15 September 2022
EMA/786523/2022

Assessment report

Beyfortus

International non-proprietary name: nirsevimab

Procedure No. EMEA/H/C/005304/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Non-clinical

Abbreviation or Specialized Term	Definition
1G7	non-YTE version of nirsevimab (MEDI8897)
ADA	antidrug antibody
BAL	bronchoalveolar lavage
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum observed concentration
EC_{90}	90% effective concentration
F	Fusion
Fc	fragment crystallisable
FcRn	neonatal Fc receptor
GLP	Good Laboratory Practice
HCl	Hydrochloride
IC_{50}	half-maximal inhibitory concentration
IgG	immunoglobulin G
$IgG1\kappa$	immunoglobulin G1 kappa
IM	intramuscular(ly)
IV	intravenous(ly)
K_D	equilibrium dissociation constant(s)
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
MEDI-524	anti-RSV F mAb, motavizumab
MEDI-557	anti-RSV F mAb, YTE modified motavizumab
NOAEL	no-observed-adverse-effect level
NW	nasal wash
PK	pharmacokinetic(s)
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
$t_{1/2}$	terminal half-life
TK	Toxicokinetics
YTE	M257Y/S259T/T261E triple amino acid substitution

Clinical

Fc: Fragment crystallizable

F protein (F): Fusion protein of RSV

HRP: Horseradish peroxidase

LRTI: Lower respiratory tract infections

mAb: Monoclonal antibody

MARM: Monoclonal antibody resistance mutant

MPV: Metapneumovirus (human)

Palivizumab: Marketed anti-RSV mAb (synagis)

RSV: Respiratory syncytial virus (human)

RSV A: The "A" subtype of RSV

RSV B: The "B" subtype of RSV

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 28 January 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Beyfortus, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "Beyfortus is indicated to immunise infants from birth entering their first Respiratory Syncytial Virus (RSV) season for the prevention of RSV lower respiratory tract disease."

1.2. Legal basis, dossier content

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0296/2021 the agreement of a paediatric investigation plan (PIP) including a deferral and the granting of a (product-specific) waiver applying to the paediatric population from 2 years to less than 18 years.

At the time of submission of the application, the PIP P/0296/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Derogation(s) from market exclusivity

Not applicable.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

The applicant requested the active substance nirsevimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Beyfortus (nirsevimab) was granted eligibility to PRIME on 31-01-2019 in the following indication: Prevention of lower respiratory tract infection caused by respiratory syncytial virus.

Eligibility to PRIME was granted at the time in view of the following:

1. RSV is the most important cause of LRTI in infants worldwide. Available prophylaxis options in the EU and worldwide are currently limited and targeted to some high-risk paediatric age subgroups. Therefore, an unmet need can be agreed in a broader population including healthy pre-term infants where the data has been generated so far.
2. Data on preclinical activity, both in vitro and in vivo, have been provided in support of the proof of principle.
3. Data from the presented phase 2b showed that a single intramuscular dose of 50 mg yielded a relative risk reduction in the incidence of medically attended RSV confirmed LRTI through D151 of 70,2% [52,4-81,3%, p<0.0001]
4. Similar results were observed using 2 different statistical methods and subgroup analyses showed consistent results.
5. Therefore, the overall data can support both proof of principle and proof of concept

Upon granting of eligibility to PRIME, Mark Ainsworth was appointed by the CHMP as rapporteur and was later replaced by Thalia Marie Estrup Blicher.

A kick-off meeting was held on 24 June 2019. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

6. Data from analytical comparability study to support the change from vial to prefilled syringe;
7. Exposure-response and Population PK modelling and simulation plan;
8. Extrapolation plan to support extending the efficacy and safety data in preterm and term infants to the target palivizumab eligible population;
9. Plans for post-authorisation measures;
10. engagement with HTA bodies/EUnetHTA including engagement prior to the start of Phase 3 studies.

1.7. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 March 2019	EMEA/H/SA/4047/1/2019/PED/III	*Dr Jens Reinhardt, Dr Mair Powell*
30 April 2020	EMEA/H/SA/4047/2/2020/PED/PR/I	*Dr Mogens Westergaard, Dr Cristina Migali*
10 December 2020	EMEA/H/SA/4047/1/FU/1/2020/PED/PR/II	*Dr Mair Powell, Dr Jens Reinhardt*

The Scientific advice pertained to the following *quality, preclinical and clinical* aspects:

1. *Preclinical program supporting clinical development and MAA*
2. *Dose regimen selection*
3. *Design of the pivotal trials*
4. *Extrapolation plan to support an indication for use of MEDI8897 in high-risk paediatric populations*
5. *Extend of safety database*
6. *Immunogenicity testing strategy, methods and analyses for assessing ADA responses*
7. *Strategy for evaluation of resistance emergence*
8. *Indication statement and SmPC*
9. *Concurrence with the primary analysis and the proposed pooled analyses of the secondary efficacy endpoint of hospitalisation*
10. *The proposed analytical-based bridging strategy and data package to support registration with the pre-filled syringe*
11. *Changes to the Nirsevimab clinical development programme aiming to mitigate the impact of the pandemic*
12. *Updated clinical data package to support a marketing application*
13. *Proposed changes to the SAPs for the ongoing Phase 3 MELODY and Phase 2/3 MEDLEY studies.*

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	28 January 2022
Accelerated Assessment procedure was agreed-upon by CHMP on	16 December 2021
The procedure started on	17 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP	21 April 2022

and PRAC members on	
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 April 2022
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 May 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	07 July 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 September 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Beyfortus on	15 September 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	15 September 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Respiratory syncytial virus (RSV) is an enveloped RNA virus and the principal pathogen responsible for LRTI in infants and young children. All infants, including healthy infants born at term, are at risk for severe RSV LRTI with primary RSV infection in infancy. Respiratory syncytial virus LRTI is the most common reason for admission to hospital in infants < 1 year of age.

2.1.2. Epidemiology and risk factors

Based on global estimates from 2015, an estimated 33 million episodes of RSV-associated LRTI occur in children < 5 years of age, with 3.2 million episodes necessitating hospitalisation. Approximately 59600 in-hospital deaths are estimated for this age group, of which 43600 are reported in lower-middle income countries. Whilst the mortality rate due to RSV infection is low in high-income countries, the inpatient disease burden is high, with the highest burden occurring in young infants.

Respiratory syncytial virus is the principal pathogen responsible for LRTI in infants and young children, estimated to cause up to 90% of childhood bronchiolitis and up to 40% of paediatric pneumonias (Hall 2001). In infants < 1 year of age, mean hospitalisation rates for RSV infection in the USA were 16 times higher than rates for influenza viral infections. Among German children 0 to 3 years of age, RSV hospitalisation rates were found to be 4 and 9 times greater than the hospitalisation rates associated with parainfluenza and influenza viral infections, respectively.

All infants, including healthy infants born at term, are at risk for severe RSV LRTI with primary RSV infection in infancy. Respiratory syncytial virus LRTI is the most common reason for admission to hospital in infants < 1 year of age (Hall 2001, 2012, Murray et al 2014, Rha et al 2020). The majority of infants admitted to hospital with RSV LRTI were born at term, and have no underlying serious comorbidity as illustrated with data from England in Figure 1 (Murray et al 2014). This observation is further supported by data series from Europe and North America (Bont et al 2016, Hall 2012, Murray et al 2014, Rha et al 2020). The burden of RSV disease is focused on the first year of life. Average annual RSV-coded admission rates ranged from 8.6 to 22.3 per 1000 children aged < 1 year across 7 European countries studied (namely Denmark, England, Finland, Italy, Netherlands, Norway, and Scotland), whereas in children aged 1 to 4 years, rates ranged from 0.2 to 2.24 per 1000 children. Admissions peaked in the second month of life but were considerable throughout infancy (Reeves et al 2020). Comparable rates and patterns were derived from a systematic review of epidemiological studies in North America and Europe: annual hospitalisation rates for RSV-associated acute respiratory infections in the first year of life ranged from 3.2/1000/year to 42.7/1000/year and decreased with increasing age to 0.6/1000/year to 1.78/1000/year in children aged 1 to 4 years (Bont et al 2016). Of note, the reported rates of RSV-associated hospitalisation varied considerably between studies and across seasons within the same study (Bont et al 2016).

Whilst the hospitalisation burden is focused in young infants, the outpatient burden is considerable and extends throughout the first year of life (Forster et al 2004, Hall et al 2013, Lively et al 2019). Disease that is managed in the outpatient setting is almost as severe as that observed in the hospital setting with laboured respiration in 73% and 85% of children with office or emergency room visits, respectively (Hall et al 2009). In a study in the USA, it was estimated that RSV accounted for 18% of emergency room visits and 15% of outpatient visits for acute respiratory infections in children < 5 years of age during the RSV season (Hall et al 2009). In England, among children < 5 years of age, overall 16% of all general practitioner consultations for acute respiratory illness throughout the year were attributed to RSV (Cromer et al 2017).

The socioeconomic costs from paediatric RSV infection on family and workplace productivity are also high. Among working parents of infants < 1 year of age hospitalised for RSV studied in Canada, Finland, and the USA, mean absenteeism ranged from 49% to 73%, and mean overall work impairment ranged from 78% to 81% (Heikkinen et al 2017, Mitchell et al 2017, Pokrzywinski et al 2019).

Controlling RSV disease in infants may have added benefits that may become apparent in the long term. Infant RSV LRTI has been associated with long-term respiratory morbidity (eg, wheezing, asthma, and impaired lung function in adult life). Long-term studies that have prospectively followed

cohorts from infancy until childhood have suggested an association with increased incidence of subsequent wheezing episodes and/or development of asthma in subjects with a history of RSV bronchiolitis in infancy (Escobar et al 2013, Pérez-Yarza et al 2007, Romero et al 2010, Ruotsalainen et al 2010, Sigurs et al 2005).

RSV LRTI Seasonality

Respiratory syncytial virus occurs in largely predictable annual epidemics worldwide. In Europe, whilst RSV transmission is active from October to May (ie, approximately Week 40 to Week 20), the majority of disease is typically focused in the 4 months of December through to March (ie, approximately Week 49 to Week 12) (Li et al 2019, Obando-Pacheco et al 2018). In the majority of countries, the start, end, and/or peak of RSV activity usually differed by only 1 to 3 weeks from season to season (**Table 1**) (Obando-Pacheco et al 2018). These seasonal peaks lead to intense pressure on health care services and in particular paediatric intensive care beds.

Table 1 RSV Seasonality Description per European Country

Country	Season week			Season length (week[s])	Period studied	Regional variability
	Start	Peak	End			
Belgium	39–43	49–50	7–13	18–22	2004–2014	No
France (official, syndromic-based)	35–37	48–52	10–14	25–31	2011–2017	No
France (unofficial RSV surveillance)	October–November	December	February–March	20–24	2011–2014	No data
Finland	50–1 [a]	7–10	17–20	19–21	2010–2015	Yes
Germany	Early 40–47	52	11–15	19–21	2010–2017	No
	Late 50–52	52–16 [b]	18	16–22		
Greece	December	February	April/May	20	1999–2013	No data
Italy	October	January/ February	April/May	24–30	2000–2014	Yes
The Netherlands	45–49	51–8 [b]	15–17	19–23	2010–2016	No data
Spain	44–45	50–52	6–12	12–19	2010–2017	No
United Kingdom	43–45	49–52	4–6	11–15	2010–2016	No

[a] Depending on the season, the start or end of the epidemic is seen in the previous epidemiological year or the next.

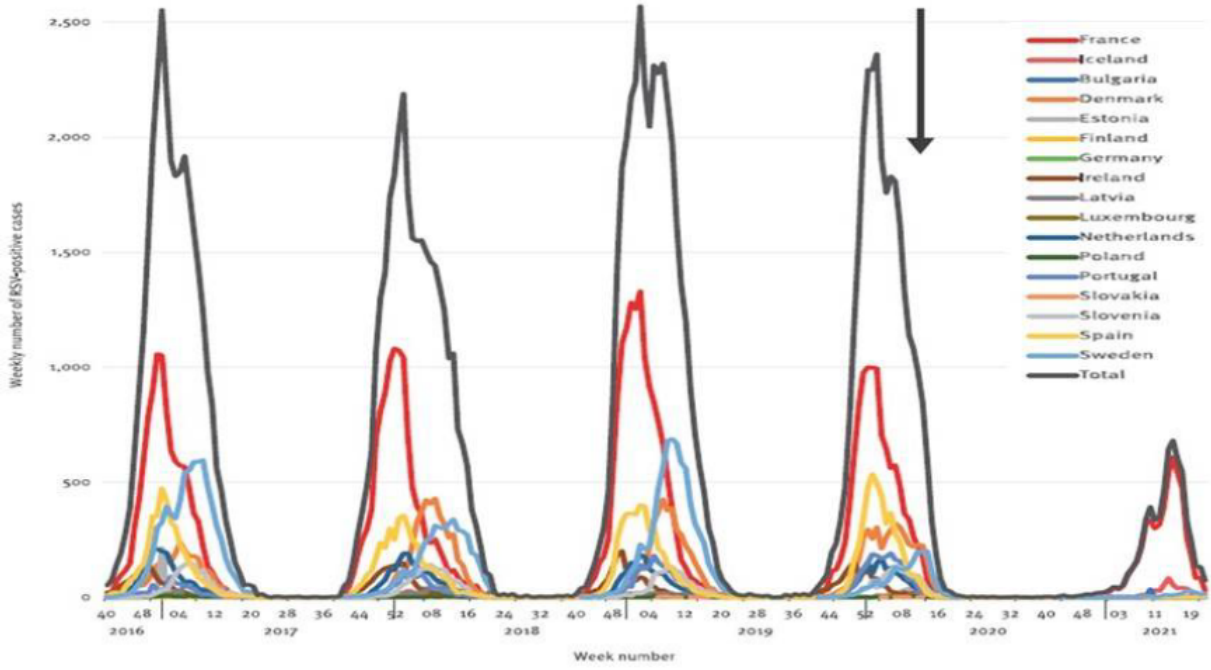
[b] Depending on the season, peak is seen in the previous epidemiological year or the next.

Each range represents the earliest and the latest epidemiological week or month where the start, end, or peak was observed during the seasons studied per country. Duration is presented as a range were the shortest and the longest epidemic of the seasons studied per country are shown.

Source: (Obando-Pacheco et al 2018).

This predictable pattern of annual RSV epidemics is illustrated across European countries for recent years preceding the COVID-19 pandemic (**Figure 1**). Unusually, RSV activity dramatically declined during the 2020/2021 season, as COVID-19 mitigation measures impacted RSV circulation. As exposure decreased there was a consequent increase in the susceptible population of infants and children who did not have the typical level of exposure during the COVID-19 restrictions. Epidemiological models predicted that this increase in RSV susceptibility would affect the timing and increase the severity of future RSV incidence (Baker et al 2020). Such off-season outbreaks have occurred widely (CDC 2021a, 2021b, Ujiie et al 2021, van Summeren et al 2021, Williams et al 2021).

Figure 1 Respiratory Syncytial Virus Activity in Europe, Wek 40 2016 to Week 20 2021, across 17 European Countries



The 17 countries represented were selected based on data completeness. The 'total' line represents the weekly number of RSV-positive cases in the 17 countries. Data were extracted via the surveillance atlas, which uses the infrastructure of TESSy by the European Centre for Disease Prevention and Control and the World Health Organisation. The TESSy surveillance network is described in detail elsewhere (Broberg et al 2018). Respiratory syncytial virus-positive cases in Week 53 2020/2021 were added to Week 52 2020/2021. The black arrow represents the declaration of the COVID-19 pandemic.

COVID-19 = coronavirus disease 2019; RSV = respiratory syncytial virus; TESSy = the European Surveillance System.

Source: (van Summeren et al 2021).

Seasonal surges in RSV infection, potentially compounded by unseasonal increases in the incidence and severity of RSV disease due to COVID-19 mitigation measures, place intense pressure on primary care, emergency department, and paediatric critical care services (ACPRC 2021). In data from Europe and North America for infants < 2 years of age hospitalised with RSV, the median length of hospital stay ranged from 2 to 12 days, with approximately 2% to 12% of infants admitted to the intensive care unit (Bont et al 2016).

Based on National Health Service England analysis of Paediatric Intensive Care Audit Network data from 2011 to 2015, annual demand for paediatric intensive care peaked in November and December largely driven by unplanned admission due to respiratory infection such as bronchiolitis and pneumonia primarily in infants < 1 year of age (NHS 2017). This can be impactful, leading to the delay of elective surgery in children.

2.1.3. Biologic features, aetiology and pathogenesis

Respiratory syncytial virus (RSV) is an enveloped non-segmented negative-sense single stranded RNA virus that belongs to the family of *Paramyxoviridae.* Its name is derived from the large cells known as syncytia that form when infected cells fuse.

RSV replication initially occurs in the epithelial cells of the nasopharynx, from where it may spread into the lower respiratory tract.

2.1.4. Clinical presentation, diagnosis and prognosis

Respiratory syncytial virus LRTI is a potentially serious and life-threatening disease characterised by infection and inflammation of the alveoli and bronchioles. It is associated with necrosis and sloughing of the epithelium of the small airways, with oedema and increased secretion of mucus. This can lead to airway obstruction and a typical clinical picture of hyperinflation, atelectasis, and wheezing (Hall 2001). It is most severe when the disease occurs in the first year of life associated with smaller airway diameter in infants. Known factors increasing the risk of hospitalisation with RSV include male sex, age under 6 months, crowding, siblings, and daycare exposure (Bont et al 2016). Some infants with serious underlying comorbidities are at higher risk of severe disease, including prematurity, CLD, CHD, cystic fibrosis, neuromuscular conditions, Down syndrome, or immunocompromise (Kristensen et al 2012). Lung immaturity, impaired vascular or pulmonary function, inability to clear secretions, or immunocompromise can all exacerbate the pathophysiology of RSV LRTI increasing the severity of the disease (Chaw et al 2020a, Chaw et al 2020b).

2.1.5. Management

Management of RSV infection as an outpatient is essentially supportive with the maintenance of hydration. Inpatient treatment of RSV infection in an infant who has been hospitalised may include oxygen supplementation, nasal CPAP or HFNC therapy, or mechanical ventilation, depending on the severity of disease (eg, hypoxaemia, respiratory failure) (Baraldi et al 2014, Turnham et al 2017). Bronchodilators and corticosteroids have not shown a benefit for the management of RSV bronchiolitis and, therefore, are not recommended (NICE 2021).

The only approved treatment for severe RSV disease is ribavirin for inhalation, licensed in several EU countries, the United Kingdom, and the USA (EMA 2018b, Medicines Complete 2021, PHE 2021, Virazole PI 2019). It is a synthetic guanosine nucleoside analogue that inhibits RSV replication and needs to be initiated early in the course of the disease. Ribavirin has a number of limitations, including the need for prolonged aerosol administration, potential toxic effects among exposed healthcare personnel, and cost. More importantly, efficacy has not been established due to limited clinical study data (Hoover et al 2018), and its use is not recommended. It is evident that improved modes of therapy are needed for children with serious RSV illness.

Prevention of RSV illnesses in all infants is a major public health priority (Giersing et al 2019). Whilst non-pharmaceutical interventions may temporarily reduce RSV incidence, as observed in response to the COVID-19 pandemic, they are not a sustainable long-term preventive approach. Despite more than 60 years of attempted vaccine development (Ruckwardt et al 2019), there is no licensed vaccine. The only currently approved prophylaxis for RSV is palivizumab (Synagis; USA authorisation 1998, EU authorisation 1999), licensed only for infants who are at the highest risk for severe RSV disease (ie, preterm infants born at $\leq$ 35 wGA under 6 months of age at the start of the RSV season, children < 2 years of age with CLD of prematurity or hemodynamically significant CHD) (Synagis PI 2020, Synagis SmPC 2021). Palivizumab is a humanised RSV mAb directed against the F protein of RSV (Johnson et al 1997). With a half-life of approximately 1 month, palivizumab must be administered monthly (IM injection) throughout the RSV season. The burden of monthly healthcare visits during the season can be a barrier to compliance, diminishing the benefits of palivizumab (Wong et al 2018). National recommendations for use are more restrictive. As palivizumab is indicated only for use in the relatively small population of higher-risk infants, its effect on limiting the total disease burden of RSV infection is limited.

2.2. About the product

Nirsevimab is a fully human, anti-RSV neutralising monoclonal antibody (IgG1/kappa isotypes for the heavy/light chains), isolated from memory B cells from human donors.

It binds to a discontinuous epitope displayed by the native, quaternary structure on the apex of the prefusion conformation of the F protein (F protein residues 62-96 and 196-212, within antigenic site Ø, site zero). Site Ø is lost as the F protein transitions to the post-fusion conformation, i.e. nirsevimab is specific for the pre-fusion state of F (McLellan 2013 and 2015, Zhu 2017, Swanson 2014).

Nirsevimab was engineered with 9 aminoacid substitutions to increase affinity for the F protein and reduce antigenicity, and a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Binding to human Fc receptors is maintained, and the mAb is expected to exhibit normal Fc-mediated effector functions (complement activation, mediation of phagocytosis, antibody-mediated killing of virus-infected cells, etc).

The mAb exhibits neutralising activity against both RSV subtype A and B strains, by locking the F protein in the pre-fusion conformation, thereby inhibiting entry of free virions into cells, as well as inhibiting spread of cell-associated virus by cell fusion. The mAb does not inhibit attachment of virions to cells. This mode of action is similar to the mode of action for palivizumab (palivizumab targets epitope site II, binds pre- as well as postfusion conformations of the RSV F protein, and likely neutralizes virus by sterically inhibiting the cell fusion step).

Contribution of Fc-mediated effector functions to protection against RSV disease cannot be ruled out (in the opinion of the rapporteur, the preclinical data from the cotton rat model appears ambiguous as regards this; see report ID8897-0031 and Zhu 2017).

The prefusion form of F is the main target for the virus-neutralizing antibody responses generated by natural RSV infection in humans (Magro 2012, Ngwuta 2015), and mAbs against prefusion-specific antigenic sites (e.g. Ø and V) have been found to exhibit higher in vitro neutralization potency than mAbs against antigenic sites which are shared between the pre- and postfusion conformations of F (McLellan 2013 and 2015, Zhu 2017).

The mechanism by which the YTE Fc mutation extends serum half-life is known (increased binding to neonatal Fc receptor, allowing rescue and recycling of mAbs from lysosomal degradation) and the YTE modification is employed in several marketed mAbs. Also, engineering for increased binding affinity and reduced antigenicity is standard in the mAb field (Zhu 2017).

In short, nirsevimab exhibits the biochemical and mode-of-action characteristics expected for a second-generation anti-RSV mAb intended for long-acting prophylaxis against RSV disease.

2.3. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

"There is an unmet medical need in the prevention of RSV infections in infants that have no risk factors. For the infants with risk factors, palivizumab is indication for the prevention of RSV infection.

The burden of the disease is acknowledged, both in terms of inpatient and outpatient resources spent on the disease.

The clinical development program seems appropriate for the accelerated assessment procedure and no major gaps were identified."

Therefore, it has been sufficiently demonstrated that nirsevimab constitutes a major interest from the point of view of public health and from the viewpoint of therapeutic innovation.

2.4. Quality aspects

2.4.1. Introduction

Nirsevimab, the active substance in Beyfortus, is a recombinant neutralising human immunoglobulin G1 kappa (IgG1κ) long-acting monoclonal antibody binding to the prefusion conformation of the respiratory syncytial virus (RSV) fusion (F) protein to prevent the infection of human cells by RSV.

Nirsevimab finished product is a sterile, preservative-free, solution for intramuscular injection. It is supplied as a single-dose pre-filled syringe (PFS) in two strengths: 50 mg (in 0.5 mL solution) and 100 mg (in 1 mL solution). Nirsevimab is formulated with L-histidine, L-histidine hydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80 (PS80) and water for injections (pH 6.0).

The PFS is presented without needle at the time of placing Beyfortus on the market. The needles are either co-packaged or provided separately.

Beyfortus is proposed in packs of 1 or 5 PFSs for each strength.

2.4.2. Active Substance

2.4.2.1. General information

Nirsevimab is composed of two identical heavy chains and two identical light chains.

Nirsevimab targets a different site of the RSV F-protein compared to palivizumab in Synagis (EMEA/H/C/257). Nirsevimab binds to a region within antigenic site Ø on prefusion RSV F and this binding site does not overlap with the binding site targeted by palivizumab (antigen site A).

Nirsevimab has been modified with a triple amino acid substitution (YTE) in the Fc region, enhancing its affinity to the neonatal Fc receptor (FcRn) and thus extending serum half-life.

There is a single N-linked glycosylation site in each heavy chain located within the CH_2 domain of the Fc constant region (Asn-306). Glycosylation is predominantly of complex type.

The molecular weight of nirsevimab is approximately 150 kDa including glycosylation.

Nirsevimab is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturing process and process controls

Nirsevimab is manufactured and QC tested at AstraZeneca Pharmaceuticals LP, Frederick in USA. All sites involved in the manufacture, control and storage of the cell banks and the active substance operate in accordance with EU GMP.

Nirsevimab is manufactured using a CHO cell line. A comprehensive process flow and description of the manufacturing process has been provided. The commercial process is standard for manufacturing of monoclonal antibodies, with inoculation and expansion of cells from a well-characterised working cell bank (WCB), cultivation, harvest and purification. The active substance is stored until further processing to finished product.

Control of materials

The generation of the nirsevimab cell substrate and master cell bank (MCB) and WCB establishment has been adequately described. The chosen cell line was expanded and stored as the research cell bank (RCB). Vials from the RCB were tested for the presence of bacteria, fungi, mycoplasma, and virus contamination, and no contaminating microorganisms or viruses were detected.

MCB, WCB and end-of-production cell bank (EOPCB) and limit-of-in-vitro-cell-age (LIVCA) cell bank have been prepared and tested for identity, purity and safety in accordance with ICH Q5A, Q5B and Q5D and the CHMP guidance on *Virus Safety Evaluation of Biotechnological Investigational Medicinal Products*. No bacterial, microplasma, fungi or viral contamination has been detected in the cell banks. All test methods for cell bank identity, purity and safety testing have been briefly described and results have been provided. Tests for bacteriostasis and fungistasis, mycoplasma and sterility are conducted according to current compendial methods. Non-compendial analytical methods were evaluated to ensure that appropriate controls are incorporated into the assay. The methods were confirmed to be suitable for the characterisation of the cell banks. Genetic and phenotypic stability of the cell banks have been analysed, confirming that the cells can stably express nirsevimab during culture after MCB thaw.

All raw materials used in the active substance manufacturing process, including cell banking and cell culturing are purchased from Quality-approved suppliers. Upon receipt supplier certificates of analysis are reviewed and materials are inspected, tested and released according to specifications.

No material of human origin was used in host cell culture, cell line development, banking of the MCB and WCB, or in active substance manufacturing. No material of animal origin was used in cell line development or cell banking after this. Certificate of analysis, certificate of origin and TSE certificate equivalent information has been submitted and is found acceptable.

Control of critical steps and intermediates

Critical process parameters (CPPs), Non-CPPs (NCPPs), in-process controls (IPCs) and performance attributes have been listed for each process step with acceptable limits, ranges or action limits for each parameter. In general, the acceptable ranges for CPPs and NCPPs have been validated in verified small-scale studies for each manufacturing step. Some acceptable ranges have not been assessed in the small-scale studies for nirsevimab manufacturing but are instead based on previous process characterisation results of other CHO cell lines used by the Applicant. This approach for setting acceptable ranges is acceptable. Microbial control is ensured throughout the down-stream active substance manufacturing process by control of bioburden and endotoxin at all steps with defined action limits, in addition to the microbial and viral IPC performed at the production bioreactor stage. As for the bioburden test method, the endotoxin test method has been product-specifically validated. A low-pH treatment virus inactivation step and a virus filtration step are part of the active substance manufacturing process to ensure clearance of any potential viral contamination. Effectiveness of these steps have been verified in acceptable viral clearance studies.

A short description of components in and preparation of cell culture medium and nutrient feeds has been provided, along with qualitative composition of the culture mediums, nutrient feeds and buffers used during cell culture and active substance manufacturing. The medium used for inoculum expansion and production and the nutrient feed are either filtered into pre-sterilised containers for storage or are filtered directly into the bioreactors.

Process validation

Three active substance batches of have been manufactured for active substance process validation (PV). The process parameters and process outputs of all three batches were within the predefined validation acceptance criteria.

A small-scale hold time study has been conducted, using samples of process intermediate from the three PV batches stored in small-scale containers.

Results from microbial challenge studies have been provided to demonstrate effective sanitisation of resins, and small-scale studies support the proposed resin lifetimes. Commercial scale studies are on-going to verify the number for cycles established in the small-scale studies which is acceptable.

Bubble point and microbial retention have been validated, confirming suitability of the filter for the intended use. Filter compatibility and extractable evaluation have been adequately assessed.

A shipping qualification study, including thermal qualification, distribution qualification, performance qualification and microbial integrity study has been conducted and is acceptable. The studies confirm that the containers used for active substance storage can maintain product temperature for the entire shipping duration and can withstand the physical rigors of shipping. Finished product manufactured from active substance included in the shipping qualification study was tested according to the proposed finished product release specification and were within specification limits.

Manufacturing process development

A severity assessment has been conducted to identify critical and non-critical quality attributes (CQAs and Non-CQAs) of the nirsevimab manufacturing process. Severity scores have been calculated for each quality attribute (i.e. product-related impurities, process-related impurities, product-related substances, and specification test parameters) based on the attribute's impact on clinical performance (biological activity, PK, safety, and immunogenicity) and uncertainty regarding the information on the attribute.

Process characterisation studies were performed using scale-down models that were verified to predict the performance of the commercial-scale process. These studies determined the impact of the process parameters on product quality, resulting in their classification as CPPs or NCPPs. This approach for defining CPPs and setting acceptable ranges is considered acceptable.

The commercial control strategy is based on a systematic risk assessment using Failure Mode and Effects Analysis (FMEA). Each quality attribute is evaluated with regard to severity (impact on safety if the attribute if not well controlled), occurrence (likelihood that a quality attribute will be outside of its appropriate limit or range) and detectability (ability to identify whether a quality attribute is outside of its appropriate limit or range). Finally, a detectability score is added depending on the ability to test each quality attribute. The combined risk prioritisation number (RPN) (severity x occurrence x detectability) indicates whether the individual quality attribute is well controlled and thus does not pose a risk to patients.

The defined CQAs for nirsevimab and the identified CPPs are considered acceptable; Overall, the proposed control strategy is considered adequate to ensure that the CQAs are maintained within their defined acceptable limits or ranges.

From the provided data, the comparability of the nirsevimab active substance, manufactured according to the different processes is supported.

It is evaluated that there is a low risk for leachables from the product-contact materials used in active substance manufacturing based on vendor-provided extractable data, and that no individual leachables would exceed the threshold of toxicological concern (TTC).

Characterisation

Overall, the structural and physiochemical characterisation of nirsevimab active substance is considered comprehensive and sufficient.

The characterisation studies include release testing using the proposed commercial release analytical methods and extended characterisation methods to assess the primary, secondary and higher order structure, as well as post-translational modifications. Physiochemical characteristics have also been addressed; the molecular weight has been confirmed and the extinction coefficient has been determined. The biological and immunological characteristics of nirsevimab have been sufficiently addressed. Based on characterisation of ADCC and CDC activity, it is considered demonstrated that effector function is not part of the mechanism of action (MOA) for nirsevimab. The MOA for nirsevimab

is neutralisation. The Fab domains of nirsevimab bind to the pre-fusion conformation of the RSV F protein, neutralises the RSV, and thereby prevents RSV infection and infection-induced cell death.

Furthermore, nirsevimab active substance was subjected to stressed conditions to understand degradation pathways and identify changes in the molecule upon exposure to stress conditions. Degradation pathways and the predominant degradation products have been identified. The Applicant has combined the knowledge gained on degradation pathways/products with experience from manufacturing and/or storage and has selected variants for further assessment of criticality.

Structural characterisation

Primary structure
The primary structure and composition of nirsevimab was confirmed.

Disulfide bonding pattern

Nirsevimab contains a total of 16 disulfide bonds, which is consistent with the expected structure of an IgG1 molecule. Further the identity of the disulfide linked peptides was confirmed; all predicted disulfide linked peptides were observed and no unexpected disulfide linkages were detected.

Higher Order Structure
The secondary structure of nirsevimab was investigated. The spectrum of nirsevimab showed a profile consistent with predominantly beta-sheet structures structure, as expected for a typical IgG molecule. Based on deconvolution analysis spectrum, the major secondary structure elements are β-sheets, β-turns, random coil, and α-helix. The spectrum showed features typical of an IgG molecule; a dominant antiparallel β-sheet band, smaller features corresponding to β-turns, and a minor side chain band. The spectrum and indicate that nirsevimab is in a folded state with a defined secondary structure.

Tertiary structure was investigated.

Size heterogeneity
The size distribution profile of nirsevimab was evaluated.

Post translational modifications

Carbohydrate Structure

The glycosylation of nirsevimab was characterised

Isoform pattern

The charge distribution profile of nirsevimab was evaluated

Biological activity and immunological characteristics

The biological properties of nirsevimab including potency, Fcγ receptors binding, FcRn binding, and Fc effector functions have been characterised.

Product-related substances/impurities

Product variants are categorised as a product-related substance or product-related impurity based on their potential impact on safety and efficacy.

Product-related impurities detected in the active substance and finished product are formed during manufacturing and/or under forced degradation conditions.

Fragments

Nirsevimab fragmentation was measured using several orthogonal techniques.

Process-related impurities

The safety risk due to process-related impurities was found to be minimal.

All stated impurities have been presented in product used in clinical studies.

Residual HCP and HCP assay development

Throughout clinical development and process validation, the levels of HCP in the Active substance were monitored. The Applicant has included a short description of the characterisation of the HCP assay.

2.4.2.3. Specification

Specifications

The proposed active substance release and shelf-life specifications for nirsevimab have been provided, The parameters included in the active substance release and shelf-life specification are found adequate to control the quality of the nirsevimab.

Justification of specification

The selection of the attributes included in the active substance specification is based on the overall control strategy presented. Nirsevimab product quality attributes were evaluated for potential impact on safety and efficacy to determine their severity. Severity was then considered along with occurrence and detectability to determine the control strategy for each attribute. For attributes for which the control strategy includes active substance and finished product release and stability testing, acceptance criteria have been established. The acceptance criteria for active substance and finished product were established using a combination of approaches. Overall, the selection of specification attributes and setting of the acceptance criteria are found in line with ICH Q6B and are acceptable.

Change during finished product manufacturing

In cases where formulation characterisation studies show an impact for a given quality attribute within the ranges allowed for a given formulation parameter, the acceptance criteria may be set to accommodate these ranges in routine manufacturing.

Analytical procedures

The analytical procedures are described in sufficient detail. System suitability criteria are specified where relevant and the acceptance criteria have been confirmed during validation of the methods. The system suitability criteria are found adequate to confirm that the methods are in control during routine testing.

Validation of analytical procedures

The compendial analytical procedures for the active substance are performed in accordance with the methods described in the relevant pharmacopoeia current at the time of testing. The compendial procedures for Appearance/Clarity and Colour, Osmolality and pH were verified to be suitable for use.

The applicant has provided validation overviews as well as validation reports for the non-compendial methods. The method applied both for the active substance and finished product are validated using active substance samples. This is accepted since the composition of the active substance and finished product are identical, no additional formulation or compounding steps is part of the finished product manufacturing process. The non-compendial analytical methods have been appropriately validated according to ICH Q2 to control nirsevimab.

Batch analysis

The batch data overall confirm batch-to-batch consistency and process comparability. Low levels of both product and process related impurities are observed in all batches.

Reference standard

A two-tiered reference standard system, with a primary reference standard (PRS) and a working reference standard (WRS), will be implemented for nirsevimab. Currently, the PRS, is used for routine active substance and finished product release and stability testing. A WRS will be introduced for use in routine testing according to the provided protocol.

Current PRS

The preparation, qualification, characterisation, storage and monitoring of the currently applied PRS has been described in sufficient detail.

Future reference standards

A short description of the preparation, qualification, storage and monitoring of the future PRS and WRS has been provided.

Container closure

Nirsevimab active substance is filled into container closure system and stored. The active substance is shipped frozen from the active substance manufacturing site to the finished product manufacturing site.

The Applicant has assessed the suitability of the for its intended use as an active substance storage container with regards to: protection of the active substance from environmental exposure and shipping stress, safety of the components of the container closure system, compatibility of the active substance with the container closure system, and further the performance of the container closure system.

The Applicant has evaluated the safety by extractables and leachables studies.

The container closure is appropriate for storage of nirsevimab active substance.

2.4.2.4. Stability

The proposed active substance shelf life is stated for the long-term storage condition. Long-term stability studies are on-going for three manufacturing process validation active substance batches.

Stability data for three active substance validation batches manufactured with the commercial manufacturing process at long-term and accelerated conditions are provided for The stability data was evaluated against the proposed commercial acceptance criteria. The data for the long-term stability study show that the batches meet specification acceptance.

The post-approval stability protocol and stability commitment are acceptable. The batches included in the study will be tested according to the active substance shelf-life specification.

Taken together, the stability studies are designed in accordance with ICH Q5C Stability testing of biotechnological/biological products.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

Nirsevimab finished product is a sterile, preservative-free, liquid dosage form intended for intramuscular injection. It is supplied as a single-dose PFS without needle in two presentations: 50 mg

in 0.5 mL or 100 mg in 1 mL of nirsevimab per PFS. The PFS is considered a medical device in accordance with the Medical Device Regulation (Regulation (EU) 2017/745) and a revised Notified Body Opinion (NBOp) on the device, confirming full compliance with the relevant general safety and performance requirements (GSPRs), has been provided. The CE marked needles are co-packaged or provided separately.

