A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age

Sponsor Protocol Number: D5290C00008

Investigational Product: Nirsevimab (MEDI8897)

Sponsor: AstraZeneca AB, SE-151 85 Södertälje, Sweden

Medical Monitor: PPD
AstraZeneca, BioPharmaceuticals R&D

Contract Research Organization: IQVIA

Protocol History, Date:
Original Protocol, 27 Jan2020
Amendment 1, 24Apr2020
Amendment 2, 17Dec2020
Amendment 3, 23June2021

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (CSP for global use)	23 June 2021
Amendment 2	17 Dec 2020
Amendment 1	24 April 2020
Original Protocol	27 Jan 2020

Descriptions of Amendments 1 and 2 are included in Section 9.

Protocol Amendment 3 (dated 23 June 2021)

The principal reason for this amendment is to revise the protocol to be globally applicable, in line with the decision to expand the study to include countries other than Japan, where the study is currently ongoing. At the time of the original protocol and Amendments 1 and 2, the study was planned to be conducted in Japan only. By expanding the study to additional countries and increasing the sample size, immunocompromised children with different underlying causes from different countries can be included in the study, supporting the safety evaluation in a diverse population. Additionally the increase in sample size aligns with the design and number of participants pre-determined for other high risk populations under study within the program.

Section(s)	Description of Change	Brief Rationale
Title Page	Study title revised to not include 'Japanese'	For global applicability.
Title Page	Name of medical monitor changed.	Assignment of new medical monitor.
Title page 1 Introduction 4.5 Investigational Product	Sponsor name changed from MedImmune to AstraZeneca	To clarify that MedImmune is a fully owned subsidiary of AstraZeneca.
Synopsis 2.2 Secondary Objectives 3.2.2 Rationale for Endpoints 4.8.4 Analysis of Pharmacokinetics	Pharmacokinetic endpoints revised to include only concentration of nirsevimab.	The sparse PK sampling in this study does not allow for accurate non-compartmental analysis.
Synopsis 2.3 Exploratory Objectives 4.3.4 Healthcare Resource Utilisation 4.8.7.4 Healthcare Resource Utilisation	Duration of use for prescription and OTC medications has been deleted from the description of the exploratory objective related to healthcare resource utilization.	To be consistent with other nirsevimab studies on data analysis.
Synopsis 3.1 Description of Study	Additional countries added to study description.	Additional countries added to support global recruitment and data collection in this

Section(s)	Description of Change	Brief Rationale
		immunocompromised population with varying underlying causes of this condition and to meet the increase in sample size.
Synopsis 3.1 Description of Study 4.1.1. Number of Subjects 4.8.2 Sample Size	Increased sample size from 30 to approximately 100 subjects.	The revision to 100 subjects allows for the study of immunocompromised children and the various causes for this condition globally. Further, the data from this study will support the evaluation of safety in a diverse population, which could potentially facilitate the examination of subpopulations.
Synopsis 4.8.1 General Considerations 4.8.8 Interim Analysis	Addition of interim analysis.	An interim analysis will be conducted to allow for an early assessment of PK and safety in this study population.
Synopsis 4.8.1 General Considerations	Text added that data will be summarized for the overall study population, as well as for Japan only.	To include summaries as per original protocol (Japan only) in addition to summaries for the global study population.
4.2.2 Treatment and Follow-up Period Previous 4.3.7 Clinical Laboratory Tests	Clinical chemistry and hematology removed from visit schedule (Section 4.2.2). Previous Section 4.3.7 removed (not applicable).	In order to minimize the volume of blood collected, and to harmonize with other nirsevimab studies in children with RSV, clinical laboratory data will not be collected outside of Japan. Considering that nirsevimab is a monoclonal antibody with no endogenous target, available data from previous nirsevimab studies, and experience from other drugs (palivizumab and motavizumab) in the same pharmacological class, the risk of observing laboratory abnormalities associated with nirsevimab is considered to be very low, and routine monitoring of clinical laboratory measurements is not deemed necessary.
4.2.2 Treatment and Follow-up Periods	Study Visit 3 replaced with telephone call, consecutive visits renumbered accordingly.	To reduce the number of visits at the clinic and to harmonize with other nirsevimab studies in children with RSV.
4.3.6 Estimate of Volume of Blood to be Collected	Estimated volume of blood to be collected has been revised.	Revised in line with no clinical laboratory data collected outside of Japan.
4.5.1.4 Reporting Product Complaints	Contact details for report complaints updated.	Mail address has changed.
Previous 4.7.3 Guidance for Additional Palivizumab	Section deleted.	Section is applicable to Japan only.

Section(s)	Description of Change	Brief Rationale
Administration after Day 151		
New section 4.8.9 Data Monitoring Committee	New section describing an independent data monitoring committee, which will review safety data.	To provide additional safety oversight by an independent monitoring committee for this global study.
5.3.1.1 Immediate Hypersensitivity, Including Anaphylaxis 5.7.3.1 Immediate Hypersensitivity, Including Anaphylaxis	Description of hypersensitivity revised to be more specific.	To provide more specific information to Investigators.
5.7.3.3 Thrombocytopenia	Revised text regarding reporting of thrombocytopenia.	To provide clearer information to Investigators for reporting events of unexpected thrombocytopenia when considered by the Investigator to be clinically relevant with unknown etiology.
Previous 5.7.5 Defect Reporting	Section deleted.	Section applicable to Japan only.
7.1 Ethical Conduct of the Study	Description of Japan-specific regulations removed.	For global applicability.
Appendix C	Revised to align with no collection of laboratory data.	For global applicability.
Throughout	Minor editorial revisions.	Minor, therefore, were not summarized.

RSV = respiratory syncytial virus; OTC = over the counter; PK = pharmacokinetic.

PROTOCOL SYNOPSIS

TITLE

A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age

OBJECTIVES AND ASSOCIATED ENDPOINTS

Type	Objective	Endpoint
Primary		
Safety	To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age	All treatment-emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and new onset chronic diseases (NOCDs)
Secondary		
PK	To evaluate the PK of nirsevimab	Summary of nirsevimab serum concentrations
Antidrug antibody (ADA)	To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum
Efficacy	To assess the efficacy of nirsevimab when administered as a single intramuscular (IM) dose to infants ≤ 24 months of age	Incidence of medically attended lower respiratory tract infection (LRTI; inpatient and outpatient) and hospitalizations due to reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed respiratory syncytial virus (RSV) through 150 days after administration of nirsevimab
Exploratory		
CCI [redacted]		
Healthcare resource utilization (HRU)	To assess HRU for nirsevimab recipients	Magnitude of HRU (eg, number of admissions to hospitals and intensive care units [ICUs] and duration of stay; number of subjects who require respiratory support and supplemental oxygen and duration of use; number and type of outpatient visits, eg, emergency room [ER], urgent care, outpatient clinic; and number of prescription and over-the-counter [OTC] medications) for nirsevimab recipients

STUDY DESIGN

Study D5290C00008 is a Phase 2, open-label, uncontrolled, single-dose study, planned to be conducted in South Africa, the United States, and the European Union, in addition to Japan, where the study in currently ongoing, to evaluate the safety and tolerability, PK, occurrence of ADA, and efficacy of nirsevimab in immunocompromised children who are ≤ 24 months of age at the time of dose administration. Approximately 100 subjects will be enrolled. Subjects will be followed for approximately 1 year after dose administration.

