaths/minute; age > 6 months, ≥ 40 breaths/minute), OR
- Hypoxemia (in room air: oxygen saturation < 95% at altitudes ≤ 1,800 meters or < 92% at altitudes > 1,800 meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid).

A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV. Testing for RSV will be performed centrally in China using an RT-PCR assay.

Figure 1 Study Flow Diagram



ADA = antidrug antibody; IM = intramuscular; LRTI = lower respiratory tract infection; PK = pharmacokinetics.
Blood samples for PK and ADA will be collected at screening or Day 1 predose, on Days 15 (PK only), 151, and 361, and from subjects hospitalized for a respiratory infection through Day 361.
Safety assessments will be performed through Day 361.

The endpoints to be measured in this study are described in Section 2.

3.1.2 Treatment Regimen

Subjects will be randomly assigned in a 2:1 ratio to receive a single IM dose of nirsevimab (N = 530) or placebo (N = 270). The nirsevimab dose level will be stratified by body weight at time of dosing: 50 mg nirsevimab for infants < 5 kg or 100 mg nirsevimab for infants ≥ 5 kg.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

A single fixed 50-mg IM dose was shown to be efficacious in the Phase 2b Study D5290C00003 in preterm infants (29 to < 35 wGA) in their first RSV season (see Section 1.4.3). Model-based analyses of the Phase 2b clinical PK and efficacy data identified a projected serum $AUC_{0-\infty}$ of 13.4 day.mg/mL as the protective exposure threshold. The risk of medically attended RSV-confirmed LRTI over the course of the RSV season was significantly

lower in infants with higher projected $AUC_{0-\infty}$. Infants with $AUC_{0-\infty}$ above 13.4 day.mg/mL had a statistically significant higher probability of protection based on exposure-response analysis using Cox-proportional hazard regression. Although, the fixed 50 mg dose resulted in clinically efficacious exposures for 97.0% of infants weighing < 5 kg in the Phase 2b study, this dose was suboptimal for infants weighing ≥ 5 kg in this study. Overall, 3.0% and 59.0% of the infants in groups weighing < 5 kg and ≥ 5 kg, respectively, were in the lowest $AUC_{0-\infty}$ quartile (4.5 to 13.4 day.mg/mL) that was determined to be suboptimal. Based on these analyses, a stratified fixed dosing strategy by weight bands will be implemented to ensure an adequate dose to maintain nirsevimab serum concentrations above the target AUC throughout the RSV season. Based on dose optimization analysis designed to maximize the proportion of infants with clinically efficacious nirsevimab serum exposure, a single fixed 50-mg IM dose will be administered for infants < 5 kg in their first RSV season, whereas a single fixed 100-mg dose will be administered for those weighing ≥ 5 kg entering their first RSV season.

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. A dose of 50 mg nirsevimab was first evaluated in healthy preterm infants 29 to < 35 wGA (per US FDA advice), including a small number of Asian subjects, in the pivotal Phase 2b Study D5290C00003 with favorable benefit-risk results (see Section 1.4.3). This study proposes to further extend the population to healthy preterm and term infants (≥ 29 weeks 0 days GA) in China to meet the overall goal of evaluating nirsevimab for prevention of RSV disease in all infants entering their first RSV season.

3.2.3 Rationale for Endpoints

The global clinical development program of nirsevimab is intended to include all infants, including high-risk infants and children. This study will evaluate nirsevimab for RSV immunoprophylaxis in healthy preterm and term infants born ≥ 29 weeks 0 days GA and entering their first RSV season. The primary endpoint is the incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season). This endpoint will examine the efficacy of nirsevimab compared to placebo in preventing LRTI due to RSV. The secondary efficacy endpoint is the incidence of RSV hospitalization through 150 days after dosing. This endpoint will examine the efficacy of nirsevimab compared to placebo in preventing hospitalization due to RSV. RSV results in a significant burden of disease consisting of hospitalization, visits to the ER, and visits to outpatient clinics. The primary and secondary endpoints are designed to allow the capture of the total burden of RSV disease and the efficacy of nirsevimab in reducing that burden.

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

Serum concentration of nirsevimab at selected time points will be evaluated as a secondary endpoint to confirm that adequate serum exposures are maintained for at least 5 months after dosing. Additionally, serum concentration data will be used to characterize the PK of nirsevimab in infants using a separate population PK approach. For infants who require hospitalization for LRTI or any respiratory infection, an additional serum sample for measurement of nirsevimab concentration and ADA will be obtained contemporaneous with time of hospitalization. Exposure-response analysis will be performed to relate nirsevimab serum concentrations and efficacy endpoints (LRTI including RSV-associated hospitalization).

To determine nirsevimab serum levels post dosing and correlation with the development of ADA, serum concentrations will be measured up to 360 days post dose. ADA will be measured at selected time points throughout the study and at 360 days post dose as well.