An overfill is applied when filling nirsevimab the finished product into the PFS. The overfill volume was determined based on the average hold-up volume in the syringe after administration combined with the fill equipment capability. Target fill volumes are applied which is acceptable. There is no overage of the active pharmaceutical ingredient in the finished product. The finished product formulation contains 100 mg/mL nirsevimab in L-histidine/L-histidine hydrochloride monohydrate, L-arginine hydrochloride, sucrose, PS80, pH 6.0.

An acceptable description of the finished product and the composition of both 50 mg/PFS and 100 mg/PFS has been provided. All excipients are of compendial grade. No novel excipients or excipients of human or animal origin are used.

Pharmaceutical development

Appropriate documentation was provided to support formulation and manufacturing process development of Beyfortus finished product.

Container closure

The intended commercial primary packaging components consist of a PFS clear and colourless borosilicate Type I glass barrel with a polycarbonate Luer Lock adapter closed at one end with a tip cap and at the other end with an elastomer plunger stopper. Two device secondary packaging components which do not contact the finished product solution are attached to the PFS: a plunger rod is threaded into the plunger stopper, and a backstop is attached to the syringe to provide additional support and leverage during manual injection.

The glass barrel is Type 1 glass (compliant with Ph. Eur. 3.2.1) with silicone oil (compliant with Ph. Eur. for "Dimeticone") on the inner surface. The elastomer plunger stopper is qualified according to Ph. Eur. 3.2.9. Both the syringe with tip cap and the plunger stopper are supplied ready-to-use and pre-sterilised in accordance with ISO standards (further information on sterilisation of the PFS is provided in section P.7).

Both the syringe with tip cap and the plunger stopper are supplied ready-to-use and pre-sterilised. The syringe is sterilised using ethylene oxide and tested according to Ph. Eur. 2.6.1; the plunger stopper is sterilised by gamma irradiation and tested according to relevant ISO standard with a validated test method.

The PFS is packed in a paperboard carton to protect the finished product from light exposure.

Container closure integrity (CCI) has been validated during finished product process validation. All units tested met acceptance criteria.

Extractables and leachables from the PFS were analysed. It is evaluated that there is very low risk for leachables from the PFS.

The two needles co-packed in some of the packaging configurations are made of stainless steel and polypropylene. The needles are covered with silicone oil on the exterior part of the needle for comfort during insertion. It has been adequately justified that the collective amount of silicone to which the patient is exposed during one dose injection does not exceed PDE limit for silicone.

An extractable study has been conducted on the polypropylene needle hub and the stainless steel needle separately. Compatibility of the needles with the PFS has also been studied to ensure no leakage between the PFS and needle when pressure is applied. A valid declaration of conformity and a valid CE certificate for the needles has been provided.

Manufacturing process characterisation

Each step of the finished product manufacturing process has been evaluated through a Process Failure Mode and Effects Analysis (pFMEA) to determine the impact of each process parameter on the product quality. No impact to relevant CQAs was observed for the initial steps of the manufacturing process; filtration flow rate over the sterile filter and vacuum stoppering pressure applied during the PFS stoppering were defined as CPPs as they are essential for microbial product safety. The proven acceptable ranges for each process parameter have been adequately validated.

Sensitivity to light exposure and room temperature of the active substance/finished product during manufacture was evaluated to be within acceptable ranges at worst case conditions when compared to light protected control samples.

All product contact material used in finished product manufacturing have been evaluated for extractables and leachables. No leachables above the TTC for genotoxic impurities described in ICH M7 for products administered less-than-lifetime were detected.

2.4.3.2. Manufacture of the product and process controls

Manufacturing process and process controls

Batch release in the EEA is performed by AstraZeneca AB, Gärtunavägen, SE-151 85 Södertälje, Sweden. All sites involved in finished product operations comply with EU GMP.

The batch size range for the finished product manufacturing process is stated.

The finished product manufacturing process standard for monoclonal antibodies. It consists of thawing of active substance, pooling, mixing, bioburden reduction filtration, sterile filtration and aseptic filling and stoppering of the PFS. The filled PFSs are 100% visually inspected.

Each step of the finished product manufacturing process has been adequately described.

The commercial control strategy and the FMEA risk assessment presented in the active substance section covers the entire nirsevimab manufacturing process and all quality attributes of nirsevimab, i.e. both active substance and finished product. The control strategy, including the defined CPPs and IPCs for both active substance and finished product were evaluated and are found acceptable.

Process validation

The finished product manufacturing process has been validated at the commercial manufacturing site. All CPPs and IPCs were within their acceptable ranges. The results were comparable between batches and between filling time point within each batch. Media fill qualifications were also performed at the finished product manufacturing site and are found acceptable.

After the bioburden reduction filtration the filtered finished product can be held prior to the sterile filtration. The in-process hold time) has been validated.

Overall, the finished product process validation is considered acceptable. Defect categories were explained and internal action limits are provided. It is clarified that PFSs with both critical and non-critical defects are discarded.

All product-contact materials are single-use, therefore no cleaning validation has been performed. Description and documentation for validation of product contact material sterilisation (gamma irradiation) performed by the vendors of the materials has been provided. The sterile filter has been validated with regards to rinsing and product bubble point, compatibility with finished product, microbial retention and extractables from the filter. All results support the suitability of the sterile filter.

The simulated transportation studies were conducted in accordance with American Standard for Testing and Materials (ASTM D4169). The provided shipping qualification data support sustained quality after simulated shipping.

2.4.3.3. Product specification

Specifications

The proposed finished product release and shelf-life specifications for nirsevimab finished product have been provided. Overall, the parameters included in the specification are found adequate to control the quality of the nirsevimab finished product.

The general approach for selection of the attributes included in the finished product specification is based on the overall control strategy. The approach for setting of the acceptance criteria is holistic considering both the active substance and finished product release and stability acceptance criteria and the approach is described in the active substance part of the dossier. The overall approach for selection of specification attributes and setting of the acceptance criteria are found in line with ICH Q6B and are acceptable.

Analytical procedures

The analytical procedures specific to the finished product are described in sufficient details. Information on the reference standards are included where relevant. System suitability criteria are specified where relevant and the acceptance criteria have been confirmed during validation of the methods. The system suitability criteria are in general found adequate to confirm that the methods are in control during routine testing.

The compendial analytical procedures for the active substance are performed in accordance with the methods described in the relevant pharmacopoeia applicable at the time of testing. The compendial procedures were verified to be suitable for use. The method for Bacterial endotoxins was verified The method for sterility was verified for use with the finished product demonstrating the product is not bacteriostatic or fungistatic.

The Applicant has provided validation overviews as well as validation reports for the non-compendial methods specific for the finished product; The method applied both for the active substance and finished product are validated using active substance samples. The non-compendial analytical methods have been appropriately validated according to ICH Q2 to control nirsevimab finished product.

Characterisation of impurities

The finished product formulation is identical to the active substance formulation and no additional formulation or compounding step take place as part of the finished product manufacturing process. No new impurities are generated during the finished product manufacturing process and all impurities observed in the finished product were characterised for the active substance.

In accordance with ICH Q3D guideline for elemental impurities, a risk assessment has been conducted on the manufacturing process and container closure of the active substance and finished product. The elemental impurity risk assessment has confirmed that the existing control measures for nirsevimab active substance and finished product manufacture adequately control the levels of metal impurities to below 30% control threshold of the PDE limits. Based on this it is acceptable that no new measures to further control elemental impurities in the nirsevimab manufacturing process are established.

The nirsevimab manufacturing process has been evaluated for nitrosamines risk, based on risk factors for biologicals. Based on the risk evaluation the Applicant has determined the risk of nitrosation or the presence of nitrosating reagents during the active substance or finished product manufacturing to be very low. It is agreed that the nitrosamines risk can be considered negligible for the nirsevimab and no additional testing is considered necessary.

Leachables risk Assessment for active substance manufacturing has been provided. No risk was found for the combined active substance and finished product processes.

Reference standards

The reference standard used for finished product and the active substance are the same.

Batch analysis

Information on the use of the different batches have been provided and it has been specified which batches are used in the different clinical studies. All batches met the acceptance criteria in place at the time of release.

2.4.3.4. Stability of the product

The proposed shelf-life for the finished product is 15 months when stored at 2-8°C. Considering the real time stability data provided, this is acceptable.

A photostability study has been conducted in accordance with ICH Q1B (Option 2). Samples were subsequently tested using suitable stability indicating methods. The study confirmed the secondary packaging can protect the finished product from light exposure.

Elemental impurities and tungsten and silicone levels were tested. These elemental impurity data are considered acceptable to support the proposed shelf-life.

The post-approval stability protocol and commitment to continue the finished product stability studies through the scheduled months is acceptable.

Beyfortus may be kept at room temperature (20°C-25°C) when protected from light for a maximum of 8 hours. After this time, the syringe must be discarded.

Considering the real time stability data provided, the shelf-life for the finished product of 15 months when stored at 2-8°C is acceptable.

2.4.3.5. Post-approval change management protocol(s)

A post-approval change management protocol (PACMP) is proposed.

The PACMP includes the following: description and rationale for the proposed change(s), comparability protocol for the proposed change(s), manufacturing process validation protocol, analytical methods technical transfer protocol, as well as justification for the variation application reporting category and the information and data to be provided in the implementing Type IB variation application.

Overall, the strategy provided in the PACMP is considered adequate and acceptable.

2.4.3.6. Adventitious agents

Viral clearance is performed at active substance process. The small-scale models used in viral clearance studies are considered verified. Also, the same or more conservative conditions were set for the small-scale studies compared to the commercial process. Four model viruses, representing different viral families, sizes, genome types and degree of physicochemical resistance were used in the studies, in accordance with ICH Q5A.

At each clearance step significant viral reduction was shown and the cumulative viral log10 reduction value (LRV) of the process was determined for each model virus.

There is no TSE/BSE risk identified in the nirsevimab manufacturing process.

The adventitious agents' safety of nirsevimab is considered adequately evaluated through assessment of the viral and non-viral safety of incoming materials and the manufacturing and purification process. The following points have been evaluated by the Applicant and are found sufficient to ensure adventitious agents' safety of nirsevimab:

- No material of animal origin are used during manufacture of nirsevimab.

- Raw materials used in the manufacturing process are controlled and the process is run under aseptic conditions.
- Sterility of MCB and WCB has been confirmed. IPC testing of mycoplasma, bioburden and adventitious viruses is performed on a sample of the unprocessed bulk prior to harvest. No microplasma, bioburden or viral contamination has been found in unprocessed bulk samples in the three PPQ batches for which data has been submitted, and the Applicant states that no contamination has been found in any of the lots manufactured.
- No microbial contamination has been detected for any of the lots manufactured.
- A high degree of clearance of potential viral adventitious agents has been confirmed in verified small-scale models using relevant model viruses.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier presented in support of the MAA for Beyfortus is of good quality.

The control strategy for the nirsevimab active substance manufacturing process was established in line with ICH guidance. Overall, the manufacturing process is considered adequately described and the applied process parameters and IPCs, as well as their ranges, and the control of starting materials are considered adequate to control the process and ensure formation of active substance of adequate and consistent quality. The approach taken to validate nirsevimab manufacturing process is considered adequate. The process is demonstrated to perform consistently and nirsevimab active substance meets all the biochemical, functional and microbiological acceptance criteria. The process development, including development of the control strategy, is overall considered adequately described and justified. Comparability studies confirm product comparability throughout development.

The selection of the attributes included in the active substance specification is based on the overall control strategy. Overall, the approach for selection of specification attributes and setting the acceptance criteria for both active substance and finished product specifications is endorsed and found in line with ICH Q6B.

The finished product manufacturing process is standard. The description is comprehensive and acceptable. The submitted process validation data demonstrate that the process is well controlled with little variation in the reported results.

A finished product shelf-life of 15 months at 2°C-8°C is proposed. This is acceptable following the review of additional data provided by the Applicant during the procedure.

As requested during the procedure (Major Objection), the Applicant provided a revised NBOp confirming full compliance with the relevant GSPRs.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Beyfortus is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Beyfortus is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

Nirsevimab (also known as MEDI8897) is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) of approximately 150 kDa that binds the prefusion conformation of the RSV F protein. Nirsevimab was derived from a human mAb D25 that was isolated directly from human B cells and binds the prefusion conformation of the RSV F protein in site Ø. The similar mAB, IG7 was also derived from D25 by optimizing for RSV neutralisation activity against RSV A and RSV B strains in vitro and differs only slightly from nirsevimab in the protein sequence, as nirsevimab contains a 3 amino acid substitution, M257Y/S259T/T261E, referred to as "YTE" in the heavy chain CH2 fragment crystallizable (Fc) region of the mAb. The YTE modification was added to the mAb to prolong the terminal half-life of the antibody in humans, though the modification significantly decreases antibody exposure in rodents resulting in decreased serum antibody levels relative to the native human Fc. Therefore, the parental molecule, 1G7, was utilized for nonclinical pharmacology studies conducted in rodents. As nirsevimab and its parental mAb 1G7 exhibit equivalent in vitro antiviral activity in cell culture both were studied in the non-clinical pharmacology studies included in the Marketing Authorisation Application.

GLP:

Safety pharmacology investigations as well as the pivotal toxicity studies were conducted in an OECD member country and in general appeared to be GLP compliant.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In an antibody competition study, it was confirmed that nirsevimab/1G7 and D25 bind to the same region within antigenic site Ø on prefusion RSV F. None of the mAbs that bind to previously characterized RSV F binding sites I (131-2A), II (palivizumab), and IV (133-1H) competed with the binding of biotinylated 1G7 to RSV-infected HEp-2 cells, confirming the specific binding to site Ø. It was also shown that 1G7 binds to both RSV subtype A2 and B9320 F protein with high affinity. The binding site of nirsevimab on RSV A or B is primarily composed of residues 62–69 in the F2 subunit and residues 196–212 in the F1 subunit. Further, genotypic analysis identified critical residues associated with ≥5-fold significant reduction of viral susceptibility to nirsevimab neutralisation in RSV A F (residues K68 and N208) and RSV B F (residues K68, N201, I206, and N208) proteins.

To identify the mechanism of antiviral activity of nirsevimab, two in vitro studies were conducted to assess the inhibition of entry and spread of recombinant RSV A2 using human airway epithelial (HAE) tissues. It was shown that by binding to the prefusion RSV F protein, nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion in HAE tissues with in vitro potencies 10- and 20-fold higher than palivizumab, respectively. The improvement in neutralisation potency exhibited by nirsevimab/1G7 was furthermore documented in a microneutralisation assay in HEp-2 cells against D25 and benchmark mAbs palivizumab and motavizumab, which showed that 1G7 is approximately 4-fold more potent than D25 and 20- and 150-fold more potent than motavizumab and palivizumab, respectively, against RSV A and B laboratory strains in vitro, confirming that binding site Ø elicits a more potent response that e.g. binding site II for palivizumab. When tested in vitro in a panel of 70 RSV A and 49 RSV B clinical HEp-2 cell isolates, 1G7 neutralized all viruses tested across the most common RSV F sequence polymorphisms found

among currently circulating strains, demonstrating a highly potent and broad antiviral activity (calculated median EC50 values of 3.2 ng/mL (range, 0.48 to 15 ng/mL) and 2.9 ng/mL (range, 0.3 to 59.7 ng/mL) against RSV A and B isolates, respectively).

Nirsevimab/1G7 also exhibits binding to Fc-gamma receptors (FcγRs; FcγRI, FcγRIIA, FcγRIIB, or FcγRIIIA-158V) on innate immune cells in vitro and based on the article by van Erp et al, 2019, it was theorized that an Fc-mediated antibody effector function response may be involved in limiting virus replication and spread in vivo. However, in an in vitro microneutralizing study against laboratory strains RSV A2 and B9320, it was demonstrated that the antiviral activity of nirsevimab, 1G7 and a modified version of 1G7 with reduced FcγR binding and effector function (1G7-TM) were similar, showing that the YTE modification in nirsevimab does seem not affect binding affinity or neutralisation activity as compared to 1G7 or 1G7-TM. This was further demonstrated in vivo in a cotton rat model of RSV infection, as it was shown that 1G7 and 1G7-TM exhibited comparable dose-dependent reduction in RSV replication in the lungs and nasal turbinates, further suggesting that protection from RSV infection is dependent on nirsevimab neutralisation activity rather than Fc-mediated effector function. Contribution from FcγR-binding and effector function on neutralization activity can however not completely be ruled out.

In Zhu et al, 2017, the antiviral activity of 1G7 was investigated in vivo by administering 1G7 i.m. at 8 different dose levels to cotton rats 1 day prior to challenging with RSV A2 or RSV B9320 strains at doses up to 3 mg/kg and 1.5 mg/kg, respectively. Palivizumab were evaluated in parallel experiments. 1G7 potently inhibited viral replication, also significantly more potently than palivizumab. Further, 1G7 was highly active in reducing viral titers in the noses or nasal turbinates of infected cotton rats, whereas palivizumab failed to inhibit viral replication in the upper airways even at high doses. It was also demonstrated in vivo that 1G7 is 9-fold more potent in reducing pulmonary viral loads by >3-logs yielding a 90% protection (EC90) in RSV A- and RSV B-infected cotton rats compared to palivizumab. A target serum concentration of 6.8 µg/ml of nirsevimab was estimated based on the calculated EC90 value, to ensure optimal protection against RSV in patients.

Antiviral resistance was investigated in vitro in cell culture of RSV A2 and B9320 strains to identify amino acid changes that could lead to possible viral escape from nirsevimab neutralization. Analysis of F protein sequences from RSV A and B variants revealed several natural polymorphisms, which were all located in the nirsevimab binding site AA 62-69 and 196-212, for which one unique RSV A variant and 6 unique RSV B variants were identified, indicating that RSV B appears to have a faster mutation rate than RSV A. Investigations of the binding kinetics of 1G7 to RSV A2 or B9320 pre-F protein containing the resistance-associated substitutions showed a correlation between antibody binding and virus neutralisation, suggesting that the primary mechanism of viral resistance is linked to amino acid changes which prevent or weaken antibody binding. All identified variants exhibited significantly reduced susceptibility to nirsevimab neutralization in vitro (ranging from 412- to > 125000-fold). Though the development of antiviral resistance raises some concern, the Applicant was able through surveillance virology studies to demonstrate that the identified nirsevimab resistance-associated substitutions were only rarely identified among RSV isolates collected since 1956.

For RSV A as well as B subtypes, F protein polymorphisms reducing the in vitro neutralization potency of nirsevimab were rare in circulating strains (< approx. 1.3% in global sequences), and these potentially concerning strains were detected only sporadically, with no evidence for increased frequency over time. It also appears that nirsevimab neutralisation escape variants does not have altered growth properties compared to parental strains in vitro, and as previously described, the RSV F protein appears to be well preserved, and data in general supports that nirsevimab can be expected to exhibit activity against most currently circulating RSV strains (both A and B subtypes).

To evaluate the antiviral resistance in vivo of a specific polymorphism, cotton rats were administered 1G7 (0.3 to 6 mg/kg) and palivizumab i.m. 1 day prior to challenging with recombinant RSV B9320 harbouring K65Q:S211N in the nirsevimab binding site. It was shown that both 1G7 and palivizumab exhibited dose-dependent antiviral activity in preventing RSV replication in the lungs of cotton rats infected with RSV B9320 harbouring K65Q:S211N, however, IG7 exhibited an approximate 4.4-fold reduced potency at inhibiting viral replication compared to RSV B9320. Thus, it was shown that the reduced potency observed in vitro due to amino acid changes in the nirsevimab binding site is translatable to reduced in vivo efficacy in cotton rats. Currently, it is not known what impact the potential neutralization escape RSV variants may have on treatment of patients regarding prophylactic protection, though based on in vivo non-clinical data it is expected that some reduction in potency will occur, which should be monitored closely in the clinic.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies were conducted by the applicant as nirsevimab is directed against a viral target that is not endogenously expressed in healthy animal or human tissues. In tissue cross-reactivity studies in a full panel of adult human tissue and adult cynomolgus monkey tissues as well as in a panel of selected juvenile, neonatal and fetal human tissues no cross-reactivity binding occurred. Thus, due to the specificity of the exogenous antigen target (RSV prefusion F protein), unintended immunological reactions are not expected.

A high concern for the development of vaccine-associated enhanced disease (VAED) exists for all new RSV vaccines. This is a result of a series of clinical trials conducted in the 1960s, evaluating a formalin-inactivated (FI) RSV vaccine in RSV-naïve infants, for which enhancement of the RSV disease was observed, which resulted in a higher rate of hospitalization and death among infants compared to the control group. RSV disease enhancement was only observed after pre-treated naïve infants were subsequently infected with RSV for the first time. Subsequent evaluations identified low ratios of neutralizing and fusion-inhibiting activity to total anti-RSV-F binding antibody among vaccinees as well as peribronchiolar monocytic infiltration and prominence of eosinophils (Browne et al, 2020[1]).

A variant of VAED termed antibody-dependent enhancement (ADE) of disease and infection has been observed in connection with antibody-based vaccines against for example Dengue and Zika viruses and is suspected to potentially also occur in connection with RSV viruses. The in vivo mechanisms of ADE are largely unknown, however, in investigations of Dengue vaccines, ADE has been associated with antibodies with poor neutralising activity that bind heterotypic virions without achieving neutralisation, potentially resulting in an increased ability of the opsonized viral particle to infect Fcy-R-bearing cells (i.e. facilitated entry), thus enhancing infection and disease. In in vitro and animal models, a peak enhancement titer (i.e., a specific concentration of antibodies that most efficiently enhances Dengue virus infection) has been observed (Munoz et al, 2021[2]). By contrast, higher antibody concentrations effectively neutralize virions, whereas sub-therapeutic concentrations elicit no effect. Besides the role of level of neutralization (antibody titers) in development of ADE, it has also been pointed out by van Erp et al (2019) that, Fc-mediated effector function may have a role in ADE of RSV disease, through either cytotoxicity (ADCC), phagocytosis (ADCP) or complement activation. It is therefore important to investigate both the neutralization activity and the Fc-mediated effector function when evaluating the potential for ADE of an RSV vaccine agent (van Erp et al, 2019[3]). Thus, the applicant has provided

[1] Browne, SK. Summary of the Vaccines and Related Biological Products Advisory Committee meeting held to consider evaluation of vaccine candidates for the prevention of respiratory syncytial virus disease in RSV-naïve infants. Vaccine 38 (2020) 101–106
[2] Munoz, FM. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine; 2021 May 21; 39(22): 3053-3066.
[3] van Erp EA. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. Front Immunol. 2019;10548.

additional in vitro data assessing the capability of nirsevimab and palivizumab to induce antibody-dependent cellular phagocytosis (ADCP), antibody-dependent complement deposition (ADCD), antibody-dependent neutrophil phagocytosis (ADNP) and antibody-dependent NK cell activation (ADNKA). Nirsevimab slightly induced ADNP and ADNKA and to a greater extend ADCP and ADCD, in a comparable range as palivizumab. However, no known cases of enhanced RSV disease in clinical studies and post-marketing surveillance of palivizumab were reported. Animal models have however identified antibody response patterns that are associated with low risk of VAED including a high ratio of neutralizing vs. antigen binding antibodies anti-receptor binding domain (RBD) antibodies of high affinity (nanomolar range), and antibody kinetics showing sustained IgG responses over time (Munoz et al, 2021).

The risk for antibody-dependent enhancement of disease was explored in a cotton rat model of disease. The applicant showed that 1G7 did not induce viral titers above those measured for the control group over the range of doses tested, including at the lowest doses of 1G7 of 0.125 mg/kg for RSV A2 and 0.03125 mg/kg for RSV B9320. In a subsequent study in cotton rats, the impact of 1G7 on the development of anti-RSV immune memory and a subsequent immune response was investigated after re-challenge with RSV A2 virus following complete clearance of 1G7 after the initial dosing. It was shown that the immune memory and anti-RSV neutralizing antibody titers induced by the first challenge were fully protective against detectable RSV replication in the lungs or nasal turbinates of all animals. Thus, it appears that 1G7 efficiently neutralizes the viral load of RSV in vivo (EC50, RSV A2 = 2.9 µg/mL; EC50,RSV B9320 = 5.6-5.8 µg/mL) and that none of the tested dose levels of 1G7 appear to enhance the viral titers in vivo. To substantiate that the effect of nirsevimab is independent of Fc-mediated effector function, the Applicant carried out in vitro and in vivo studies in cotton rats. In vitro, it was demonstrated that nirsevimab binds with differing binding affinities to FcγRI (8.94 nM), FcγRIIA (18.7 µM), FcγRIIB (530 µM), or FcγRIIIA-158V (CD16; 16.7 µM). In vivo in cotton rats, no difference was observed in efficacy of 1G7 and 1G7-T, a mAb with reduced Fc effector function, which leads the Applicant to conclude that Fcγ-binding likely plays a minor role in protection from RSV virus. Finally, the Applicant informs that no unanticipated worsening of RSV has been observed in the clinical trials to date. Though histopathological evaluations of lung tissue were not conducted in cotton rats, which could have provided further information on the potential occurrence of alveolitis with (neutrophilic) infiltrates, which is an acknowledged marker of ADE in the cotton rat model, the overall weight of evidence presented by the Applicant indicates a low risk of ADE of disease for nirsevimab. The risk of ADE will further be monitored in the clinic after marketing authorization and is included in the RMP.

2.5.2.3. Safety pharmacology programme

In accordance with ICH guidelines S6(R1) and S7A no stand-alone safety pharmacology studies were performed.

Based on the one-month repeat-dose GLP toxicologic study in cynomolgus monkeys there were no clinical signs nor microscopic findings indicating any nirsevimab-related effects on the central nervous or respiratory systems and there were no adverse treatment-related effects on qualitative or quantitative ECG parameters.

2.5.2.4. Pharmacodynamic drug interactions

Due to the specificity of nirsevimab targeting the exogenous RSV prefusion F protein, it is accepted that no studies investigating pharmacodynamic interactions are submitted.

2.5.3. Pharmacokinetics

Method of analysis

The ELISA methods developed to measure nirsevimab and anti-nirsevimab antibody (ADA) in cynomolgus monkey serum in support of the GLP pivotal toxicological study has been suitably validated to GLP. The method measuring nirsevimab was validated across the concentrations ranging from 0.50 to 32.00 µg/mL. Validation of the ADA assay demonstrated that ADA levels of>62.5 ng/mL were detectable in the presence of 10 µg/mL of nirsevimab and in the presence of 100 µg/mL nirsevimab, ADA levels of 500 ng/mL were reproducibly detectable, which is acceptable as serum concentrations of nirsevimab were >500 µg/mL. Incurred sample reproducibility is found to comply with guidelines in the assessed pivotal study and the accuracy and precision of within-run and between-run values is acceptable and in line with relevant guidance (*EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2).* Furthermore, dilution integrity and minimum required dilution (MRD) as well as stability during freeze thaw cycles was sufficiently addressed. Serum samples containing nirsevimab are stable during 5 freeze-thaw cycles at -80º C, 20 hours at room temperature, and up to 7 days refrigerated while anti-nirsevimab antibody samples are stable during 5 freeze-thaw cycles at ≤-70º C, 20 hours at room temperature, and up to 7 days refrigerated. Long-term stability sufficiently demonstrated for nirsevimab in serum samples, demonstrates stability for 374 days. Long-term stability was not investigated for ADA to nirsevimab in cynomolgus monkey serum quality control samples as it was indicated that the long-term stability of antibodies in serum at ≤-20º C is generally well documented. It is acknowledged that recommendations on antibody stability testing is in general lacking. However, with reference to the available body of data on long-term stability of ADA, it is accepted that immunoglobulins are generally considered stable for several years when maintained under controlled storage conditions, i.e. ≤-20º C (Myler H et al, 2022[4]). Therefore, no further specific information on the long-term stability of anti-nirsevimab antibodies in serum samples is required. The ELISA method developed for detection of nirsevimab in cynomolgus monkey nasal wash samples (study 1468-038) is considered suitably qualified and supports a quantitative range of 50 to 6400 ng/mL nirsevimab. Further, the ELISA method for detection of nirsevimab, MEDI-524 and MEDI-557 in cynomolgus monkey serum, nasal wash and BAL samples (non-GLP, study 20089726) is considered suitably qualified.

Absorption

Toxicokinetics after single and repeat i.m. dosing with nirsevimab was investigated as part of the 1-month repeat-dose GLP study in cynomolgus monkeys. The study showed that over the dose range of 50 mg/kg i.v. to 300 mg/kg i.v., nirsevimab exhibited linear and dose proportional TK after the first i.v. dose, but TK exposure increased in slightly less than dose-proportional manner after the last (5th) weekly dose on Day 29. Only minor accumulation was observed from first to fifth dose. Mean T_{max} was observed approximately 2.3 days following administration of 300 mg nirsevimab i.m. after the first dose. Mean $t_{1/2}$ was 40.45 and 39.91 days, following administration of 300 mg/kg i.v. and 300 mg i.m., respectively. Anti-drug antibodies (ADA) was observed in the high dose groups administered 300 mg/kg i.v. (2/3 animals) and 300 mg i.m. (2/3 animals) only during the recovery phase. In 2 of the 4 animals that tested positive for ADA (1 in 300 mg/kg i.v. and 1 in 300 mg i.m.), serum concentrations declined faster while PK in the other 2 animals remained unimpacted. In general, there were no significant gender differences, however, in the recovery groups, males had slightly higher exposures compared to females in the 300 mg/kg i.v. group and females had slightly higher exposures in the 300 mg i.m. group as compared to males, probably due to ADA. Given the long half-life, steady-state concentrations were not achieved within the dosing period of 28 days in this study. As a result, steady-state parameters such as CLss, Vz and Vss were not reported.

Distribution

[4] Myler H et al. White Paper - Anti-drug Antibody Validation Testing and Reporting Harmonization. The AAPS Journal (2022) 24: 4

Standard tissue distribution studies with nirsevimab have not been conducted, which is considered acceptable in accordance with ICH S6 for mAbs. Lung biodistribution in male cynomolgus monkeys (5 male animals/group) following i.v. administration was however investigated for nirsevimab in comparison to two other human IgG1κ mAbs, MEDI-524 (motavizumab) and MEDI-557 (YTE modification of motavizumab), both targeting the A epitope of the F glycoprotein of RSV, in order to benchmark the distribution of nirsevimab. All three mAbs were detected in nasal wash (NW) samples at 24 hours and 72 hours and in bronchoalveolar lavage (BAL) samples at 72 h in all animals dosed with the respective compounds, however, high individual variability was observed. In general, nirsevimab concentrations were lower than the comparator mAbs, though absolute mean concentrations of nirsevimab in NW were within 2- to 3-fold of the comparator mAbs at 24 hours and within 2- to 7-fold at 72 hours, while the absolute mean concentrations of nirsevimab in BAL were within 1- to 2-fold of the comparator mAbs. The mean concentration ratios of nirsevimab in NW samples compared to nirsevimab serum concentrations was approximately 1:10000.

Metabolism and excretion

In accordance with ICH S6 it is acceptable that no dedicated metabolism or excretion studies have been conducted. Nirsevimab is a monoclonal antibody and therefore its expected metabolism is degradation to small peptides and amino acids that is eliminated through the intrinsic clearance by the reticuloendothelial system in the same way as that for an endogenous IgG. No renal excretion is expected for nirsevimab since the molecular weight is higher than the glomerular filtration.

Pharmacokinetic drug interactions

It is considered acceptable that no nonclinical studies investigating pharmacokinetic drug interactions have been submitted due to the specific mode of action of nirsevimab, which is not likely to impact expression levels of metabolic enzymes such as cytochrome P405 enzymes. It is furthermore not considered likely that metabolism of nirsevimab is affected by concomitant medication as nirsevimab is likely degraded via normal protein catabolism which is not dependent on cytochrome P405 enzymes.

2.5.4. Toxicology

The non-clinical safety programme consisted of a 1-month repeat-dose toxicity study in cynomolgus monkeys and tissue cross-reactivity studies in human tissues (adult, juvenile, neonatal and foetal tissues). The antigen for nirsevimab (RSV F protein) is not endogenously expressed in humans or monkeys. Therefore, use of cynomolgus monkeys as the relevant animal species for the non-clinical in vivo program of nirsevimab is endorsed based on the comparable affinity of nirsevimab to human and cynomolgus FcRn and the fact that the YTE substitution decreases antibody exposure in rodents. Furthermore, it is supported that in the absence of adverse local or systemic effects of nirsevimab and in the absence of cross-reactivity with human tissues, additional non-clinical studies to support the use of nirsevimab in the proposed patient population were considered not necessary.

2.5.4.1. Single dose toxicity

No dedicated single-dose studies were performed. Single-dose toxicity was evaluated as a part of the one-month repeat study in cynomolgus monkeys and no adverse local or systemic effects of nirsevimab were observed based on clinical observations and clinical pathology. This is considered acceptable. In general, single-dose studies are not recommended.

2.5.4.2. Repeat dose toxicity

A repeat-dose toxicology study was conducted in cynomolgus monkeys to evaluate the potential toxicity of nirsevimab (study No 1468-038). The pivotal toxicity study was stated to be GLP-compliant with the exception of the nasal wash analysis according to the GLP compliance statement. However, it

was also noted that the formulation analysis and clinical pathology report were not conducted according to GLP. Apart from these discrepancies, the study was considered to be in compliance with GLP.

In the 4-week toxicity study with a 25-week recovery period once weekly i.v. or i.m. administration (5 doses total) of nirsevimab of 0, 300 mg/kg/week i.v. or 0 and 300 mg/kg/week i.m (6 monkeys/sex/group) or 50 mg/kg/week i.v. to (3 monkeys/sex/group) led to no adverse local or systemic effects of nirsevimab through recovery (3 monkeys/sex/group) to necropsy on Day 169.

Minor nirsevimab-related findings at terminal necropsy on Day 31 included minimal increases in globulin (males at 300 mg/kg, i.v.) that were not associated with effects on other clinical pathology or microscopic endpoints. These findings were considered test article-related but were not associated with effects on leukocytes and had no microscopic correlates, hence they were not regarded as biologically relevant. They may have been in-part related to the presence of the test article which is an immunoglobulin. In the recovery period (Days 57 to 169), globulin values continued to be mildly increased in males receiving 300 mg/kg i.v. and were also statistically increased in the 300 mg i.m. group. These observations similarly did not have other correlative findings suggesting these were biologically relevant effects. Microscopic changes in the spleen (red pulp macrophage hypertrophy/hyperplasia) were noted at the terminal necropsy in some animals (one female and two males receiving 300 mg i.m.). This microscopic finding is commonly seen with the administration of foreign proteins to monkeys and may be related to the clearance of antibodies from circulation. The NOAEL was considered to be the top dose of 300 mg/kg/week i.v. and 300 mg/week i.m.

Toxicokinetics from the 1 month repeat dose study in monkeys were assessed in the PK section.

Interspecies comparison data was presented as a comparison of exposures over a 1-month treatment period in cynomolgus monkeys and human infants and adults. Based on the NOAEL of 300 mg/week i.m. calculated safety margins for a dose of 50 mg i.m. for infants weighing <5 kg and 100 mg i.m. for those weighing ≥5 kg entering their first RSV season was 44-fold based on Cmax and 8-fold based on AUC. Given that the toxicity profile did not differ between i.m. and i.v. routes in the cynomolgus monkey, safety margins were also calculated for the NOAEL of 300 mg/kg/week i.v. which was 118-fold based on Cmax and 18-fold based on AUC. A relative low safety margin (8-fold) was noted observed at a dose of 50 mg i.m. for infants weighing <5 kg and 100 mg i.m. for those weighing ≥5 kg.

2.5.4.3. Genotoxicity

The lack of genotoxicity studies is acceptable in accordance with ICH guideline S6(R1).

2.5.4.4. Carcinogenicity

Nirsevimab binds a non-endogenous viral-specific target that is not expressed in non-clinical models or in humans, and is intended for intermittent clinical use. Thus, in accordance with ICH guideline S6(R1) the omission of carcinogenicity studies is considered acceptable.

2.5.4.5. Reproductive and developmental toxicity

In accordance with ICH guideline S6(R1), no dedicated studies have been conducted to evaluate the effects of nirsevimab on fertility, embryo-foetal, and prenatal and postnatal development. Nirsevimab binds a viral-specific target that is not expressed endogenously in non-clinical models or in humans, and the intended clinical population (infants and children) does not include women of childbearing potential. In addition, nirsevimab did not show any adverse effects on reproductive tissues in the repeat-dose toxicity study (study No 1468-038) and did not bind to any evaluated human reproductive tissues (including placenta) in the tissue cross-reactivity study (study No 20046491).

In the absence of adverse local or systemic effects of nirsevimab and in the absence of cross-reactivity with human tissues the omission of dedicated non-clinical fertility, embryo-foetal and prenatal and postnatal development studies is supported.

The currently available clinical and non-clinical safety data are considered sufficient to support the planned paediatric development and registration of nirsevimab. Although the current indication includes very young children, the nature of the target and therapeutic modality and knowledge from conducted non-clinical studies, a juvenile study is not expected to provide any added value.

2.5.4.6. Toxicokinetic data

Toxicokinetics from the 1 month repeat dose study in monkeys were assessed in the PK section.

2.5.4.7. Local Tolerance

Local tolerance after i.v. and i.m. injection was assessed as a part of the 1-month repeat-dose study in monkeys. Injection sites were evaluated for erythema/eschar and oedema changes according to the dermal Draize score. There were no nirsevimab-related signs of local irritation in the non-clinical studies conducted.