TARGET SUBJECT POPULATION

Neonates, infants, and young children ≤ 24 months of age at the time of dose administration, with immunodeficiency.

TREATMENT GROUPS AND REGIMENS

Subjects entering their first RSV season will receive a single fixed IM dose of nirsevimab 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg (n = ~ 50), and subjects entering their second RSV season will receive a single fixed IM dose of nirsevimab 200 mg (n = ~ 50).

STATISTICAL METHODS

Sample Size

A total of approximately 100 subjects are planned to receive a single IM dose of nirsevimab to evaluate the safety, PK, ADA, and efficacy, which will be assessed descriptively. The originally proposed sample size of 30 was based on a similarly designed palivizumab study in a similar population, and it is expected to be sufficient in establishing a PK profile that allows extrapolation of efficacy and safety data from the Phase 2b (D5290C00003) and Phase 3 (CCI studies in healthy preterm and term infants to the target immunocompromised population. The updated sample size of 100 allows for the collection of data from a larger, global cohort of immunocompromised children with different underlying conditions.

CCI [redacted]

Statistical Analyses

There are 2 planned analyses for this study: an interim analysis and a final analysis. The interim analysis will be conducted when subjects enrolled globally by end of 2021 have been followed through Day 151. For the interim analysis, all safety, PK, ADA and efficacy data available at the time of the data cut-off for subjects enrolled by end of 2021 will be analyzed. A minimum of approximately of 30 subjects is expected to be sufficient in establishing a PK profile for efficacy and safety extrapolation at the time of the interim analysis. The final analysis will be conducted after all subjects have completed the last visit of the study (ie, Day 361).

Data will be summarized for the overall study population, as well as for Japan only.

Safety Analyses

Adverse events 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 according to the Medical Dictionary for Regulatory Activities, 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 immediate hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) 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.

Antidrug Antibody Analyses

The incidence of ADA to nirsevimab will be assessed and summarized by number and percentage of subjects who are ADA positive. The impact of ADA on PK, and the association with TEAEs and TESAEs, will be assessed, if data permit.

Efficacy Analyses

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

The incidence of RSV hospitalization through 150 days after dose will also be summarized. Additional analyses will include summarizing RSV positive LRTI endpoints using results from either the central or local laboratory.

Additional Analyses

CCI

[redacted]

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, urgent care, outpatient clinic; and number of prescriptions and OTC medications use) will be summarized.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
CHD	congenital heart disease
CI	confidence interval
CLD	chronic lung disease
CSR	clinical study report
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GA	gestational age
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
hMPV	human metapneumovirus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular(ly)
IRB	Institutional Review Board
IV	intravenous(ly)
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Specialized Term	Definition
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
$t_{1/2}$	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
YTE	M257Y/S259T/T261E

1 INTRODUCTION

1.1 Disease Background

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) among infants and young children, resulting in annual epidemics worldwide (Hall et al, 2009; Shay et al, 1999; Shi et al, 2017; Stockman et al, 2012). 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). Children < 1 year of age had an estimated 2.3 million hospital admissions. The overall mortality due to RSV LRTI was estimated to be as high as 118,200 (uncertainty range, 94,600 to 149,400) (Shi et al, 2017).

Children with congenital or acquired immunodeficiencies, transplant recipients, and those receiving immunosuppressive therapy are at increased risk for severe RSV-associated LRTI with prolonged viral shedding and higher viral loads (Resch et al, 2009), resulting in prolonged hospitalizations (11.5 to 24 days), admissions to the intensive care unit (ICU), and the need for mechanical ventilation (Asner et al, 2013; Manzoni et al, 2017; Moyes et al, 2013). Among immunocompromised children hospitalized with RSV, ICU admission rates of 19% or higher have been reported (Asner et al, 2013; Rowan et al, 2018). In addition, RSV-associated mortality rates can reach 60% in untreated children with immunodeficiencies, compared to a mortality rate of less than 0.5% in healthy infants with RSV (Asner et al, 2013).

Prevention of RSV illness in all infants is a major public health priority. However, despite many years of attempted vaccine development (Kim H. W. et al, 1969), there is no licensed vaccine for these children. Currently, the primary management of RSV-associated LRTI includes supportive care such as supplemental oxygen and mechanical ventilation. Other therapies such as ribavirin and immunoglobulins may be used to treat RSV infection in immunocompromised patients, but their effectiveness remains unclear (Asner et al, 2013; Kim E. et al, 2014; Rowan et al, 2018).

Palivizumab (Synagis®) is the only approved agent for RSV prophylaxis, and its use is limited internationally to high-risk children: preterm infants ≤ 35 weeks gestational age (GA),

children with chronic lung disease (CLD) of prematurity (also known as bronchopulmonary dysplasia), and children with hemodynamically significant congenital heart disease (CHD). In Japan, palivizumab received approval in 2013 for an additional indication in children ≤ 24 months of age with immunocompromised medical conditions or Down syndrome. Approval of this new indication was based on an open-label study that evaluated the efficacy, pharmacokinetics (PK), and safety of palivizumab in 28 immunocompromised Japanese children. In that study, the serum trough concentrations were comparable with Western-approved, indicated pediatric populations and Japanese-approved, indicated pediatric populations (preterm infants and children with bronchopulmonary dysplasia or hemodynamically significant CHD) (Mori et al, 2014). A larger postmarketing surveillance study with 312 Japanese children ≤ 24 months of age with immunocompromised medical conditions or Down syndrome demonstrated that palivizumab is generally safe and effective in this population (Kashiwagi et al, 2018). However, because its half-life ($t_{1/2}$) is approximately 1 month, infants and young children need to receive monthly intramuscular (IM) doses of palivizumab throughout the RSV season to maintain protection. This constitutes a significant burden on healthcare providers as well as the infants/children and their families.