Exploratory endpoints will examine the magnitude of healthcare resource utilization (HRU) due to RSV illness in the studied population. This will allow the determination of social and economic resources that are required for infants who have RSV-confirmed LRTI. To monitor for RSV resistance, the F protein from collected RSV isolates will be genetically characterized and novel variants will be phenotypically characterized for nirsevimab susceptibility. The incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 through Day 361 will be assessed to determine if there is a possible effect of nirsevimab past Day 151.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of approximately 800 infants will be randomized in a 2:1 ratio to receive a single IM dose of nirsevimab (N = 530) or placebo (N = 270).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Healthy Chinese preterm and term infants in their first year of life and born ≥ 29 weeks 0 days GA (infants who have an underlying illness such as cystic fibrosis or Down syndrome with no other risk factors are eligible)
2 Infants who are entering their first RSV season at the time of screening
3 Written informed consent and any locally required authorization obtained from the subject's parent(s)/legal representative(s) prior to performing any protocol-related procedures, including screening evaluations

4 Subject's parent(s)/legal representative(s) able to understand and comply with the requirements of the protocol including follow-up visits as judged by the Investigator
5 Subject is available to complete the follow up period, which will be approximately 1 year after receipt of investigational product

4.1.3 Exclusion Criteria

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

1 Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or acute illness within 7 days prior to investigational product administration
2 Any history of LRTI or active LRTI prior to, or at the time of, randomization
3 Known history of RSV infection or active RSV infection prior to, or at the time of, randomization
4 Any drug therapy (chronic or other) within 7 days prior to randomization or expected receipt during the study with the exception of: a) multivitamins and iron; b) infrequent use of over-the-counter (OTC) medications for the systemic treatment of common childhood symptoms (eg, pain relievers) that may be permitted according to the judgment of the Investigator
5 Any current or expected receipt of immunosuppressive agents including steroids (except for the use of topical steroids according to the judgment of the Investigator)
6 History of receipt of blood products, or immunoglobulin products, or expected receipt through the duration of the study
7 Hospitalization at the time of randomization, unless discharge is expected within the 7 days after randomization
8 Known renal impairment
9 Known hepatic dysfunction including known or suspected active or chronic hepatitis infection
10 History of CLD/bronchopulmonary dysplasia
11 Clinically significant congenital anomaly of the respiratory tract
12 CHD, except for children with uncomplicated CHD (eg, patent ductus arteriosus, small septal defect)
13 Chronic seizure, or evolving or unstable neurologic disorder
14 Prior history of a suspected or actual acute life-threatening event
15 Known immunodeficiency, including human immunodeficiency virus (HIV)
16 Mother with HIV infection (unless the child has been proven to be not infected)
17 Any known allergy or history of allergic reaction to immunoglobulin products, blood products, or other foreign proteins, or history of allergic reaction
18 Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination
19 Receipt of any monoclonal or polyclonal antibody (for example, hepatitis B immune globulin, IV immunoglobulin) or anticipated use during the study

20 Receipt of any investigational product
21 Concurrent enrollment in another interventional study
22 Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product or interpretation of study results
23 Children of 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 or administered investigational product. The Investigator must consult with the Sponsor before a subject who has failed screening may be considered for rescreening.

4.1.5 Withdrawal from the Study

Subjects may at any time be withdrawn from the study without prejudice to further treatment (withdrawal of consent). The caregivers of such subjects will always be asked about the reason(s) for withdrawal and the presence of any AEs. If possible, 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 electronic case report form (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). Subjects who have not received investigational product, regardless of reason, will not be followed.

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 the subject's parent(s)/legal representative(s) fails to return him or her 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's parent(s)/legal representative(s) 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's parent(s)/legal representative(s) and reschedule the missed visit as soon as possible and counsel the subject's parent(s)/legal representative(s) on the importance of maintaining the assigned visit schedule.
- Repeated attempts must be made to regain contact with the subject's parent(s)/legal representative(s) 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's parent(s)/legal representative(s) should continue until the end of the study.

The subject will be classified as lost to follow-up only if his/her parent(s)/legal representative(s) fail to return his/her 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's parent(s)/legal representative(s) 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's parent(s)/legal representative(s) 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 subject's parent(s)/legal representative(s) 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's parent(s)/legal representative(s) 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

Whenever vital signs and blood draws are scheduled for the same nominal time, vital signs should occur prior to blood draws.

4.2.1 Enrollment/Screening Period

Table 4 shows all procedures to be conducted at the screening visit.

Table 4 Schedule of Screening Procedures

Study Period	**Screening**
Visit Number	**V1**
Procedure / Study Day	**Day -30 to Day 1**
Written informed consent/ assignment of SID number	X
Medical history	X
Physical examination	X
Weight	X
Vital signs	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Verify eligibility criteria	X

Table 4 Schedule of Screening Procedures

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Day -30 to Day 1**

AE = adverse event; SAE = serious adverse event; SID = subject identification; V = visit.