2.5.4.8. Other toxicity studies

The translational value of ADA formation in animal models are limited. Nevertheless, formation of ADA was assessed based on data from the 1-month repeat-dose study in cynomolgus monkeys with a 25-week recovery period. None of the animals in the control or treated groups tested positive for ADA at any time point during the treatment phase. ADAs to nirsevimab was only observed in the recovery period and in a limited number of animals (four (22.2%) of the recovery animals). Although it is unclear what effect ADAs had on the TK, sufficient exposures appear to have been achieved.

There was no evidence of potential nirsevimab-related immunotoxicity in parameters evaluated. The lack of dedicated immunotoxicity studies was considered acceptable.

In contrast to centrally active small molecules, available data suggests that monoclonal antibodies, as a drug class, are unlikely to cause dependence. Consistent with ICH guideline M3(R2) the absence of studies to evaluate the potential for nirsevimab abuse or misuse is accepted.

Nirsevimab is a monoclonal antibody and expected to be fully metabolized into small peptides and amino acids via catabolic pathways in the body. Therefore, the absence of studies to determine metabolites is accepted.

No concern was identified with regard to impurities.

Tissue cross-reactivity of nirsevimab was assessed by immunohistochemical methods in a GLP-compliant study using a full panel of frozen human tissues from normal human donors (study No 20046491). Results revealed no staining with nirsevimab, and therefore, no tissue cross-reactivity was observed.

Tissue cross-reactivity of nirsevimab was determined by immunohistochemical methods in a GLP-compliant study against cryosections of selected juvenile, neonatal and foetal human tissues (study No 20060018). Results revealed no staining with nirsevimab, and therefore, no tissue cross-reactivity was identified against a panel of normal human juvenile, neonatal and foetal tissues.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided an acceptable justification for not conducting a full Environmental Risk Assessment. Since nirsevimab is a monoclonal antibody with effect on the prefusion conformation of

the respiratory syncytial virus F protein, it is expected to be fully metabolized into small peptides and amino acids via catabolic pathways in the body with negligible excretion of intact, biologically active protein. In accordance to the guideline (EMEA/CHMP/SWP/4447/00 corr 21*), nirsevimab is therefore considered to be no particular hazard to the environment and no special precautions in terms of use and disposal are needed.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The pharmacology of nirsevimab was thoroughly described in the provided non-clinical package and no other concerns has been raised. The non-clinical documentation shows that nirsevimab efficiently binds to the prefusion conformation of the RSV F protein in binding site Ø with high affinity and inhibits the essential membrane fusion step in the viral entry process, neutralizing the virus and blocking cell-to-cell fusion, which has been shown both in vitro and in vivo in a cotton rat model of disease. Several polymorphisms of RSV subtype A and B were identified. However, it was shown that the occurrence of the polymorphisms is rare and that nirsevimab can be expected to exhibit activity against most currently circulating RSV strains (both A and B subtypes). The Applicant performed in vitro and in vivo studies to investigate the risk of antibody-dependent enhancement (ADE) of disease, and the documentation is considered sufficient.

Pharmacokinetics

Overall, the pharmacokinetics of nirsevimab are well described.

Toxicology

The toxicological profile of nirsevimab was characterized in a 1-month repeat-dose toxicity study in cynomolgus monkeys and two tissue cross-reactivity studies in human tissues (adult, juvenile, neonatal and foetal tissues). The antigen for nirsevimab (RSV F protein) is not endogenously expressed in humans or monkeys. Therefore, the use of cynomolgus monkeys as the relevant animal species for the non-clinical in vivo program of nirsevimab is endorsed based on the comparable affinity of nirsevimab to human and cynomolgus FcRn and the fact that the YTE substitution decreases antibody exposure in rodents. Furthermore, it is endorsed that in the absence of adverse local or systemic effects of nirsevimab and in the absence of cross-reactivity with human tissues, additional non-clinical studies to support the use of nirsevimab in the proposed patient population were considered not necessary. All pivotal non-clinical safety studies were performed according to the principles of GLP, appropriate ICH guidelines and were in line with Scientific Advice given on March 2019.

In the 4-week toxicity study with a 25-week recovery period once weekly i.v. or i.m. administration (5 doses total) of nirsevimab to monkeys, up to and including 300 mg/kg i.v. or 300 mg i.m. dose levels, was not associated with any treatment-related adverse effects both locally and systemically. Thus, the NOAEL was considered to be 300 mg/kg/week i.v. and 300 mg/week i.m. Calculated safety margins for a dose of 50 mg i.m. for infants weighing <5 kg and 100 mg i.m. for those weighing ≥5 kg was 44-fold based on Cmax and 8-fold based on AUC. Given that the toxicity profile did not differ between i.m. and i.v. routes in the cynomolgus monkey, safety margins were also calculated for the NOAEL of 300 mg/kg/week i.v. which was 118-fold based on Cmax and 18-fold based on AUC. A relative low safety margin (8-fold) was noted for a dose of 50 mg i.m. for infants weighing <5 kg and 100 mg i.m. for those weighing ≥5 kg, however, this did not give rise to concern considering that it was established at the top dose level at which no safety signals were observed.

Tissue cross-reactivity results showed no staining of any normal human adult, juvenile, neonatal and foetal tissues as expected given the target for nirsevimab was a non-endogenous viral-specific target.

In accordance with ICH guideline S6(R1) no genotoxicity and carcinogenicity studies were conducted.

In the absence of adverse local or systemic effects of nirsevimab and in the absence of cross-reactivity with human tissues the omission of dedicated non-clinical fertility, embryo-foetal and prenatal and postnatal development studies is supported.

No concern regarding local tolerance, antigenicity, immunotoxicity, dependence, metabolites and impurities were identified.

ERA

The active substance is considered a natural substance (as a protein), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, nirsevimab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* pharmacology was conducted for nirsevimab, including a disease model, supporting the intended clinical use of nirsevimab. Non-clinical proof of concept as an antibody-mediated prophylactic treatment for the prevention of RSV seems established.

Pharmacokinetics of nirsevimab is well described.

Overall, the toxicology program of nirsevimab revealed no major concerns. The toxicity studies supporting the market authorization of nirsevimab to immunise infants from birth entering their first RSV season for the prevention of RSV lower respiratory tract disease were performed according to appropriate ICH guidelines, taking into consideration the nature of the product being a monoclinal antibody directed at a foreign target. Intravenous or i.m. administration of nirsevimab to monkeys in GLP repeat-dose toxicity study was not associated with any treatment-related adverse effects both locally and systemically. For the proposed indication in the paediatric population, the safety margin for nirsevimab was 8-fold based on AUC. Nirsevimab was not considered to be genotoxic. No concern regarding reproductive and developmental toxicity, local tolerance, antigenicity, immunotoxicity, dependence, metabolites and impurities were identified. Tissue cross-reactivity results with nirsevimab showed no staining of any human tissues tested, neither adult, paediatric nor fetal tissues. Nirsevimab is not expected to pose a risk to the environment.

In conclusion, the non-clinical part of the dossier is considered approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 2 Summary of Nirsevimab Clinical Studies Referred to in the Summary of Clinical Pharmacology

Study number/ abbreviation Phase (Status)	Study design (including primary/secondary objectives)	Study Population	Dosage regimen and route of administration	Sampling time points [a]	Number of subjects included in the analysis
D5290C00001/Study 1 Phase I (Completed)	Dose-escalation, Randomised, Double-blind, Placebo-controlled, safety, PK/ADA	Healthy adults, aged ≥18 to < 50 years	Nirsevimab: 300, 1000, or 3000 mg IV; 100 or 300 mg IM Placebo: IM/IV Single dose	PK Pre dose and 8 hours post dose on Day 1 and on Study Days 2, 4, 6, 8, 15, 22, 31, 61, 91, 121, 151, 181, 271, and 361. ADA Pre dose, Study Day 15, 31, 91, 181, 271, and 361.	Total dosed: 136 Nirsevimab: 102 Placebo: 34 Included in PK/ADA analyses Nirsevimab: 102
D5290C00002/Study 2 Phase Ib/IIa (Completed)	Dose-escalation, Randomised, Double-blind, Placebo-controlled, safety, PK/ADA	Preterm infants born ≥ 32 to < 35 wGA	Nirsevimab: 10, 25, or 50 mg IM Placebo: IM Single dose	PK Screening, Study Day 8, 31, 151, 361. ADA Screening, Study Day 31, 151, and 361.	Total dosed: 89 Nirsevimab: 71 Placebo: 18 Included in PK/ADA analyses Nirsevimab: 71
D5290C00003/Study 3 Phase IIb pivotal (Completed)	Randomised, Double-blind, Placebo-controlled, safety, efficacy, PK/ADA	Very and moderately preterm infants born ≥ 29 to < 35 wGA	Nirsevimab: 50 mg IM Placebo: IM Single dose	PK Screening, Study Day 91, 151, and 361. ADA Screening, Study Day 91, 151, and 361.	Total dosed: 1447 Nirsevimab: 968 Placebo: 479 As treated population: 1447

Study number/ abbreviation Phase (Status)	Study design (including primary/secondary objectives)	Study Population	Dosage regimen and route of administration	Sampling time points [a]	Number of subjects included in the analysis
				Resistance analyses Nasal samples were to be collected for all LRTI within 2 days and up to 14 days after the diagnosis.	Included in PK/ADA analyses Nirsevimab: 968 (572 infants < 5 kg dosed per Phase III regimen) Placebo: 479 Included in resistance analyses Nirsevimab: 40, including 16 infants weighing < 5 kg Placebo: 58, including 33 infants weighing < 5 kg
D5290C00004/MELODY Phase III pivotal (Ongoing)	Randomised, Double-blind, Placebo-controlled, safety, efficacy, PK/ADA	Term and late preterm infants born ≥ 35 wGA [b]	Nirsevimab: 50 or 100 mg IM [c] Placebo: IM Single dose	PK Screening or Day 1 pre dose and Days 8 (Japan only), 15 (EU only) and/or 31 (non-EU), 151, and 361. ADA Screening, Day 31, 151, and 361.	Primary cohort, As-treated, at data cut-off 11 March 2021: Included in PK/ADA analyses: 1478 Nirsevimab: 987 Placebo: 491

Study number/ abbreviation Phase (Status)	Study design (including primary/secondary objectives)	Study Population	Dosage regimen and route of administration	Sampling time points [a]	Number of subjects included in the analysis
				Resistance analyses Nasal samples were to be collected from all subjects with LRTIs (inpatient or outpatient) and from all subjects hospitalised with any respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis.	Included in resistance analyses Nirsevimab: 31 Placebo: 46

Study number/ abbreviation Phase (Status)	Study design (including primary/secondary objectives)	Study Population	Dosage regimen and route of administration	Sampling time points [a]	Number of subjects included in the analysis
D5290C00005/MEDLEY Phase II/III pivotal (Ongoing)	Randomised, Double-blind, palivizumab-controlled, safety, PK/ADA, descriptive efficacy	Infants eligible to receive palivizumab; preterm infants born < 35 wGA and infants with CLD of prematurity or haemodynamically significant CHD	Nirsevimab: First RSV season: 50 or 100 mg IM [c] Second RSV season: 200 mg IM One dose nirsevimab followed by 4 once-monthly IM doses placebo Palivizumab: 15 mg/kg IM; 5 once-monthly doses	PK Screening or Day 1 pre dose and Days 8 (Japan only), 15 (EU only) and/or 31 (non-EU), Days 151, and 361. ADA Screening or Day 1 pre dose, Day 31, 151, and 361. Resistance analyses Nasal samples were to be collected from all subjects with LRTIs (inpatient or outpatient) and from all hospitalised subjects with any new	Overall population Total dosed: 918 [d] Nirsevimab: 614 Palivizumab: 304 Included in PK/ADA analyses: Season 1, As-treated at data cut-off 03 May 2021: Total: 918 Preterm cohort: Nirsevimab: 406 Palivizumab: 206 CLD/CHD cohort: Nirsevimab: 208 Palivizumab: 98 Included in resistance analyses Nirsevimab: 5, including 3 in the preterm cohort + 2 in the CLD/CHD cohort Palivizumab: 6, including 3 in the

Study number/ abbreviation Phase (Status)	Study design (including primary/secondary objectives)	Study Population	Dosage regimen and route of administration	Sampling time points [a]	Number of subjects included in the analysis
				respiratory infection (upper or lower) within approximately 2 days after the initial healthcare provider assessment and diagnosis	preterm cohort + 3 in the CLD/CHD cohort

[a] PK/ADA at un-scheduled visits in Study 3, MELODY, and MEDLEY (hospitalisation): blood samples for PK and ADA were to be collected from all subjects hospitalised with LRTI within approximately 2 days following hospital admission.

[b] Preterm infant population not eligible to receive palivizumab per local guidelines. In the European Union, infants entering their first RSV season were to be ≤ 8 months of age.

[c] Based on body weight at time of dosing: 50 mg nirsevimab for infants < 5 kg or 100 mg nirsevimab for infants ≥ 5 kg.

[d] Only data for the first RSV season are included in the analyses.

ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular; IV = intravenous; PK = pharmacokinetics; RSV = respiratory syncytial virus; wGA = weeks gestational age.

2.6.2. Clinical pharmacology

2.6.2.1. Clinical virology:

In the three pivotal clinical studies (study 3, MELODY and MEDLEY), for children with lower respiratory tract infections requiring medical attention or hospitalization through 150 days post the nirsevimab dose, based on RSV RNA obtained from nasal swabs, RSV strains were characterized genetically as regards conservation of nirsevimab and palivizumab epitope sites and genotype (based on sequences for F and G proteins, respectively), and susceptibility to nirsevimab and palivizumab neutralization in vitro was examined (in vitro neutralization in HEp-2 cells using recombinant RSV viruses engineered to express the F proteins of clinical strains of interest).

The documentation that the Lyra RT-PCR assay used to confirm RSV infection in children remained able to detect RSV strains circulating during the three pivotal clinical studies is largely satisfactory (some data is outstanding, and a question has been raised as to this).

In cases where RSV breakthrough infections occurred in nirsevimab-treated children, nirsevimab resistance-associated substitutions in the F protein (MARMs) were seen only in study 3, at a frequency of 2 of the 25 breakthrough infection cases in the study. While RSV A and B subtypes contributed equally to the breakthrough infections (11 and 14 caused by RSV A and B subtypes, respectively), the 2 MARM cases were both of the B subtype, and in both cases the MARMs were essentially completely resistant to nirsevimab neutralization in vitro (N208S >387-fold loss in neutralization potency; I64T+K68E+I206M+Q209R >447-fold loss in neutralization potency).

The emergence of RSV B MARMs but not RSV A MARMs in nirsevimab-treated children is in agreement with the surveillance virology data and knowledge for RSV biology and the structure of the nirsevimab epitope: (i) Amongst naturally circulating RSV strains, the RSV B subtype exhibits a higher degree of polymorphism in its F protein than does the RSV A subtype, and RSV B may have a faster evolution rate than RSV A (Langedijk 2020 and 2021, Lu 2015, Tabor 2020, Zhu 2017, Lin 2021), and (ii) the nirsevimab epitope site locates to the most variable part of the F protein; Magro 2012, Ngwuta 2015, McLellan 2013, Mas 2018, Hause 2017).

The Company considers that there were no signs of unusual clinical course of RSV disease in the 2 nirsevimab-treated children experiencing breakthrough infections with RSV B MARMs, and this is of course encouraging.

On the other hand, the current data from the MELODY and MEDLEY studies is not informative as regards the risk of emergence of MARMs, especially for the RSV B subtype where this risk is likely highest (for MELODY, due to preponderance of RSV A cases in the study, for MEDLEY, due to the low RSV infection incidence, maybe related to social distancing measures during the COVID-19 pandemic).

Thus, a more comprehensive picture of the risk of RSV breakthrough infections in nirsevimab-treated children is expected to be provided by the final reports from the MELODY and MEDLEY studies.

Finally, the potential of nirsevimab treatment to interfere with rapid RSV antigen detection assays was examined (done for 5 assays employing detection mAbs targeting epitope sites I, II and IV in the F protein; Remel X/pect RSV test kit, Quidel QuickVue RSV test kit, Meriden True RSV test, BD Directigen EZ RSV test kit, and Binax NOW RSV test kit). The results were satisfactory, but information on whether these assays are representative for RSV diagnostics in Europe is relevant.

2.6.2.2. Pharmacokinetics

Analytical methods

Nirsevimab is a human IgG1 monoclonal antibody that contains YTE amino acid substitutions in the Fc portion of the molecule to extend serum half-life. Five clinical studies contributed data to the PK/PD evaluation namely studies 1, 2 and 3, and ongoing studies MELODY and MEDLEY.

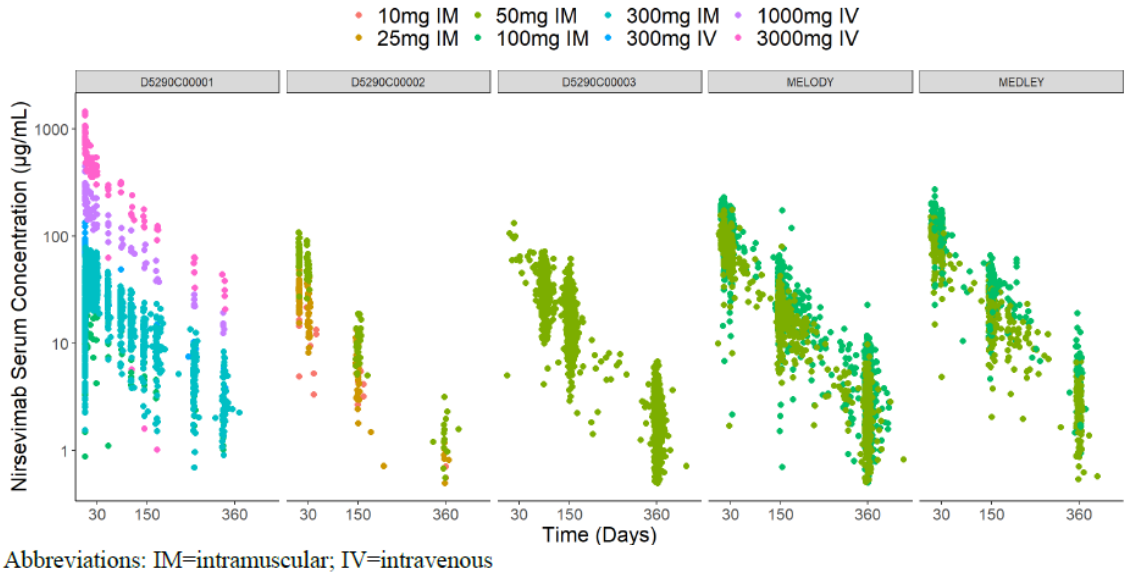
For quantification of nirsevimab in human serum, a validated ELISA based method utilising a monoclonal anti-idiotypic antibody for capture was used. The nirsevimab assay was transferred to a different analytical site, optimised and re-validated to include samples from paediatric (infant) patients. The quantification assay was not tolerant for ADAs against nirsevimab at ADA concentrations >100 ng/mL. Even 100 ng/mL ADA was shown to interfere with measurement of nirsevimab concentrations ≤1000 ng/mL. This will be relevant for interpretation of Day365 serum concentration data in ADA positive subjects in the target population. Several methods were validated for detection of ADAs to nirsevimab (screening/confirmation), NAbs to nirsevimab and ADAs to the YTE-substitution. For the ADA screening methods, the drug tolerance for detection of 100 ng/mL ADA was established to 10-12.5 µg/mL drug using goat polyclonal antibody as the positive control. The median nirsevimab systemic concentration falls below the 100 ng/ml ADA drug tolerance level after about 200 days following a 50 mg dose or after about 275 days following a 100 mg dose, thus most samples with low ADA titre would not be positive within 200-275 days post-dose. Drug tolerance for detection of 100 ng/mL NAb was 62.2 ng/mL drug (method applied in study 3) or 50 µg/mL drug (method applied in studies MELODY and MEDLEY). One electro-chemiluminescent based assay was validated for the detection of anti-drug antibodies specific against the YTE domain of nirsevimab in human serum samples. Drug tolerance was established in the method applied in MELODY and MEDLEY to 100 ng/mL YTE-antibody positive control could be detected in the presence of 100 µg/mL drug. ELISA methods were validated for quantification of palivizumab and for detection of ADAs to palivizumab. A micro-neutralization assay was developed for detection of anti-RSV neutralizing antibodies (RSV-NAb). A multiplexed ECL method for the detection of IgG antibodies specific for the pre-F, post-F, N, Ga and Gb antigens of RSV in human serum were also developed.

Population PK modelling

Nonlinear mixed-effects modelling software (NONMEM® version 7.4.3), was used for popPK modelling. Nirsevimab PK have previously been described by a linear 2-compartment model with variance terms estimated for CL and V2, based on data from studies 1, 2 and 3. IM absorption was estimated by use of adult IV data and modelled using a first-order rate constant. Residual error was described by a proportional error model. Effect of postmenstrual age (PAGE) on CL was modelled by a maturation function. Effect of body weight on disposition parameters was allometrically scaled with estimated exponents.

Data as a result of weight-band dosing of infants in studies MELODY and MEDLEY were included sequentially to the previous model with data from MELODY first. The updated complete PK dataset included 8239 PK observations from 2643 subjects, of these were 102 adults with dense PK profiles. The remaining data came from sparsely sampled infants.

Figure 2 Nirsevimab Serum Concentration Versus Time by Study



Abbreviations: IM=intramuscular; IV=intravenous

A model was first developed after inclusion of additional Study 3 data and data from MELODY. MELODY contributed 2539 observations from 962 healthy infants. MEDLEY contributed 1375 observations from 592 high-risk palivizumab-eligible infants. Using the base MELODY model, data from MEDLEY was included followed by a new covariate analysis for the final MEDLEY Pop PK model. No parameters changed notably by inclusion of MEDLEY data and GoF plots and VPCs were comparable. Significant covariates were body weight on CL, V2, Q, and V3; postmenstrual age (maturation) on CL; race on both CL and V2; and ADA on CL. Weight and postmenstrual age had large impact on nirsevimab CL. Parameter estimates and selected GoF plots and VPCs are presented for MELODY in Table **3**, **Error! Reference source not found.**for MEDLEY in Table 4, Figure 3, Figure 4, Figure 5 respectively.

Table 3 MELODY Final Model Parameter Estimates

Parameters	**Estimates**	**%RSE**	**95% CI**
Clearance (CL, mL/day)	37.6	10	30.52, 44.7
Central volume (V2, mL)	2070	33	740, 3400
Intercompartmental clearance (Q, mL/day)	612	13	453.4, 771.2
Peripheral volume (V3, mL)	2330	11	1840, 2830
Absorption rate constant (KA, day^{-1})	0.367	9	0.300, 0.433
Bioavailability (F)	0.781	8	0.664, 0.898
Covariate	**Estimates (CL and V2)**	**%RSE (CL and V2)**	**95% CI (CL and V2)**
Fractional clearance (BETACL)[a]	0.422	6	0.372, 0.472
Maturation half-life (TCL, months)[a]	10.3	17	6.79, 13.7
Body weight effect on clearances and volumes	$(WT/70)^{0.674}$, $(WT/70)^{0.868}$	4, 2	0.623, 0.726 0.836, 0.901
Race effect (Black or African American)	CL_{pop}* (1+0.118), $V2_{pop}$* (1-0.0457)	24, 67	0.0826, 0.154 -0.105, 0.0138
Race effect (Other)	CL_{pop}* (1+0.175), $V2_{pop}$* (1+0.0263)	15, 225	0.112, 0.239, -0.0897, 0.142
Race effect (American Indian or Alaskan Native)	CL_{pop}* (1-0.0740), $V2_{pop}$* (1-0.313)	19, 28	-0.132, -0.016, -0.484, -0.142
Race effect (Asian)	CL_{pop}* (1-0.117), $V2_{pop}$* (1-0.251)	40, 34	-0.189, -0.0459, -0.420, -0.0815
Race effect (Multiple)	CL_{pop}* (1-0.142), $V2_{pop}$* (1-0.219)	31, 48	-0.230, -0.0536, -0.427, -0.0111
Categorical ADA effect (yes or no per subject) on CL	CL_{pop}* (1+0.0837)	32	0.0439, 0.124
Random Effects	**Estimates (%CV)**	**%RSE [%Shrinkage]**	**95 % CI**
IIV on CL	27	4 [10%]	0.0607, 0.0816
ηV2-ηCL correlation	r=0.742	-	
IIV on V2	45	25 [27%]	0.00341, 0.409
IIV on KA	88	10 [74%]	0.481, 1.072
Residual Error	**Estimates**	**%RSE**	
Proportional error	20%	2	0.192, 0.2105

[a]Maturation function: 1-(1-BETACL) *exp (-((postmenstrual age) -(40/4.35)) *log(2)/TCL)

Table 4 Summary of Final Population PK Model Parameter Estimates

Parameters	**Estimates**	**%RSE**	**Bootstrap 95% CI**
Clearance (CL, mL/day)	39.8 [a]	7	30.4, 44.1
Central volume (Vc, mL)	2370 [a]	11	729, 2990
Intercompartmental clearance (Q, mL/day)	663 [a]	9	480, 844
Peripheral volume (Vp, mL)	2300 [a]	5	1970, 2700
Absorption rate constant (KA, day-1) [b]	0.425	7	0.216, 0.517
Bioavailability (F)	0.851	7	0.634, 0.946
Covariate	**Estimates (CL, Vc)**	**%RSE (CL, Vc)**	**Bootstrap 95% CI (CL and Vc)**
Fractional clearance (BETACL) [c]	0.400	6	0.343, 0.448
Maturation half-life (TCL, months) [c]	11.3	11	8.18, 16.3
Body weight effect [d] on clearances (CL, Q)	0.644	3	0.579, 0.699
Body weight effect [d] on volumes (Vc, Vp)	0.853	1	0.829, 0.874
Race effect (Black or African American) [d]	CL_{pop}* (1 + 0.107), Vc_{pop}* (1 - 0.0650)	16, 43	0.0754, 0.137 -0.129, 0.0122
Race effect (Other) [e]	CL_{pop}* (1 + 0.171), Vc_{pop}* (1 + 0.0247)	17, 200	0.117, 0.235 -0.0933, 0.147
Race effect (Asian) [e]	CL_{pop}* (1 - 0.0823), Vc_{pop}* (1 - 0.199)	53, 44	-0.138, -0.0220 -0.582, -0.122
Race effect (American Indian or Alaskan Native) [e]	CL_{pop}* (1 - 0.0666), Vc_{pop}* (1 - 0.281)	77, 30	-0.112, -0.0102 -0.523, -0.189
Race effect (Multiple) [e]	CL_{pop}* (1 - 0.126), Vc_{pop}* (1 - 0.129)	44, 83	-0.204, -0.0279 -0.344, 0.0595
Categorical ADA effect (yes or no per subject) on CL	CL_{pop}* (1 + 0.100)	21	0.0605, 0.140
Random Effects	**Estimates (%CV)**	**%RSE [%Shrinkage]**	**Bootstrap 95 % CI**
IIV on CL	27	3 [11%]	0.0621, 0.0780
ηVc-ηCL correlation	r=0. 785	-	
IIV on Vc	40	15 [27%]	0.105, 0.673
IIV on KA	46	15 [83%]	0.0407, 0.344
Residual Error	**Estimates**	**%RSE**	
Proportional error	20%	1	0.193, 0.215

[a] Parameter estimates for a 70 kg adult. The derived parameters for an infant of 5 kg, 11.1 months postmenstrual age are CL= 3.38 mL/day, Vc = 249 mL, Q= 121 mL/day, Vp= 241 mL.

[b] Absorption $t_{1/2}$ (ln(2)/KA) = 1.6 days

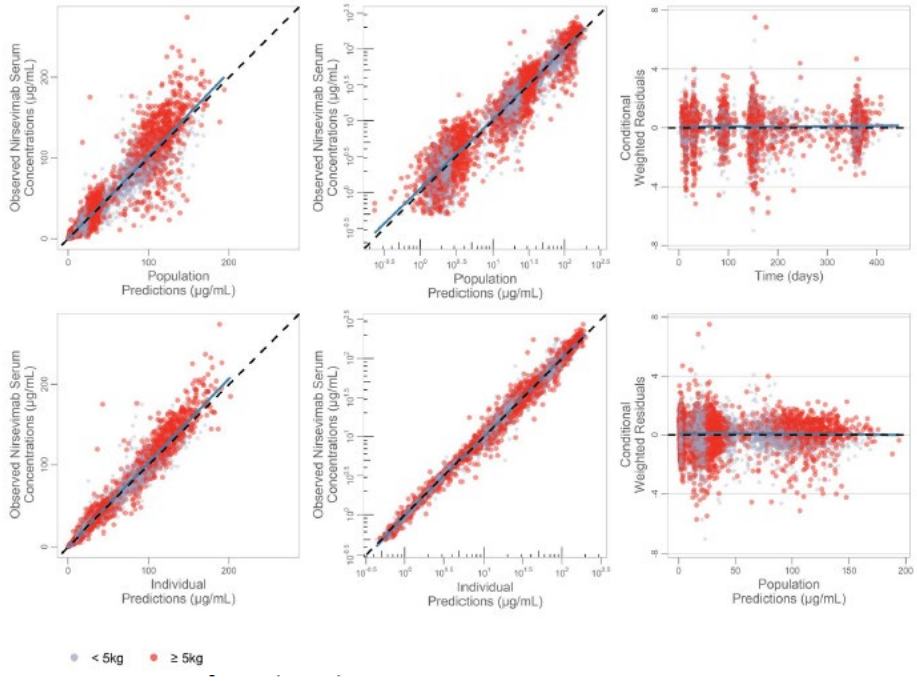
[c] Maturation function: 1-(1-BETACL) *exp (-((postmenstrual age) -(40/4.35)) *ln(2)/TCL)

[d] Body weight effect: $(WT/70)^{WTeffect}$.

[e] Reference group is White or Native Hawaiian/Pacific Islander.

ADA = anti-drug antibodies; η = eta; CI = confidence interval; CV = coefficient of variation; IIV = inter-individual variability; PK = pharmacokinetics; r = correlation coefficient; RSE = relative standard error; Vc = central volume; Vp = peripheral volume; WT = body weight.

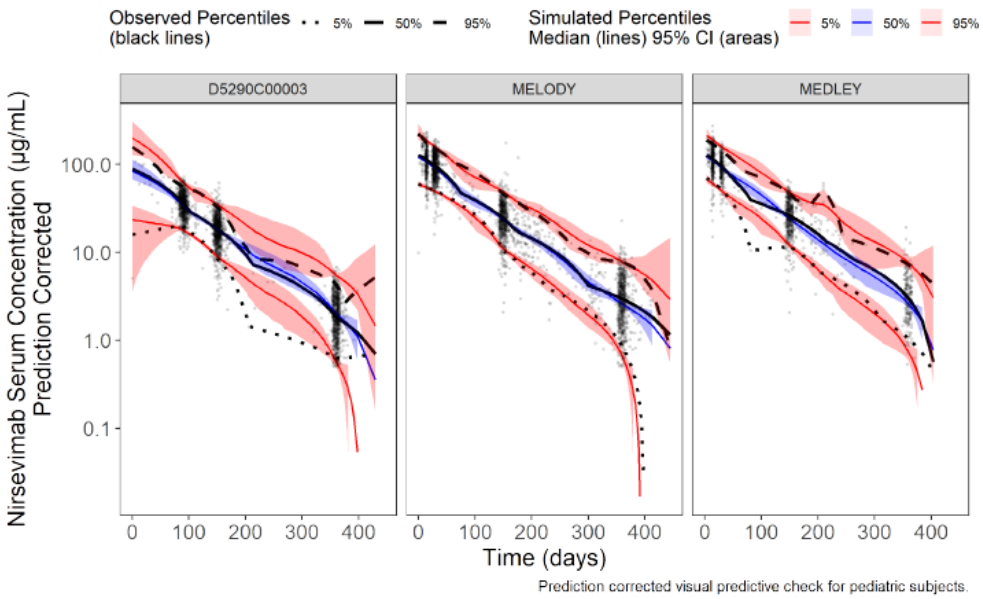
Figure 3 GOF Plots for Pediatric Subjects in the Final MEDLEY Model by Weight Group



Notes: Dots are individual data points for pediatric subjects (red: ≥5 kg, gray: <5 kg), and solid blue lines are smoothed LOESS lines. The dashed lines in columns 1 and 2 are lines of identity. In the 2 plots on the right, horizontal lines are reference lines.

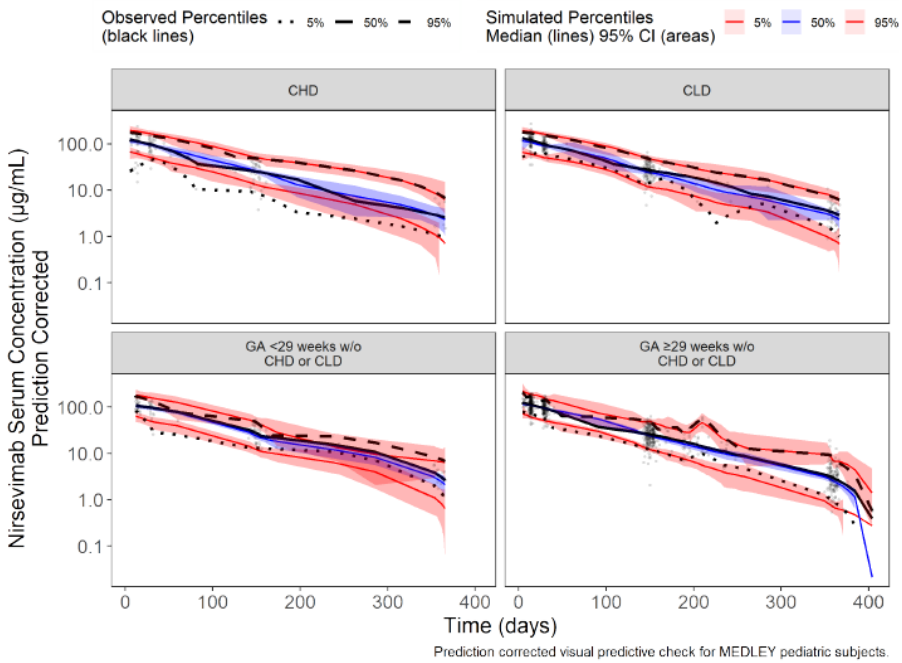
Abbreviations: CWRES=conditional weighted residuals; GOF=goodness of fit; LOESS=locally weighted smoothing

Figure 4 Prediction-Corrected VPC for MEDLEY final model stratified by study



Notes: Black dots are observed data points; black solid line is the observed median; black dotted and dashed lines are observed 5th and 95th percentiles. The blue shaded area is the 95% PI of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).
Abbreviations: CI=confidence interval; PI=prediction interval; VPC=visual predictive check

Figure 5 Prediction-Corrected VPC for MEDLEY final model stratified by CHD



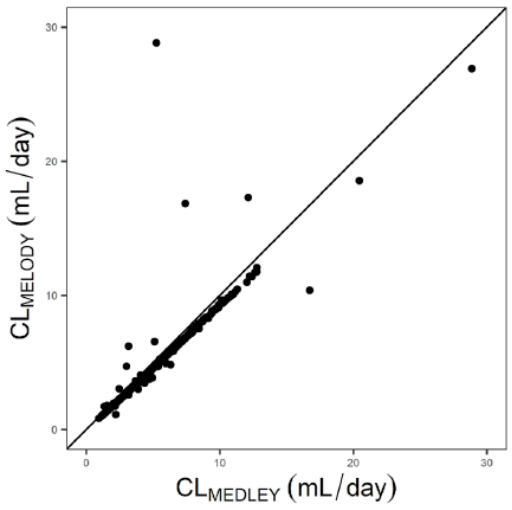
Prediction corrected visual predictive check for MEDLEY pediatric subjects.

Notes: Black dots are observed data points; black solid line is the observed median; black dotted and dashed lines are observed 5th and 95th percentiles. The blue shaded area is the 95% prediction interval (PI) of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).
Abbreviations: CHD=congenital heart disease; CI=confidence interval; CLD=chronic lung disease; GA=gestational age; PI=prediction interval; VPC=visual predictive check; w/o=without

GoF plots did not indicate any trends in the paediatric data. VPCs showed both models could adequately describe observations across the paediatric age range. Eta distributions of parameter estimates for paediatrics were close to normal with low shrinkage, except for Ka. Use of fixed exponents was tested using the final MEDLEY model (all data) but raised the OFV and gave a net decrease in CL of 25%.

A scatterplot of individual derived post hoc CL values in paediatric subjects for MELODY versus MEDLEY indicated PK comparability (Figure 6).