1.2 Nirsevimab Background

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

Nirsevimab is a recombinant human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against the prefusion conformation of the RSV F protein. The antibody has been engineered with a triple amino acid substitution (YTE; M257Y/S259T/T261E [M252Y/S254T/T256E, according to the European Union {EU numbering system}) in the fragment crystallizable (Fc) region to prolong the $t_{1/2}$, 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 PK of 1G7, the non-YTE version of

nirsevimab, was evaluated in cotton rats following a single 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 the RSV season.

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

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

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

1.4 Summary of Clinical Experience

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

1.4.1 Phase 1a Study D5290C00001

Study D5290C00001 was a first-time-in-human Phase 1a, randomized, double-blind, placebo-controlled, dose-escalation study conducted to evaluate the safety, tolerability, PK, and ADA of nirsevimab compared to placebo in healthy adult volunteers (Griffin et al, 2017). This study was completed in June 2015. A total of 136 subjects were randomized and received a single fixed dose of nirsevimab (6 subjects each at doses of 300 mg IV, 1,000 mg IV, 3,000 mg IV, 100 mg IM, and 78 subjects at 300 mg IM) or placebo (34 subjects). All subjects were followed for approximately 360 days after dosing.

Safety

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

Pharmacokinetics

A 2-compartment PK model adequately described the PK profile following both IV and IM administrations. Body weight was determined to be a significant covariate on systemic clearance and volume of distribution with allometric exponents. The mean population clearance and volume of distribution were 42.3 mL/day and 2.8 L, respectively. The mean $t_{1/2}$ of nirsevimab ranged from 85 to 117 days across dose groups, and bioavailability after IM administration was 77%. The predicted 3- to 4-fold increase in the $t_{1/2}$ of nirsevimab compared to a standard IgG antibody was confirmed.

Antidrug Antibody

Post-baseline ADA was detected in 13.7% of subjects in the nirsevimab total group and 15.2% of subjects in the placebo group, with a maximum titer of 1:800 and 1:400, respectively. On Day 361, ADA was detected in 5.3% of nirsevimab subjects and 10.7% of

placebo subjects. The highest titer at Day 361 was 1:200 for both the nirsevimab and placebo groups. The presence and titer of ADA had no effect on the PK or safety profiles.

1.4.2 Phase 1b/2a Study D5290C00002

Study D5290C00002 was a Phase 1b/2a, randomized, double-blind, placebo-controlled, single ascending-dose study to evaluate the 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 United States (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.

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 substitution and 4 of the 20 subjects with samples available had neutralizing ADA.

There was no impact of the presence of ADA on safety. ADAs did not appear to impact PK for 150 days after dosing. Serum anti-RSV neutralizing antibody 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 neutralizing antibody across all the dose levels, confirming anti-RSV activity of nirsevimab.

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 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 approximately 360 days after dosing.

Efficacy

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

Safety

The safety profile of nirsevimab was similar to that of placebo, with no new 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 numerically 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 considered to be 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 group 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 5,176.3 (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 apparent effect on PK 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 NAb on Day 361.

1.5 Rationale for Conducting the Study

Prevention of RSV illnesses in all infants is a major public health priority; however, despite more than 50 years of attempted vaccine development, there are no licensed vaccines. While RSV prevention exists in the form of a specific RSV IgG (palivizumab) requiring 5 once-monthly injections, it is licensed only for infants who experience the greatest morbidity and mortality from RSV: preterm infants born ≤ 35 weeks GA, children with CLD of prematurity, children with hemodynamically significant CHD and, in Japan, children ≤ 24 months of age with immunocompromised conditions and Down syndrome. 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 clinical development program includes 2 pivotal studies for infants entering their first RSV season: the completed Phase 2b study (D5290C00003) and an ongoing Phase 3 study (D5290C00004) in healthy late term and term infants. Because of the significant advantage of one dose per RSV-season that nirsevimab would provide, the Sponsor recognizes the potentially important benefits for the pediatric population receiving palivizumab who must receive monthly injections during the RSV-season for protection. A Phase 2/3 study (D5290C0005) is currently being conducted in the high-risk palivizumab-eligible population entering their first and second RSV seasons. In addition, this Phase 2 study is planned to support an indication for a single dose of nirsevimab at the start of the RSV season in immunocompromised children who are ≤ 24 months of age.

Primarily, the PK data in this study will be used to assess whether nirsevimab systemic exposure is altered in this population as compared to healthy infants. The effects of immune

status on exposure will be evaluated using population PK methods. Assuming similar exposure-response relationship, exposure matching principles will be used to support extrapolation of the observed clinical efficacy of nirsevimab from the Phase 2b, and Phase 3 studies in heathy infants.

1.6 Benefit-Risk and Ethical Assessment

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

To evaluate the clinical benefit-risk balance for nirsevimab, nonclinical and clinical data have been taken into consideration. Based on the risk of serious RSV disease in infants and high-risk children, there is an established unmet medical need for the use of nirsevimab for prophylaxis in all infants entering their first RSV season and in high-risk preterm infants and children ≤ 24 months of age with CLD or CHD. Additionally, in Japan, palivizumab is approved for use in immunocompromised children ≤ 24 months of age. Children in this study (ie, ≤ 24 months of age with an immunocompromised medical condition) who receive nirsevimab may potentially benefit by being protected against serious RSV disease. Nirsevimab is expected to provide similar efficacy benefits as palivizumab with the advantage of requiring a single IM dose instead of the 5 IM doses required for palivizumab.

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

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

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

The primary objective and associated endpoints are described in Table 1.

Table 1 Primary Objective and Associated Endpoints

Type	Objective	Endpoint
Safety	To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age	All TEAEs, TESAEs, AESIs, and NOCDs

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

2.2 Secondary Objectives and Associated Endpoints

The secondary objectives and associated endpoints are described in Table 2.

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
PK	To evaluate the PK of nirsevimab	Summary of nirsevimab serum concentrations
ADA	To evaluate ADA responses to nirsevimab in serum	Incidence of ADA to nirsevimab in serum
Efficacy	To assess the efficacy of nirsevimab when administered as a single IM dose to infants ≤ 24 months of age	Incidence of medically attended LRTI (inpatient and outpatient) and hospitalizations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab

ADA = antidrug antibody; IM = intramuscular; LRTI = lower respiratory tract infection; PK = pharmacokinetics; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction.

2.3 Exploratory Objectives and Associated Endpoints

The exploratory objectives and associated endpoints are described in Table 3.