4.2.2 Treatment and Follow-up Periods

Investigational product is administered on Day 1. Table 5 shows all procedures to be conducted during the treatment and follow-up periods.

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures

Study Period	**Treatment Period**							**Follow-up Period**					
Visit Number	**V2** [a]	**TC**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**TC**		**LRTI**	**Skin Reaction**
Procedure / Study Day	**D1**	**D8 (± 2 days)**	**D15 (± 2 days)**	**D31 (± 2 days)**	**D61 (± 2 days)**	**D91 (± 2 days)**	**D121 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**D1-151 Q2W (± 5 days)**	**D152-361 monthly (± 5 days)**	**D1-361 as needed**	**D1-361 as needed**
Medical history update	X		X	X	X	X	X	X	X				
Physical examination	X		X	X	X	X	X	X	X				
Weight	X		X	X	X	X	X	X	X				
Vital signs	X[b]		X	X	X	X	X	X	X				
Blood sample for PK, ADA	X[c]		X (PK only)					X	X			X[d]	
Assessment of AEs/SAEs, AESIs, NOCDs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X												
Randomization	X												
IP administration	**X**												
Assessment of LRTI or any respiratory infection that requires hospitalization												X[d]	
Nasal swab collection												X[d]	
Assessment of skin reaction													X[e]
Telephone contact[f]		X								X	X		
HRU[g]												X	

Table 5 Schedule of Treatment Period and Follow-up Period Study Procedures

Study Period	Treatment Period							Follow-up Period					
Visit Number	V2 [a]	TC	V3	V4	V5	V6	V7	V8	V9	TC		LRTI	Skin Reaction
Procedure / Study Day	D1	D8 (± 2 days)	D15 (± 2 days)	D31 (± 2 days)	D61 (± 2 days)	D91 (± 2 days)	D121 (± 2 days)	D151 (± 7 days)	D361 (± 7 days)	D1-151 Q2W (± 5 days)	D152-361 monthly (± 5 days)	D1-361 as needed	D1-361 as needed

ADA = anti-drug antibody; AE = adverse event; AESIs = adverse events of special interest; D = study day; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; IP = investigational product; LRTI = lower respiratory tract infection; NOCDs = new onset chronic diseases; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every 2 weeks; SAE = serious adverse event; TC = telephone call; V = visit.

[a] Visit 2/Day 1 and Visit 1/Screening can occur on the same day.

[b] All vital signs (temperature, blood pressure, heart rate, and respiratory rate) should be obtained within 60 minutes prior to dosing, and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post dose.

[c] PK and ADA samples will only be collected predose in randomized subjects.

[d] Nasal samples will be collected from all subjects with LRTIs (inpatient or outpatient) and from all hospitalized subjects with any new respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis.
Blood samples will be collected from all subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospital admission.

[e] Skin reaction assessment will be done for any post-dosing skin or skin-related reaction regardless of severity, duration, time of onset post dosing, or relationship to IP.

[f] Telephone contact must be verbal communication and documented. Written communication via text, email, or other written form is not acceptable.

[g] HRU includes admission and duration of hospital and ICU stay, number of subjects who require respiratory support and supplemental oxygen use, duration of respiratory support and supplemental oxygen use, number and type of outpatient visits (eg, ER, outpatient clinic), and number and days of prescription and OTC medication.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Lower Respiratory Tract Infection

Subjects will be monitored throughout the study for LRTI (see Table 5). All subjects seeking medical attention for a respiratory illness (in either the inpatient or outpatient setting) will be evaluated for the occurrence of LRTI (Table 6). All subjects found to have an LRTI and all subjects who require hospitalization for a respiratory infection, even if there is not a diagnosis of LRTI, should have respiratory samples obtained and respiratory assessment forms completed. Samples should be collected for all of these respiratory events even those not meeting the protocol definition of LRTI. Subjects who have a primary hospitalization for a respiratory infection (ie, upper or lower tract) or a respiratory deterioration during a hospitalization, or who seek outpatient medical attention (including ER visits) for a lower respiratory illness, will be assessed clinically for the presence of LRTI and for RSV by central laboratory diagnostic testing of respiratory secretions. A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV. Testing for RSV will be performed centrally in China using an RT-PCR assay.

In addition to the clinical assessment of LRTI, there is a protocol definition using objective criteria for the determination of protocol-defined medically attended LRTI. To meet the protocol-defined endpoint of medically attended LRTI, subjects with signs of LRTI must have documented at least one physical examination finding of rhonchi, rales, crackles, or wheeze AND at least one of the following clinical signs:

- Increased respiratory rate at rest (age: < 2 months, ≥ 60 breaths/min; 2 to 6 months, ≥ 50 breaths/min; > 6 months, ≥ 40 breaths/min), OR
- Hypoxemia (in room air: oxygen saturation $< 95\%$ at altitudes $\leq 1{,}800$ meters or $< 92\%$ at altitudes $> 1{,}800$ meters), OR
- Clinical signs of severe respiratory disease (eg, acute hypoxic or ventilatory failure, new onset apnea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid).