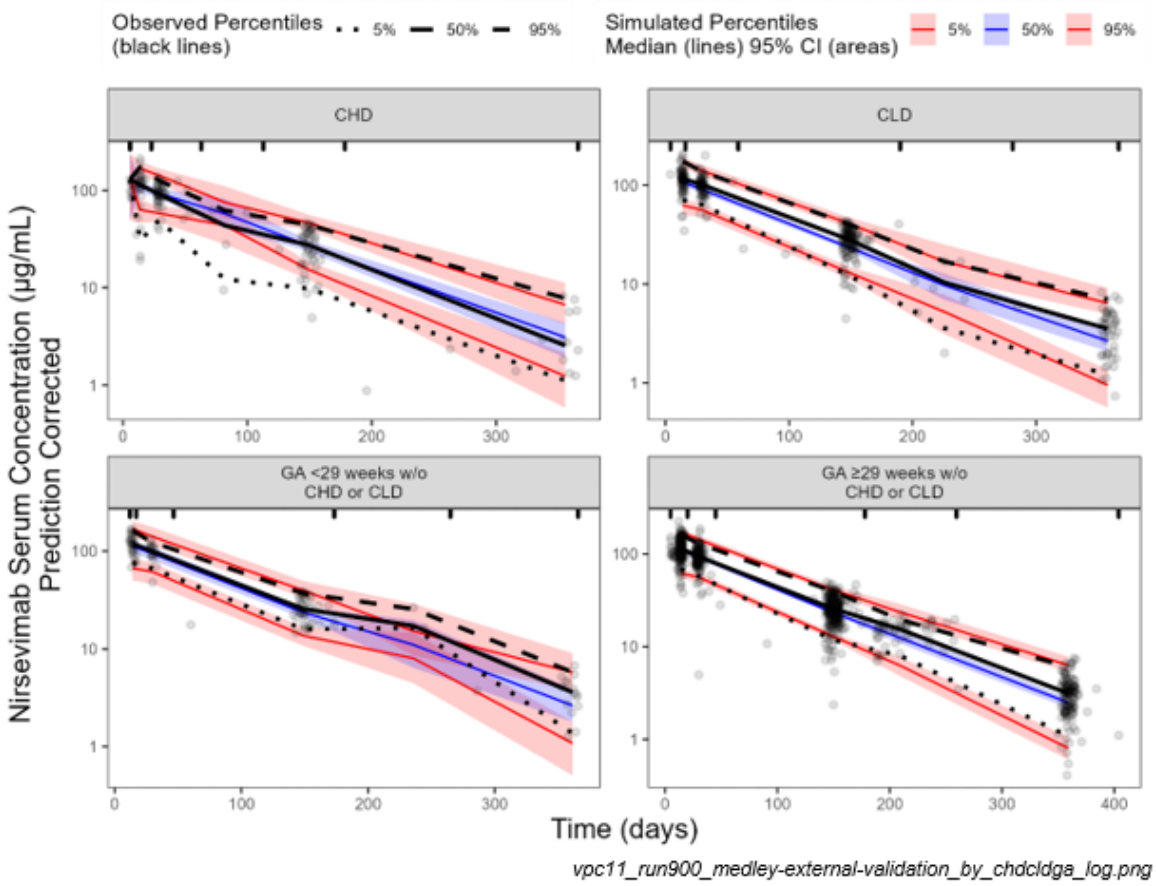
Figure 6 Scatterplot of post Hoc CL values at baseline for the MELODY final PopPK model versus post hoc CL values at baseline for the MEDLEY final PopPK



Notes: Dots are individual post hoc CL values at baseline in pediatric subjects.
Abbreviations: CL=clearance; popPK=population pharmacokinetics

For further confirmation of PK comparability, the final MELODY Pop PK model parameter estimates were used to predict the MEDLEY study data through external validation. **Figure 7** shows VPCs stratified by subgroups.

Figure 7 VPC: MEDLEY subjects predicted from the final MELODY Pop PK model (external validation) -stratified by subgroups

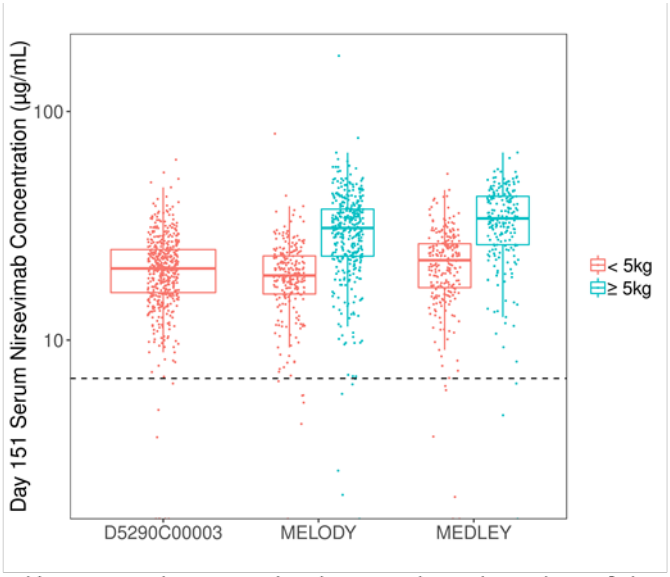


CHD = congenital heart disease; CI = confidence intervals; CLD = chronic lung disease; GA = gestational age pop PK = population pharmacokinetics; VPC = visual predictive check.

Exposure after 5 months (Day 151)

Serum nirsevimab concentrations at Day 151 for subjects from Study 3 weighing <5kg, MELODY, and MEDLEY are shown in **Figure 8**. The percentage of subjects with day 151 concentrations above the nonclinical IC90 are summarised in Table 5.

Figure 8: Day 151 serum nirsevimab concentrations by study and weight group



Dashed line:6.8 µg/mL; samples drawn within +/- 14 days of the nominal visit day

Table 5 Percent of subjects with Day 151 serum nirsevimab concentrations above the nonclinical IC90, by weight group

Weight group	N	N (%) above 6.8 µg/mL
< 5kg	1009	989 (98)
≥ 5kg	597	588 (98.5)

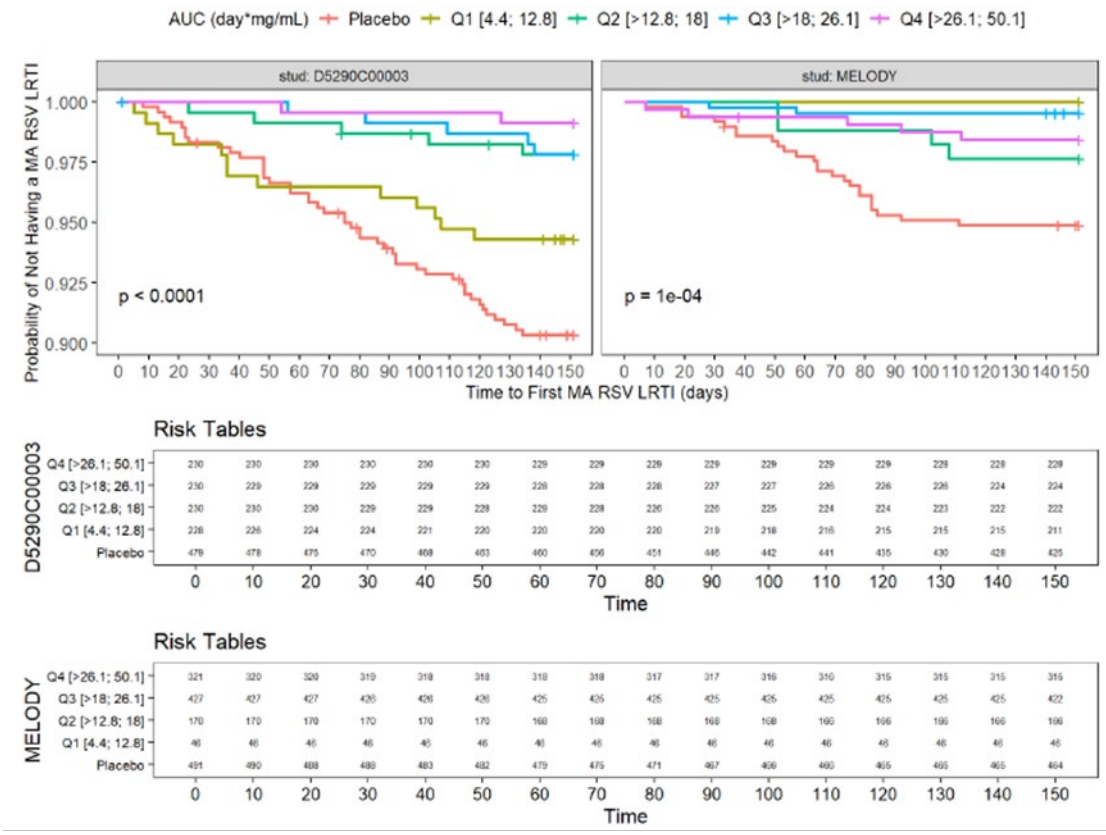
Samples drawn within +/- 14 days of the nominal visit day
IC90 = concentration producing 90% inhibition; N = number of subjects

Exposure-response modelling

A previous exposure-response analysis assessed the relationship between AUCbaseline CL and "medically attended RSV-confirmed lower respiratory tract infection" (MA RSV LRTI) over a 5-month RSV season using Cox proportional hazards modelling. Stepwise univariate covariate analysis was conducted to determine relevant factors or exposure metrics that were predictive of efficacy in this study population. Exposure evaluated as AUC quartiles was a statistically significant predictor of MA RSV LRTI risk.

Efficacy (and safety) of Study 3 and MELODY were extrapolated as per approved PIP, to the MEDLEY palivizumab-eligible population based on PK bridging. The target exposure (AUC 12.8 day·mg/mL) was the upper limit of the lowest exposure quartile (Q1), based on individual data from Study 3 in which all infants received 50 mg IM. Efficacy was demonstrated if serum nirsevimab exposures in MEDLEY were at or above the target exposure in >80% of the study population throughout a 5-month period. Specific subgroups in MEDLEY included infants with CLD of prematurity, infants with haemodynamically significant CHD, and extremely preterm infants < 29 weeks GA without CLD/CHD.

Figure 9 Kaplan-Meier plot of MA RSV LRTI outcome in studies D5290C00003 and MELODY stratified by study D5290C00003 $AUC_{baseline\ CL}$ quartiles



Note: p-value method is log rank. AUC quartiles were derived based on Study D5290C00003 data. MELODY AUC data were mapped to the AUC quartiles.

Abbreviations: AUC=$AUC_{baseline\ CL}$=area under the serum concentration-time curve derived from post hoc clearance values at baseline from the MELODY final population pharmacokinetic model; CL=clearance; MA RSV LRTI= medically attended respiratory syncytial virus-confirmed lower respiratory tract infection; Q1=first quartile; Q2= second quartile; Q3=third quartile; Q4=fourth quartile

A Cox proportional hazards model was also estimated based on data from the proposed dose only with AUC quartiles as predictor. This E-R analysis included data from Study 3 (infants <5kg) and all data from MELODY. All AUC quartiles were significantly different from 1 ($p<0.01$ or $p < 0.001$) with point estimates of HR <0.3.

Absorption

The estimated absorption half-life following IM administration was 1.6 days, based on population PK analysis. Bioavailability (F) and absorption rate constant (KA) after IM administration were 85% and 0.425 day -1, respectively, corresponding to an absorption t½ of 1.6 days, based on population PK analysis (note: these are defined primarily based on adult data but are assumed to be the same in infants). Interindividual variability on KA was 46%.

In study 2, mean Cmax after administration of 50 mg IM in pre-term healthy subjects was 71.7 µg/ml. Predicted Cmax from final popPK model was 113 µg/ml. In the SmPC, no statement on Cmax is given. As absorption information is mainly based on adult data and predicted Cmax might be over- or underestimated, this is agreed.

Distribution and elimination

The central and peripheral volumes of distribution for a typical infant weighing 5 kg and a postmenstrual age of 11.1 months were 249 mL and 241 mL, respectively, based on population PK analysis.

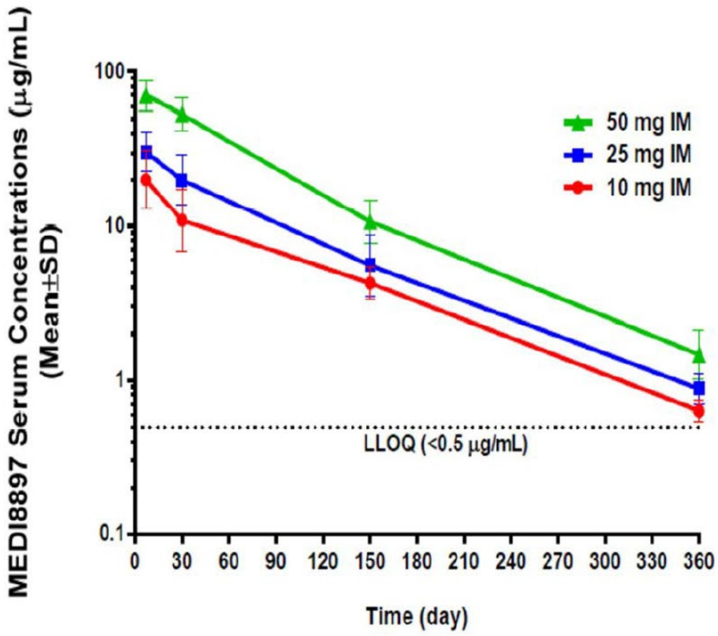
Nirsevimab is a human mAb that is degraded by proteolytic enzymes widely distributed in the body. Nirsevimab is not metabolised by hepatic enzymes. Based on population PK analyses, the estimated CL for nirsevimab is 3.38 mL/day for a typical infant weighing 5 kg and a postmenstrual age of 11.1 months. The model-predicted mean (SD) terminal elimination half-life of nirsevimab was 69 (10) days for infants.

In the target population, there is a strong impact of body weight (and maturation) on volume of distribution and clearance. The volume of distribution in infants weighing 2.2 kg and 8.3 kg were 50% and 155% of that of a 5 kg infant. Clearance in infants weighing 2.2 kg and 8.3 kg were predicted to be 59% and 139%, respectively, of the CL in a 5 kg infant.

Dose proportionality and time dependencies

The PK of nirsevimab were dose-proportional following single IV doses of 300 to 3000 mg and single IM doses of 100 mg to 300 mg in adults. In infants, dose proportional PK was seen after single IM doses of 25 mg to 50 mg.

Figure 10 Mean Nirsevimab serum concentration-time profiles following a single fixed IM dose of 10,25 or 50mg Nirsevimab in preterm infants ≥ 32 to < 35wGA – Study 2



IM = intramuscular; LLOQ = lower limit of quantification; MEDI8897 = nirsevimab; SD = standard deviation; wGA = weeks gestational age.
Source: Figure 11.4.4.1-1, Study 2 CSR, Module 5.3.3.1.

Nirsevimab is intended for one-time administration only, time dependency has not been studied.

Interindividual variability implemented on CL, central volume, and KA, were 27%, 40%, and 46%, respectively. The intended population are infants and represented in 4 of the 5 studies conducted.

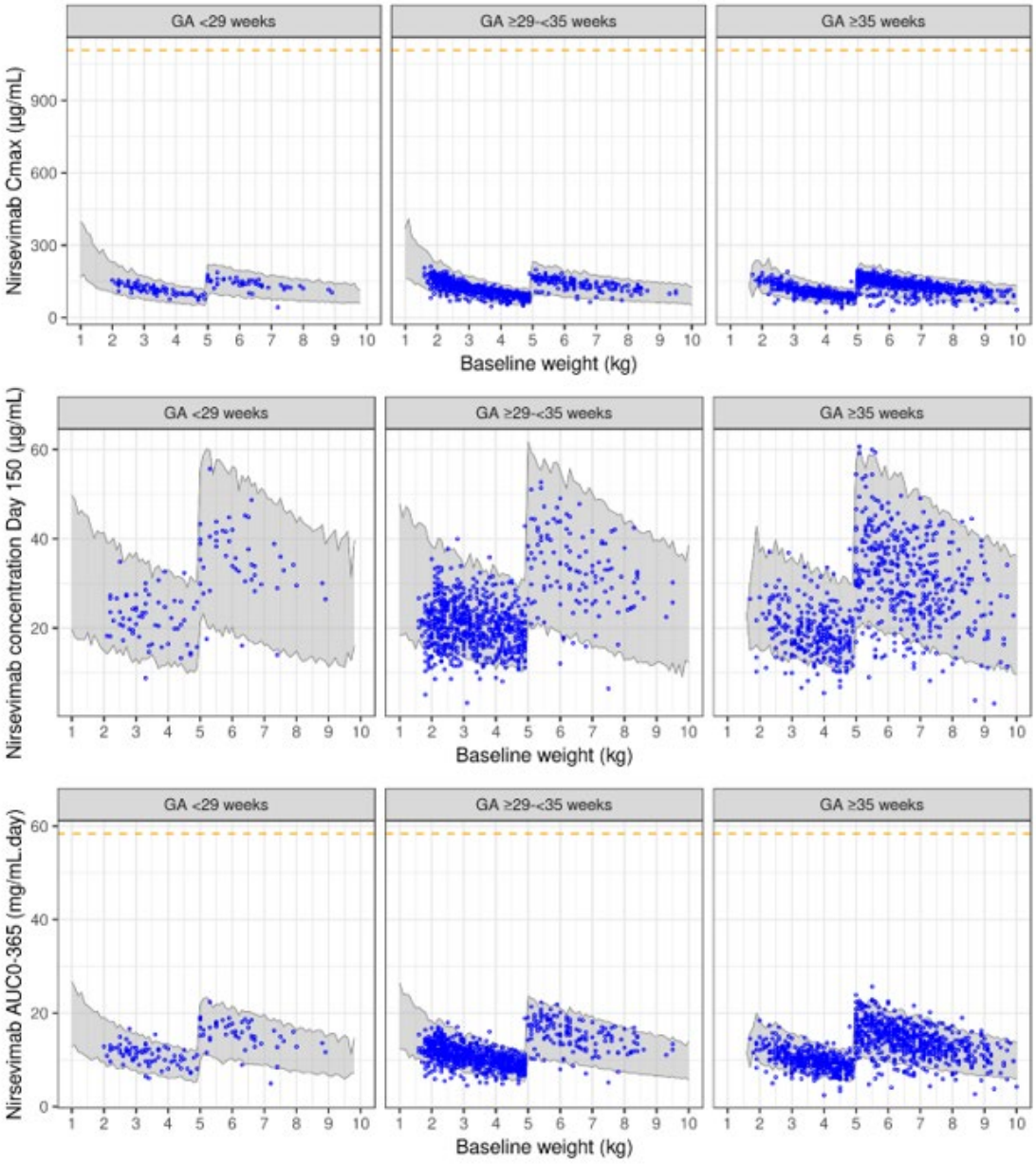
Special populations

No studies in special populations have been conducted. Covariates affecting the PK of nirsevimab were identified from the PopPK model. Race was identified as a statistically significant covariate on the clearance and central volume of nirsevimab in the population PK analysis; however, the estimated effects of race (independent of body weight) were generally small relative to the overall variability. Predicted exposures per race group for weight-band dosed infants indicated no clinically relevant differences between race groups. Clearance and volume of distribution increase with increase in body weight.

Exposure simulations versus body weight

Simulations were performed for the full nirsevimab serum concentration time course following a single dose, according to the proposed weight-band dosing regimen (ie, 50 mg dose for infants weighing < 5 kg; 100 mg dose for infants weighing ≥ 5 kg). Models included time-varying body weight, based on growth curves for preterm and term infants with a minimum weight of 1 kg at the time of dosing**.**

Figure 11 Predicted Nirsevimab serum exposures versus body weight at baseline 90% prediction interval (grey band), individual predictions (blue points), median adult exposures from 3000 mg IV (orange broken line); C_{max} (top), concentration day 150 (middle), AUC_{0-365} (bottom)



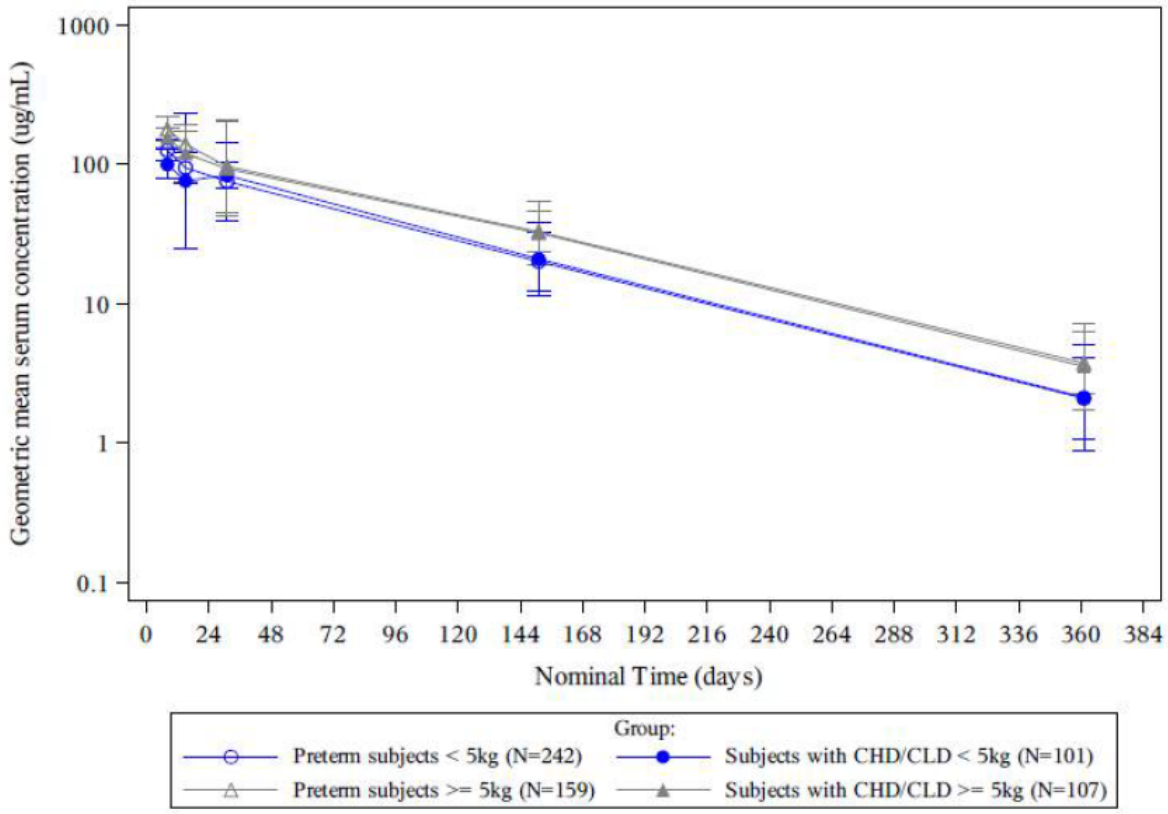
Individual predictions for subjects in Study 3 (< 5 kg), MELODY, and MEDLEY are overlaid for reference.

Nirsevimab has been studied in adults and preterm and term infants. There is a high correlation between age and body weight. An effect of postmenstrual age was estimated in the population PK analysis. The effect of postmenstrual age (PAGE) gave an estimated 60% lower CL for a term infant at birth (40 weeks GA) compared to complete maturation, and a maturation t½ of 11.3 months, resulting in a 26% lower CL for a term infant at 12 months of age (postmenstrual age 21 months).

Infants with CLD or CHD

CLD or CHD were not significant covariates in the popPK model, and in MEDLEY, infants with CLD and/or CHD had similar nirsevimab exposure as preterm infants (**Figure 12**). In this study, infants were dosed with the proposed dose.

Figure 12 Geometric mean serum concentration (µg/mL) of Nirsevimab versus time by group (log-linear scale) (Season 1) – as treated population



Vertical lines represent the geometric mean ± gSD. Geometric mean is derived from planned visit day ± 14 days.
Geometric mean – gSD=exp(mean(log(PK Conc)) – SD(log(PK Conc))). Geometric mean + gSD=exp(mean(log(PK Conc)) + SD(log(PK Conc))).
Subjects < 5 kg received 50 mg, subjects ≥ 5 kg received 100 mg nirsevimab.
Subjects redosed after heart surgery were included. Subjects with important protocol deviations of accidentally receiving a second dose of nirsevimab on Day 31 were excluded (n = 4).
Conc = concentration; gSD = geometric standard deviation; PK = pharmacokinetics; N = number of subjects; SD = standard deviation.
Source: Figure 14.5.1.2.

Pharmacokinetic interaction studies

No DDI studies have been conducted with nirsevimab. As a mAb, nirsevimab is eliminated by intracellular catabolism and not primarily cleared via hepatic or renal pathways. Based on the mechanism of action of nirsevimab, which specifically neutralises RSV pre-F to provide protection in vivo (and prevent viral entry into target cells), it is unlikely that it could interfere with the immune response to vaccines.

2.6.2.3. Pharmacodynamics

Mechanism of action

Nirsevimab is a fully human, anti-RSV neutralising monoclonal antibody (IgG1/kappa isotypes for the heavy/light chains), isolated from memory B cells from human donors.

It binds to a discontinuous epitope displayed by the native, quaternary structure on the apex of the prefusion conformation of the F protein (F protein residues 62-96 and 196-212, within antigenic site Ø, site zero). Site Ø is lost as the F protein transitions to the post-fusion conformation, i.e. nirsevimab is specific for the pre-fusion state of F (McLellan 2013 and 2015, Zhu 2017, Swanson 2014).

Nirsevimab was engineered with 9 aminoacid substitutions to increase affinity for the F protein and reduce antigenicity, and a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Binding to human Fc receptors is maintained, and the mAb is expected to exhibit normal Fc-mediated effector functions (complement activation, mediation of phagocytosis, antibody-mediated killing of virus-infected cells, etc).

The mAb exhibits neutralising activity against both RSV subtype A and B strains, by locking the F protein in the pre-fusion conformation, thereby inhibiting entry of free virions into cells, as well as inhibiting spread of cell-associated virus by cell fusion. The mAb does not inhibit attachment of virions to cells. This mode of action is similar to the mode of action for palivizumab (palivizumab targets epitope site II, binds pre- as well as postfusion conformations of the RSV F protein, and likely neutralizes virus by sterically inhibiting the cell fusion step).

Primary and Secondary pharmacology

Following administration of a single dose of nirsevimab in infants in Study 2, Study 3, and MELODY, dose-dependent increases in serum anti-RSV-neutralising antibody levels were seen, similar to the increases in nirsevimab serum concentrations. Serum anti-RSV neutralising antibody levels were correlated with nirsevimab serum concentrations across all dose levels. The RSV-neutralising antibody levels for infants passively immunised with nirsevimab decreased between days 151 and 361 but remained more than 5 times greater than baseline levels in subjects in both Study 3 and MELODY.

Immune response to nirsevimab was described in terms of ADA prevalence (percentage of subjects who were ADA-positive at any time point during the study, including at baseline) and incidence (treatment-emergent ADA or percentage of subjects who were positive post baseline only or subjects positive at baseline with post-baseline titre increased by a factor of ≥ 4).

Based on analyses of pooled data from the primary cohort of subjects in MELODY and Study 3 entering their first RSV season, who received the proposed dose of nirsevimab,

Anti-drug antibody prevalence was 5.7% (88/1556). Treatment-emergent ADA (incidence) were detected in 5.6% (84/1498) of subjects with a median of the maximum titre of 200.0.

The prevalence and incidence of neutralising antibodies to nirsevimab were 0.9% (14/1556) and 1.0% (14/1423), respectively. Anti-drug antibodies against the nirsevimab YTE substitution were detected with prevalence and incidence of 4.4% (68/1556) and 4.8% (68/1423), respectively. The majority of

nirsevimab-treated subjects who had positive ADA results were positive only 361 days post baseline (and not at 151 days).

Anti-drug antibody results were generally comparable between subgroups (term/preterm, weight, CHD/CLD). On Day 361, serum nirsevimab concentrations were generally lower in participants with ADA, including a larger proportion being below the limit of quantification, compared with those who tested negative; this indicates an influence of ADA on nirsevimab PK between Days 151 and 361.

An exposure-response analysis performed based on pooled data from MELODY and Study 3 (all subjects, figure 15) showed a positive correlation between AUC and a reduction in the risk of MA RSV LRTI through 150 days post dose with a target AUC of 12.8 mg*day/mL. The AUCs were divided into quartiles based on Study 3 data. MELODY applied weight-band dosing to achieve exposures above the serum Q1 efficacy target and the individual AUCs for MELODY subjects were mapped into the quartiles defined based on Study 3. Exposures (AUCs) for subjects in the MEDLEY study were derived using post hoc estimates of CL at baseline from the MEDLEY final popPK model. Nirsevimab exposures in the MEDLEY study were compared to the adjusted target exposure threshold of 12.8 day·mg/mL. Under these conditions, AUCbaseline CL was determined to be above the target in >80% of the overall MEDLEY population (94.3%) and for all subgroups of special interest: infants with CLD (94.1%), infants with hemodynamically significant CHD (80.3%), and extreme preterm infants <29 weeks GA (93.6%) (**Table 6**).

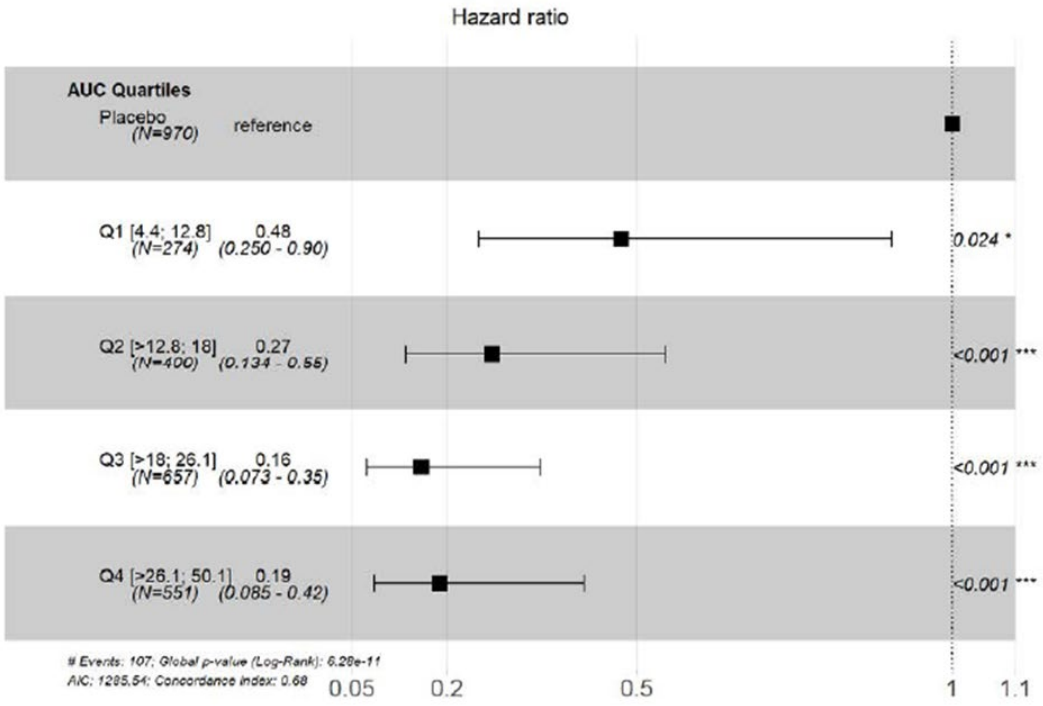
Table 6 Extrapolation results for Paediatric subjects in MEDLEY stratified by gestational CHD/CLD status

	CHD (N=66)	CLD (N=136)	Total (N=202)
$AUC_{baseline\ CL} \geq$ Threshold	53 (80.3%)	128 (94.1%)	181 (89.6%)
$AUC_{baseline\ CL} <$ Threshold	13 (19.7%)	8 (5.9%)	21 (10.4%)

Note: target exposure threshold 12.8 day·mg/mL, CHD group includes 9 subjects with CHD/CLD.
Abbreviations: $AUC_{baseline\ CL}$=area under the serum concentration-time curve derived from post hoc CL values at baseline from the MEDLEY final popPK model; CHD=congenital heart disease; CL=clearance; CLD=chronic lung disease; N=number

Thus, weight-band dosing (ie, 50 mg for infants weighing < 5 kg and 100 mg for infants weighing ≥ 5 kg) resulted in exposures above the target in > 80% of the infants studied. No further relationship between nirsevimab exposure and the risk of MA RSV LRTI was evident based on data from the proposed weight-band dose.

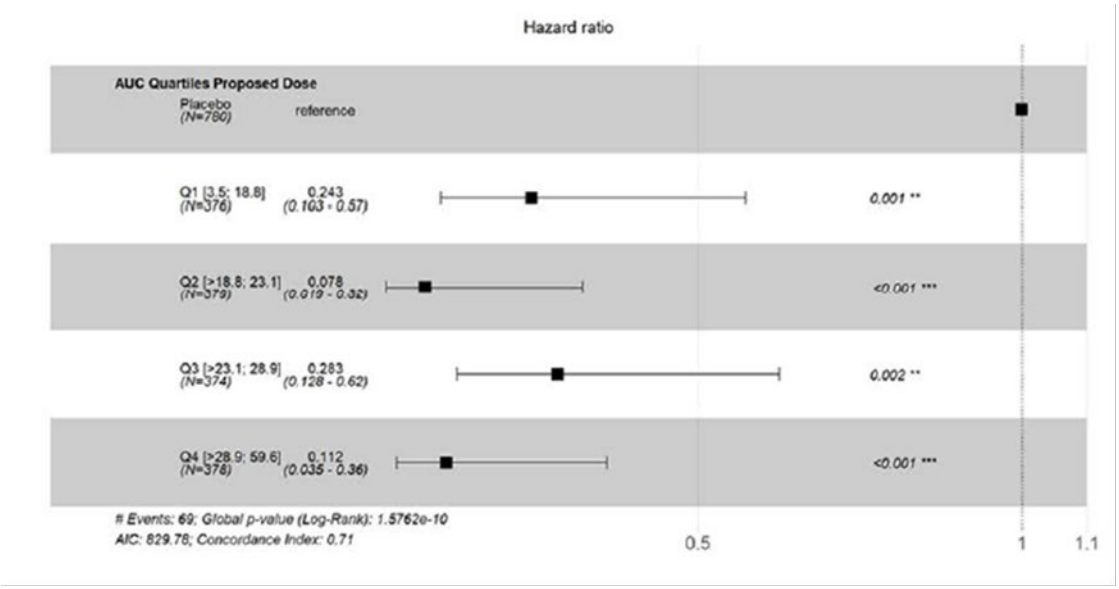
Figure 13 forest plot predictors in the final exposures-response model for MA RSV LRTI through Day 151 (MELODY and study 3), hazard ratio (95%CI)



Note: AUC quartiles were derived based on Study 3 data. MELODY AUC data were mapped to the AUC quartiles. P-values based on the Wald test show testing of each quartile versus placebo; *=p-value <0.05, ***=p-value <0.001.
AIC = Akaike information criterion; AUC = area under the serum concentration-time curve derived from post-hoc clearance values at baseline from the population PK model based on Study 1, Study 2, Study 3 and MELODY; CI = confidence interval; CL = clearance; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects; PK = pharmacokinetics; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; RSV = respiratory syncytial virus.

No exposure-response were demonstrated when only data based on the proposed dose were included (Study 3 data from infants ≥5kg excluded). All AUC quartiles were significantly different from placebo treatment (**Figure 14**).

Figure 14 exposure response based on proposed dose for MA RSV LRTI through day 151, hazard ratio (95% CI)



Notes: P-values based on the Wald test show testing of each quartile versus placebo; **=p<0.01; ***=p<0.001
AIC = Akaike information criterion; AUC = area under the serum concentration-time curve derived from post-hoc clearance values at baseline from the population PK model based on Study 1, Study 2, Study 3 and MELODY; CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects; PK = pharmacokinetics; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile.

2.6.3. Discussion on clinical pharmacology

ELISA based methods were developed and validated for determination of nirsevimab serum concentrations, detection of ADAs to nirsevimab (screening/confirmation), NAbs to nirsevimab and ADAs to the YTE-substitution of nirsevimab. The quantification assay was not tolerant for ADAs at ADA concentrations >100 ng/mL. The drug tolerance of the ADA assay was 12.5 µg/mL for detection of 100 ng/mL ADA against nirsevimab, which allows detection of sustained ADA positivity after Day 151. The Applicant will submit final bioanalytical reports covering MELODY and MEDLEY once they are available.

Rank-based analysis of Study 3 data identified the optimal 5 kg cut-point for body weight of the proposed weight-band dosing, 50 mg <5 kg, 100 mg ≥5kg, applied in the phase 3 trials.

The final Pop PK models including data from Study 3 (all dosed 50 mg), MELODY and MEDLEY (weight-band dosing, 50 or 100 mg) are considered to be of high impact. No formal hypothesis testing for efficacy of nirsevimab in the higher-risk infant subgroups of MEDLEY was conducted. Individual model derived exposure metrics for MELODY and for MEDLEY using post-hoc estimates of CL at baseline, were used for extrapolation of efficacy from MELODY to MEDLEY by PK bridging as per approved PIP. A scatterplot of individual derived post hoc CL values in paediatric subjects for MELODY versus MEDLEY indicated PK comparability. Further PK comparability was demonstrated by fitting the MEDLEY data through external validation using the final MELODY Pop PK model. Nirsevimab serum concentration time curves following a single dose were simulated using a model that included time-varying body weight based on growth curves for preterm and term infants. The predicted exposure metrics indicated that the smallest infants of 1 kg could experience a 75% higher Cmax, a 10% lower Day 150 concentration and a 15% higher AUC0-365 after 50 mg, than a 5 kg child receiving 100 mg. From the simulated exposure data for infants down to 1 kg, it is agreed that no dose adaptation is necessary in the lightest individuals. A sensitivity analysis for the 41 extremely preterm (≤ 29 wGA at birth) infants who received nirsevimab within the first 3 months of life, assuming F=100% and ka*5 only had a minimal effect on predicted AUC365 and increased predicted Cmax approximately 1.5-fold. Considering

the safety margin compared to phase 1 adult data (with doses up to 3000 mg applied), this is still more than 3-fold for both, Cmax and AUC365, for the infant with the highest exposure in the extreme scenario (Kax5 and 100% bioavailability).