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
CCI [redacted]		

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
CCI		
HRU	To assess HRU for nirsevimab 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 duration of use; number and type of outpatient visits, eg, ER, urgent care, outpatient clinic; and number of prescription and OTC medications) for nirsevimab recipients

ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; OTC = over-the-counter; RSV = respiratory syncytial virus.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

Study D5290C00008 is a Phase 2, open-label, uncontrolled single-dose study to assess the safety and tolerability, PK, occurrence of ADA, and efficacy of nirsevimab in immunocompromised children who are ≤ 24 months of age at the time of dose administration. The study is planned to be conducted in South Africa, the US, and the EU, in addition to Japan, where the study is currently ongoing. Approximately 100 subjects will be enrolled. Approximately 50 subjects entering their first RSV season will receive nirsevimab as a single, fixed IM dose of 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg. Approximately 50 subjects entering their second RSV season will receive nirsevimab as a single, fixed IM dose of 200 mg. Subjects will be followed approximately 1 year after dose administration.

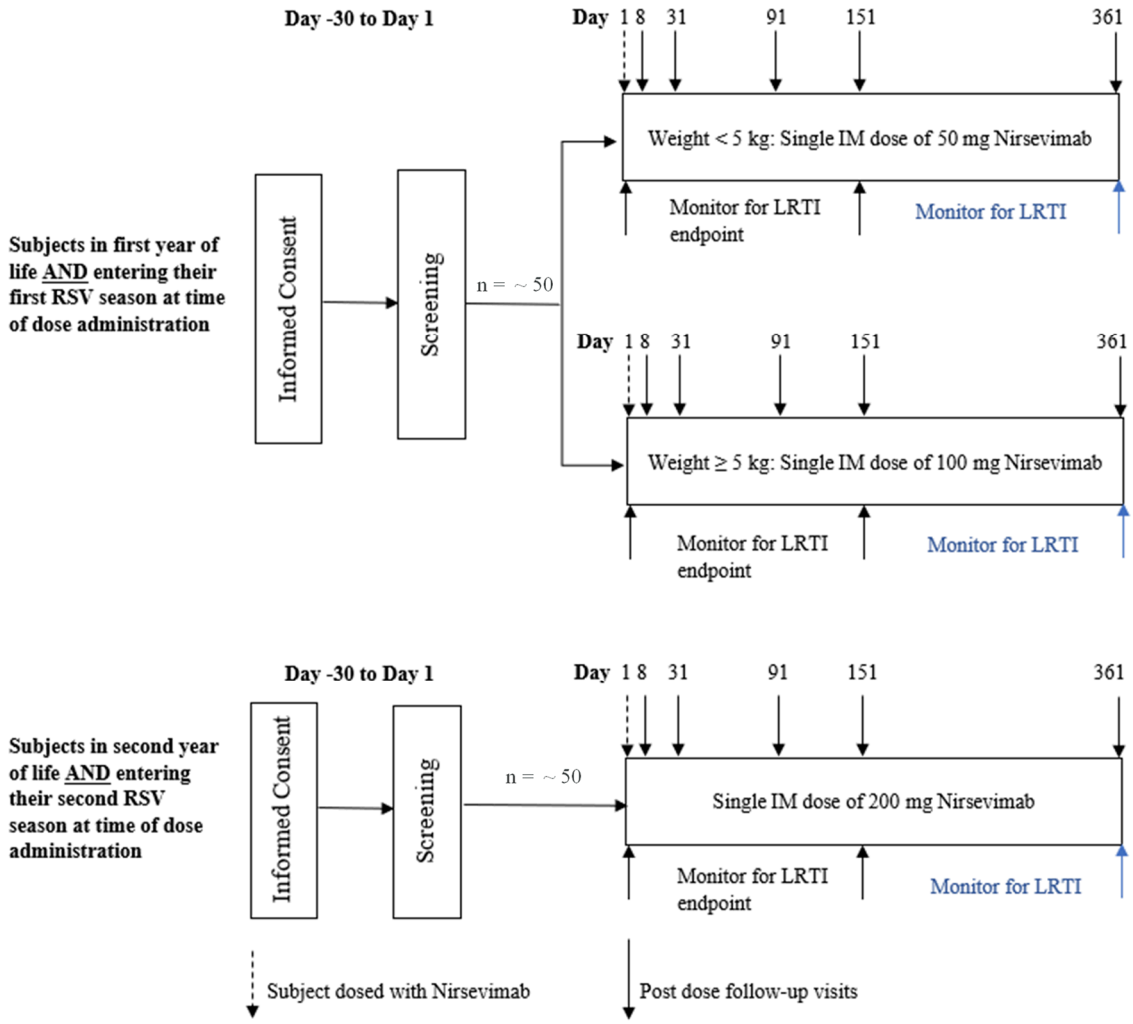
Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness (inpatient or outpatient setting) will be evaluated for the occurrence of LRTI. All subjects found to have a LRTI and all subjects who require hospitalization for a respiratory infection, 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 1 of the following clinical signs:

- Increased respiratory rate at rest (age < 2 months, ≥ 60 breaths/min; age 2 to 6 months, ≥ 50 breaths/min; age > 6 months, ≥ 40 breaths/min), 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).

Testing for RSV will be performed centrally using the US Food and Drug Administration (FDA)-cleared and Conformité Européenne or European Conformity-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV Assay, Quidel, San Diego, CA; www.quidel.com). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR.

Figure 1 Study Flow Diagram



IM = intramuscular; LRTI = lower respiratory tract infection; n = number of patients; RSV = respiratory syncytial virus.

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

3.1.2 Treatment Regimen

As this is a single-arm study, all subjects will receive nirsevimab. Subjects who are in their first year of life AND entering their first RSV season at the time of dose administration will receive nirsevimab as a single, fixed IM dose of 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg (n = ~ 50). Subjects in their second year of life AND entering their second RSV season at the time of dose administration will receive nirsevimab as a single, fixed IM dose of 200 mg (n = ~ 50).

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 weeks GA) in their first RSV season. 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% of infants weighing < 5 kg in the Phase 2b study, this dose was suboptimal for infants weighing ≥ 5 kg in this study. Overall, 3% and 59% 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. Additionally, a cut point analysis of the weight-normalized doses of all treated infants revealed that a 10 mg/kg dose was the corresponding clinically efficacious and protective threshold dose. Henceforth, based on these analyses, a stratified fixed dosing strategy by weight bands is proposed to ensure an adequate dose to maintain nirsevimab serum concentrations above the target area under the concentration-time curve throughout the RSV season. Based on dose optimization analysis designed to maximize the proportion of infants with clinically efficacious nirsevimab serum exposure, for infants entering their first RSV season a single fixed 50-mg IM dose is proposed for infants with body weight < 5 kg, while a single fixed 100-mg dose is proposed for infants weighing ≥ 5 kg. The body weight range for the majority of children entering their second RSV season is expected to be approximately 8.5 to 15 kg at the time of dosing. Therefore, with the same rationale, a single fixed 200-mg dose of nirsevimab is proposed for subjects entering their second RSV season to achieve and maintain efficacious exposure during the entire second RSV season. There have been no reports that IgG1 kappa mAb compounds show obvious ethnic differences.