Table 6 Criteria for Meeting the Protocol-defined Endpoint of Medically Attended RSV LRTI

RSV	Lower Respiratory Tract	Medical Significance
RSV Confirmed: • Positive by central laboratory RT-PCR assay	**Documented PE findings localizing to lower respiratory tract**: • Rhonchi • Rales • Crackles • Wheeze	**Objective measures of clinical severity**: • Increased respiratory rate • Hypoxemia • Acute hypoxic or ventilatory failure • New onset apnea • Nasal flaring • Retractions • Grunting • Dehydration due to respiratory distress

LRTI = lower respiratory tract infection; PE = physical examination; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.
Note: One item from each column is required to meet the protocol-defined endpoint of RSV LRTI.

RSV Hospitalization

An RSV hospitalization is defined as either (1) a respiratory hospitalization with a positive RSV test within approximately 2 days of hospital admission (primary) or (2) a new onset of respiratory symptoms in an already hospitalized subject, with an objective measure of worsening respiratory status and positive RSV test (nosocomial). Primary and nosocomial RSV hospitalization are further defined below.

Primary RSV Hospitalization

RSV diagnostic testing will be performed on respiratory secretions obtained within approximately 2 days before or after admission for subjects hospitalized for respiratory infection (upper or lower respiratory tract). If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the hospitalization will be classified as a primary RSV hospitalization. Deaths that can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) will also be considered as primary RSV hospitalization endpoints.

Nosocomial RSV Hospitalization

Subjects hospitalized for a respiratory illness or non-respiratory illness whose RSV diagnostic test is negative may develop nosocomial RSV illness during the study.

If signs (such as retractions, rhonchi, wheezing, crackles or rales) of a new lower respiratory illness occur during a hospitalization, whatever the reason for hospitalization, and there is an objective measure of worsening respiratory status (that is, new requirement for supplemental oxygen, increase in supplemental oxygen requirement from prior to the onset of symptoms, or

need for new or additional mechanical ventilation), a specimen will be collected within approximately 2 days from worsening of respiratory status for RSV diagnostic testing by the central laboratory. For any subject who is hospitalized for a respiratory infection (upper or lower respiratory tract), the subject must return to his/her baseline respiratory status or be clearly resolving the preceding respiratory illness before a subsequent respiratory deterioration for a nosocomial RSV hospitalization event can be determined.

If the RSV diagnostic test (performed centrally via RT-PCR) is positive, the subsequent hospital days will count as a nosocomial RSV hospitalization. The days of RSV hospitalization will be counted beginning with the start of the respiratory deterioration that resulted in the RSV diagnostic test.

RSV LRTI Outpatient Events

Subjects who seek outpatient medical attention, including ER visits, for an LRTI should have respiratory secretions obtained within approximately 2 days after the initial healthcare provider assessment.

Respiratory Secretions for RSV Detection

Respiratory secretions for RSV testing must be collected from all subjects with LRTIs (inpatient or outpatient) and from all hospitalized subjects with any new respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis. Nasal secretions will be obtained unless the subject is intubated, and then tracheal secretions may be obtained.

Respiratory secretions will be tested in a central laboratory in China for RSV using an RT-PCR assay. Testing may include other respiratory pathogens.

Monitoring for RSV Resistance

As an exploratory endpoint, novel RSV F variants identified in RSV positive nasal specimens collected from study subjects will be evaluated by genotypic and phenotypic methods to monitor potential susceptibility changes to nirsevimab neutralization. The subtype and genotypic determination of RSV will be performed directly on the nasal specimens that are collected from all subjects who are confirmed RSV-positive using an RT-PCR assay. The full-length F gene will be amplified using a standard, single-tube population-based RT-PCR method and sequenced by Sanger and Next-Generation sequencing methodology to detect polymorphisms and minor variants, respectively. Amino acid (aa) substitution(s) within the nirsevimab binding site (aa 62-69 and aa 196-212) and outside the binding site in the extracellular regions of mature F protein (aa 24-109 and aa 137-524) will be reported and compared to F protein sequences of contemporary reference RSV A or RSV B strains. In vitro phenotypic analysis (susceptibility to nirsevimab neutralization) will be attempted using an

RSV neutralization assay (performed at Viroclinics Biosciences, Rotterdam, The Netherlands) with recombinant RSV viruses constructed through site-directed mutagenesis of the F gene and reverse genetics into laboratory-adapted RSV A2 or B9320 strains.

4.3.2 Medical History and Physical Examination, Weight, and Vital Signs

A complete medical history will be obtained at screening and a medical history update will be obtained on the day of dosing and during the follow-up period as defined in Section 4.2. Assessment will include history and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

A physical examination will be performed at screening, on the day of dosing, and during the follow-up period as defined in Section 4.2. The physical examination will include assessment of weight at screening and at each study visit mentioned above.