The efficacy measure "Medically attended RSV-confirmed lower respiratory tract infection" (MA RSV LRTI) over a 5-month RSV season was explored using Cox proportional hazards modelling. Exposure evaluated as AUC quartiles, was a statistically significant predictor of MA RSV LRTI risk. Due to inclusion of additional Study 3 data, the AUC quartiles were updated using the final MELODY Pop PK model and a new and lower exposure threshold was defined (AUC 12.8 day·mg/mL). The exposure quartiles used in the updated E-R analysis included data from subjects who were not treated using weight-band dosing as applied in MEDLEY. A "proposed dose" E-R analysis excluding Study 3 data from infants weighing ≥5kg did not indicate any relation of AUC quartile to efficacy. In this analysis the upper limit of the AUCbaseline CL first quartile was 18.8 mg·day/mL.

Overall, it can be agreed that an extrapolation of efficacy based on exposure is reasonable, as nirsevimab has an external target and viral aetiology as well as exposure-response are expected to be comparable between populations. Simulations indicate that the AUC 12.8 day·mg/mL threshold value was reached in >80% of infants in all investigated subgroups in study MEDLEY. From 66 infants with CHD, 53 reached threshold while 13 did not; thus, objective of extrapolation was only just met (80.3%).

Positive exposure-response relationship was shown for efficacy: between AUC and a reduction in the risk of MA RSV LRTI through 150 days post dose. No dose-exposure-response analysis for safety has been conducted. As nirsevimab aims at an exogenous target, no target-related AEs are expected. For safety parameters investigated (e.g. systemic hypersensitivity, SAEs by PT, deaths), incidence was low and exposure-safety analyses are not expected to be robust. Thus, it is acceptable not to perform exposure-safety analyses for safety endpoints.

The metabolic pathways of nirsevimab have not been investigated. This is acceptable for an IgG antibody. Commonly the t½ reported for human IgG is around 20 days, though there is a wide range in the reported values. Because of the YTE modification that was added to this monoclonal antibody to prolong the terminal t1/2 in humans, the terminal elimination half-life of nirsevimab was 69 (10) days for infants. The PK of nirsevimab were dose-proportional following single IV doses of 300 to 3000 mg and single IM doses of 100 mg to 300 mg in adults. In infants, dose proportional PK was seen after single IM doses of 25 mg to 50 mg.

About ¾ of intramuscularly administered nirsevimab becomes systemically available based on adult data. This is well in line with what has been reported for other mAbs (52 -80% after SC or IM application).

Due to the chosen route of administration, Cmax (113 µg/ml based on final popPK model) is reached with lag time, which is considered acceptable for a pre-exposure prophylaxis setting. Furthermore, much lower values were estimated to be sufficient for treatment effect (6.8 µg/mL).

Currently, only data after a single dose of nirsevimab are available; PK data on planned re-application in the 2nd season are outstanding. No analysis of PK under steady state conditions has been performed; the potential for accumulation has not been investigated.

No dedicated studies have been conducted to investigate the pharmacokinetics of nirsevimab in special populations. The effects of renal or hepatic impairment on the clearance of nirsevimab were not studied which is considered acceptable since intact nirsevimab is not expected to undergo renal elimination or to be metabolised by hepatic enzymes. No clinically relevant effects of race, ADA, or concomitant CLD or CHD on the PK of nirsevimab were identified. Age and weight are important covariates on the PK of nirsevimab. Baseline body weight and baseline postmenstrual age (PAGE) were strongly correlated. PAGE was included in the Pop PK model using a maturation function on CL. A 60% lower CL were estimated for a newborn child compared to complete maturation. This is of special interest for the infants born <29GA receiving their nirsevimab dose in their first month of life where the highest exposure is expected. Thus, the absolute numbers of exposure in these patients have been presented and were lower than those in the term infants dosed with the 100mg dose. As seen with

other mAbs and thus expected for fixed dosing regimens, exposure decreased with increasing body weight. Considering the presumed weight ranges of the target population, there will be great differences in exposure after the planned weight-band dosing. Based on data presented it is agreed that CHD and CLD do not have a relevant impact on nirsevimab PK in infants.

For study MEDLEY, mean serum concentrations by time point were presented separately for CLD/CHD cohorts within each weight/dose group. Results from CLD/CHD cohorts were well in line with results obtained in subjects without these pre-existing conditions. However, for all subgroups, inter-subject variability was high at some time points. Thus, the applicant presented the overlay of individual PK profiles of study MEDLEY for the subgroups CHD/CLD <5kg, and CHD/CLD ≥5 kg, respectively. These plots demonstrate that CHD/CLD children covered the extreme ranges of concentrations obtained after application of 50 mg and 100 mg nirsevimab, respectively. No apparent outliers were identified. Thus, as in overall population, high variability seen in CHD/CLD cohorts is supposed to be mainly attributed to the broad range of weights and ages (maturation) treated with the same flat-doses. The treatment regimen might therefore also be acceptable for CHD/CLD children.

Based on data obtained with palivizumab, surgery with cardiopulmonary bypass is expected to result in decreased exposure. Within study MEDLEY there were 9 infants that underwent surgery, 8 of them received a replacement dose. However, only for 4 infants pre- and post-surgery PK data (prior to next nirsevimab dose) were available. For these subjects only a small decrease (within assay variation) in nirsevimab serum concentration was seen. Thus, a data-based recommendation on an additional dose in infants undergoing cardiac surgery with cardiopulmonary bypass cannot be given. However, it can be agreed that an additional dose might be needed to facilitate RSV protection in infants that underwent cardiac surgery with cardiopulmonary bypass and that these children are of particular vulnerability. As no safety problems occurred in the limited number of subjects, an additional dose at the discretion of the treating clinician to be included in the SmPC is acceptable.

Due to the nature of the product DDIs are not expected and it is accepted, that no DDI studies have been conducted. The PK of nirsevimab is well-described in the target population. Regarding concomitantly administration with routine paediatric vaccines it is accepted, that interactions/interference with the immune response to those is unlikely. Furthermore, routine vaccines were given in the safety pool.

The primary PD effect of nirsevimab has been assessed by increase in serum anti-RSV neutralising antibody levels. These were correlated with nirsevimab serum concentrations across all dose levels in study 2, 3 and MELODY and ~93% of the infants with samples measured for RSV-neutralising antibodies experienced a ≥ 4- fold rise. This is accepted as a satisfactory PD response.

The RSV-neutralising antibody levels for infants passively immunised with nirsevimab decreased between days 151 and 361 as expected but remained more than 5 times greater than baseline levels in subjects in study 3 and MELODY. The impact of maternal antibodies (detected as baseline level of anti-RSV antibodies in infants) on efficacy endpoints was investigated in exploratory analyses. The distribution of maternal antibodies was similar between treatment arms in each study and no correlation between baseline antibody level and efficacy endpoints was observed.

Immunogenicity is a minor concern, if the product is intended for one time administration only. ADA incidence was low and did not affect the PK of nirsevimab before day 151. Beyond day 151 there is indication of changed PK due to ADA as serum concentrations of nirsevimab were lower in ADA positive subjects at day 361. In the target population, the impact of ADAs on exposure seems to be mainly present in elimination phase post day 151 and might presumably be attributed to ADAs against YTE substitution. Furthermore, it has to be kept in mind that the nirsevimab PK assay was not tolerant of antibody concentrations above 100 ng/mL for detection of nirsevimab concentrations ≤1 µg/mL. Thus, nirsevimab concentrations BLOQ post day 151 might also be a matter of assay deficiency in ADA positive subjects. As exposure until day 151 was not obviously affected in the large majority of ADA positive subjects, findings do not raise a certain concern.

The surveillance virology data as well as the literature, supports that nirsevimab can be expected to exhibit activity against most currently circulating RSV strains (A as well as B subtypes), and the

Applicant has informed that continued monitoring of breakthrough RSV infections in nirsevimab-treated children will continue in the EU after a potential marketing authorization.

2.6.4. Conclusions on clinical pharmacology

ELISA based methods were developed and validated for determination of nirsevimab serum concentrations, detection of ADAs to nirsevimab (screening/confirmation), NAbs to nirsevimab and ADAs to the YTE-substitution of nirsevimab. Final bioanalytical reports covering MELODY and MEDLEY are awaited and will be provided post-authorisation (PAM).

The PK elimination phase of the half-life extended antibody nirsevimab has been adequately described in the target population. The absorption phase after the planned IM administration is mainly described by adult data due to sparse sampling in infants. PK of nirsevimab highly depends on weight and maturation of infants, which is considered by the popPK model developed by the Applicant.

Clinical data on neutralising RSV antibodies indicate that sufficiently high values for a treatment effect will be obtained for up to 5 months. A good correlation between nirsevimab plasma concentration and neutralising RSV antibody titers was expected (as kind of concept proof) and is seen with clinical data. The prevalence of variants harbouring nirsevimab resistance-associated substitutions was low in the surveillance studies conducted.

The incidence of anti-drug antibodies (ADA) was overall low within the clinical trial program.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The Applicant agrees to submit the final bioanalytical reports covering MELODY and MEDLEY PK, ADA, anti-YTE and nAb analysis, when they become available.

2.6.5. Clinical efficacy

The study programme for the assessment of efficacy includes 1 pivotal trial (MELODY), where the primary analysis has been completed (follow-up at day 151) and 1 phase IIb study (named Study 3). Additionally, a phase II/III study (MEDLEY) is ongoing in preterm infants born < 35 wGA (without CLD or CHD) and term and preterm infants with CLD or CHD. This study will only provide data to the extrapolation of efficacy. The submitted data provides information on efficacy in subjects entering their first RSV season. The Table below shows the details of the 3 studies.

Table 7

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects randomised/ treated	Healthy subjects or diagnosis of patients	Duration of treatment	CSR synopses Location in Module 5
Controlled Clinical Studies								
Efficacy	D5290C00003 (Study 3)	Efficacy Safety PK ADA	Phase IIb R, DB, PC	Nirsevimab: 50 mg IM Placebo: IM Single dose	1453/1447 Nirsevimab, 969/968 Placebo, 484/479	Very and moderately preterm infants, born ≥ 29 to < 35 wGA	Single dose	Module 5.3.5.1
Efficacy	D5290C00004 (MELODY) [a]	Safety Efficacy PK ADA	Phase III R, DB, PC	Nirsevimab: 50 or 100 mg IM Placebo: IM Single dose	Primary cohort (complete through Day 361): 1490/1478 Nirsevimab, 994/987 Placebo, 496/491 Safety cohort (enrolment complete): 1524/1522	Term and late preterm infants born ≥ 35 wGA entering their first RSV season	Single dose	Module 5.3.5.1
Safety	D5290C00005 (MEDLEY) [b]	Safety PK ADA Descriptive efficacy	Phase II/III R, DB, palivizumab controlled	**RSV Season 1:** Nirsevimab: 50 or 100 mg IM; single dose followed by 4 once-monthly IM doses placebo Palivizumab: 15 mg/kg IM; 5 once-monthly doses **RSV Season 2:** Nirsevimab: 200 mg IM; single dose followed by 4 once-monthly IM doses placebo Palivizumab: 15 mg/kg IM; 5 once-monthly doses	**RSV Season 1 (complete):** 925/918 Nirsevimab, 616/614 Preterm, 407/406 CLD/CHD, 209/208 (70 with CHD) Palivizumab, 309/304 Preterm, 208/206 CLD/CHD, 101/98 (33 with CHD)	Infants eligible to receive palivizumab; preterm infants born < 35 wGA and infants with CLD of prematurity or haemodynamically significant CHD **RSV Season 1:** 1. Preterm infants born ≤ 35 wGA (without CLD or CHD) 2. Infants with CLD of prematurity or haemodynamically significant CHD **RSV Season 2:** [c] Children ≥ 12 and ≤ 24 months of age with CLD of prematurity or haemodynamically significant CHD who received nirsevimab or palivizumab in their first RSV season	**RSV Season 1:** Nirsevimab: single IM dose followed by 4 once-monthly IM doses placebo Palivizumab: 5 once-monthly doses **RSV Season 2:** Children with CLD or CHD who: 1. Received nirsevimab in RSV Season 1 will receive a single fixed dose of nirsevimab 200 mg IM followed by 4 once-monthly IM doses placebo 2. Received palivizumab in RSV Season 1 will be randomised 1:1 to receive either: • Nirsevimab: single fixed dose 200 mg IM followed by 4 once-monthly IM doses of placebo or • Palivizumab: 15 mg/kg IM; 5 once-monthly doses	Module 5.3.5.1

[a] Only results from the primary cohort of MELODY are included.

[b] Only results from RSV Season 1 of MEDLEY with a data cut-off of 03 May 2021 are included.

[c] RSV Season 2 data are planned for submission in a variation to support extending the indication to cover children at high risk for severe RSV disease in their second RSV season.

ADA = antidrug antibody; CHD = (haemodynamically significant) congenital heart disease; CLD = chronic lung disease (of prematurity); CSR = clinical study report; DB = double blind; IM = intramuscular; PC = placebo controlled; PK = pharmacokinetic(s); R = randomised; RSV = respiratory syncytial virus; wGA = weeks gestational age.

2.6.5.1. Dose response studies

In study 3, a predefined subgroup analysis was conducted, and efficacy in subjects with a body weight higher than 5 kg was lower than subjects with a body weight lower than 5 kg. Furthermore, modelling and simulation study showed that nirsevimab exposure (AUC) was dependent on body weight, and a large proportion of infants weighing ≥ 5 kg had suboptimal exposure in Study 3 where only the 50 mg dose was used.

Therefore, a higher dose (100 mg) was selected for MELODY in subjects weighing ≥ 5 kg.

2.6.5.2. Main studies

The main studies include 3 studies. In the following, MELODY (phase 3 study) and Study 3 (phase 2b study) are evaluated in the same section due to the similarity of the study designs. Additionally, the pooled analysis of the secondary endpoint is presented in the same section, as this is part of the main prespecified analyses.

MEDLEY is evaluated in a separate section, and the extrapolation methods are described in the pharmacology section.

MELODY: A Phase III Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants

Study 3: A Phase IIb Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants

Methods

1. **Study Participants**

MELODY included healthy infants born at term or late preterm ≥ week 35 gestational age, and **Study 3** included preterm infants born between week 29+0 and week 34+6 gestational age.

The infants had to enter their first RSV season when entering screening phase. In study 3 in EU, the infants had to be below 8 months of age when entering the season to be eligible.

2. **Treatments**

The solution was 50 mg nirsevimab/ml. Corresponding saline solution was used for placebo. The treatment was a single dose.

In **MELODY**, the dose was stratified by bodyweight. In infants weighing < 5 kg 50 mg was administered, and in infants weighing ≥ 5 kg, 100 mg was administered.

In **Study 3**, 50 mg was used in all subjects, including subjects weighing ≥ 5 kg. Hence, only in subjects weighing less than 5 kg the proposed dose was used.

3. **Objectives**

MELODY:

Primary: To assess the efficacy of nirsevimab when administered as a single fixed IM dose to term/late preterm infants ≥ 35 weeks 0 days GA and entering their first RSV season, in reducing medically attended respiratory syncytial virus lower respiratory tract infection (MA RSV LRTI), compared to placebo

Secondary: To assess the efficacy of nirsevimab in reducing MA RSV LRTI with hospitalisation, compared to placebo

Exploratory: To assess the incidence of MA RSV LRTI, compared to placebo after Day 151

Study 3:

Primary: Assessed the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo

Secondary: Assessed the efficacy of MEDI8897 for the reduction of hospitalizations due to RT- PCR-confirmed RSV, compared to placebo

4. **Outcomes/endpoints**

In **MELODY**, the primary endpoint was: Incidence of MA RSV LRTI (inpatient and outpatient) through 150 days after dosing (ie, during a typical 5-month RSV season).

In **Study 3**, the primary endpoint was: Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season.

In both studies, the RSV infection should be confirmed by RT PCR and in both studies, the primary analyses were conducted when subjects had reached day 150.

Additionally, in **MELODY**, RSV infection after 150 days is stated as an exploratory efficacy endpoint. Furthermore, in both studies health care resources were prespecified as exploratory endpoints, e.g. ICU admission, duration of stay, respiratory support, oxygen supplementation. Specifically, the Applicant defined an endpoint of severe LRTI (MA RSV LRTI very severe), which included hospitalised patients with RSV LRTI who required oxygen supplementation or intra venous fluid.

5. **Sample size**

For both studies, the sample size was aiming at 99% power to detect a 70% relative risk reduction. In both studies, the incidence rate in the placebo group was assumed to be 8%.

In **MELODY**, the sample size was driven by safety database requirement, and 3000 infants should be included, of which 2000 should be exposed to nirsevimab. In study 3, 1500 infants should be included of which 1000 should be exposed to nirsevimab.

6. **Randomisation and Blinding (masking)**

In both studies, infants were randomised 2:1 to either nirsevimab or placebo. The randomisation was stratified by Northern and Southern hemisphere and age (≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months). An interactive web response system was used for the randomisation.

Both **MELODY** and **Study 3** were double-blind studies. **MELODY** was blinded until data base lock at day 511, except for one single Japanese subject that had completed the day 361 visit.

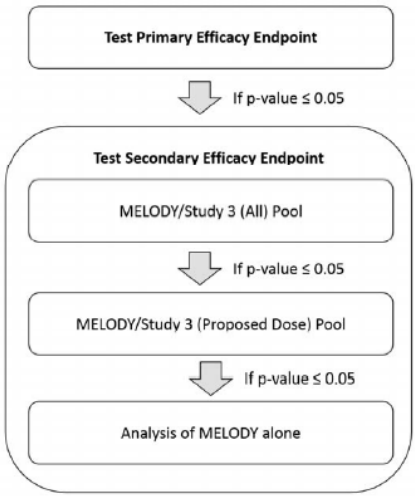
7. **Statistical methods**

Intention to treat was used. Estimands were not defined but the influence of drop-outs was assessed using imputation methods. Dropout was minimal.

Poisson regression with Zou's variance estimator is appropriate and standard under the circumstances. The implementation with the repeated statement in sas proc genmod is according to Zou's paper.

Pooling of MELODY and Study 3: The secondary endpoint was analysed in a pooled analysis of MELODY and Study 3 using hierarchical testing (Figure 15)

Figure 15 Hierarchical testing for primary and secondary efficacy endpoints, prespecified in the MELODY SAP and study protocol



Primary endpoint = MA RSV LRTI.
Secondary endpoint = MA RSV LRTI with hospitalisation.
LRTI = lower respiratory tract infection; MA = medically attended; SAP = statistical analysis plan; RSV = respiratory syncytial virus.

Several subgroup analyses were planned and those were not multiplicity-adjusted.

Results

1. **Participant flow**

Disposition of subjects are shown in **Table 8**.

Overall, the disposition was similar between treatment arms within each study and across studies. The completion rate at day 151 was high (97.5% in MELODY and 98.0% in Study 3). In the nirsevimab arms there were 4 and 2 deaths in MELODY and Study 3, respectively. This is addressed in the safety section.

Table 8 Subject disposition – MELODY, study 3, and MEDLEY

Statistic	Number (%) of Subjects							
	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA				Infants at higher risk for severe RSV disease	
	MELODY		Study 3 (All subjects)		Study 3 (Proposed Dose)		MEDLEY	
	Placebo	Nirsevimab	Placebo	Nirsevimab	Placebo	Nirsevimab	Palivizumab	Nirsevimab
Subjects screened (Total) [a]	1626		1540		860		960	
Screen failures (Total) [b]	136 (8.4)		87 (5.6)		0 (0.0)		35 (3.6)	
Did not meet inclusion/exclusion criteria [c]	98 (72.1)		66 (75.9)		0 (0.0)		22 (62.9)	
Lost to follow-up [c]	6 (4.4)		1 (1.1)		0 (0.0)		0	
Withdrawal of consent [c]	25 (18.4)		13 (14.9)		0 (0.0)		9 (25.7)	
Other [c]	7 (5.1)		7 (8.0)		0 (0.0)		4 (11.4)	
Subjects randomised	496	994	484	969	290	570	309	616
Subjects randomised, not dosed	5 (1.0)	7 (0.7)	3 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.6)	2 (0.3)
Subjects randomised and dosed	491 (99.0)	987 (99.3)	481 (99.4)	966 (99.7)	290 (100.0)	570 (100.0)	304 (98.4)	614 (99.7)
Study phase status								
Completed Day 151 follow-up	488 (98.4)	977 (98.3)	472 (97.5)	945 (97.5)	285 (98.3)	560 (98.2)	293 (94.8)	593 (96.3)
Completed Day 361 follow-up	453 (91.3)	914 (92.0)	454 (93.8)	913 (94.2)	273 (94.1)	542 (95.1)	NA	NA
Completed the study	43 (8.7)	89 (9.0)	454 (93.8)	913 (94.2)	273 (94.1)	542 (95.1)	NA	NA
Early discontinuation from study	21 (4.2)	40 (4.0)	30 (6.2)	56 (5.8)	17 (5.9)	28 (4.9)	25 (8.1)	44 (7.1)
Death	0 (0.0)	4 (0.4)	4 (0.8)	2 (0.2)	4 (1.4)	2 (0.4)	1 (0.3)	5 (0.8)
Lost to follow-up	3 (0.6)	9 (0.9)	11 (2.3)	26 (2.7)	5 (1.7)	12 (2.1)	1 (0.3)	7 (1.1)
Withdrawal by parent/legal/representative	14 (2.8)	20 (2.0)	11 (2.3)	21 (2.2)	5 (1.7)	9 (1.6)	17 (5.5)	28 (4.5)
COVID-19 pandemic	1 (0.2)	3 (0.3)	NA	NA	NA	NA	2 (0.6)	0 (0.0)
Other [d]	3 (0.6)	4 (0.4)	4 (0.8)	7 (0.7)	3 (1.0)	5 (0.9)	4 (1.3)	4 (0.6)

2. **Recruitment**

Study 3 was conducted between 3 November 2016 and 6 December 2018. In **MELODY**, the first subject was enrolled 23 July 2019, and the follow-up is not completed yet.

3. **Conduct of the study**

There were several protocol deviations due to the COVID-19 pandemic. Most of them were subjects missing at least one visit. In **MELODY**, 1.5% were excluded from the per protocol population and in **Study 3**, 0.2% were excluded from the per protocol population due to missed dose.

Overall, the proportion of protocol deviations were similar between treatment groups. The Applicant has conducted several sensitivity analyses in order to address the missing visits due to COVID-19.

4. **Baseline data**

The distribution of baseline variables was similar between treatment groups within each study (**Table 9**).

In **MELODY**, median age at randomisation (min;max) was 2.6 months (0.03;11.10). In **Study 3**, median age at randomisation (min;max) was 2.8 months (0.1;11.9).

In Study 3, 22 children with a gestational age of 29 weeks were exposed to nirsevimab during the first 3 months of life, but no children with a gestational age of 29 weeks were exposed before the age of 1 month in this study. In the MEDLEY study (described below), 17 children with a gestational age between 24 weeks and ≤29 weeks were exposed to nirsevimab within the first 3 months of life and only 13 children within the age of 2 months. In the posology section in the SmPC, it is stated that there is limited data available in extremely preterm infants less than 8 weeks of age, and that no

clinical data is available in infants with a postmenstrual age (gestational age at birth plus chronological age) of 32 weeks.

In **MELODY,** 40% of the subjects had a body weight < 5 kg, and 15.6% had a body weight ≤ 2.5 kg. The minimum bodyweight was 1.8 kg in the nirsevimab group. In **Study 3**, mean bodyweight was 4.6 kg and the minimum bodyweight was 1.6 kg in the nirsevimab group.

In the posology section in the SmPC it is stated that safety and efficacy of nirsevimab in infants with body weight below 1.6 kg have not been established and no clinical data are available. Furthermore, it is stated that dosing in infants with a body weight from 1.0 kg to <1.6 kg are based on extrapolation.

In **MELODY**, 7.7% of subjects had a history of respiratory, thoracic and mediastinal disorders, 6.7% had a history of gastrointestinal disorders, 6.3% had a history of infections and infestations, and 6.1% had a history of jaundice neonatal. In **Study 3**, the overall medical history was similar in both treatment groups. However, for atrial septal defects, the prevalence was higher (30/484 (6.2%)) for placebo than for nirsevimab (38/969 (3.9%)), and for neonatal respiratory distress syndrome the prevalence was 93/484 (19.2%) in the placebo group and 162/969 (16.7%) in the nirsevimab group and thereby the prevalence was also higher in the placebo group than nirsevimab for history of neonatal respiratory distress syndrome. In order to rule out that the results are confounded by medical history of atrial septal defects or neonatal respiratory distress syndrome, the Applicant has conducted a post hoc sensitivity analysis in which those two factors were added to the model.

Table 9 Selected demographic and baseline characteristics-MELODY, study 3 (all subjects), study 3 (proposed dose)

Statistic	Term and late preterm infants born ≥ 35 wGA (MELODY)			Very and moderately preterm infants born ≥ 29 to < 35 wGA (Study 3; All subjects)			(Study 3; Proposed dose)		
	Placebo (N = 496)	Nirsevimab (N = 994)	Total (N = 1490)	Placebo (N = 484)	Nirsevimab (N = 969)	Total (N = 1453)	Placebo (N = 290)	Nirsevimab (N = 570)	Total (N = 860)
Age at randomisation, months									
Mean	3.01	2.91	2.95	3.28	3.29	3.29	1.79	1.84	1.83
SD	2.25	2.21	2.22	2.31	2.22	2.25	1.17	1.10	1.12
Median (min, max)	2.60 (0.03, 10.97)	2.60 (0.03, 11.10)	2.60 (0.03, 11.10)	2.80 (0.1, 11.3)	2.90 (0.1, 11.9)	2.80 (0.1, 11.9)	1.55 (0.1, 6.4)	1.70 (0.1, 5.7)	1.60 (0.1, 6.4)
Age at randomisation stratum, n (%)									
≤ 3.0 months	285 (57.5)	577 (58.0)	862 (57.9)	257 (53.1)	516 (53.3)	773 (53.2)	246 (84.8)	489 (85.8)	735 (85.5)
> 3.0 to ≤ 6.0 months	162 (32.7)	317 (31.9)	479 (32.1)	153 (31.6)	320 (33.0)	473 (32.6)	42 (14.5)	81 (14.2)	123 (14.3)
> 6.0 months	49 (9.9)	100 (10.1)	149 (10.0)	74 (15.3)	133 (13.7)	207 (14.2)	2 (0.7)	0	2 (0.2)
Sex, n (%)									
Female	257 (51.8)	464 (46.7)	721 (48.4)	224 (46.3)	468 (48.3)	692 (47.6)	140 (48.3)	272 (47.7)	412 (47.9)
Male	239 (48.2)	530 (53.3)	769 (51.6)	260 (53.7)	501 (51.7)	761 (52.4)	150 (51.7)	298 (52.3)	448 (52.1)
Race, n (%) [a]									
American Indian or Alaska Native	26 (5.2)	57 (5.8)	83 (5.6)	1 (0.2)	0	1 (0.1)	0	0	0
Asian	18 (3.6)	36 (3.6)	54 (3.6)	10 (2.1)	5 (0.5)	15 (1.0)	6 (2.1)	3 (0.5)	9 (1.0)
Black or African American	136 (27.4)	286 (28.9)	422 (28.4)	67 (13.8)	189 (19.5)	256 (17.6)	40 (13.8)	120 (21.1)	160 (18.6)
Native Hawaiian or other Pacific Islander	5 (1.0)	6 (0.6)	11 (0.7)	3 (0.6)	8 (0.8)	11 (0.8)	3 (1.0)	6 (1.1)	9 (1.0)
White	272 (54.8)	524 (52.9)	796 (53.5)	355 (73.3)	693 (71.6)	1048 (72.2)	206 (71.0)	395 (69.4)	601 (70.0)
Other	38 (7.7)	70 (7.1)	108 (7.3)	43 (8.9)	61 (6.3)	104 (7.2)	32 (11.0)	39 (6.9)	71 (8.3)
Multiple categories	1 (0.2)	12 (1.2)	13 (0.9)	5 (1.0)	12 (1.2)	17 (1.2)	3 (1.0)	6 (1.1)	9 (1.0)
Ethnicity, n (%)									
Hispanic or Latino	51 (10.3)	100 (10.1)	151 (10.2)	91 (18.8)	225 (23.2)	316 (21.8)	44 (15.2)	118 (20.7)	162 (18.9)
Not Hispanic or Latino	443 (89.7)	890 (89.9)	1333 (89.8)	393 (81.2)	743 (76.8)	1136 (78.2)	246 (84.8)	451 (79.3)	697 (81.1)

Weight group on Day 1, n (%)									
< 5 kg	192 (38.7)	403 (40.6)	595 (40.0)	290 (60.3)	570 (59.1)	860 (59.5)	290 (100.0)	570 (100.0)	860 (100.0)
≥ 5 kg	304 (61.3)	589 (59.4)	893 (60.0)	191 (39.7)	394 (40.9)	585 (40.9)	0	0	0
Birth weight group n (%)									
≤ 2.5 kg	88 (17.7)	145 (14.6)	233 (15.6)	454 (93.8)	905 (93.4)	1359 (93.5)	276 (95.2)	541 (94.9)	817 (95.0)
> 2.5 kg	408 (82.3)	848 (85.4)	1256 (84.4)	30 (6.2)	64 (6.6)	94 (6.5)	14 (4.8)	29 (5.1)	43 (5.0)
Gestational age group, n (%)									
< 29 weeks	NA	NA	NA	NA	NA	NA	NA	NA	NA
≥ 29 to < 32 weeks	NA	NA	NA	101 (20.9)	193 (20.1)	294 (20.3)	64 (22.1)	125 (22.2)	189 (22.2)
≥ 32 to < 35 weeks	NA	NA	NA	383 (79.1)	769 (79.9)	1152 (79.7)	226 (77.9)	438 (77.8)	664 (77.8)
≥ 35 weeks	NA	NA	NA	NA	NA	NA	NA	NA	NA
≥ 35 weeks to < 37 weeks	76 (15.4)	132 (13.3)	208 (14.0)	NA	NA	NA	NA	NA	NA
≥ 37 weeks	419 (84.6)	861 (86.7)	1280 (86.0)	NA	NA	NA	NA	NA	NA
Multiple birth, n (%)									
Yes	45 (9.1)	96 (9.7)	141 (9.5)	185 (38.2)	366 (37.8)	551 (37.9)	119 (41.0)	213 (37.4)	332 (38.6)
No	451 (90.9)	897 (90.3)	1348 (90.5)	299 (61.8)	603 (62.2)	902 (62.1)	171 (59.0)	357 (62.6)	528 (61.4)
Subjects ever breastfed, n (%)									
Yes	433 (87.3)	884 (89.0)	1317 (88.4)	NE	NE	NE	NE	NE	NE
No	63 (12.7)	109 (11.0)	172 (11.6)	NE	NE	NE	NE	NE	NE
Smokers in household currently, n (%)									
Yes	120 (24.2)	215 (21.7)	335 (22.5)	NE	NE	NE	NE	NE	NE
No	375 (75.8)	778 (78.3)	1153 (77.5)	NE	NE	NE	NE	NE	NE
Currently in day care, n (%)									
Yes	29 (5.9)	56 (5.6)	85 (5.7)	NE	NE	NE	NE	NE	NE
No	466 (94.1)	937 (94.4)	1403 (94.3)	NE	NE	NE	NE	NE	NE

a Each race category counts subjects who selected only that category; "Multiple categories checked" counts subjects who selected more than one race category.

The n's and totals for the number of subjects with data for each individual characteristic are provided in the source tables.

max = maximum; min = minimum; NA = not applicable; NE = not evaluated; SD = standard deviation; wGA = weeks gestational age.

Source: Table 14.1.4.a, MELODY iCSR, Module 5.3.5.1; Table 14.1.4 Study 3 CSR, Module 5.3.5.1; Tables 66.1 and 77.1, Appendix 2.7.3.6, Module 5.3.5.3.

5. Numbers analysed

The ITT populations were used for the primary analyses. Furthermore, a pooled population with individuals from MELODY and Study 3 were defined for the secondary endpoint (hospitalisation). Additionally, a pooled population with individuals dosed with the proposed dose was defined. This population consists of all subjects from MELODY and subject < 5 kg in Study 3, as subjects ≥ 5 kg in study 3 received 50 mg, which is lower than the proposed dose, which is 100 mg.

6. Outcomes and estimation

Primary endpoint

In **MELODY**, 12/994 subjects in the nirsevimab group and 25/496 subjects in the placebo group met the primary endpoint, and the relative risk reduction was 74.5% (95% CI: 49.6%, 87.1%) with nirsevimab compared with placebo (**Table 10**).

In **Study 3**, 25/969 subjects in the nirsevimab group and 46/484 subjects in the placebo group met the primary endpoint, and the relative risk reduction was 70.1% (95% CI: 52.3%, 81.2%) with nirsevimab compared with placebo (**Table 11**).

Results on the primary endpoints from both studies were statistically significant.

Table 10 incidence of MA RSV LRTI though 150 days post dose (ITT1)

Analysis	Placebo (N = 496)	Nirsevimab (N = 994)	Relative risk reduction (95% CI)	p-value
Poisson regression with robust variance (Primary Analysis)				
Subjects with observed events, n (%)	25 (5.0)	12 (1.2)	NA	
Subjects requiring imputation [a], n (%)	6 (1.2)	15 (1.5)	NA	
Efficacy [b]			74.532 (49.626, 87.124)	<0.0001
Poisson regression with robust variance with adjustment of follow-up time				
Observed events	25 (5.0)	12 (1.2)	NA	
Efficacy [c]			76.539 (53.240, 88.229)	<0.0001
Stratified Cochran-Mantel-Haenszel test				
Observed events	25 (5.0)	12 (1.2)	NA	
Efficacy [d]			76.100 (52.729, 87.916)	<0.0001

[a] Subjects who had no events and were not followed through 150 days post dose.

[b] Relative risk reduction of nirsevimab versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including stratification factor [age at randomisation] as covariate) obtained from PROC MIANALYZE after missing data imputation.

[c] Relative risk reduction of nirsevimab versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance adjusting for the stratification factor of age at randomisation with log (follow-up time) as offset.

[d] Relative risk reduction of nirsevimab versus placebo, the 95% CI, and p-value were estimated based on stratified CMH test (adjusted for the stratification factor [age at randomisation]).

CI = confidence interval; ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects in treatment group; n = number of subjects in analysis; NA = not applicable; RSV = respiratory syncytial virus.

Source: Table 14.2.1.1.a, Table 14.2.1.3.a, and Table 14.2.1.4.a.

Table 11 Incidence of medically attended RSV-confirmed LRTI through 150 days post dose (ITT population)

Analysis	Placebo N = 484	MEDI8897 N = 969	Relative Risk Reduction (95% CI)	P value
Poisson regression with robust variance (primary analysis)				
Observed events	46 (9.5%)	25 (2.6%)	NA	
Subjects requiring imputation[a]	11 (2.3%)	24 (2.5%)	NA	
Efficacy			70.1% (52.3%, 81.2%)	< 0.0001
Poisson regression with robust variance with adjustment of follow-up time				
Observed events	46 (9.5%)	25 (2.6%)	NA	
Efficacy			73.9% (57.5%, 84.0%)	< 0.0001
Cochran-Mantel-Haenszel test				
Observed events	46 (9.5%)	25 (2.6%)	NA	
Efficacy			72.9% (56.5%, 83.1%)	< 0.0001

CI = confidence interval; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; NA = not applicable; RSV = respiratory syncytial virus.

[a] Subjects who had no events and were not followed through 150 days post dose.

Source: Table 14.2.1.1, Table 14.2.1.3, and Table 14.2.1.4.

Secondary endpoint

The secondary endpoints were analysed in the pooled population of MELODY and Study 3 according to the statistical analysis plan for MELODY (**Table 12**).

First, a pooled analysis of the total population of MELODY and Study 3 was conducted. In this population, 14/1963 (0.7%) in the nirsevimab group and 28/980 (2.9%) in the placebo group met the secondary endpoint (MA RSV LRTI hospitalisation 150 days post dose). The relative risk reduction reached statistical significance with an estimate (95% CI) of 73.5% (50.2%; 85.9%). The absolute difference was low with an estimated treatment difference of around 2.2% point.

The Applicant also defined a pooled population of individuals receiving the proposed dose – that is all subjects in MELODY and subjects <5 kg in Study 3. In this pooled population, the RRR was marginally higher (77.3%), and the treatment difference was 2.1% point.

In MELODY alone, the RRR reduction was lower (62.1%) and not statistically significant, and the treatment difference was around 1.0% point.

In Study 3 alone, the relative risk reduction was 78.4% (95% CI: 51.9%;90.3%).

Table 12 Analysis of incidence of RSV LTI hospitalisation (protocol-defined) through 150 days post dose using poisson regression with robust variance

Population		Placebo	MEDI8897	Relative Risk Reduction (95% CI)[a]	P-value[a]
Subjects from Phase 2b (ITT) and Phase 3 (ITT1)	Number of Subjects	980	1963		
	Subjects with Observed events	28 (2.9)	14 (0.7)		
	Subjects requiring imputation[b]	17 (1.7)	39 (2.0)		
	Efficacy			73.458 (50.157, 85.866)	<0.0001
Subjects Weighing < 5 kg from Phase 2b (ITT) and All Phase 3 (ITT1) Subjects	Number of Subjects	786	1564		
	Subjects with Observed events	21 (2.7)	9 (0.6)		
	Subjects requiring imputation[b]	10 (1.3)	25 (1.6)		
	Efficacy			77.313 (50.259, 89.653)	0.0002
Phase 3 (ITT1) Subjects Alone	Number of Subjects	496	994		
	Subjects with Observed events	8 (1.6)	6 (0.6)		
	Subjects requiring imputation[b]	6 (1.2)	15 (1.5)		
	Efficacy			62.148 (-8.568, 86.803)	0.0708

CI=confidence interval; LRTI=lower respiratory tract infection; RSV=respiratory syncytial virus.
[a]Relative risk reduction of MEDI8897 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study as covariate for pooled studies) obtained from PROC MIANALYZE after missing data imputation.
[b]Subjects who had no events and were not followed through 150 days post dose.