3.2.2 Rationale for Study Population

Children with immunodeficiencies are at increased risk for severe RSV disease, leading to prolonged hospitalizations, admission to the ICU, and mechanical ventilation (Manzoni et al, 2017; Welliver, 2003). Currently, there is no specific treatment for RSV infection. In Japan, palivizumab is approved for the prevention of RSV infection in children with immunocompromised conditions. Palivizumab has been found to be generally safe and effective in this population (Kashiwagi et al, 2018; Mori et al, 2014), but because of its $t_{1/2}$ of approximately 1 month, infants and young children need to receive monthly IM doses of palivizumab throughout the RSV-season to maintain protection.

Nirsevimab has the potential to provide significant improvement over palivizumab based on its demonstrated increased potency and extended $t_{1/2}$. Because of the significant advantage of one dose per RSV season that nirsevimab would provide, the Sponsor recognizes the potentially important benefits for the current pediatric population receiving palivizumab. This Phase 2 study is planned to evaluate the safety and tolerability, PK, ADA, and efficacy of nirsevimab in immunocompromised children ≤ 24 months of age.

3.2.3 Rationale for Endpoints

Nirsevimab is being developed to provide RSV immunoprophylaxis for all infants and young children, including immunocompromised children ≤ 24 months of age. The primary endpoint for this study is safety and tolerability. The standard measures of TEAEs/TESAEs, AESIs, and NOCDs will be used for this assessment. All subjects will be followed for approximately 1 year after dosing with nirsevimab.

Serum concentrations of nirsevimab at selected time points will be evaluated as a secondary endpoint to confirm that serum concentrations are maintained at an efficacious level for at least 5 months after dosing. PK data will be summarized by descriptive statistics. PK data obtained in this study will be compared to the PK data from the Phase 2b, Phase 3, and the Phase 2/3 studies. For infants and children 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.

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

This study will also summarize efficacy of nirsevimab in terms of incidence of RSV LRTI. RSV results in a significant burden of disease consisting of hospitalization, visits to the ER, and visits to outpatient clinics. This endpoint is designed to allow the capture of this total burden of disease. A separate endpoint of RSV hospitalization will also be evaluated.

Exploratory endpoints will examine CCI [redacted].

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of approximately 100 subjects will be enrolled.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Neonate, infant, or young child ≤ 24 months of age who, per Investigator judgment, are:
   (a) In their first year of life AND entering their first RSV season at the time of dose administration

   OR

   (b) In their second year of life AND entering their second RSV season at the time of dose administration
2. The subject must meet at least 1 of the following conditions at the time of informed consent.
   (a) Diagnosed with combined immunodeficiency (severe combined immunodeficiency, X-linked hyper-immunoglobulin M [IgM] syndrome, etc); antibody deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndromes, etc); or other immunodeficiency (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc), or
   (b) Diagnosed with human immunodeficiency virus infection, or
   (c) History of organ or bone marrow transplantation, or
   (d) Subject is receiving immunosuppressive chemotherapy, or
   (e) Subject is receiving systemic high-dose corticosteroid therapy (prednisone equivalents ≥ 0.5 mg/kg every other day, other than inhaler or topical use), or
   (f) Subject is receiving other immunosuppressive therapy (eg, azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc)

   All efforts will be made to recruit subjects for representation across all the immunocompromised conditions indicated in inclusion criteria (a) - (f).
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 nirsevimab.

4.1.3 Exclusion Criteria

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

1. Subject who meets any of the indications other than (including those approved for palivizumab in Japan) the immunocompromised conditions below.
   (a) Subject born at ≤ 28 weeks gestation and is ≤ 12 months of age
   (b) Subject born at 29 to 35 weeks gestation and is ≤ 6 months of age
   (c) Age ≤ 24 months with a history of bronchopulmonary dysplasia requiring medical management within the past 6 months
   (d) Age ≤ 24 months with current hemodynamically significant CHD
   (e) Age ≤ 24 months with Down syndrome
2. Requirement for oxygen supplementation, mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support at screening.
3. A current, active infection, including RSV infection, at the time of screening or at the time of investigational product administration.
4. Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or acute illness within 7 days prior to investigational product administration.
5. Any serious concurrent medical condition (renal failure, hepatic dysfunction, suspected active or chronic hepatitis infection, seizure disorder, unstable neurologic disorder, etc), except those resulting in an immune deficiency condition.
6. Clinically significant congenital anomaly of the respiratory tract.
7. Receipt of palivizumab.
8. Any known allergy or history of allergic reaction to any component of nirsevimab.
9. Any known allergy or history of allergic reaction to immunoglobulin products, blood products, or other foreign proteins.
10. Concurrent enrollment in another interventional study, or prior receipt of any investigational agent.
11. Anticipated survival of less than 1 year at the time of informed consent.
12. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product or interpretation of study results.
13. 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, 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), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive 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 are free to withdraw their consent to participate in the study at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the Investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

Each subject will receive a single IM dose of investigational product. An individual subject will not receive investigational product if any of the following occur in the subject in question:

- Withdrawal of consent
- Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation

Subjects who have received any investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation (Section 4.1.5) or the subject is lost to follow-up. Subjects who have not received investigational product, regardless of reason, will not be followed.

4.1.7 Replacement of Subjects

Subjects will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

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

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

The Principal Investigator:

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

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

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

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

Table 4 Schedule of Screening Procedures

Study Period	Screening
Procedure / Study Day or Week	**Day -30 to Day -1**
Written informed consent/assignment of SID number	X
Medical history	X
Physical examination	X
Weight	X
Vital signs	X
Blood sample for PK, ADA, CCI [redacted][a]	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Verify eligibility criteria	X

ADA = antidrug antibody; AE = adverse event; PK = pharmacokinetics; RSV = respiratory syncytial virus; SAE = serious adverse event; SID = subject identification.

[a] If Visit 1/Screening and Visit 2/Day 1 do not occur on the same day, blood sample for PK/ADA/CCI [redacted] can be collected at either Visit 1/Screening or Visit 2/Day 1 predose.

4.2.2 Treatment and Follow-up Periods

Investigational product is administered on Day 1/Visit 2. Table 5 shows all procedures to be conducted on Day 1 and during the post-dose follow-up period, respectively.