Vital signs (temperature, blood pressure, respiratory rate, and heart rate measurements) will be collected at screening, on the day of dosing, and during the follow-up period as defined in Section 4.2. On Day 1, vital signs will be monitored before and after administration of investigational product.

Baseline information will be collected on breastfeeding, smoking in the household, and if the infant attends day care.

4.3.3 Pharmacokinetics and Antidrug Antibody

A blood sample for assessment of PK and ADA will be collected through Day 361 according to the schedule defined in Section 4.2. 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.

4.3.3.1 Pharmacokinetic Evaluation

Blood samples to evaluate the PK of nirsevimab in serum will be collected according to scheduled time points. Blood samples for PK evaluation will also be collected from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days following hospitalization. See the collection schedule in Section 4.2. The concentration of nirsevimab in serum will be measured using validated assays.

4.3.3.2 Antidrug Antibody Evaluation

Blood samples to evaluate ADA responses to nirsevimab in serum will be collected according to scheduled time points. Blood samples will also be collected for ADA response from subjects hospitalized with LRTI or any respiratory infection within approximately 2 days

following hospitalization. ADA samples may also be further tested for characterization of the ADA response. See the collection schedule in Section 4.2. Evaluations will be performed using validated immunoassays.

4.3.4 Healthcare Resource Utilization

Information on HRU will be collected for all events of medically attended LRTI through Day 361 (see Section 4.2). This will include admission to and duration of hospital and intensive care unit stay, number of subjects who require respiratory support and supplemental oxygen use, duration of respiratory support and supplemental oxygen use, number and type of outpatient visits (eg, ER, outpatient clinic), and the number of prescription and OTC medications and their duration of use.

4.3.5 Skin Reactions

Skin reaction assessment will be done for any post-dosing skin or skin-related reaction through Day 361 to assist in determination of the etiology of the reaction (see Section 4.2). Information will be collected regardless of event severity, duration, time of onset post dosing, or relationship to investigational product. Parents/legal representatives of study subjects will be given a hypersensitivity card and instructed to call the study site immediately for signs of hypersensitivity or allergic reaction. Sites must notify the Sponsor within 24 hours of knowledge of such events. For any skin or skin-related reactions, including all rashes that occur within 7 days after dosing, the infant will be brought to the study site as soon as possible for evaluation.

4.4 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study at any time. The reasons for temporarily suspending or permanently 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 (in this case the study will be paused for the Sponsor safety review committee to evaluate the events)
2 Anaphylactic reaction that is related to investigational product (see Appendix B for a definition of anaphylaxis; in this case the study will be paused for the Sponsor safety review committee to evaluate the events)
3 Grade 3 and/or 4 hypersensitivity AEs based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale that are assessed as related to nirsevimab in 2 or more subjects
4 Two serious adverse events (SAEs) of the same type that are assessed as related to nirsevimab
5 Other events that, in the judgment of the Sponsor or site Investigator, are deemed serious enough to warrant immediate review by the Sponsor safety review committee

6 Subject enrollment is unsatisfactory
7 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 all participating Investigators (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 all Investigators, heads of the medical institutions (where applicable), and/or institutions 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, 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.02% (w/v) 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.

Investigational product should be stored at 2°C to 8°C.

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

Investigational product will be supplied to the site in open-labeled 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.

4.5.1.1 Investigational Product Inspection

Each vial selected for dose administration 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 Administration 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 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 A dose of 50 mg (ie, 0.5 mL) of nirsevimab will be obtained by withdrawing the entire contents of 1 investigational vial with an appropriately sized syringe.
2 A dose of 100 mg (ie, 1.0 mL) of nirsevimab will be obtained by withdrawing the entire contents of 2 investigational vials with an appropriately sized syringe.
3 For subjects randomized to placebo, a corresponding volume of placebo (0.5 mL for infants < 5 kg or 1.0 mL for infants ≥ 5 kg) should be administered.
4 Switch the needle prior to administration.
5 Administer investigational product using the appropriate size needle ranging from 22 to 25 gauge and 5/8 to 1.0 inches based on muscle size and weight of the subject.

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 labeled to reveal treatment identity.

Investigational product (nirsevimab or placebo) should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections.

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 at 60 minutes (± 5 minutes) post dose.

As with any antibody, 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 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: productcomplaints3@astrazeneca.com

Phone: +1-301-398-2105

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 at a 2:1 ratio to receive nirsevimab (N = 530) or placebo (N = 270). Randomization will be stratified by subject age at the time of randomization (≤ 3 months, > 3 to ≤ 6 months, > 6 months), and by GA (< 35 wGA, ≥ 35 wGA). The number of randomized infants > 6 months of age will be limited to approximately 100.

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 sites are using commercially available saline as the placebo. Nirsevimab and placebo are visually indistinguishable once in syringes. Neither the subjects' parent(s)/legal representatives 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 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.