Table 13 Efficacy against the secondary endpoint MA RSV LRTI with hospitalisation through 150 days post dose in term and preterm infants born ≥29 wGA – MELODY, study 3 (proposed dose), and the MELODY/Study 3 (proposed dose) Pool

Statistic	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA				Term and preterm infants born ≥ 29 wGA	
	MELODY		Study 3 (All subjects)		Study 3 (proposed dose) [a]		MELODY/Study 3 (Proposed Dose) [a] Pool	
	Placebo N = 496	Nirsevimab N = 994	Placebo N = 484	Nirsevimab N = 969	Placebo N = 290	Nirsevimab N = 570	Placebo N = 786	Nirsevimab N = 1564
Poisson regression with robust variance (Secondary endpoint: MA RSV LRTI with hospitalisation)								
Subjects with events n (%)	8 (1.6)	6 (0.6)	20 (4.1)	8 (0.8)	13 (4.5)	3 (0.5)	21 (2.7)	9 (0.6)
Subjects requiring imputation n (%)	6 (1.2)	15 (1.5)	11 (2.3)	24 (2.5)	5 (1.7)	10 (1.8)	10 (1.3)	25 (1.6)
RRR (95% CI) p-value	62.1% (-8.6% to 86.8%) p = 0.0708 [b]		78.4% (51.9% to 90.3%) p = 0.0002 [b]		86.5% (53.5% to 96.1%) [c]		77.3% (50.3% to 89.7%) p = 0.0002 [d]	

a Analysis includes all randomised subjects who received the proposed dose (ie, subjects weighing ≥ 5 kg weight at time of dosing, who may have received a suboptimal dose, are excluded from the analysis).

b Multiplicity-protected analysis of the secondary endpoint, prespecified in the MELODY and Study 3 study protocols.

c Post-hoc analysis (not multiplicity protected).

d Multiplicity-protected analysis of the secondary endpoint, prespecified in the MELODY study protocol.

Data presented for the Number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; n = number of events observed N = number of subjects; RRR = relative risk reduction vs placebo; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Source: Table 14.2.2.1.a, MELODY CSR, Module 5.3.5.1; Table 14.2.2.1, Study 3 CSR, Module 5.3.5.1; Table 30.6, Appendix 2.7.3.6, Module 5.3.5.3.

7. **Ancillary analyses**

Exploratory endpoints

The analyses of RSV subtype were predefined, and the results showed a numerically higher event rate for both RSV A and RSV B in placebo group than nirsevimab group in both studies and in the pooled population with the proposed dose (**Table 14**). The efficacy related to RSV subtype is further addressed in the pharmacology section.

Table 14 Incidence of MA RSV LRTI by RSV Subtype and reporting period on term and preterm infants born ≥29 wGA – MELODY, study 3 (All subjects), Study 3 (proposed dose), and MELODY/Study 3 (proposed dose) Pool

RSV Subtype	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA				Term and preterm infants born ≥ 29 wGA	
	MELODY		Study 3 (All subjects)		Study 3 (Proposed Dose) [a]		MELODY/Study 3 (Proposed Dose) [a] Pool	
	Placebo (N = 496)	Nirsevimab (N = 994)	Placebo N = 484	Nirsevimab N = 969	Placebo N = 290	Nirsevimab N = 570	Placebo N = 786	Nirsevimab N = 1564
Total	25 (5.0)	12 (1.2)	46 (9.5)	25 (2.6)	26 (9.0)	7 (1.2)	51 (6.5)	19 (1.2)
RSV A	21 (4.2)	12 (1.2)	24 (5.0)	11 (1.1)	14 (4.8)	2 (0.4)	35 (4.5)	14 (0.9)
RSV B	4 (0.8)	0 (0.0)	22 (4.5)	14 (1.4)	12 (4.1)	5 (0.9)	16 (2.0)	5 (0.3)

a Analysis includes all randomised subjects who received the proposed dose (ie, subjects weighing ≥ 5 kg weight at time of dosing, who may have received a suboptimal dose, are excluded from the analysis).

b The incidence rate was calculated using the number of ITT subjects who had Day 151 visit as denominator. N = 488 (placebo) and 977 (nirsevimab) in MELODY; N = 472 (placebo) and 945 (nirsevimab) in Study 3. N = 285 (placebo) and 560 (nirsevimab) in Study 3 (Proposed Dose).

c One subject had 2 events (one prior to Day 151, one after Day 151) and was included in the numerator when reporting by each period.

Data presented for the Number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.

ITT = Intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; RSV = respiratory syncytial virus; wGA = weeks gestational age.

Source: Table 14.2.1.7.a, MELODY iCSR, Module 5.3.5.1; Table 14.2.1.7, Study 3 CSR, Module 5.3.5.1; Table 1.2.4.2, IEA, Module 5.3.5.3: Table 57.3, Appendix 2.7.3.6, Module 5.3.5.3.

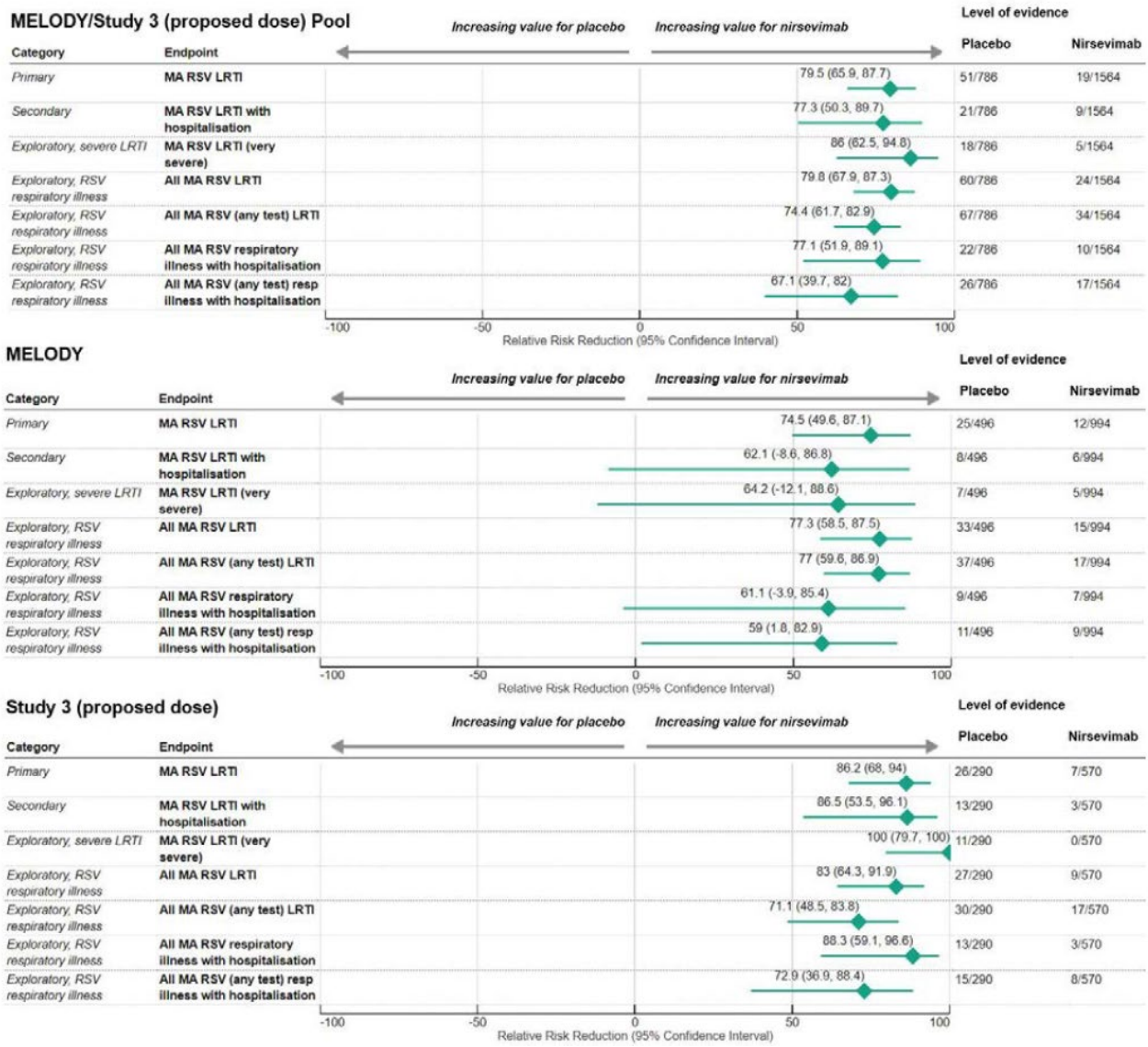
Pooled analysis

The Applicant has conducted a wide range of explorative analyses and explorative endpoints have been defined.

Severity of RSV was defined prior to unblinding and included hospitalisation plus requirement for supplemental oxygen or IV fluids. In MELODY, 5/994 subjects (0.5%) in nirsevimab and 7/496 subjects (1.4%) in placebo met the endpoint with a relative risk reduction of 64.2% (-12.1%;88.6%) with nirsevimab compared to placebo. In Study 3, the estimate was numerically higher, and 4/969 subjects (0.4%) and 16/484 subjects (3.3%) met the endpoint, and the relative risk reduction was 87.5% (62.9%;95.8%). When pooling the analyses of patients with the proposed dose, the estimate was 88.3% (50.3;89.7%). Hence, the exploratory analyses of severity pointed towards an effect against severe respiratory illness.

For alternative case definitions of MA RSV LRTI, a higher number of events were included when LRTI was also permitted to be defined by investigator judgement (All MA RSV LRTI), and when RSV was permitted to be defined by any (local or central) testing (All MA RSV [any test] LRTI). As shown in **Figure 16**, the estimates were of similar magnitude as the primary and secondary endpoint definition.

Figure 16 Overview of efficacy endpoints – MELODY/Study 3 (Proposed Dose) Pool, MELODY, Study 3 (Proposed dose)



Health care utilisation

In MELODY and Study 3, numerically fewer patients were admitted to ICU, required supplemental oxygen, CPAP or mechanical ventilation in the nirsevimab group than the placebo group (**Table 15**).

Table 15 Healthcare Resource Utilisation for MA RSV LRTI through 150 days post dose – MELODY, Study 3 (All subjects), Study 3 (Proposed dose), and MELODY/Study 3 (Proposed dose) Pool

HRU parameter	Term and late preterm infants born ≥ 35 wGA		Very and moderately preterm infants born ≥ 29 to < 35 wGA)				Term and preterm infants born ≥ 29 wGA	
	MELODY		Study 3 (All Subjects)		Study 3 (Proposed Dose) [a]		MELODY/Study 3 (Proposed Dose) [a] Pool	
	Placebo (N = 496)	Nirsevimab (N = 994)	Placebo (N = 484)	Nirsevimab (N = 969)	Placebo (N = 290)	Nirsevimab (N = 570)	Placebo (N = 786)	Nirsevimab (N = 1564)
Admission to hospitals	8 (1.6)	6 (0.6)	20 (4.1)	8 (0.8)	13 (4.5)	3 (0.5)	21 (2.7)	9 (0.6)
Admission to ICU	1 (0.2)	0 (0.0)	5 (1.0)	0 (0.0)	5 (1.7)	0 (0.0)	6 (0.8)	0 (0.0)
Respiratory support use	1 (0.2)	1 (0.1)	4 (0.8)	0 (0.0)	4 (1.4)	0 (0.0)	5 (0.6)	1 (0.1)
CPAP	1 (0.2)	1 (0.1)	4 (0.8)	0 (0.0)	4 (1.4)	0 (0.0)	5 (0.6)	1 (0.1)
Mechanical ventilation	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Supplemental oxygen use	6 (1.2)	4 (0.4)	15 (3.1)	4 (0.4)	11 (3.8)	0 (0.0)	17 (2.2)	4 (0.3)
Outpatient visit	23 (4.6)	10 (1.0)	38 (7.9)	20 (2.1)	20 (6.9)	4 (0.7)	43 (5.5)	14 (0.9)
Outpatient ED	6 (1.2)	1 (0.1)	11 (2.3)	4 (0.4)	4 (1.4)	0 (0.0)	10 (1.3)	1 (0.1)
Urgent care	2 (0.4)	1 (0.1)	5 (1.0)	2 (0.2)	3 (1.0)	1 (0.2)	5 (0.6)	2 (0.1)
Outpatient clinic	18 (3.6)	9 (0.9)	28 (5.8)	18 (1.9)	15 (5.2)	4 (0.7)	33 (4.2)	13 (0.8)

a Analysis includes all randomised subjects who received the proposed dose (ie, subjects weighing ≥ 5 kg weight at time of dosing, who may have received a suboptimal dose, are excluded from the analysis).
Data presented for number (%) of subjects. Subjects were counted once for each category regardless of the number of events. Incidence rate was calculated using the number of ITT subjects followed through 150 days post dose as the denominator.
CPAP = continuous positive airway pressure (includes CPAP and high frequency nasal cannula); ED = emergency department; HRU = healthcare resource utilisation; ICU = intensive care unit; ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; RSV = respiratory syncytial virus; wGA = weeks gestational age.
Source: Tables 62.10, 79.2, 62.9 and 72.1, Appendix 2.7.3.6, Module 5.3.5.3.

Sensitivity analyses

Imputation of missing data showed results consistent with the main analysis. Even with the most conservative analysis, where missing events was counted as an event in the nirsevimab group and as no event in the placebo group, the effect was statistically significant, although the estimate for relative risk reduction was lower 46.1% (8.2;68.4) than the main analysis as anticipated. Sensitivity analysis using principal stratum estimand, hypothetical estimand and using laboratory data after intercurrent event showed similar results as the main analysis.

In a requested post-hoc sensitivity analysis atrial septal defects and neonatal respiratory distress syndrome were included as covariates in order to analyse whether the results were driven by those factors due to the imbalance of those two medical conditions at baseline. The estimate for this analysis is 73.1% (56.7%, 83.2%) and is similar to the estimate of the main analysis of 70.1% (52.3%, 81.2%).

Subgroup analyses

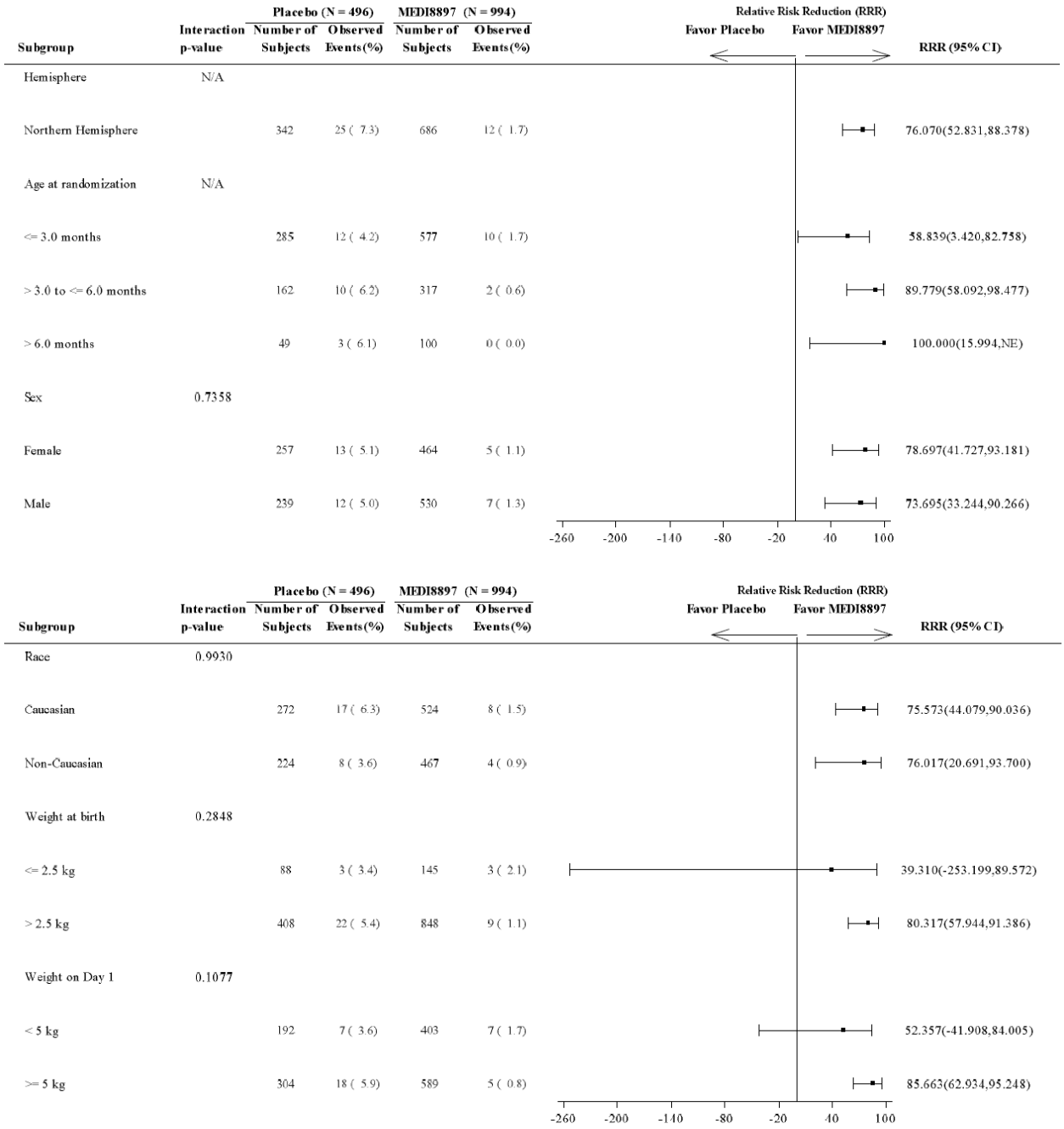
MELODY (**Figure 17**) Subgroup analyses of the primary endpoint in MELODY showed a lower estimate for children with low birthweight (≤ 2.5 kg) of 39.3% (- 253.2;89.6), as 3/145 subjects in the nirsevimab group and 3/88 subjects in the placebo group met the endpoint. In children with a birthweight > 2.5 kg, the relative risk reduction was 80%.

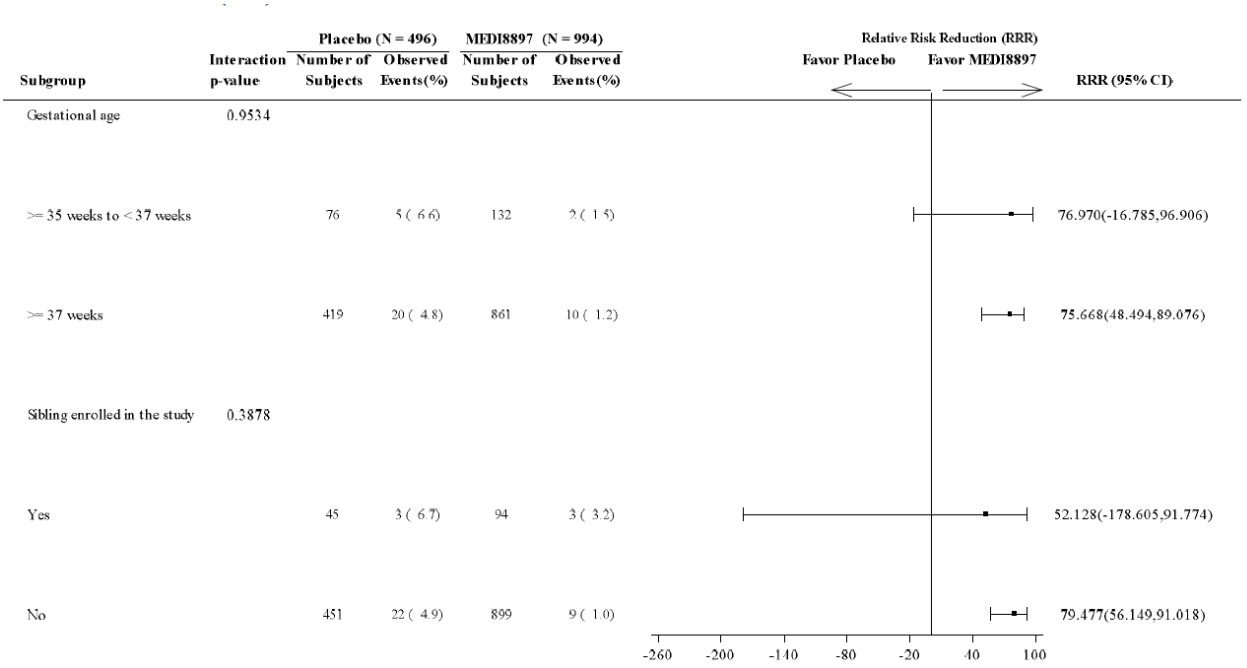
Additionally, children with a body weight <5 kg at randomisation had a lower effect (RRR of 52.4%, 95% CI: -41.9;84.0) than children >5 kg.

Study 3 (**Figure 18**) In children with birth weight ≤ 2.5 kg no differences in effect was seen compared with birthweight >2.5 kg. In study 3 it seems that dosing early after birth and in children with low weight at time of dosing, there is a tendency towards a higher effect, although not statistically significantly different. This is opposite to what is shown in the pooled analysis.

In neither of the studies, the interaction terms were statistically significant and the confidence intervals were overlapping

Figure 17 Forest Plot for Subgroup Analysis for the Incidence of MA RSV LRTI (Observed) Through 150 days post dose (ITT)



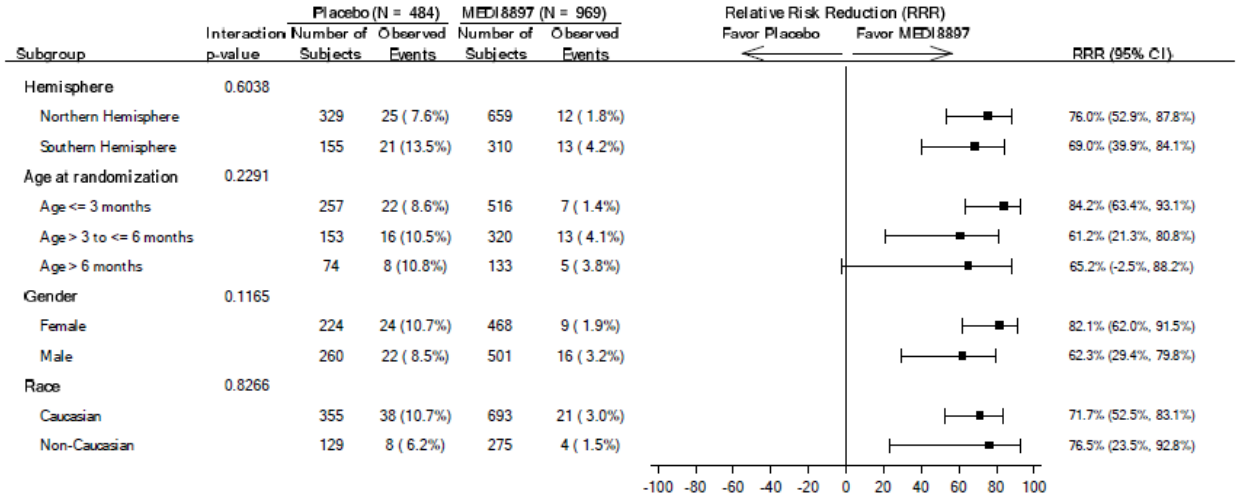


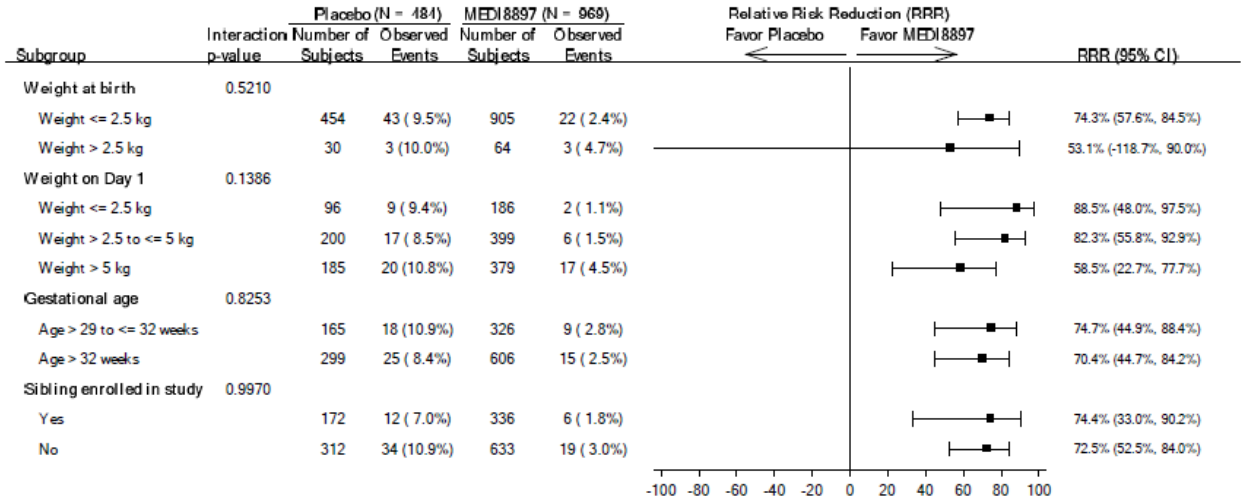
The interaction p-value was obtained from Poisson regression with robust variance, including the terms of treatment group, age group, subgroup being tested, and treatment-by-subgroup interaction. The relative risk reduction and its 95% CI (mid-p adjusted) were estimated based on exact conditional method using PROC GENMOD with no strata. If RRR - 100% or - Infinity, one-sided 97.5% CI was reported.

CI = confidence interval; ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; N = number of subjects; RSV = respiratory syncytial virus.

Source: Figure 14.2.1.14.a.

Figure 18 Forest Plot for Subgroup Analysis for Incidence of Medically attended RSV – confirmed LRTI (Observed Through 150 days post dose (ITT population)





CI = confidence interval; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; RRR = relative risk reduction; RSV = respiratory syncytial virus.

8. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of Efficacy in the Proposed Indication: MELODY

Title	**A Phase III Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants**	
Study identifier	D5290C00004; MELODY; EudraCT number 2019-000114-11	
Design	A Phase III, randomised, double-blind, placebo-controlled study to evaluate efficacy, safety, PK, and ADA of nirsevimab versus placebo in term and late preterm infants born ≥ 35 wGA, entering their first RSV season. Randomisation was done 2:1 for nirsevimab to placebo. At the time of this submission, the Primary Analysis is completed; the Safety Cohort is ongoing.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	Follow up of 150 days after dosing for efficacy Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Nirsevimab	50 mg (infants weighing < 5 kg at time of dosing) or 100 mg (infants weighing ≥ 5 kg at time of dosing) single IM dose 994 randomised infants

Table 16 Summary of Efficacy in the Proposed Indication: MELODY

	Placebo		Single IM dose 496 randomised infants
Endpoints and definitions	Primary endpoint	MA RSV LRTI through 150 days post dose	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
	Secondary endpoint	MA RSV LRTI with hospitalisation through 150 days post dose	Incidence of hospitalisations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
	Exploratory endpoint	MA RSV LRTI (very severe) through 150 days post dose	Incidence of hospitalisations with supplementary oxygen or IV fluids due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Database lock	14 April 2021		
Results and Analysis: MELODY (ITT1)			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**MELODY (ITT1)** The intent-to-treat population 1 (ITT1), which included all randomised subjects, was used as the primary population for the efficacy analyses. Subjects were analysed according to the treatment assigned at randomisation. The designation of ITT1 indicates that this is the ITT population in the Primary Cohort used for the Primary Analysis. Efficacy results up through 150 days post dose (Day 151) are summarised for the Primary Analysis		
Descriptive statistics and estimate variability	Treatment group	Placebo	Nirsevimab
	Number of subjects	496	994
	MA RSV LRTI through 150 days post dose Subjects with events n (%)	25 (5.0)	12 (1.2)
	MA RSV LRTI with hospitalisation through 150 days post dose Subjects with events n (%)	8 (1.6)	6 (0.6)
	MA RSV LRTI (very severe) through 150 days post dose Subjects with events n (%)	7 (1.4)	5 (0.5)

Table 16 Summary of Efficacy in the Proposed Indication: MELODY

Effect estimate per comparison	Primary endpoint MA RSV LRTI through 150 days post dose (Multiplicity-protected analysis of the primary endpoint, prespecified in the MELODY protocol)	Comparison groups	Nirsevimab versus placebo
		RRR	74.5%
		95% CI	49.6%, 87.1%
		P-value Poisson regression with robust variance	< 0.0001
	Secondary endpoint MA RSV LRTI with hospitalisation through 150 days post dose (Multiplicity-protected analysis of the secondary endpoint, prespecified in the MELODY protocol).	Comparison groups	Nirsevimab versus placebo
		RRR	62.1%
		95% CI	-8.6%, 86.8%
		P-value Poisson regression with robust variance	0.0708
	Exploratory endpoint MA RSV LRTI (very severe) through 150 days post dose (Prespecified in MELODY SAP addendum, not multiplicity protected).	Comparison groups	Nirsevimab versus placebo
		RRR	64.2%
		95% CI Poisson regression with robust variance	-12.1%, 88.6%
Notes	**Patient disposition**: Over 99% of the randomized subjects in MELODY were dosed, and over 98% of the randomized subjects completed the Day 151 follow-up, with similar results in the two treatment groups.		

Data presented for the number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
ADA = anti-drug antibodies; CI = confidence interval; IM = intramuscular; ITT = intent-to-treat; ITT1 = intent-to-treat analysis set for Primary Analysis Population 1 in MELODY; IV = intravenous; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; PK = pharmacokinetic(s); RRR = relative risk reduction versus placebo; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase polymerase chain reaction; SAP = statistical analysis plan; wGA = weeks gestational age.

Table 17 Summary of Efficacy in the Proposed Indication: Study 3 (All and Proposed Dose)

Title	**A Phase IIb Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants**		
Study identifier	D5290C00003; Study 3; EudraCT number 2016-001677-33; DOI: 10.1056/NEJMoa1913556		
Design	A Phase IIb randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, PK, and ADA of nirsevimab versus placebo in very and moderately preterm infants born ≥ 29 to < 35 wGA, entering their first RSV season. Randomisation was done 2:1 for nirsevimab to placebo. This study is completed.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		Follow up of 150 days after dosing for efficacy not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Nirsevimab		50 mg single IM dose 969 randomized infants of which 570 infants with weight < 5 kg at time of dosing
	Placebo		Single IM dose 484 randomized infants of which 290 infants with weight < 5 kg at time of dosing
Endpoints and definitions	Primary endpoint	MA RSV LRTI through 150 days post dose	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
	Secondary endpoint	MA RSV LRTI with hospitalisation through 150 days post dose	Incidence of hospitalisations due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
	Exploratory endpoint	MA RSV LRTI (very severe) through 150 days post dose	Incidence of hospitalisations with supplementary oxygen or IV fluids due to RT-PCR-confirmed RSV through 150 days after dosing (ie, during a typical 5-month RSV season)
Database lock	14 February 2019		
Results and Analysis: Study 3 (All Subjects)			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**<u>Study 3 (All Subjects)</u>** All subjects in Study 3 were randomized to receive a single IM dose of either nirsevimab 50 mg or placebo regardless of weight at the time of dosing. The All Subjects population is the Intent-to-Treat (ITT) population defined in the protocol which includes all		

Table 17 Summary of Efficacy in the Proposed Indication: Study 3 (All and Proposed Dose)

	randomised subjects. Subjects were analysed according to the treatment assigned at randomisation. Efficacy results up through 150 days post dose (Day 151) are summarised for the Primary Analysis.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Nirsevimab
	Number of subjects	484	969
	MA RSV LRTI through 150 days post dose Subjects with events n (%)	46 (9.5)	25 (2.6)
	MA RSV LRTI with hospitalisation through 150 days post dose Subjects with events n (%)	20 (4.1)	8 (0.8)
	MA RSV LRTI (very severe) through 150 days post dose Subjects with events n (%)	16 (3.3)	4 (0.4)
Effect estimate per comparison	Primary endpoint MA RSV LRTI through 150 days post dose (Multiplicity-protected analysis of the primary endpoint, prespecified in the Study 3 protocol)	Comparison groups	Nirsevimab versus placebo
		RRR	70.1%
		95% CI	52.3%, 81.2%
		P-value Poisson regression with robust variance	< 0.0001
	Secondary endpoint MA RSV LRTI with hospitalisation through 150 days post dose (Multiplicity-protected analysis of the secondary endpoint, prespecified in the Study 3 protocol).	Comparison groups	Nirsevimab versus placebo
		RRR	78.4%
		95% CI	51.9%, 90.3%
		P-value Poisson regression with robust variance	0.0002
	Exploratory endpoint MA RSV LRTI (very severe) through 150 days post dose	Comparison groups	Nirsevimab versus placebo
		RRR	87.5%
		95% CI Poisson regression with robust variance	62.9%, 95.8%

Table 17 Summary of Efficacy in the Proposed Indication: Study 3 (All and Proposed Dose)

	(Post-hoc analysis, not multiplicity protected).		
Notes	**Patient disposition**: Over 99% of the randomized subjects in the Study 3 (All Subjects) population were dosed, and over 97% of the randomized subjects completed the Day 151 follow-up, with similar results in the two treatment groups.		
Results and Analysis: Study 3 (Proposed Dose)			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Study 3 (Proposed Dose)** All subjects in Study 3 were randomized to receive a single IM dose of either nirsevimab 50 mg or placebo regardless of weight at the time of dosing. The Proposed Dose population includes all randomised subjects weighing < 5 kg at the time of dosing. Subjects weighing ≥ 5 kg at time of dosing, who may have received a suboptimal dose, are excluded from the Proposed Dose analysis. Subjects were analysed according to the treatment assigned at randomisation. Efficacy results up through 150 days post dose (Day 151) are summarised for the Primary Analysis.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Nirsevimab
	Number of subjects	290	570
	MA RSV LRTI through 150 days post dose Subjects with events n (%)	26 (9.0)	7 (1.2)
	MA RSV LRTI with hospitalisation through 150 days post dose Subjects with events n (%)	13 (4.5)	3 (0.5)
	MA RSV LRTI (very severe) through 150 days post dose Subjects with events n (%)	11 (3.8)	0 (0)
Effect estimate per comparison	Primary endpoint	Comparison groups	Nirsevimab versus placebo
	MA RSV LRTI through 150 days post dose (Post-hoc analysis, not multiplicity protected)	RRR	86.2%
		95% CI Cochran-Mantel-Haenszel test (used because primary Poisson regression model did not converge)	68.0%, 94.0%
	Secondary endpoint	Comparison groups	Nirsevimab versus placebo
		RRR	86.5%

Table 17 Summary of Efficacy in the Proposed Indication: Study 3 (All and Proposed Dose)

	MA RSV LRTI with hospitalisation through 150 days post dose (Post-hoc analysis, not multiplicity protected).	95% CI Poisson regression with robust variance	53.5%, 96.1%
	Exploratory endpoint	Comparison groups	Nirsevimab versus placebo
	MA RSV LRTI (very severe) through 150 days post dose (Post-hoc analysis, not multiplicity protected)	RRR	100.0%
		97.5% (1-sided) CI Generated using exact conditional method due to the extreme distribution of cases	79.7%, NE
Notes	**Patient disposition:** All randomized subjects in the Study 3 (Proposed Dose) population were dosed, and over 98% of the randomized subjects completed the Day 151 follow-up, with similar results in the two treatment groups.		

Data presented for the number (%) of subjects with events; for subjects with multiple events, only the first event is included in the analysis.
ADA = anti-drug antibodies; CI = confidence interval; IM = intramuscular; ITT = intent-to-treat; IV = intravenous; LRTI = lower respiratory tract infection; MA = medically attended; MEDI8897 = nirsevimab; NE = not evaluated; PK = pharmacokinetic(s); RRR = relative risk reduction versus placebo; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase polymerase chain reaction; wGA = weeks gestational age.

MEDLEY: A Study to Evaluate the Safety of MEDI8897 for the Prevention of Medically Attended Respiratory Syncytial Virus (RSV) Lower Respiratory Tract Infection (LRTI) in High-risk Children.

1. Study participants

The population consisted of two cohorts: preterm infants ≤ 35+0 weeks gestational age with no lower limit of gestational age, besides for the population in Japan in which the gestational age was 29-35 weeks.

The second cohort consisted of term and preterm infants in their first year of life with either chronic lung disease of prematurity or congenital heart disease.

2. Treatments

Subjects were randomised to weight-based dose of nirsevimab (50 mg or 100 mg) or palivizumab 15mg/kg once monthly x 5. Relevant placebo injections were used.

Administration of other medication were allowed at the discretion of the investigators and were recorded.

3. Objectives

The primary objective was to evaluate safety. One of the secondary objectives was to assess the effect of nirsevimab on MA LRTI and hospitalization in the first and second RSV season.

4. Outcomes/endpoints

The primary endpoint in the MEDLEY trial was safety. Efficacy endpoints were part of the secondary endpoint or explorative endpoints. Criteria for the MA LRTI is the same as in MELODY and Study 3, with an addition of prescription of new or increased dose of medications (bronchodilators, steroids, diuretics, cardiac medication) because the CLD/CHD cohort were on this background treatment.