Table 5 Schedule of Treatment and Post-Dose Follow-up Procedures

Study Period	Dosing	Post-dose Follow-up								
Visit Number	**V2 [a]**	**Telephone Call**	**V3**	**V4**	**V5**	**V6**	**Telephone Call**	**Telephone Call**	**LRTI**	**Skin Reaction**
Procedure/ Study Day	**D1**	**D8 (± 2 days)**	**D31 (± 2 days)**	**D91 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**Q2W D1-151 (± 5 days)**	**Monthly after D151-361 (± 5 days)**	**D1-361**	**D1-361**
Medical history update	X		X	X	X	X				
Physical examination	X		X	X	X	X				
Weight	X		X	X	X	X				
Vital signs	X[b]		X	X	X	X				
Blood sample for PK, ADA, CCI [redacted]	X[c]		X		X	X			X[d]	
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Assessment of AESIs and NOCDs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Verify eligibility criteria	X									
Investigational product administration	X									
Assessment of LRTI or any respiratory infection that requires hospitalization									X[d]	
Nasal swab collection									X[d]	

Table 5 Schedule of Treatment and Post-Dose Follow-up Procedures

Study Period	Dosing	Post-dose Follow-up								
Visit Number	**V2 [a]**	**Telephone Call**	**V3**	**V4**	**V5**	**V6**	**Telephone Call**	**Telephone Call**	**LRTI**	**Skin Reaction**
Procedure/ Study Day	**D1**	**D8 (± 2 days)**	**D31 (± 2 days)**	**D91 (± 2 days)**	**D151 (± 7 days)**	**D361 (± 7 days)**	**Q2W D1-151 (± 5 days)**	**Monthly after D151-361 (± 5 days)**	**D1-361**	**D1-361**
Assessment of skin reaction										X[e]
Telephone contact[f]							X	X		
HRU [g]									X	

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; D = Day; ER = emergency room; HRU = healthcare resource utilization; ICU = intensive care unit; LRTI = lower respiratory tract infection; NOCDs = new onset chronic diseases; OTC = over-the-counter; PK = pharmacokinetic; Q2W = once every 2 weeks; RSV = respiratory syncytial virus; SAE = serious adverse event; V = visit.

[a] V2/D1 and V1/Screening can occur on the same day.

[b] 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] If V1/Screening and V2/D1 do not occur on the same day, blood sample PK/ADA/CCI [redacted] can be collected at either V1/Screening or V2/D1.

[d] Nasal samples will be collected for all LRTIs (inpatient or outpatient) and all subjects hospitalized with any respiratory infection (upper or lower) within 2 days after the diagnosis by a healthcare provider. Blood samples will be collected from all subjects hospitalized with LRTI or any respiratory infection within 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 investigational product.

[f] Telephone contact must be verbal communication. 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, urgent care, 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. Testing for RSV will be performed centrally using the US FDA-cleared and Conformité Européenne or European Conformity-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV assay, Quidel Corporation, San Diego, CA). A diagnosis of RSV LRTI requires having a respiratory sample positive for RSV by the central laboratory RT-PCR.

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 ≤ 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 and urgent care 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 for RSV using the US FDA-cleared and Conformité Européenne or European Conformity-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + hMPV assay; Quidel Corporation, San Diego, CA). Testing may include other respiratory pathogens.

The respiratory samples will be retained at AstraZeneca or designee for a maximum of 15 years following the issue of the CSR to properly address potential questions from regulatory authorities.

CCI [redacted]

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, Antidrug Antibody, and CCI [redacted]

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.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements to properly address potential questions from regulatory authorities, after which they will be destroyed.

- Pharmacokinetic and ADA samples will be disposed of 6 months after issuance of the draft Bioanalytical Report.
- Remaining PK sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR.

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. See the collection schedule in Section 4.2. Evaluations will be performed using validated immunoassays.

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[redacted]

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 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, urgent care, outpatient clinic), and the number of prescription and over-the-counter (OTC) medications.

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.

4.3.6 Estimate of Volume of Blood to be Collected

Blood volume estimates are provided in Table 7 by visit/study day. For all subjects hospitalized with LRTI or any respiratory infection, an additional blood sample will be collected within 2 days following hospital admission.

Table 7 Volume of Blood to be Collected

Visit/Study Day	Estimated Blood Volume
Visit 1/Screening or Visit 2/Day 1	1.5 mL
Visit 3/Day 31	1.5 mL
Visit 5/Day 151	1.5 mL
Visit 6/Day 361	1.5 mL
Total	6.0 mL

4.4 Study or Study Component Suspension or Termination

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

- 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's safety review committee to evaluate the events).
- 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's safety review committee to evaluate the events).
- 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.

- Two serious adverse events (SAEs) of the same type that are assessed as related to nirsevimab.
- Other events that, in the judgment of the Sponsor or the Principal Investigator, are deemed serious enough to warrant immediate review by the Sponsor's safety review committee.
- Subject enrollment is unsatisfactory.
- 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, head of the medical institution (where applicable), and/or institution conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs, when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

The Sponsor will provide the Investigator(s) with investigational product (Table 8) using designated distribution centers.

Table 8 Identification of Investigational Product

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Nirsevimab	AstraZeneca AB	Supplied as 50 mg (nominal) per vial solution. CCI [redacted]

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).

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

4.5.1.1 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. Refer to Table 8 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 4.5.1.4) for further instructions.

4.5.1.2 Dose Preparation Steps and Treatment Administration

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

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

The dose administration steps are as follows:

1. **Infants in the first year of life and entering their first RSV season at time of dosing**
   (a) Infants < 5 kg body weight at time of dosing:

   A dose of 50 mg (ie, 0.5 mL) nirsevimab will be obtained by withdrawing the entire contents of 1 investigational product vial with an appropriately sized syringe, and administered as 1 single (ie, 0.5 mL) injection.

   (b) Infants ≥ 5 kg body weight at time of dosing:

   A dose of 100 mg (ie, 1.0 mL) nirsevimab will be obtained by withdrawing the entire contents of 2 investigational product vials with an appropriately sized syringe and administered as 1 single (ie, 1.0 mL) injection.
2. **Children in the second year of life and entering their second RSV season at time of dosing**

   A dose of 200 mg (ie, 2.0 mL) nirsevimab will be obtained by withdrawing the entire contents of 4 investigational product vials with an appropriately sized syringe and administered as 2 injections (1.0 mL each).

3. Switch the needle prior to administration.
4. Nirsevimab should be administered in the anterolateral aspect of the thigh according to standard practice procedures for IM injections. The injection should be given using standard aseptic technique. Subjects receiving the 200-mg dose (administered as 2 injections) should receive 1 injection in each thigh. The maximum volume to be administered with each injection is 1.0 mL.
5. Nirsevimab should be administered 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.

The investigational product will not be delivered until the contract is completed between the study site and Sponsor (and/or designee). The investigational product manager, who is designated by the head of the study site, is responsible for managing the investigational product from receipt by the study site until the return of all unused investigational product, after the contract is concluded between the study site and the Sponsor (and/or designee).