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 end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care including routine vitamins and iron.

4.7.2 Prohibited Concomitant Medications

Use of concomitant medications including OTC medications (except for routine vitamins and iron), herbal supplements, etc from Day 1 through Day 15 post dose is discouraged. Subjects' parent(s)/legal representatives should be instructed not to administer any medications, including OTC products, without first consulting with the Investigator.

4.8 Statistical Evaluation

4.8.1 General Considerations

There are 2 planned analyses for this study: the primary analysis and the final analysis. The primary analysis will be conducted after all randomized subjects have completed the Day 151 visit, and the final analysis will be conducted when all subjects have completed the last visit of the study (Day 361).

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 ITT Population will include all subjects who are randomized. In this population, data will be analyzed according to the randomized treatment. All efficacy and HRU analyses will be performed on the ITT Population unless otherwise specified.

The As-treated Population will include all subjects who are randomized and who receive any amount of investigational product. In this population, data will be analyzed according to the treatment actually received. All safety and ADA analyses will be performed on the As-treated Population.

The Per-protocol Population will include subjects in the ITT Population who receive the correct dose of randomized treatment and who do not have a serious protocol violation. Detailed criteria defining this population will be determined and documented prior to performing the primary analysis.

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 performed on the PK Population.

4.8.2 Sample Size

This study will randomize approximately 800 subjects of whom approximately 530 subjects will receive nirsevimab and approximately 270 subjects will receive placebo. Considering 10% attrition, this sample size has at least 90% power to detect 70% RRR, assuming a placebo

medically attended RSV LRTI incidence of 8%, with a 2-sided $\alpha = 0.05$ based on a Poisson regression model with robust variance (Zou 2004). The assumption of 8% incidence is supported both by the literature (Paramore et al 2010, Yan et al 2017) and the observed placebo incidence rate (9.5%) in the Phase 2b Study (D5290C00003). The 70% RRR assumption is based on the Phase 2b Study D5290C00003 in which nirsevimab prophylaxis resulted in 70.1% RRR in the incidence of medically attended RSV LRTI (9.5% placebo, 2.6% nirsevimab; $p < 0.0001$) and 78.4% RRR in the incidence of RSV hospitalization (4.1% placebo, 0.8% nirsevimab; $p = 0.0002$).

To evaluate risk, a sample size of 530 subjects exposed to nirsevimab will provide a > 95% probability of observing at least one AE if the true event rate is 0.6%; if no AEs are observed, this study provides 95% confidence that the true event rate is < 0.6%.

The sample size necessary to achieve the power for the incidence of medically-attended RSV LRTI is calculated based on the assumed placebo event rate and the RRR of nirsevimab over placebo using Poisson regression model with robust variance. To mitigate the uncertainty around these assumptions, a blinded sample size re-estimation will be conducted prior to the last subject being randomized into the study.

The overall event rate, as well as the data from external sources (eg, RRR of nirsevimab over placebo in the global Phase 3 study D5290C00004), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed.

4.8.3 Efficacy

The primary and secondary efficacy hypotheses will be assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis will be tested at a significance level of 0.05 only if the treatment effect on the primary efficacy endpoint is demonstrated at the significance level of 2-sided 0.05. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

4.8.3.1 Primary Efficacy Analysis

The primary endpoint is the incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose. For subjects with multiple events, only the first occurrence will be used in the primary analysis. The determination of medically attended RSV LRTI will be based on RSV test results (performed centrally using RT-PCR) and protocol-defined objective clinical LRTI criteria.

The primary efficacy analysis of the primary endpoint will be performed on the ITT Population using a Poisson regression model with robust variance (Zou 2004). The model contains the term of treatment group and age at randomization (ie, age ≤ 3 months, age > 3 to ≤ 6 months, age > 6 months) and GA group (< 35 wGA, ≥ 35 wGA) as covariates. The RRR, defined as 1-Relative Risk, and its corresponding 2-sided 95% CI, will be estimated from the model. In addition, the 2-sided p-value testing null hypothesis that the incidence of medically attended RSV LRTI between nirsevimab and placebo groups are the same will be obtained from the model. Statistical significance will be achieved if the 2-sided p-value is ≤ 0.05.

RSV LRTI that occurs through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a medically attended RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation techniques and will be described in the statistical analysis plan.

If convergence cannot be achieved using the Poisson regression analysis model, the stratified Cochran-Mantel-Haenszel (CMH) test will be used as the primary analysis model.

The above described analysis on the primary efficacy endpoint will also be conducted on the Per-protocol Population.

4.8.3.2 Secondary Analyses of the Primary Endpoint

A CMH test stratified by the 2 stratification factors will be used to compare the incidence of RSV LRTI through 150 days post dose between treatment groups as a secondary analysis for the primary endpoint. The RRR and its associated 95% CI will be provided. This analysis will be performed without imputation. The Breslow-Day test and Zelen's exact test will be used to test the homogeneity of the odds ratios across strata and the corresponding p-values will be presented.