Efficacy was based on extrapolation as agreed by the PDCO.

5. Sample size

The sample size calculation was based on safety, and 600 subjects were to be exposed to nirsevimab and 300 to palivizumab. Superiority and noninferiority design in terms of efficacy was not feasible.

6. Randomisation and blinding

The randomization was stratified by age group and hemisphere as in the MELODY and Study 3. The randomization was not stratified by CLD/CHD disease. The two cohorts (preterm and CLD/CHD) were balanced between treatment groups. The study was double-blinded.

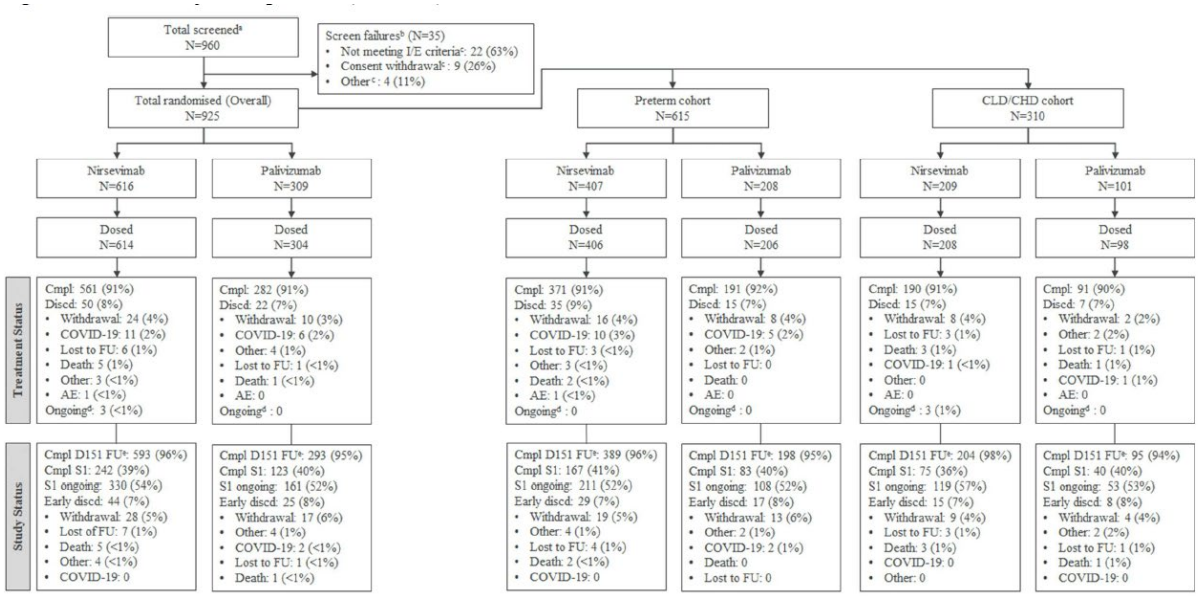
7. Statistical methods

Descriptive statistics were used for efficacy variables. Furthermore, extrapolation was used to assess efficacy. Please refer to the pharmacology section.

Results

8. Participant flow

Figure 19 Subject Disposition (Season 1)



[a] Subjects signed the informed consent.
[b] Denominator is the number of subjects screened.
[c] Denominator is the number of screen failures.
[d] Subjects who did not receive Day 121 dose up to the data cutoff date and did not have end of treatment page.
[e] Numerator includes subjects whose study status was ongoing on Season 1 Day 151.
AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; Cmpl = completed; COVID-19 = coronavirus disease 2019; D151 = Day 151; Discd = discontinued; FU = follow-up; I/E = inclusion/exclusion; S1 = Season 1.
Source: Table 14.1.1.1 and Listing 16.2.1.4.

9. Recruitment

The first subject was enrolled on 30 July 2019, and the study is still ongoing.

Subjects were enrolled at 126 sites in 25 countries, and 497 subjects were enrolled in EU countries.

10. Conduct of the study

Of the total study population 15.7% had at least 1 important protocol deviation. The deviations were balanced between treatment groups, but subjects in the CLD/CHD cohort had a lower frequency of protocol deviations (10.3% vs 18.4%).

11. Baseline data

The baseline characteristics were balanced between the two treatment arms in both cohorts. In the CLD/CHD, the median age at baseline was 1.8 months higher than the preterm group. As such, the median body weight was also marginally higher (0.7 kg). Minimum bodyweight in the nirsevimab group at baseline was 1.8 kg and the minimum age at dosing was 0.07 months corresponding to 2 days. No minimum bodyweight is stated in the SmPC.

Even though subjects with a gestational age of 22 weeks were included in the study, the minimum bodyweight was 1.8 kg. Hence, none of the extremely preterm children were treated with nirsevimab early in life. The age of nirsevimab dosing is shown in Table 3 for MEDLEY, Study 3 and MELODY.

Table 18 Nirsevimab recipients by age of dosing (MEDLEY, MELODY, and Study 3)

	Number of subjects [a]																					
wGA at birth / age at dosing (months)	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**Total**
MEDLEY																						
<1								1	3	1	7	12	27	9		1		1		1		63
1						1	6	5	7	9	18	13	27	7	1		5	3	1	1		104
2					6	7	8	7	11	11	8	15	17	3			1	2	1	2		99
3			2	4	1	7	5	4	8	5	11	8	14	4	1	1	1	4		1		81
Total (≤ 3 months)			2	4	7	15	19	17	29	26	44	48	85	23	2	2	7	10	2	5		347
Study 3																						
<1	Not applicable								3	7	19	36	70	4	Not applicable							139
1								11	13	24	33	62	64	1								208
2								6	10	24	26	31	59									156
3								5	3	15	22	35	54	2								136
Total (≤ 3 months)								22	29	70	100	164	247	7								639
MELODY																						
<1	Not applicable													15	21	39	51	60	42	14	3	245
1														14	9	18	35	41	35	12	1	165
2														7	11	25	25	40	35	12	2	157
3														4	14	12	24	38	21	10	2	125
Total (≤ 3 months)														40	55	94	135	179	133	48	8	692

a For clarity of data presentation, blank cell = 0 subjects.
Source: IEMT 94 Tables 94.1.5, 94.1.6, 94.1.7 in Appendix A.

Median gestational age was 32 weeks in preterm subjects and 30 weeks in CLD/CHD subjects, and the lowest gestational age was 22 weeks. Overall, 21.1% of the included subjects in the nirsevimab group (n=130) were born earlier than week 29 gestational age. Hence, a reasonable large population of extremely preterm children were included in the MEDLEY study.

Table 19 Demographic and Baseline Characteristics for overall population, preterm and CLD/CHD Cohorts (Season 1) – ITT population

Characteristic	Overall			Preterm			CLD/CHD		
	Palivizumab (N=309)	Nirsevimab (N=616)	Total (N=925)	Palivizumab (N=208)	Nirsevimab (N=407)	Total (N=615)	Palivizumab (N=101)	Nirsevimab (N=209)	Total (N=310)
Age at randomisation, months									
n	309	616	925	208	407	615	101	209	310
Mean	3.840	3.947	3.911	3.499	3.487	3.491	4.541	4.842	4.744
SD	2.4607	2.5513	2.5206	2.3922	2.3666	2.3734	2.4631	2.6632	2.5996
Median	3.483	3.462	3.462	2.769	2.858	2.793	4.238	4.698	4.615
Min, Max	0.07, 12.25	0.07, 11.14	0.07, 12.25	0.07, 10.35	0.07, 11.07	0.07, 11.07	0.33, 12.25	0.20, 11.14	0.20, 12.25
Age group, n (%)									
≤ 3.0 months	144 (46.6)	274 (44.5)	418 (45.2)	113 (54.3)	214 (52.6)	327 (53.2)	31 (30.7)	60 (28.7)	91 (29.4)
> 3.0 to ≤ 6.0 months	101 (32.7)	210 (34.1)	311 (33.6)	59 (28.4)	126 (31.0)	185 (30.1)	42 (41.6)	84 (40.2)	126 (40.6)
> 6.0 months	64 (20.7)	132 (21.4)	196 (21.2)	36 (17.3)	67 (16.5)	103 (16.7)	28 (27.7)	65 (31.1)	93 (30.0)
Sex, n (%)									
Female	133 (43.0)	297 (48.2)	430 (46.5)	93 (44.7)	201 (49.4)	294 (47.8)	40 (39.6)	96 (45.9)	136 (43.9)
Male	176 (57.0)	319 (51.8)	495 (53.5)	115 (55.3)	206 (50.6)	321 (52.2)	61 (60.4)	113 (54.1)	174 (56.1)
Race, n (%) [a]									
American Indian or Alaska Native	5 (1.6)	11 (1.8)	16 (1.7)	5 (2.4)	11 (2.7)	16 (2.6)	0	0	0
Asian	14 (4.5)	36 (5.8)	50 (5.4)	9 (4.3)	26 (6.4)	35 (5.7)	5 (5.0)	10 (4.8)	15 (4.8)
Black or African American	29 (9.4)	59 (9.6)	88 (9.5)	24 (11.6)	49 (12.0)	73 (11.9)	5 (5.0)	10 (4.8)	15 (4.8)
Native Hawaiian/ other Pacific Islander	1 (0.3)	4 (0.6)	5 (0.5)	1 (0.5)	3 (0.7)	4 (0.7)	0	1 (0.5)	1 (0.3)
White	249 (80.8)	483 (78.4)	732 (79.2)	160 (77.3)	305 (74.9)	465 (75.7)	89 (88.1)	178 (85.2)	267 (86.1)
Other	6 (1.9)	17 (2.8)	23 (2.5)	6 (2.9)	10 (2.5)	16 (2.6)	0	7 (3.3)	7 (2.3)
Multiple categories checked	4 (1.3)	6 (1.0)	10 (1.1)	2 (1.0)	3 (0.7)	5 (0.8)	2 (2.0)	3 (1.4)	5 (1.6)
Ethnicity, n (%)									
Hispanic or Latino	41 (13.3)	99 (16.1)	140 (15.2)	35 (16.9)	77 (18.9)	112 (18.2)	6 (5.9)	22 (10.5)	28 (9.0)
Not Hispanic or Latino	267 (86.7)	517 (83.9)	784 (84.8)	172 (83.1)	330 (81.1)	502 (81.8)	95 (94.1)	187 (89.5)	282 (91.0)
Weight on Day 1, kg									
n	304	613	917	206	405	611	98	208	306
Mean	4.64	4.74	4.71	4.50	4.56	4.54	4.93	5.11	5.05
SD	1.785	1.863	1.837	1.886	1.827	1.846	1.523	1.883	1.775
Median	4.50	4.60	4.50	4.20	4.30	4.30	4.80	5.00	5.00
Min, Max	1.7, 9.5	1.8, 12.2	1.7, 12.2	1.7, 9.5	1.8, 12.2	1.7, 12.2	2.3, 9.3	1.8, 11.4	1.8, 11.4
Weight group on Day 1, n (%)									
< 5 kg	174 (57.2)	344 (56.1)	518 (56.5)	123 (59.7)	243 (60.0)	366 (59.9)	51 (52.0)	101 (48.6)	152 (49.7)
≥ 5 kg	130 (42.8)	269 (43.9)	399 (43.5)	83 (40.3)	162 (40.0)	245 (40.1)	47 (48.0)	107 (51.4)	154 (50.3)
Gestational age, weeks									
n	309	616	925	208	407	615	101	209	310
Mean	31.4	31.7	31.6	31.5	31.9	31.7	31.2	31.3	31.2
SD	3.68	3.74	3.72	2.27	2.47	2.41	5.58	5.41	5.46
Median	32.0	32.0	32.0	32.0	32.0	32.0	31.0	30.0	30.0
Min, Max	23, 40	22, 41	22, 41	25, 35	24, 40	24, 40	23, 40	22, 41	22, 41
Gestational age group, n (%)									
< 29 weeks	70 (22.7)	130 (21.1)	200 (21.6)	28 (13.5)	49 (12.0)	77 (12.5)	42 (41.6)	81 (38.8)	123 (39.7)
≥ 29 to < 32 weeks	71 (23.0)	128 (20.8)	199 (21.5)	59 (28.4)	91 (22.4)	150 (24.4)	12 (11.9)	37 (17.7)	49 (15.8)
≥ 32 to < 35 weeks	126 (40.8)	262 (42.5)	388 (41.9)	114 (54.8)	235 (57.7)	349 (56.7)	12 (11.9)	27 (12.9)	39 (12.6)

≥ 35 weeks	42 (13.6)	96 (15.6)	138 (14.9)	7 (3.4)	32 (7.9)	39 (6.3)	35 (34.7)	64 (30.6)	99 (31.9)
Birth weight group, n (%)									
≤ 2.5 kg	274 (88.7)	534 (86.7)	808 (87.4)	203 (97.6)	375 (92.1)	578 (94.0)	71 (70.3)	159 (76.1)	230 (74.2)
> 2.5 kg	35 (11.3)	82 (13.3)	117 (12.6)	5 (2.4)	32 (7.9)	37 (6.0)	30 (29.7)	50 (23.9)	80 (25.8)
Multiple birth, n (%)									
Yes	107 (34.6)	189 (30.7)	296 (32.0)	90 (43.3)	149 (36.6)	239 (38.9)	17 (16.8)	40 (19.1)	57 (18.4)
No	202 (65.4)	427 (69.3)	629 (68.0)	118 (56.7)	258 (63.4)	376 (61.1)	84 (83.2)	169 (80.9)	253 (81.6)
Underlying lung disease, n (%)									
Yes	70 (22.7)	148 (24.0)	218 (23.6)	0	0	0	70 (69.3)	148 (70.8)	218 (70.3)
No	239 (77.3)	468 (76.0)	707 (76.4)	208 (100.0)	407 (100.0)	615 (100.0)	31 (30.7)	61 (29.2)	92 (29.7)
CHD, n (%)									
Yes	34 (11.0)	70 (11.4)	104 (11.2)	0	0	0	34 (33.7)	70 (33.5)	104 (33.5)
No	275 (89.0)	546 (88.6)	821 (88.8)	208 (100.0)	407 (100.0)	615 (100.0)	67 (66.3)	139 (66.5)	206 (66.5)
CLD, n (%)									
Yes	70 (22.7)	148 (24.0)	218 (23.6)	0	0	0	70 (69.3)	148 (70.8)	218 (70.3)
No	239 (77.3)	468 (76.0)	707 (76.4)	208 (100.0)	407 (100.0)	615 (100.0)	31 (30.7)	61 (29.2)	92 (29.7)
Down syndrome, n (%)									
Yes	3 (1.0)	9 (1.5)	12 (1.3)	0	2 (0.5)	2 (0.3)	3 (3.0)	7 (3.3)	10 (3.2)
No	306 (99.0)	607 (98.5)	913 (98.7)	208 (100.0)	405 (99.5)	613 (99.7)	98 (97.0)	202 (96.7)	300 (96.8)
Cystic fibrosis, n (%)									
Yes	0	2 (0.3)	2 (0.2)	0	2 (0.5)	2 (0.3)	0	0	0
No	309 (100.0)	614 (99.7)	923 (99.8)	208 (100.0)	405 (99.5)	613 (99.7)	101 (100.0)	209 (100.0)	310 (100.0)

[a] Each race category counts subjects who selected only that category; "Multiple categories checked" counts subjects who selected more than one race category.
CHD = congenital heart disease; CLD = chronic lung disease; ITT = Intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation.
Source: Table 14.1.6.1.1.

12. Numbers analysed

In the ITT population, 925 subjects were included. In the CLD/CHD cohort, 310 children were included and in the preterm cohort, 615 children were included.

13. Outcomes and estimation

The proportion of subjects with a MA RSV LRTI through 150 days post first dose was similar in the two treatment groups (1.0% in palivizumab group and 0.6% in nirsevimab group) (Table 20). This was also the case when the data was stratified by CHD/CLD and a similar pattern was seen with hospitalisation due to MA RSV LRTI (**Table 21**). The Applicant has not shown the data for health care utilisation for the prespecified endpoint. When using the broader definition of endpoint (ALL MA LRTI), the incidence of respiratory support use was higher in nirsevimab than palivizumab (0.6% vs 0.3%), and supplemental oxygen was also higher (1.9% vs 1.6%) (**Table 22**). The differences were primarily seen in the CLD/CHD cohort. However, the endpoint is not based on RSV, and the numbers are low. No formal statistical analysis has been conducted.

Table 20 Incidence of MA RSV LRTI by RSV Subtype and reporting period in overall population, preterm and CLD/CHD cohorts (Season 1) – ITT Population

Reporting period RSV subtype	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivi-zumab (N=309)	Nirse-vimab (N=616)	Palivi-zumab (N=208)	Nirse-vimab (N=407)	Palivi-zumab (N=101)	Nirse-vimab (N=209)
Through 150 days post first dose [95% CI] [a]	3 (1.0) [0.20, 2.81]	4 (0.6) [0.18, 1.65]	1 (0.5) [0.01, 2.65]	2 (0.5) [0.06, 1.76]	2 (2.0) [0.24, 6.97]	2 (1.0) [0.12, 3.41]
RSV A	1 (0.3)	4 (0.6)	1 (0.5)	2 (0.5)	0	2 (1.0)
RSV B	2 (0.6)	0	0	0	2 (2.0)	0
From 151 to 360 days post first dose [b]	1/293 (0.3)	1/593 (0.2)	1/198 (0.5)	1/389 (0.3)	0/95 (0.0)	0/204 (0.0)
RSV A	1/293 (0.3)	1/593 (0.2)	1/198 (0.5)	1/389 (0.3)	0/95 (0.0)	0/204 (0.0)
RSV B	0/293 (0.0)	0/593 (0.0)	0/198 (0.0)	0/389 (0.0)	0/95 (0.0)	0/204 (0.0)
Through 360 days post first dose	4 (1.3)	5 (0.8)	2 (1.0)	3 (0.7)	2 (2.0)	2 (1.0)
RSV A	2 (0.6)	5 (0.8)	2 (1.0)	3 (0.7)	0	2 (1.0)
RSV B	2 (0.6)	0	0	0	2 (2.0)	0

[a] Two-sided 95% (or one-sided 97.5% for incidence rates of 0% or 100%) CIs were calculated using the Clopper-Pearson method.

[b] The incidence rate was calculated using the number of ITT subjects who were followed for at least 151 days post first dose as a denominator.

CHD = congenital heart disease; CI = confidence interval; CLD = chronic lung disease; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; RSV = respiratory syncytial virus.

Source: Table 14.2.1.1.1 and Table 14.2.1.5.1.

Table 21 Incidence of MA RSV LRTI with Hospitalisation by RSV Subtype and reporting period in overall population, preterm and CLD/CHD cohorts (Season 1) – ITT Population

Reporting period RSV subtype	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivi-zumab (N=309)	Nirse-vimab (N=616)	Palivi-zumab (N=208)	Nirse-vimab (N=407)	Palivi-zumab (N=101)	Nirse-vimab (N=209)
Through 150 days post first dose	2 (0.6)	2 (0.3)	0	0	2 (2.0)	2 (1.0)
RSV A	0	2 (0.3)	0	0	0	2 (1.0)
RSV B	2 (0.6)	0	0	0	2 (2.0)	0
From 151 to 360 days post first dose [a]	0/293 (0.0)	1/593 (0.2)	0/198 (0.0)	1/389 (0.3)	0/95 (0.0)	0/204 (0.0)
RSV A	0/293 (0.0)	1/593 (0.2)	0/198 (0.0)	1/389 (0.3)	0/95 (0.0)	0/204 (0.0)
RSV B	0/293 (0.0)	0/593 (0.0)	0/198 (0.0)	0/389 (0.0)	0/95 (0.0)	0/204 (0.0)
Through 360 days post first dose	2 (0.6)	3 (0.5)	0	1 (0.2)	2 (2.0)	2 (1.0)
RSV A	0	3 (0.5)	0	1 (0.2)	0	2 (1.0)
RSV B	2 (0.6)	0	0	0	2 (2.0)	0

[a] The incidence rate was calculated using the number of ITT subjects who were followed for at least 151 days post first dose as a denominator.

CHD = congenital heart disease; CLD = chronic lung disease; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; RSV = respiratory syncytial virus.

Source: Table 14.2.1.5.1 and Table 14.2.2.1.1.

Table 22 Healthcare Resource Utilisation for All MA LRTI (Any Cause) through 150 days post first dose in overall population, preterm and CLD/CHD cohorts (Season 1) – ITT Population

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivi-zumab (N=309)	Nirse-vimab (N=616)	Palivi-zumab (N=208)	Nirse-vimab (N=407)	Palivi-zumab (N=101)	Nirse-vimab (N=209)
Admission to hospital	8 (2.6)	17 (2.8)	2 (1.0)	5 (1.2)	6 (5.9)	12 (5.7)
Admission to ICU	2 (0.6)	1 (0.2)	1 (0.5)	0	1 (1.0)	1 (0.5)
Respiratory support use	1 (0.3)	4 (0.6)	0	0	1 (1.0)	4 (1.9)
CPAP	0	3 (0.5)	0	0	0	3 (1.4)
Initial	0	3 (0.5)	0	0	0	3 (1.4)
Increased	0	0	0	0	0	0
Mechanical ventilation	1 (0.3)	2 (0.3)	0	0	1 (1.0)	2 (1.0)
Initial	0	2 (0.3)	0	0	0	2 (1.0)
Increased	1 (0.3)	0	0	0	1 (1.0)	0
Supplemental oxygen use	5 (1.6)	12 (1.9)	1 (0.5)	3 (0.7)	4 (4.0)	9 (4.3)
Initial	3 (1.0)	11 (1.8)	1 (0.5)	3 (0.7)	2 (2.0)	8 (3.8)
Increased	2 (0.6)	2 (0.3)	0	0	2 (2.0)	2 (1.0)
Outpatient visit	20 (6.5)	43 (7.0)	13 (6.3)	33 (8.1)	7 (6.9)	10 (4.8)
Outpatient ED	5 (1.6)	8 (1.3)	1 (0.5)	6 (1.5)	4 (4.0)	2 (1.0)
Urgent care	4 (1.3)	13 (2.1)	2 (1.0)	10 (2.5)	2 (2.0)	3 (1.4)
Outpatient clinic	13 (4.2)	24 (3.9)	11 (5.3)	19 (4.7)	2 (2.0)	5 (2.4)
Medications	22 (7.1)	44 (7.1)	12 (5.8)	30 (7.4)	10 (9.9)	14 (6.7)
OTC	4 (1.3)	12 (1.9)	3 (1.4)	11 (2.7)	1 (1.0)	1 (0.5)
Prescribed	22 (7.1)	41 (6.7)	12 (5.8)	28 (6.9)	10 (9.9)	13 (6.2)
Other	0	0	0	0	0	0

[a] Subjects were counted once for each category regardless of the number of events.
CHD = congenital heart disease; CLD = chronic lung disease; CPAP = continuous positive airway pressure; ED = emergency department; ICU = intensive care unit; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; OTC = over-the-counter.
Source: Table 14.2.4.1.1.

14. Extrapolation

In the pharmacology section, the popPK model used to extrapolate results from MELODY and Study 3 to high risk population in MEDLEY is addressed.

In MEDLEY 21.6% of the study population was extremely preterm. Of those, 130 subjects were exposed to nirsevimab. The median bodyweight and range are similar to the study population of Study 3, which is acknowledged in terms of PK and extrapolation. However, none of the extremely preterm children were dosed early in life, as the minimum bodyweight in the nirsevimab group was 1.6 kg in Study 3, and 1.8 kg in MELODY and MEDLEY.

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

See pharmacology section.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

See secondary analyses and explorative analyses of MELODY and Study 3 for the pooled analyses and the pharmacology section for dose-response relationship.

2.6.5.6. Supportive studies

Anti-drug antibodies

In the pooled analysis, the occurrence of ADA was approximately 6% and 3% in nirsevimab-treated and placebo-treated arms, and the occurrence of ADA was comparable amongst the different patient populations receiving nirsevimab (i.e. no substantial effect of gestational age and body weight on ADE-development).

The occurrence of neutralising antibodies in nirsevimab-treated patients was 1%, and the occurrence of YTE-targeting antibodies was approximately 3%-5%. Thus, the occurrence of YTE-targeting antibodies was comparable to the occurrence of ADA, which is not surprising, because (i) essentially the same assay format was employed for measurement of these 2 parameters, (ii) the YTE modification, comprising a surface-exposed non-germline modification of nirsevimab, is expected to comprise a major target for ADA. In contrast, the occurrence of neutralizing antibodies was lower than the occurrence of ADA. This again is not surprising, as nirsevimab has a high binding affinity for the F protein, i.e. the fluid-phase competition assays employed to detect neutralizing antibodies would be expected to measure primarily high-affinity neutralizing antibodies.

There was a tendency of a higher incidence of MA RSV LRTI +/- hospitalisation in subjects with ADA compared with subjects without ADA in MELODY (Table 23). As such 13.3% of subjects with ADA had an event whereas only 1.0% of subjects without ADA had an event. For hospitalisation, the incidence was 6.7% vs 0.5% for ADA positive and ADA negative subjects, respectively.

This tendency was although not so clear in Study 3, where 3.8% of ADA positive had an event and 2.5% of ADA negative had an event. For hospitalisation, the opposite was seen 0% vs 0.8%.

Table 23 Summary of Incidence of MA RSV LRTI (Primary Endpoint) and RSV LRTI Hospitalisation (Secondary Endpoint) Through 150 Days Post Dose by Immunogenicity Subgroups – MELODY and Study 3 (All)

Subgroup	Placebo			Nirsevimab		
	N	MA RSV LRTI	MA RSV LRTI with hosp.	N	MA RSV LRTI	MA RSV LRTI with hosp.
MELODY						
Post-baseline positive ADA through 150 days post dose						
Yes	2	0 (0.0)	0 (0.0)	15	2 (13.3)	1 (6.7)
No	494	25 (5.1)	8 (1.6)	979	10 (1.0)	5 (0.5)
Post-baseline positive ADA through 360 days post dose						
Yes	5	0 (0.0)	0 (0.0)	58	2 (3.4)	1 (1.7)
No	491	25 (5.1)	8 (1.6)	936	10 (1.1)	5 (0.5)
Study 3 (All subjects)						
Post-baseline positive ADA through 150 days post dose						
Yes	9	0 (0.0)	0 (0.0)	26	1 (3.8)	0
No	475	46 (9.7)	20 (4.2)	943	24 (2.5)	8 (0.8)

Data presented for number (%) of subjects with events.

ADA= anti-drug antibody; hosp. = hospitalisation; LRTI = lower respiratory tract infection; N = number of subjects; RSV=respiratory syncytial virus.

Source: Table 14.4.1.4.a, MELODY iCSR, Module 5.3.5.1; Tables 14.4.1.4.1 and 14.4.1.5.1, Study 3 CSR, Module 5.3.5.1. Also see Table 1.2.7.2, IEA, Module 5.3.5.3 for the MELODY/Study 3 (Proposed Dose) Pool.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the current application is supported by 3 studies: A phase 3 pivotal trial (MELODY), a phase 2b trial (Study 3) and a phase 2 trial (MEDLEY). The 3 studies target different parts of the paediatric population entering their first RSV season. In MELODY, healthy infants with a gestational age from week 35+0 are included. In Study 3, healthy infants with a gestational age between week 29+0 to week 35 are included. In MEDLEY, two different cohorts are included: healthy infants with a gestational age below week 29 and infants with congenital heart disease (CHD) and/or chronic lung disease (CLD).

In MELODY, which included healthy children, infants with an underlying illness such as cystic fibrosis or Down syndrome with no other risk factors were eligible to be enrolled.

MELODY and Study 3 overall have similar study design, and both studies are randomised placebo-controlled trials and subjects were randomised 2:1 to receive one dose of nirsevimab or placebo before entering the RSV season. In Study 3, a flat dose of 50 mg was administered to all children in the nirsevimab group. However, due to lower exposure and lower efficacy in subjects with a bodyweight ≥ 5 kg, the dose in the phase 3 study (MELODY) was based on bodyweight: 50 mg for children with a bodyweight < 5 kg and 100 mg for children with a bodyweight ≥ 5 kg. The proposed dosing regimen is considered sufficiently justified and is also the proposed dose stated in the SmPC.

MEDLEY is an ongoing Phase II/III study in high-risk infants eligible to receive palivizumab when entering their first or second RSV season i.e preterm infants born < 35 wGA (without CLD or CHD) and term and preterm infants with CLD or CHD. This study was designed to evaluate the safety, PK, ADA response, and descriptive efficacy of nirsevimab in comparison to palivizumab. Thus, this study will only provide data to the extrapolation of efficacy and is considered supportive in this respect. The currently submitted data provides information on efficacy in subjects entering their first RSV season.

In MEDLEY, subjects were randomised 2:1 to nirsevimab (50 mg or 100 mg and subsequently 4 monthly doses of placebo) or palivizumab 15mg/kg x 5 monthly.

The primary endpoint in MELODY and Study 3 was medically attended RSV lower respiratory tract infection (MA RSV LRTI) through day 150 post dose. The key secondary endpoint was MA RSV LRTI hospitalisation. The primary endpoint is clinically relevant, but the key secondary endpoint might be due to biases, as health care service might differ between countries and also differ within countries and

is dependent on hospital occupancy. Especially during the COVID-19 pandemic, where MELODY was conducted, this might have affected the hospitalisation rate. However, to some extend this might also be true for the primary endpoint i.e. MA visit especially during the COVID-19 pandemic. Subjects might have hesitated to visit health care facilities. Since hospitalisation rate shows a trend towards more serious disease it is acceptable that it is mentioned in the SmPC although this is not in accordance with the CHMP scientific advice.

Severity of the MA RSV LRTI is considered more relevant. As suggested by the CHMP scientific advice, the Applicant has defined an explorative endpoint (very severe RSV), which included hospitalisation and requirement of oxygen supplementation or IV fluids. This is considered clinically relevant and is included in the SmPC. Furthermore, the Applicant has been asked to consider contriving an ordinal composite severity score (4 levels).

In the original protocol (5 April 2019), thus prior to the COVID-19 pandemic, the Applicant planned a pooled analysis, in which data from MELODY and Study 3 were pooled for the secondary endpoint. The Applicant is although focusing on the population from Study 3 receiving the proposed dose and not the full population, even though the full population was included in the predefined analysis in the hierarchical testing. As stated in the CMHP scientific advice (EMA/CHMP/SAWP/182016/2019), it is important that the two studies can stand alone in order to support an indication for the full paediatric population entering their first season of RSV. Therefore, the pooled analysis should be considered supportive, only.

In MEDLEY, the primary endpoint was safety, and secondary endpoints were pharmacokinetics and descriptive efficacy endpoints. In order to establish efficacy in the MEDLEY population, extrapolation was used. This approach is considered acceptable and is in accordance with the PIP.

The design of the studies is considered adequate and is in accordance with the PIP, and the selected study population is relevant for the applied indication. The comparator used in the studies are relevant, and it is acknowledged that an active comparator was used in the MEDLEY population although non-inferiority could not be evaluated. Delayed or missed doses of palivizumab might have decreased protection against RSV in the palivizumab group and a supportive, per-protocol analysis of the relevant efficacy endpoints in MEDLEY has been requested.

Efficacy data and additional analyses

In MELODY and Study 3, 1,490 and 1,540 subjects, respectively, were randomised to nirsevimab or placebo. The proportion of subjects completing the day 151 follow-up visit was high (between 95.5% and 98.4%). Due to the COVID-19 pandemic, several subjects had at least 1 missing visit. The Applicant has conducted several sensitivity analyses to address this issue, and the results pointed in the same direction as the main analysis.

The study populations for the 3 studies were well described in terms of gestational week, bodyweight and age, and minimum gestational age was week 22, and the minimum bodyweight at dosing was 1.6 kg and minimum age at dosing was 0.03 months (~1 days). In the SmPC, no minimum age or bodyweight are included, neither for the term and preterm children. This has been discussed by the CHMP and based on the data submitted by the Applicant including the modelling of the exposure in children from 1 kg and the overall safety data, it can be concluded that efficacy and safety can be extrapolated to the youngest and lightest possible individuals both for term and preterm individuals. Hence, no minimum age or bodyweight should be included in indication, neither for term or preterm children. As requested, the Applicant has stated in the SmPC section 4.2 that no clinical data in children with a bodyweight below 1.6 kg exist, and that the dose in children down to 1 kg is based on modelling.

Across the 3 studies included in the dossier, 41 extremely preterm infants (≤29 weeks gestational age) received nirsevimab within the first 3 months of life. Only 1 subject (29 weeks gestational age) received nirsevimab below 1 month of age, 12 subjects between 1 and 2 months of age, and 28 subjects between 2 and 3 months of age. None of the children with GA of 24-25 weeks received nirsevimab below 3 months chronological age. As discussed in the pharmacology section the minimum postmenstrual age at dosing was 7.4 months. In the SmPC section 4.2 it is reflected that there is

limited data available in extremely preterm infants (Gestational Age] <29 weeks) less than 8 weeks of age, and that no clinical data is available in infants with a postmenstrual age (gestational age at birth plus chronological age) of 32 weeks.

Overall, the demographics of the study populations were well balanced between treatment arms, although an overview of medical history was missing for Study 3, which the Applicant has provided with the day 90 responses. In study 3, the medical history was similar in both treatment groups. However, for atrial septal defects, the prevalence was higher (30/484 (6.2%)) for placebo than for nirsevimab (38/969 (3.9%)), and for neonatal respiratory distress syndrome the prevalence was 93/484 (19.2%) in the placebo group and 162/969 (16.7%) in the nirsevimab group and thereby the prevalence was also higher in the placebo group than nirsevimab for history of neonatal respiratory distress syndrome. As the imbalances in history of atrial septal defects and neonatal respiratory distress syndrome could potentially have driven the effect estimates, a post hoc sensitivity analysis was requested.

The event rate of MA RSV LRTI (primary endpoint) was lower for the nirsevimab group than the placebo group. As such, 12/994 (1.2%) subjects in the nirsevimab group and 25/496 (5.0) subjects in the placebo group met the primary endpoint, and the relative risk reduction was 74.5% (95% CI: 49.6%, 87.1%) with nirsevimab compared with placebo in MELODY in subjects with GA > 35 weeks. Similar pattern was seen in subjects with GA between week 29 and week 35, where the event rate was 25/969 (2.6%) and 46/484 (9.5%) in the nirsevimab and placebo arm, respectively, corresponding to a relative risk reduction of 70.1% (95% CI: 52.3%, 81.2%). Even though the relative risk reductions are high, the absolute numbers are low. The event rates in the placebo groups are lower than expected, which also turn into a lower absolute effect. However, the relative risk reduction is as anticipated in the sample size calculation (70%).

The key secondary endpoint was MA RSV LRTI with hospitalisation. In MELODY, the relative risk reduction was not statistically significant: 62.1% (95% CI: -8.6; 86.8) with 8/496 hospitalisations in the placebo group and 6/994 hospitalisations in the nirsevimab group. In Study 3, MA RSV LRTI with hospitalization was statistically significant. The relative risk reduction was 78.4% (95% CI: 51.9; 90.3) with 20/484 hospitalisations in the placebo group and 8/969 hospitalisations in the nirsevimab group. A pooled analysis and part of the statistical hierarchy in the MELODY study was planned after the results from Study 3 were available due to anticipated low numbers of hospitalisations. The pooled analysis showed a relative risk reduction of 73.5% (50.2; 85.9). As mentioned above, a hospitalisation endpoint may be subject to external impact and as such the results are subject to bias. Therefore, a more clinically relevant endpoint is acknowledged as the predefined exploratory endpoint, very severe RSV.

This was defined as MA RSV LRTI hospitalisation and requirement of oxygen or intravenous fluid. In MELODY, 5/994 subjects (0.5%) in the nirsevimab group and 7/496 subjects (1.4%) in the placebo group had severe RSV corresponding to a relative risk reduction of 64.2% (-12.1%;88.6%) with nirsevimab compared to placebo. In Study 3, the estimate was numerically higher, and 4/969 subjects (0.4%) in the nirsevimab group and 16/484 subjects (3.3%) in the placebo group, had severe RSV; with a relative risk reduction of 87.5% (62.9%;95.8%). Hence, the exploratory analyses of severity pointed towards an effect against severe respiratory illness with nirsevimab in both studies, although the results were not statistically significant in MELODY. This was further supported by explorative analysis in Study 3 showing that numerically fewer patients were admitted to ICU, were in need of supplemental oxygen, CPAP or mechanical ventilation in the nirsevimab group than the placebo group. In MELODY, the numbers were low, and there were no differences between the treatment groups with regards to severity measures.

On request, the Applicant conducted post hoc analysis including a proportional odds model, which supported the primary analysis. Additionally, a post hoc sensitivity analysis was conducted in which atrial septal defects and neonatal respiratory distress syndrome were included as covariates in order to analyse whether the results were driven by those factors due to the imbalance of those two medical conditions at baseline. The estimate of the sensitivity analysis was similar to the main analysis.

Overall, the two studies showed an effect of nirsevimab on MA RSV LRTI and severe RSV in healthy subjects with a GA > 29 weeks, and even though the magnitude of effect compared to placebo, due to the overall low event rate, might be considered modest, it is considered clinically relevant.

For subjects with a GA < 29 weeks and subjects with CLD or CHD extrapolation of efficacy from MELODY and Study 3 was used. Furthermore, the event rates from MEDLEY were analysed descriptively. In MEDLEY, 616 children were randomised to nirsevimab, and 309 children were randomised to palivizumab. The incidence of MA RSV LRTI was lower in this population than MELODY and study 3, which was expected due to the high-risk nature of the population and thereby a focus on minimising the risk of infections e.g. by social distancing. The event rate in the nirsevimab group was 4/616 (0.6%) and in the placebo group 3/309 (1.0%).