4.5.1.3 Monitoring of Dose Administration

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

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

4.5.1.4 Reporting Product Complaints

Any defects with the investigational product must be reported immediately to the Sponsor's Product Complaint Department by the site, with further notification to the site monitor. All defects will be communicated to the Sponsor and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

Sponsor contact information for reporting product complaints:

Email PPD

Phone: PPD

Mail:AstraZeneca

Attn:PPD
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.

The site's designated investigational product manager should ensure that the investigational product supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the process outlined in the Pharmacy Manual should be followed.

4.5.5 Treatment Compliance

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

4.5.6 Accountability

The head of the study site 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

Investigational product 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 study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This study is not blinded.

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 electronic case report form (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 any new medications from Day 1 through Day 15 post dose should be avoided if possible. This includes OTC medications (except for routine vitamins and iron) and herbal supplements. Subjects' parent(s)/legal representatives should be instructed not to administer any new 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: an interim analysis and a final analysis. The interim analysis will be conducted when subjects enrolled globally by end of 2021 have been followed through Day 151. For the interim analysis, all safety, PK, ADA, and efficacy data collected for subjects enrolled globally in 2021 will be analyzed. A minimum of approximately of 30 subjects is expected to be sufficient in establishing a PK profile for efficacy and safety extrapolation at the time of the interim analysis. The final analysis will be conducted after all subjects have completed the last visit of the study (ie, Day 361).

Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, median, standard deviation, minimum, and maximum. In general, unless stated otherwise, baseline will be defined as the last non-missing value prior to dosing.

Data will be summarized for the overall study population, as well as for Japan only.

Data analyses will be conducted using the SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC) in a SAS GRID environment.

4.8.2 Sample Size

A total of approximately 100 subjects are planned to receive a single IM dose of nirsevimab to evaluate the safety, PK, ADA, and efficacy, which will be assessed descriptively. The originally proposed sample size was based on a similarly designed palivizumab study in a similar population (Mori et al, 2014), and it is expected to be sufficient in establishing a PK profile that allows extrapolation of efficacy and safety data from the Phase 2b (D5290C00003) and CCI [redacted] studies in healthy preterm and term infants to the target immunocompromised population. The updated sample size of 100 allows for the collection of PK and safety data from a larger cohort of immunocompromised children. The revised sample size of 100 subjects allows for the study of immunocompromised children and the various causes for this condition globally. Further, the data from this study will support the evaluation of safety in a diverse population, which could potentially facilitate the examination of subpopulations.

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4.8.3 Safety

AEs will be graded according to the current version of the NCI CTCAE (or Appendix A) where applicable for pediatric assessments. AEs will be coded by MedDRA and the type, incidence, severity, and relationship to study drug will be summarized. Other safety assessments will include the occurrence of AESIs defined as AEs of immediate hypersensitivity (including anaphylaxis), thrombocytopenia, and immune complex disease (eg, vasculitis, endocarditis, neuritis, glomerulonephritis) following study drug administration, and the occurrence of NOCDs following study drug administration.

4.8.4 Analysis of Pharmacokinetics

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.

4.8.5 Analysis of Antidrug Antibody

The incidence of ADA to nirsevimab will be assessed and summarized by number and percentage of subjects who are ADA positive. The impact of ADA on PK, and the association with TEAEs and TESAEs, will be assessed, if data permit.

4.8.6 Efficacy

The incidence of medically attended RSV LRTI (inpatient and outpatient) through 150 days post dose, based on RSV test results (performed centrally using RT-PCR) and objective

protocol-defined LRTI criteria, will be summarized for all dosed subjects. For subjects with multiple medically attended RSV LRTI events, only the first occurrence will be used in the analysis.

The incidence of RSV hospitalization through 150 days after dose will also be summarized. Additional analyses will include summarizing RSV-positive LRTI endpoints using results from either the central laboratory or local laboratory.

4.8.7 Additional Analyses

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[redacted]

4.8.7.4 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, urgent care, outpatient clinic; and number of prescription and OTC medications) will be summarized.

4.8.8 Interim Analysis

An interim analysis will be conducted when subjects enrolled globally by the end of 2021 have been followed through Day 151. For the interim analysis, all safety, PK, ADA and efficacy data available at the time of the data cut-off for subjects enrolled globally by end of 2021 will be analyzed. A minimum of approximately of 30 subjects is expected to be

sufficient in establishing a PK profile for efficacy and safety extrapolation at the time of the interim analysis.

4.8.9 Data Monitoring Committee

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

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 if judged by the Investigator as medically significant), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

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

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment

in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

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

5.3.1 Serious Hypersensitivity (Including Anaphylaxis and Immune Complex Disease)

5.3.1.1 Immediate Hypersensitivity, Including Anaphylaxis

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with immediate (type I) hypersensitivity (including anaphylaxis) that occurs during or after dosing. An immediate hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both that occurs during or after administration of investigational product (but does not meet the definition of anaphylaxis). 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 AEs.

5.3.1.2 Immune Complex Disease

Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Drug-induced immune complex (type III) hypersensitivity reactions can occur when the host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complexes formation and their deposition in blood vessels. Subsequently this initiates tissue damaging inflammatory reactions mediated by complement and/or leukocytes and mast cells. The pathology and clinical manifestations are dependent on the tissues/organs involved, with vascular, skin, and renal tissues being common sites of injury. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise, and polyarthralgias or polyarthritis. Symptoms typically develop 1 to 2 weeks after first exposure to antigen and usually resolve in several weeks after withdrawal of the causative agent. Serum sickness needs to be differentiated from other ‘serum-sickness-like’ reactions that have a similar clinical presentation (eg, viral infections, anti-seizure drugs), but are believed to have different pathogenic mechanisms. Both serum sickness and serum sickness-like reactions have

been reported with mAbs (eg, rituximab, infliximab). Clinical presentation and time to onset should be considered for the diagnosis and differentiation of these reactions. Diagnosis of these suspected reactions is best confirmed via biopsy of the affected tissues. See Section 5.5 for recording AEs.

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 severity and relationship to investigational product.

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

5.5.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from the time of signature of informed consent through Day 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 will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.5.3 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 aminotranserase (AST) or alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN) together with total bilirubin (TBL) $\geq 2 \times$ 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 of an SAE by the Investigator to the Sponsor 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, head of the medical institution, and Investigators.

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

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

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

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

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

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

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

If the EDC system is not available, then the Investigator or other study site personnel contacts the Sponsor representative by telephone. The Sponsor representative will give guidance on 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 that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

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

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

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

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

5.7.2 Medication Error

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

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

Medication error includes situations where an error:

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

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

- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, eg, wrong route or wrong site of administration

- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication
- Wrong drug administered to subject

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

- 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 Immediate Hypersensitivity, Including Anaphylaxis

Events of immediate (Type 1) 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 immediate 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.