4.8.3.3 Supplementary Analyses of the Primary Endpoint

A Kaplan-Meier curve for time to first medically attended RSV LRTI will be generated based on observed events. Treatment group differences in time-to-first medically attended RSV LRTI will be compared using the stratified log-rank test with the 2 stratification factors (ie, age at randomization, GA group) as the strata.

Additional analyses, including summaries for age at onset of the first medically attended RSV LRTI, inpatient/outpatient visit settings, and RSV subtypes associated with the primary endpoint will be provided.

An analysis may also include all RSV positive LRTI endpoints, using results from either the central laboratory or local laboratory.

To evaluate the impact of the missing data on the primary analyses, the following supplementary analyses will be conducted. For subjects who do not have an RSV LRTI and are not followed through 150 days post dose:

1 Count these subjects as having not met the RSV LRTI endpoint within each treatment group
2 Perform multiple imputations using the observed event rate per treatment group for their event status
3 Perform single imputation using observed placebo rate for both groups

Subgroup analysis will be performed for the primary efficacy endpoint, the incidence of medically attended RSV LRTI. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model with the terms of treatment, age group, GA, subgroup, and treatment-by-subgroup interaction. If this full model does not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction will be used. Significant treatment-by-subgroup interaction is judged at the significance level of 0.10. Within each level of a subgroup, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RRR and the 95% CI will be presented. In the event that the Poisson regression model does not converge for any stratum of a subgroup, the exact conditional method based on the number of RSV LRTIs (Breslow and Day 1987) will be used as the analytical model to generate the RRR and its corresponding CI for all subgroup strata.

The subgroup analysis will be conducted for the following subgroups on the ITT Population:

- Age at randomization stratum (age $\leq$ 3 months, age > 3 to $\leq$ 6 months, age > 6 months)
- GA group (< 35 wGA, $\geq$ 35 wGA)
- Gender
- Weight at birth (weight $\leq$ 2.5 kg, weight > 2.5 kg to < 5 kg, weight $\geq$ 5 kg)
- Weight on Day 1 (weight < 5 kg, weight $\geq$ 5 kg)
- Sibling also participating in the study (yes/no)

The details of the supplementary analyses will be described in the statistical analysis plan.

4.8.3.4 Secondary Efficacy Analyses

The secondary efficacy endpoint is the incidence of RSV LRTI hospitalization through 150 days post dose. For subjects with multiple RSV LRTI hospitalizations, only the first occurrence will be used in the analysis.

A Poisson regression model with robust variance (Zou 2004) using only the treatment term will be used to assess the treatment effect on the incidence of RSV LRTI hospitalization

between nirsevimab and placebo groups in the ITT population. RRR and its corresponding 95% CI will be estimated from the model. RSV LRTI hospitalization that occurs through 150 days post dose will contribute to the analysis. For subjects who do not have an RSV LRTI and were not followed through 150 days post dose, their event status will be imputed using the observed placebo RSV LRTI hospitalization rate following the repeated imputation procedure without involvement of stratification factors.

The additional analyses, including the CMH test with the only term of treatment for the incidence of RSV LRTI hospitalization, and the Kaplan-Meier for time-to-first RSV LRTI hospitalization will be conducted. Treatment group differences in time-to-first RSV LRTI hospitalization will be compared using log-rank test.

In addition, age at onset of the first medically attended RSV LRTI hospitalization through 150 days post dose will be analyzed similarly to that for the primary endpoint. Summary of incidence of RSV LRTI hospitalization by subgroup will also be provided.

The details of above analyses will be described in the Statistical Analysis Plan.

4.8.4 Safety

Safety of nirsevimab will primarily be assessed and measured by the occurrence of all TEAEs and TESAEs. AEs will be graded according to the current version of the NCI CTCAE where applicable for pediatric assessments. AEs will be coded by MedDRA 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. The type, incidence, severity, and relationship to study investigational product will be summarized by treatment group. In addition, summaries of deaths and SAEs will be provided. Other safety assessments will include:

- Occurrence of AESIs to include targeted AEs of anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis), or thrombocytopenia following investigational product administration
- Occurrence of NOCDs following investigational product administration

4.8.5 Analysis of Pharmacokinetics and Antidrug Antibody

4.8.5.1 Pharmacokinetic Analysis

Following a single dose of nirsevimab, individual nirsevimab serum concentration data will be tabulated by treatment group along with descriptive statistics. PK parameters, eg, maximum observed concentration, AUC, apparent clearance, and $t_{1/2}$, will be estimated using noncompartmental analysis, if data permit.

4.8.5.2 Antidrug Antibody Analysis

The incidence of ADA to nirsevimab will be assessed and summarized by number and percentage of subjects who are ADA positive by treatment group. The ADA titer will be listed by subject at different time points. The impact of ADA on PK, efficacy, and association with TEAEs and TESAEs, will be assessed.