5.7.3.2 Immune Complex Disease

Events of immune complex disease (as defined in Section 5.3.1.2) 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).

5.7.3.3 Thrombocytopenia

Events of unexpected thrombocytopenia (platelet count < 120,000 per µL) that the Investigator judges to be both clinically significant and of unknown etiology require the Investigator or other site personnel to 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)

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

6.2.1 Source Data

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

Direct Access to Source Data

The head of the study site and the Principal Investigator/Investigator will cooperate for monitoring and auditing by the Sponsor (or designee) and accept inspection by the IRB/IEC or regulatory authorities. All study documents such as raw data will be open for direct access to source data at the request of the monitor and the auditor of the Sponsor (or designee), the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before the Principal Investigator signs the eCRFs to ensure accuracy and completeness of documentation and assure that the Principal Investigator has submitted the eCRFs to the Sponsor. If the Investigator wishes to amend the collected eCRFs, the monitor will ensure that the Principal Investigator has recorded the amendment with signature and date and provided this to the Sponsor.

6.2.2 Study Agreements

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

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

6.2.3 Archiving of Study Documents

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

Document File and Period of Retention

All study documents (including letters from the Sponsor) should be retained in the study document file by the Principal Investigator. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by the Sponsor's auditor, regulatory authorities, or IRB/IEC.

Period of Record Retention

The study site (and the Principal Investigator) will retain the essential documents as specified by GCP (eg, source document such as medical records, contract, signed informed consent form). Essential documents should be retained at the study site for 15 years in principle following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the Sponsor. However, this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period, however, if needed by the Sponsor, and the specific period and method of retention will be separately discussed between the study site and the Sponsor (or designee). The Sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records must be managed by a responsible person appointed by the head of the study site.

6.3 Study Timetable and End of Study

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

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

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

6.4 Data Management

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

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

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

6.5 Medical Monitor Coverage

Each subject will be provided with contact information of the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 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 healthcare 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 medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be conducted in compliance with the Declaration of Helsinki, the clinical study protocol, ICH/GCP, and any local standard.

7.2 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.

7.3 Ethics and Regulatory Review

The IRB/IEC responsible for the site must review and approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The head of the medical institution 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 head of the medical institution must provide a copy of the written approval to the Sponsor before enrollment of any subject into the study.

The Sponsor should approve any substantive modifications to the informed consent form that are needed to meet local requirements.

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

Before the study is initiated, the Sponsor will ensure that the national regulatory authority in the respective 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.

The 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 via the head of the medical institution. The Sponsor will provide this information to the Investigator so that he/she can meet these reporting requirements. The head of study site is responsible for providing the report and on keeping the IRB apprised of the progress of the study and of any changes made to the protocol but, in any case, at least once a year.

7.4 Informed Consent

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

The Principal Investigator(s) at the site will:

- Ensure each subject'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

7.5 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 7.3) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

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

7.6 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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9 CHANGES TO THE PROTOCOL

At the time of the original protocol and Amendments 1 and 2, this study was planned to be conducted only in Japan. Amendments 1 and 2 are described below. Amendment 3, which revised the protocol for global use, is described before the Protocol Synopsis.

9.1 Protocol Amendment 1 dated 24 April 2020

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1.

The protocol was amended to include the following substantial changes:

1. Section 5.5.4 (Potential Hy's Law and Hy's Law): New section required per protocol template for studies that include laboratory assessments.
2. Section 5.6 (Reporting of Serious Adverse Events): Change in email address for SAE reporting.
3. Appendix C (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): New appendix required per protocol template for studies that include laboratory assessments.

9.2 Protocol Amendment 2 dated 17 Dec 2020

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2.

1. Cover page: updated Medical Monitor information.
2. Incorporated protocol revisions in **"Addendum for domestic use of the Clinical Study Protocol D5290C00008, Version 2.0 dated 03Jun2020".**
   (a) Section 4.1.2 "Inclusion Criteria": added clarification for inclusion criteria 2 that all efforts will be made to recruit subjects into different subtypes 2 (a) to 2 (f)
   (b) Section 4.3.7 "Clinical Laboratory Tests": newly added section
   (c) Section 4.5.1.2 "Dose Preparation Steps and Treatment Administration": removed the word "placebo" as it is not applicable to the study
   (d) Section 7.1 "Ethical Conduct of the Study": newly added section
   (e) Section 7.3 "Ethics and Regulatory Review": added at end of the section, site head's responsibility
3. Section 3.1.1 "Overview": updated the arm description in Figure 1.
4. Section 3.1.2 "Treatment Regimen": clarified target populations are "subjects in first year of life and entering their first RSV season at dose administration" and "Subjects in second year of life and entering their second RSV season at dose administration".
5. Section 4.1.2 "Inclusion Criteria": updated inclusion criteria 1 to reflect target populations, and clarified this eligibility criterion is assessed per Investigator judgment
6. Section 4.2.2 "Treatment and Follow-up Periods": Table 5, remove "as needed" from the visit number description for "LRTI" and "Skin Reactions".

7. Section 4.3.1.1 “Lower Respiratory Tract Infection”: Table 6, added reference to the footnote in table for lower respiratory tract and medical significance for clarity.
8. Section 4.3.1.1 “Lower Respiratory Tract Infection”: subsection “Respiratory Secretions for RSV Detection”, added sample storage and destruction details.
9. Section 4.3.3 “Pharmacokinetics, Antidrug Antibody, and RSV Serology”: added sample storage and destruction details.
10. Section 4.3.3.3 “RSV Neutralizing Antibody Evaluation”: clarified that Analyses will be performed using **an updated version** of the RSV NAb assay previously described.
11. Section 4.5.1.2 “Dose Preparation Steps and Treatment Administration”: clarified target population.
12. Section 4.7.3 “Guidance for Additional Palivizumab Administration after Day151”: newly added section in addendum 2.0 dated 03Jun20; further updates made to clarify the palivizumab use on study.
13. Appendix B: formatted numbering.

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

Hospitalization

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

Assessment of severity is one of the responsibilities of the Investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the Investigator based upon medical judgment and the 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 nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

Protocol related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

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

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

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

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

Appendix 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 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 ≥ 3 × ULN **together with** TBL ≥ 2 × 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 ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated 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

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

- Notify the Sponsor study representative
- Repeat the test (new blood draw) without delay
- Determine whether the participant meets potential Hy's Law criteria (see Section C 2 for definition) by reviewing any laboratory reports from all previous visits
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result.

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, as applicable.

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 medical monitor 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 medical monitor.
  - 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 medical monitor 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 medical monitor 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 iIvestigator 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 medical monitor 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, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

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