4.8.6 Exploratory Analysis

4.8.6.1 Healthcare Resource Utilization

The magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who require respiratory support and supplemental oxygen and the duration of use; number and types of outpatient visits, eg, ER, outpatient clinic; and number of prescription and OTC medications and duration of use) will be summarized overall by treatment group, and for the following subgroups: subjects with at least one medically attended LRTI caused by RT-PCR-confirmed RSV, subjects with medically attended LRTI not caused by RSV, and subjects with non-protocol defined LRTIs, which may be further broken down by RSV status.

4.8.6.2 Monitoring RSV Resistance to Nirsevimab

Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using an RT-PCR assay. RSV genotypic analysis will report the sequence changes in the mature F protein from all RSV positive isolates compared to contemporary RSV A and RSV B reference strains. Susceptibility of novel RSV variants to nirsevimab will be tested and compared to control viruses.

4.8.6.3 RSV LRTI Occurring from Day 152 to Day 361

The incidence of medically attended RSV LRTI (inpatient and outpatient) from Day 152 to Day 361 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and will be summarized by treatment group.

4.8.7 Data Monitoring Committee

An independent data monitoring committee will review safety data regularly and make recommendations regarding further study conduct.

4.8.8 Interim Analysis

No interim analyses are planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject 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 even if no study treatment 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
  - 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.
- 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 ER or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations

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 B. See Section 5.5 for recording of 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 Sections 5.2 and 5.6), or is an AESI or NOCD (see Sections 5.3, 5.4, and 5.7) and therefore requires immediate notification to the Sponsor. See Appendix A for guidelines for assessment of AE severity and relationship to investigational product. If an AE evolves into a condition that meets the 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 361.

AESIs and NOCDs will be collected from the time of dosing through Day 361.

5.5.2 Follow-up of Unresolved Adverse Events

Any AE that is unresolved at the subject's last visit are 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 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period, must be reported as SAEs. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the

Sponsor representative(s) within the usual timeframes (refer to Section 5.6 for additional information).

5.5.4 Potential Hy's Law and Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix C 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 (SUSARs) 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 have to 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 study representative(s) within one day ie, immediately but **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 the necessary information is provided to the Sponsor 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 must inform Sponsor study representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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 study representative(s).

If the EDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate Sponsor study representative by telephone. The Sponsor study 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 on the relevant AE modules in the eCRF and on the overdose eCRF module.
- An overdose associated with an SAE must be recorded as an SAE.
- An overdose without associated symptoms is only reported on the overdose eCRF module.

If an overdose on a Sponsor investigational product occurs in the course of the study, then the Investigator or other site personnel must inform appropriate Sponsor study 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 to the Sponsor's patient safety data entry site. For all overdoses, reporting to the data entry site must occur within 24 hours.

5.7.2 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 at room temperature when it should be in the refrigerator
- 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.

5.7.3 Adverse Events of Special Interest

5.7.3.1 Anaphylaxis and Other Serious Hypersensitivity Reactions Including Immune Complex Disease

Events of hypersensitivity, including anaphylaxis (as defined in Appendix B), 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. Parent(s)/legal representatives will be provided a card with this information to aid in prompt identification and reporting of these signs. Parent(s)/legal representatives 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 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).

5.7.3.2 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).

5.7.4 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 center 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 each center 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 (including telephone contact).

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 (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by the Sponsor 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 Study Physician Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a Study Physician 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a Study Physician through this system, which is managed by a third party vendor.

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 trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, 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 each 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 enrolment 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 each country 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.

Each Principal 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 Principal 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 each center will:

- Ensure each subject's legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each subject's legal guardian is notified that they are free to discontinue from the study at any time
- Ensure that each subject's legal guardian is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject's legal guardian 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's legal guardian
- Ensure that any incentives for subjects and/or their legal guardians 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 each 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 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 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 ER 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 ER or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization

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 severity categories of Grade 1 to 5 as defined below.

Grade 1 An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 An event, and/or its immediate sequelae, that is associated with an imminent risk of death.

Grade 5 Death as a result of an event.

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 non-treatment-emergent serious adverse events (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent adverse events. 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 B National Institute of Allergy and Infectious Diseases 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 and Food Allergy and Anaphylaxis Network 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 (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 (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

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

C 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. 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. For example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review 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 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 SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

C 2 Definitions

C 2.1 Potential Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase.

C 2.2 Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated alkaline phosphatase 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.

C 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 C 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

C 4 Follow-up

C 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the Sponsor study representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

C 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 on 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

C 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 in order 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 caused by the investigational product, to ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. The Sponsor's Global Clinical Lead or equivalent 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 an 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, update the previously submitted potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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 over 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 are related to the investigational product and seriousness criteria is 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 still 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

C 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 study treatment and has already met potential Hy's Law criteria at a previous on study treatment 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 C 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 C 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.

C 7 Laboratory Tests

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

C 8 References

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