The Applicant has conducted relevant subgroup analysis and the effect was consistent across subgroups of gender, gestational age, bodyweight and age at treatment.

Additional expert consultation

None

2.6.7. Conclusions on the clinical efficacy

The study design of the three studies are considered relevant for the applied indication. No data in children with a bodyweight below 1.6 kg exists, however, based on the data including the modelling of the exposure in children from 1 kg and the overall safety data, it can be concluded that efficacy and safety can be extrapolated to the youngest and lightest possible individuals both for term and preterm individuals.

Overall, an effect of nirsevimab on MA RSV LRTI and severe RSV in healthy subjects with a GA > 29 weeks was shown in the studies MELODY and Study 3, and even though the magnitude of effect compared to placebo, due to the overall low event rate, might be considered modest, it is considered clinically relevant.

2.6.8. Clinical safety

The preliminary safety evaluation is based on safety data from three pivotal studies on the use of nirsevimab (50 mg or 100 mg single IM dose) in 2569 infants in their first RSV season:

Study 3, a Phase IIb Study D5290C00003/randomised 2:1 nirsevimab: placebo, double-blind, placebo-controlled (complete). Very and moderately preterm infants born ≥ 29 to < 35 wGA (Study 3; N = 1453).

MELODY, a Phase III Study D5290C00004 /randomised 2:1 nirsevimab: placebo, double-blind, placebo-controlled (ongoing). Term and late preterm infants born ≥ 35 wGA (MELODY; N = 1490). Data cut-off date of 11 March 2021, and a data lock date of 14 April 2021.

MEDLEY, a Phase II/III Study D5290C00005/palivizumab-controlled study (ongoing). Infants at higher risk for severe RSV, including preterm infants born < 35 wGA and infants with CLD/CHD (including some infants in each cohort born < 29 wGA) (N = 925 (616 preterm cohort and 309 subjects CLD/CHD cohort). Data cut-off date of 03 May 2021 and database lock date of 10 June 2021.

The Primary Analysis in MELODY is complete and includes safety data through Day 361. The Final Analysis in Study 3 is complete and includes safety data through Day 361. The Primary Analysis in MEDLEY is complete and includes safety data for subjects followed up through at least 150 days post first dose (RSV Season 1).

Table 24 Pivotal Studies Contributing to the Evaluation of the Clinical Safety of Nirsevimab

Study number (abbreviation) Status	Study Design (primary/secondary objectives)	Study Population	Dosing Regimen	Number Randomised/Dosed
D5290C00004 (MELODY) Study ongoing; Primary Analysis complete [a]; safety cohort ongoing	Phase III, randomised, double-blind, placebo-controlled, (efficacy, safety, PK, and ADA) / through Day 361	Term and late preterm infants born ≥ 35 wGA, entering their first RSV season	**Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) IM **Placebo:** IM Single dose	Primary Cohort – Nirsevimab: 994/987 Placebo: 496/491
D5290C00003 (Study 3) Study complete; Primary Analysis complete [a]	Phase IIb, randomised, double-blind, placebo-controlled (efficacy, safety, PK, and ADA) / through Day 361	Very and moderately preterm infants born ≥ 29 to < 35 wGA, entering their first RSV season	**Nirsevimab:** 50 mg IM **Placebo:** IM Single dose	Final analysis – Nirsevimab: 969/968 (including 572 infants weighing < 5 kg who received the proposed dose) Placebo: 484/479
D5290C00005 (MEDLEY) Study ongoing; Primary Analysis (RSV Season 1) complete [b]	Phase II/III, randomised, double-blind, palivizumab-controlled (safety, descriptive efficacy, PK, and ADA) / through Day 151	Infants and children entering their first or second RSV season, eligible to receive palivizumab RSV Season 1: Preterm infants born < 35 wGA (without CLD/CHD) and term and preterm infants with CLD of prematurity or hemodynamically significant CHD. RSV Season 2: Children ≥ 12 to ≤ 24 months with CLD or CHD (who received nirsevimab or palivizumab in RSV Season 1) [c]	**Nirsevimab:** RSV Season 1 - 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) IM RSV Season 2 - 200 mg IM Single dose of nirsevimab followed by 4 once-monthly doses of placebo **Palivizumab:** RSV Season 1 and Season 2 - 15 mg/kg IM (5 once-monthly doses)	RSV Season 1 Nirsevimab: 616 (preterm 407 + CLD/CHD 209)/614 Palivizumab: 309 (preterm 208 + CLD/CHD 101)/304
Total number of infants dosed with nirsevimab in the pivotal safety studies [d]				**2569**
Total number of infants dosed with nirsevimab at proposed dosing regimen in the pivotal safety studies [e]				**2173**
Total number of infants weighing < 2.5 kg at time of dosing with nirsevimab in the pivotal safety studies				**252**
Total number of neonates dosed with nirsevimab in MELODY and Study 3				**358**

[a] Data presented from Study 3 and MELODY through 150 days post dose for efficacy and Day 361 post dose for safety, PK, and ADA.
[b] Data presented from MEDLEY through 150 days post dose for RSV Season 1.
[c] RSV Season 2 data are not currently available and are not included in the current application.
[d] Data included from MELODY, Study 3, and MEDLEY.
[e] Data included from MELODY, Study 3 < 5 kg Day 1 (at dosing), and MEDLEY.

ADA = anti-drug antibodies; CHD = congenital heart disease; CLD = chronic lung disease (of prematurity); IM = intramuscular; PK = pharmacokinetic(s); RSV = respiratory syncytial virus; wGA = weeks gestational age.

Non-clinical findings

Non-clinical data from toxicology-studies in cynomolgus monkeys, cross-reactivity studies against adult, juvenile, neonatal and foetal human tissues did not disclose any safety concerns for Nirsevimab. Also, in an RSV challenge study in a cotton rat model of RSV infection no antibody dependent enhancement (ADE) of RSV infection was observed.

Pharmacological Class Effects

As no non-clinical studies raised concern of safety concerns related to nirsevimab, the potential risks were based on the pharmacological class effect of immunoglobulins (including mAbs) and thus included focus on adverse events as immediate hypersensitivity (including anaphylaxis) and immune complex disease as AESI's. This also included thrombocytopenia as such events of were reported in post-approval use of SYNAGIS® (palivizumab).

2.6.8.1. Methods

Safety data in term and preterm infants born ≥ 29 wGA with a safety follow-up of 360 days post dose from MELODY and study 3 were analysed in 2 pools:

The **MELODY/study 3 (All) safety pool** that included pooled data of all dosed participants from Study 3 and the MELODY primary cohort ((N = 2925 dosed with either nirsevimab [n = 1955] or

placebo [n = 970]) and a subpopulation; the **MELODY/Study 3 (proposed dose) safety pool** that include pooled data of subjects receiving the proposed dose (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg at the time of dosing) weighing < 5 kg at the time of dosing from Study 3 and the MELODY primary cohort (N = 2338 dosed with either nirsevimab [n = 1559] or placebo[n = 779]). The MELODY/Study 3 (All) Safety Pool was used to evaluate the AE profile, ADRs, and potential risks comprising the largest pool of placebo-controlled data for nirsevimab. Data from the palivizumab-controlled **MEDLEY study** in infants at higher risk for severe RSV disease (including subpopulations of extremely preterm infants born < 29 wGA and infants with CLD or CHD) through at least 150 days post dose was evaluated separately due to differences in study design.

The safety evaluation was standardised across the studies and adverse events coded using the MedDRA version 23.1, evaluations including treatment-emergent AEs, SAEs, discontinuations, NOCDs, AESIs, and skin reactions.

2.6.8.2. Disposition and baseline characteristics

Dispositions

In the MELODY/Study 3 (All) Safety Pool of infants born at term and preterm (≥ 29 wGA), 3166 subjects were screened, of whom 2943 were enrolled and randomised (2:1) to nirsevimab (n = 1963) or placebo (n = 980). Of the 2943 randomised subjects, 2925 (1953 in the nirsevimab group and 972 in the placebo group) were dosed and included in the As-treated Population. Disposition data were balanced in the nirsevimab and placebo groups with similar percentages of subjects completing the Day 151 follow-up, completing the Day 361 follow-up and completing the ongoing study (. For the 96 (4.9%) subjects in the nirsevimab group and 51 (5.2%) in the placebo group who discontinued the study, the main reasons for discontinuation were withdrawal by the parent/guardian and lost to follow-up, both of which occurred in similar percentage of subjects in each group.

In the MELODY/Study 3 (Proposed Dose) Safety Pool of subjects from MELODY + subjects weighing < 5 kg at the time of dosing in Study 3, 2350 subjects were randomised (2:1) to nirsevimab (n = 1564) or placebo (n = 786). Of the 2350 randomised subjects, 2338 (1557 in the nirsevimab group and 781 in the placebo group) were dosed and included in the As-treated Population. Disposition data were balanced in the nirsevimab and placebo groups with similar percentages of subjects completing the Day 151 follow-up, completing the Day 361 follow-up and completing the ongoing study. For the 68 (4.4%) subjects in the nirsevimab group and 38 (4.9%) subjects in the placebo group who discontinued the study, the main reasons for discontinuation were withdrawal by the parent/guardian and lost to follow-up, both of which occurred in a similar percentage of subjects in each group.

In MEDLEY, 960 subjects were screened, of whom 925 were enrolled and randomised (2:1) to nirsevimab (n = 616) or palivizumab (n = 309). A total of 918 subjects (614 in the nirsevimab group and 304 in the palivizumab group) were dosed and included in the As-treated Population. Disposition data were balanced in the nirsevimab and palivizumab groups with similar percentages of subjects completing dosing, completing follow-up through at least 150 days post first dose, and reaching Day 361. For the 50 subjects in the nirsevimab group and 22 subjects in the palivizumab group who discontinued, the main reasons for discontinuation were being withdrawn by the parent/guardian and COVID-19 pandemic.

In the preterm cohort of subjects born < 35 wGA without CLD/CHD, 615 subjects were randomised to nirsevimab (n = 407) or palivizumab (n = 208). Of these subjects, 612 were dosed (1 subject in the nirsevimab group and 2 subjects in the palivizumab group were not dosed). A total of 587 subjects, including 389 in the nirsevimab group and 198 in the palivizumab group, had completed follow-up through at least 150 days post first dose and 250 subjects (40.7%), including 167 (41.0%) in the nirsevimab group and 83 in the palivizumab group, completed RSV Season 1 and are considered to have completed the study per protocol. In the CLD/CHD cohort, 310 subjects were randomised to nirsevimab (n = 209) or palivizumab (n = 101). Of these subjects, 306 were dosed (1 subject in the nirsevimab group and 3 subjects in the palivizumab group were not dosed). A total of 299 subjects, including 204 in the nirsevimab group and 95 in the palivizumab group, had completed follow-up

through at least 150 days post first dose, and 115 subjects, including 75 in the nirsevimab group and 40 in the palivizumab group, completed RSV Season 1.

Baseline characteristics

Table 25 Demographics (MELODY/Study 3 [All] Safety Pool)

Characteristic	Statistics	Placebo (N=970)	Nirsevimab (N=1955)	Total (N=2925)
Age (months) at randomisation	n	970	1955	2925
	Mean	3.145	3.091	3.109
	SD	2.2879	2.2114	2.2368
	Median	2.628	2.700	2.700
	Min	0.03	0.03	0.03
	Max	11.30	11.90	11.90
Age group, n (%)	Age ≤ 3.0 months	537 (55.4)	1090 (55.8)	1627 (55.6)
	Age > 3.0 to ≤ 6.0 months	310 (32.0)	636 (32.5)	946 (32.3)
	Age > 6.0 months	123 (12.7)	229 (11.7)	352 (12.0)
	Total	970	1955	2925
Sex, n (%)	Female	478 (49.3)	930 (47.6)	1408 (48.1)
	Male	492 (50.7)	1025 (52.4)	1517 (51.9)
	Total	970	1955	2925
Race [a], n (%)	American Indian or Alaska Native	27 (2.8)	57 (2.9)	84 (2.9)
	Asian	28 (2.9)	40 (2.1)	68 (2.3)
	Black or African American	203 (20.9)	470 (24.1)	673 (23.0)
	Native Hawaiian or Other Pacific Islander	8 (0.8)	14 (0.7)	22 (0.8)
	White	619 (63.8)	1214 (62.2)	1833 (62.8)
	Other	79 (8.1)	132 (6.8)	211 (7.2)
	Multiple Categories Checked	6 (0.6)	24 (1.2)	30 (1.0)
	Total	970	1951	2921
Ethnicity, n (%)	Hispanic or Latino	138 (14.3)	324 (16.6)	462 (15.8)
	Not Hispanic or Latino	830 (85.7)	1626 (83.4)	2456 (84.2)
	Total	968	1950	2918

[a] Each race category counts subjects who selected only that category; "Multiple Categories checked" counts subjects who selected more than one race category.

Total row includes the number of subjects with non-missing data for the corresponding characteristic and was used as the denominator for calculating percentages for all categories.

Source: Table 1.1.3.1, ISA, Module 5.3.5.3.

Table 26 Baseline Characteristics (MELODY/Study 3 [All] Safety Pool)

Characteristic	Statistics	Placebo (N=970)	Nirsevimab (N=1955)	Total (N=2925)
Weight (kg) on Day 1	n	969	1951	2920
	Mean	5.04	5.05	5.04
	SD	1.96	1.93	1.94
	Median	5.00	5.00	5.00
	Min	1.2	1.6	1.2
	Max	11.0	11.5	11.5
Weight group on Day 1, n (%)	Weight < 5 kg	478 (49.3)	974 (49.9)	1452 (49.7)
	Weight ≥ 5 kg	491 (50.7)	977 (50.1)	1468 (50.3)
	Total	969	1951	2920
Birth weight (kg)	n	970	1955	2925
	Mean	2.51	2.51	2.51
	SD	0.80	0.81	0.81
	Median	2.40	2.40	2.40
	Min	0.8	0.8	0.8
	Max	5.0	5.6	5.6
Birth weight group n (%)	Weight ≤ 2.5 kg	537 (55.4)	1048 (53.6)	1585 (54.2)
	Weight > 2.5 kg	433 (44.6)	907 (46.4)	1340 (45.8)
	Total	970	1955	2925
Gestational age (weeks)	n	970	1955	2925
	Mean	35.6	35.6	35.6
	SD	3.3	3.3	3.3
	Median	35.0	35.0	35.0
	Min	29	29	29
	Max	42	42	42
Gestational age group, n (%)	≥ 29 to ≤ 32 weeks	185 (19.1)	363 (18.6)	548 (18.7)
	> 32 to < 35 weeks	294 (30.3)	598 (30.6)	892 (30.5)
	≥ 35 to < 37 weeks	76 (7.8)	139 (7.1)	215 (7.4)
	≥ 37 weeks	415 (42.8)	855 (43.7)	1270 (43.4)
	Total	970	1955	2925
Multiple birth, n (%)	Yes	228 (23.5)	460 (23.5)	688 (23.5)
	No	742 (76.5)	1495 (76.5)	2237 (76.5)
	Total	970	1955	2925
Siblings enrolled in the study, n (%)	Yes	215 (22.2)	428 (21.9)	643 (22.0)
	No	755 (77.8)	1527 (78.1)	2282 (78.0)
	Total	970	1955	2925

Total row includes the number of subjects with non-missing data for the corresponding characteristic and was used as the denominator for calculating percentages for all categories.

Source: Table 1.1.4.1, ISA, Module 5.3.5.3.

Baseline demographics and characteristics (**Table 25** and **Table 26**) were overall similar and balanced between the nirsevimab and placebo groups among the study population included in the MELODY/Study 3 (All) Safety Pool and adequate for the intended target population of infants born at term and late preterm (≥ 35 wGA) and infants born very and moderately preterm (≥ 29 to < 35 wGA). The median age at randomisation was 2.70 months (0.03-11.90 months) in the nirsevimab group and a little less in the placebo group: 2.3 (0.03-11.30 months). The percentage of participants with weight ≤ 2.5 kg were a little fewer in the nirsevimab group: 53.6% compared to 55.4% in the placebo group.

In the subgroup of participants < 2.5 kg on Day 1, baseline demographics and characteristics were overall similar to the study population included in the MELODY/Study 3 (All) Safety Pool except the

median age at randomisation (0.7 months) and the mean weight on Day 1 (2.1 kg) (39.2% in GA groups of ≥ 29 weeks to ≤ 32 weeks and 46.3% in GA group > 32 weeks to < 35 weeks). The discrepancies were considered subject to the subgroup characteristics. This was also evident in the subgroup of neonates (all infants < 28 days at randomisation) where the median age at randomisation, which was 0.5 months and mean weight on Day 1, which was 2.8 kg in nirsevimab and 3.0 kg placebo groups for neonates compared with 5.04 kg and 5.05 kg, respectively in the overall MELODY/Study 3 (All) Safety Pool.

Medical history for the study population in the MELODY/Study 3 (All) Safety Pool were overall balanced between both treatment arms and considered representative of common pediatric conditions for the intended target population (nirsevimab 47.2% and placebo 47.0%, respectively). The majority were disorders categorised in the SOCs of Respiratory, thoracic and mediastinal disorders (17.5%, each), most frequently TEA's by PT neonatal respiratory distress syndrome (8.8% and 10.0%, respectively), nasal congestion (2.6% and 2.4%, respectively). Overall baseline demographics, characteristics and medical history for the MELODY /Study 3 (All) Safety pool were balanced between nirsevimab and placebo groups. Baseline demographics and characteristics were overall similar and balanced between the nirsevimab and placebo groups among the study population included in the MELODY/Study 3 (proposed) Safety Pool and reflecting the intended target population of infants born at term and late preterm (≥ 35 wGA) and infants born very and moderately preterm (≥ 29 to < 35 wGA). Medical history for the study population in the MELODY/Study 3 (proposed) Safety Pool were overall balanced between both treatment arms and considered representative of common pediatric conditions for the intended target population. Overall baseline demographics, characteristics and medical history for the MELODY /Study 3 (proposed) Safety pool were balanced between nirsevimab and placebo groups.

In the MEDLEY study cohort, baseline demographics and characteristics were overall similar and balanced between treatment groups and represented the intended target population of infants at higher risk for RSV disease, including infants born preterm < 35 wGA without CLD/CHD (preterm cohort) and infants with CLD or CHD, with some infants born extremely preterm < 29 wGA in both cohorts. In the CLD/CHD cohort there were fewer subjects in the weight group < 5kg in the nirsevimab treatment group (48.6% vs. 52.0%) and more in the weight group ≥5 kg (51.4% vs. 48.0%). Also, by gestational age there were numerical imbalances with fewer subjects <29 weeks in the nirsevimab group (38.8% vs. 41.6%) and more in the ≥29 to <weeks (17.7% vs. 11.9%) compared to palivizumab. Medical history for the MELODY study population was overall balanced between both treatment arms and considered representative of the more complex pediatric conditions this cohort of infants at higher risk of RSV disease. Overall baseline demographics, characteristics and medical history for the MEDLEY study were balanced between nirsevimab and placebo groups.

2.6.8.3. Patient exposure

In the MELODY/Study 3 (All) Safety Pool subjects received a single dose of nirsevimab (n=1955) or placebo (n=970). In the nirsevimab group, 70.4% (1377) received a 50 mg dose and 29.6% (578) received a 100 mg dose. In study 3 there were to subjects that incorrectly received nirsevimab and is included in the safety analysis. In the MELODY/Study 3 (Proposed Dose) Safety Pool group, 62.9% (981) in the nirsevimab group received 50 mg and 37.1% (578) received 100 mg.

Table 27 Summary of Exposure (MELODY/Study 3 [ALL] Safety Pool)

Treatment received	Statistics	Total
Placebo	n	970
Nirsevimab	n	1955
50 mg	n (%)	1377 (70.4)
100 mg	n (%)	578 (29.6)

A subject who received any nirsevimab dose will be classified into nirsevimab group.

Source: Table 1.2.1.1, ISA, Module 5.3.5.3.

Table 28 Summary of Exposure (MELODY/Study 3 [Proposed Dose] Safety Pool)

Treatment received	Statistics	Total
Placebo	n	779
Nirsevimab	n	1559
50 mg	n (%)	981 (62.9)
100 mg	n (%)	578 (37.1)

A subject who received any nirsevimab dose will be classified into nirsevimab group.

Source: Table 1.2.1.2, ISA, Module 5.3.5.3.

In the MEDLEY study, a total of 918 subjects (nirsevimab (n=614) and palivizumab (n=304) were dosed. Almost 90% of subjects received all 5 planned doses (nirsevimab:100.0% received at least one active dose; palivizumab: 90.1% received at least 5 active doses).

2.6.8.4. Adverse events

All-over in the **MELODY/Study 3 (All Safety Pool)**, the percentage of subjects that experienced at least one AE was identical (86.8%) in the nirsevimab and placebo group (overall through 360 days post dose) (Table 29). A little more in the nirsevimab group, however experienced at least one AE within the first 1,3- or 14-days post dose (2.1%, 5.9 % and 25.8% compared to 1.5%, 5.6% and 24.5% in the placebo group). All-over there were a lower percentage in the nirsevimab group that had a grade 3 event or worse (5.8% in the nirsevimab group vs. 8.4% in the placebo group), however there were a little higher percentage in the nirsevimab group that experienced grade 3 or worse events within 3- and 7-days post dose compared to placebo (0.2% and 0.3% vs. 0% and 0.2%). The percentage of IP-related AESI based on selected MedDRA PT codes, and IP-related skin reaction was also higher in the nirsevimab group; 0.6% and 0.7% vs. 0.4% and 0.6% in the placebo group.

Table 29 Overall Summary of Treatment-Emergent Adverse Events Through 360 Days Post Dose (Melody/Study 3 [All] Safety Pool)

Subjects [a] with	Number (%) of Subjects		
	Placebo (N=970)	Nirsevimab (N=1955)	Total (N=2925)
At least one event	842 (86.8)	1697 (86.8)	2539 (86.8)
occurring ≤ 1 day post dose	15 (1.5)	42 (2.1)	57 (1.9)
occurring ≤ 3 days post dose	54 (5.6)	115 (5.9)	169 (5.8)
occurring ≤ 7 days post dose	136 (14.0)	253 (12.9)	389 (13.3)
occurring ≤ 14 days post dose	238 (24.5)	505 (25.8)	743 (25.4)
At least one investigational product-related event	17 (1.8)	32 (1.6)	49 (1.7)
At least one event of ≥ Grade 3 severity [b]	81 (8.4)	113 (5.8)	194 (6.6)
occurring ≤ 1 day post dose	0	0	0
occurring ≤ 3 days post dose	0	3 (0.2)	3 (0.1)
occurring ≤ 7 days post dose	2 (0.2)	6 (0.3)	8 (0.3)
occurring ≤ 14 days post dose	6 (0.6)	9 (0.5)	15 (0.5)
At least one investigational product-related event ≥ Grade 3 severity [b]	0	1 (< 0.1)	1 (< 0.1)
occurring ≤ 1 day post dose	0	0	0
occurring ≤ 3 days post dose	0	0	0
occurring ≤ 7 days post dose	0	1 (< 0.1)	1 (< 0.1)
occurring ≤ 14 days post dose	0	1 (< 0.1)	1 (< 0.1)
Any AE with outcome death (Grade 5 severity [b])	3 (0.3)	5 (0.3)	8 (0.3)
At least one serious [c] event	117 (12.1)	175 (9.0)	292 (10.0)
At least one serious [c] and/or ≥ Grade 3 severity [b] event	130 (13.4)	197 (10.1)	327 (11.2)
At least one investigational product-related serious [c] event	0	0	0
At least 1 AESI based on investigator's assessment	3 (0.3)	6 (0.3)	9 (0.3)
At least 1 AESI based on selected MedDRA preferred term codes	254 (26.2)	503 (25.7)	757 (25.9)
At least one investigational product-related AESI based on selected MedDRA preferred term codes	4 (0.4)	11 (0.6)	15 (0.5)
At least one investigational product-related skin reaction	6 (0.6)	13 (0.7)	19 (0.6)
At least one NOCD	6 (0.6)	5 (0.3)	11 (0.4)
At least one investigational product-related NOCD	0	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.

[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

MedDRA version 23.1.

AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease.

Source: Table 1.3.1.1.1, ISA, Module 5.3.5.3.

In the MELODY/Study 3 (All Safety Pool) the frequency of AE's by SOC in the nirsevimab was generally balanced and similar to the placebo group. Only in the SOC Skin and subcutaneous tissue disorders, and General disorders and administration site conditions were the frequencies a little higher (29.6% and 14.9% in the nirsevimab group vs. 29.2% and 14.4% in the placebo group). AE's commonly reported by SOC (> 25% of subjects in the nirsevimab group and the placebo group) were Infections and infestations (75.1% and 77.5%, respectively); Skin and subcutaneous tissue disorders (29.6% and 29.2%, respectively); Gastrointestinal disorders (28.3% and 29.2%, respectively). AE's by PT most commonly in the nirsevimab groups were; (> 10% of subjects) respiratory tract infection (41.7%

vs. 39.7%), gastroenteritis (10.8% vs. 9.1%). More predominant in the placebo group were: pyrexia (13.1% vs. 12.9%), nasopharyngitis (14.9% vs. 11.7%), and bronchiolitis (11.3% vs. 7.9%).

In the MELODY/Study 3 (All) Safety Pool, AE's of grade 3 or higher severity by SOC and PT through 360 days post dose (data not shown) were overall similar or less in the nirsevimab group compared to placebo. There were fewer Grade 3 events in the nirsevimab group: 5.1% vs. 7.5% in the placebo group and 0.4% Grade 4 events compared to 0.5% in the placebo group. Numbers were generally low. There were 0.3% Grade 5 events in both treatment groups). Grade 3 events were most commonly bronchiolitis (0.7% in the nirsevimab group vs. 1.8% in the placebo group), lower respiratory tract infection (0.8% vs. 1.1%), bronchitis (0.4% vs. 0.8%,) with higher frequencies in the placebo group. In the nirsevimab group there was a higher frequency of viral pneumonia (0.4% vs. 0.1%). Grade 4 and 5 events were few and generally reported in one subject each in both treatment group were. In the nirsevimab group there were however 2 deaths (Grade 5), and 2 cases of gastroenteritis. Also, there were 2 Grade 4 AE's in two subjects; congestive heart failure on day 30 in a patient with ventricular septal defect, atrial septal defect, and peripheral pulmonary stenosis and cardiopulmonary arrest on Day 64, secondary to pulmonary vein stenosis caused by bronchopneumonia. Both could be explained by their medical history

In the MELODY/Study 3 (All Safety Pool) the frequency of participants with any IP-related AE through 360 days post dose was lower in the nirsevimab group (1.6% vs. 1.8%). Events in the nirsevimab group were most frequently by the SOCs; General disorders and administration site conditions (0.5% vs. 0.2%), Skin and subcutaneous tissue disorders (0.6% vs.0.6%) and Nervous system disorders (0.3% vs. 0.1%). Most events were Grade 1-2 in severity (one Grade 3 severity event of rash in the nirsevimab group / investigator-assessed AESI of skin-hypersensitivity) and most commonly a reflection of mild reactogenicity; rash (0.3% nirsevimab vs. 0.2% placebo), hypersomnia (0.2% nirsevimab vs. 0 placebo), injection site pain (0.1% nirsevimab and 0% placebo) pyrexia (0.1% nirsevimab vs. 0.2% placebo).

In the MELODY/Study 3 (All Safety Pool) the frequency of participants with AE's by SOC and PT in 2 or more subjects by time relative to dosing within 1, 3, 7, and 14 days post dose were overall balanced between the nirsevimab and placebo groups. There was however a trend of mild but slightly enhanced reactogenicity in the nirsevimab treated group compared to placebo within one day post dose, though they occurred infrequently: pyrexia 0.2% vs. 0.1%) and injection site reactions 0.4% vs.0%.

In **MELODY/Study 3 (Proposed Dose) Safety Pool**, the overall the distribution of common AE's resembled the MELODY/Study (ALL) Safety Pool and was balanced between the nirsevimab and placebo treatment groups (Table 14), with AEs by SOC most commonly reported being: Infections and infestations (73.6% vs. 76.3%); Skin and subcutaneous tissue disorders (31.0% vs. 31.2%); Gastrointestinal disorders (28.3% vs. 29.0%); Respiratory, thoracic and mediastinal disorders (24.3% vs. 25.4%); and General disorders and administration site conditions (14.8% vs. 13.2%). AE's were mostly Grade 1 and there were fewer Grade 3 events in the nirsevimab group (4.2% vs. 7.3%). AEs considered related to IP by the investigator, were mainly reflecting mild reactogenicity in the nirsevimab treatment group (rash (0.2% vs. 0%), injection site pain (0.1% vs. 0%), and pyrexia (0.1% vs. 0.3%). AE's by time relative to dosing within one day post dose was higher in the nirsevimab treatment group: 1.9% vs. 0.8%.

Table 30 Overall Summary of Treatment-Emergent Adverse Events Through 360 Days Post Dose (MELODY/Study 3 [Proposed Dose] Safety Pool)

Subjects [a] with	Number (%) of Subjects		
	Placebo (N=779)	Nirsevimab (N=1559)	Total (N=2338)
At least one event	671 (86.1)	1348 (86.5)	2019 (86.4)
occurring ≤ 1 day post dose	6 (0.8)	30 (1.9)	36 (1.5)
occurring ≤ 3 days post dose	39 (5.0)	89 (5.7)	128 (5.5)
occurring ≤ 7 days post dose	103 (13.2)	196 (12.6)	299 (12.8)
occurring ≤ 14 days post dose	190 (24.4)	404 (25.9)	594 (25.4)
At least one investigational product-related event	10 (1.3)	18 (1.2)	28 (1.2)
At least one event of ≥ Grade 3 severity [b]	64 (8.2)	77 (4.9)	141 (6.0)
occurring ≤ 1 day post dose	0	0	0
occurring ≤ 3 days post dose	0	3 (0.2)	3 (0.1)
occurring ≤ 7 days post dose	2 (0.3)	6 (0.4)	8 (0.3)
occurring ≤ 14 days post dose	5 (0.6)	9 (0.6)	14 (0.6)
At least one investigational product-related event ≥ Grade 3 severity [b]	0	1 (< 0.1)	1 (< 0.1)
occurring ≤ 1 day post dose	0	0	0
occurring ≤ 3 days post dose	0	0	0
occurring ≤ 7 days post dose	0	1 (< 0.1)	1 (< 0.1)
occurring ≤ 14 days post dose	0	1 (< 0.1)	1 (< 0.1)
Any AE with Outcome Death (Grade 5 severity [b])	3 (0.4)	5 (0.3)	8 (0.3)
At least one serious [c] event	97 (12.5)	137 (8.8)	234 (10.0)
At least one serious [c] and/or ≥ Grade 3 severity [b] event	105 (13.5)	149 (9.6)	254 (10.9)
At least one investigational product-related serious [c] event	0	0	0
At least 1 AESI based on investigator's assessment	0	3 (0.2)	3 (0.1)
At least 1 AESI based on selected MedDRA preferred term codes	210 (27.0)	404 (25.9)	614 (26.3)
At least one investigational product-related AESI based on selected MedDRA preferred term codes	2 (0.3)	6 (0.4)	8(0.3)
At least one investigational product-related skin reaction	3 (0.4)	7 (0.4)	10 (0.4)
At least one NOCD	4 (0.5)	1 (< 0.1)	5 (0.2)
At least one investigational product-related NOCD	0	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.

[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.

[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

MedDRA version 23.1.

AE = adverse event; AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease.

Source: Table 1.3.1.1.2, ISA, Module 5.3.5.3.

In the overall **MEDLEY** population (including preterm and CLD (CHD cohorts), the distribution ≥1 AE through at least Day 150 (up to 14 days post dose) was balanced between nirsevimab and palivizumab treatment groups (Table 31). Overall, however with a little higher percentage of ≥1 Grade 3 (or higher) AEs in the nirsevimab group (7.2% vs. 6.6%, preterm: 3.4% vs. 3.4%, CLD/CHD: 14.4% vs. 13.3%), and also more deaths: 0.8% (n=5 vs. 0.3 (n=1). In the preterm and CLD/CHD cohorts there were also more deaths in the nirsevimab group compared to palivizumab (0.5% (2) vs. 0% and 1.4% (3) vs 1.0% (1)).

Table 31 Overall Summary of Treatment-emergent Adverse Events for Overall Population, Preterm and CLD/CHD Cohorts Though at Least 150 Days Post (RSV Season 1) in MEDLEY, As-treated population

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm (< 35 wGA without CLD/CHD)		CLD/CHD	
	Palivizumab (N=304)	Nirsevimab (N=614)	Palivizumab (N=206)	Nirsevimab (N=406)	Palivizumab (N=98)	Nirsevimab (N=208)
≥ 1 event	206 (67.8)	416 (67.8)	134 (65.0)	268 (66.0)	72 (73.5)	148 (71.2)
Occurring ≤ 1 day post any dose	13 (4.3)	30 (4.9)	9 (4.4)	21 (5.2)	4 (4.1)	9 (4.3)
Occurring ≤ 3 days post any dose	37 (12.2)	77 (12.5)	27 (13.1)	52 (12.8)	10 (10.2)	25 (12.0)
Occurring ≤ 7 days post any dose	78 (25.7)	151 (24.6)	50 (24.3)	103 (25.4)	28 (28.6)	48 (23.1)
Occurring ≤ 14 days post any dose	140 (46.1)	248 (40.4)	89 (43.2)	166 (40.9)	51 (52.0)	82 (39.4)
≥ 1 IP-related event	6 (2.0)	10 (1.6)	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
≥ 1 event of ≥ Grade 3 [b]	20 (6.6)	44 (7.2)	7 (3.4)	14 (3.4)	13 (13.3)	30 (14.4)
Occurring ≤ 1 day post any dose	1 (0.3)	1 (0.2)	1 (0.5)	0	0	1 (0.5)
Occurring ≤ 3 days post any dose	4 (1.3)	2 (0.3)	2 (1.0)	0	2 (2.0)	2 (1.0)
Occurring ≤ 7 days post any dose	5 (1.6)	6 (1.0)	3 (1.5)	1 (0.2)	2 (2.0)	5 (2.4)
Occurring ≤ 14 days post any dose	10 (3.3)	14 (2.3)	3 (1.5)	2 (0.5)	7 (7.1)	12 (5.8)
≥ 1 IP-related event of ≥ Grade 3 [b]	0	0	0	0	0	0
Any AE with outcome death	1 (0.3)	5 (0.8)	0	2 (0.5)	1 (1.0)	3 (1.4)
≥ 1 serious [c] event	31 (10.2)	68 (11.1)	11 (5.3)	28 (6.9)	20 (20.4)	40 (19.2)
≥ 1 serious [c] or ≥ Grade 3 [b] event	32 (10.5)	73 (11.9)	11 (5.3)	28 (6.9)	21 (21.4)	45 (21.6)
≥ 1 IP-related serious [c] event	0	0	0	0	0	0
≥ 1 AESI based on investigator assessments	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)
≥ 1 AESI based on selected MedDRA PT codes	43 (14.1)	108 (17.6)	32 (15.5)	61 (15.0)	11 (11.2)	47 (22.6)
≥ 1 IP-related AESI based on selected MedDRA PT codes	1 (0.3)	2 (0.3)	1 (0.5)	1 (0.2)	0	1 (0.5)
≥ 1 IP-related skin reaction	2 (0.7)	2 (0.3)	1 (0.5)	1 (0.2)	1 (1.0)	1 (0.5)
≥ 1 NOCD	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)
≥ 1 IP-related NOCD	0	0	0	0	0	0
≥ 1 event related to COVID-19	2 (0.7)	10 (1.6)	1 (0.5)	8 (2.0)	1 (1.0)	2 (1.0)
≥ 1 confirmed COVID-19 [d]	2 (0.7)	9 (1.5)	1 (0.5)	7 (1.7)	1 (1.0)	2 (1.0)
≥ 1 suspected COVID-19	0	1 (0.2)	0	1 (0.2)	0	0

[b] Subjects with multiple events in the same category were counted once in that category. Subjects with events in > 1 category were counted once in each of those categories.

[c] Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal.

[d] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

[e] COVID-19 confirmed events include COVID-19 positive asymptomatic and symptomatic events.

AE = adverse event; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NOCD = new onset chronic disease; PT = preferred term; wGA = weeks gestational age.

Source: Table 14.3.2.1.1.1, MEDLEY iCSR, Module 5.3.5.1.

Overall, subjects with more than 1 SAE were more common in the nirsevimab group (11.1% vs. 10.2%), also in subjects that had ≥ 1 AE or ≥ Grade 3 event (11.9% vs. 10.5%, preterm: 6.9% vs. 5.3%, CLD/CHD: 19.2% vs. 20.4%). Overall, two subjects in the nirsevimab group (one subject each in the preterm and CLD (CHD cohort) had more than one AESI based on investigator assessment (0.3% vs. 0%) and there was also a higher percentage of subjects with more than one AESI based on selected MedDRA PT codes (17.6% vs. 14.1%). This difference was most evident in the CLD/CHD cohort where the percentage was more than double in the nirsevimab group (22.6% (47) vs. 11.2 (11).

AEs were overall balanced between the treatment groups, with small numerical imbalances, but higher percentages (>1%) of subjects receiving nirsevimab with the following PT's: pyrexia (11.6% vs. 9.9%), viral upper respiratory tract infection (4.7% vs. 3.3%), bronchiolitis (4.4% vs. 3.0%), nasal congestion (6.2% vs. 4.3%), dermatitis diaper (4.2% vs. 2.0%). The pattern of distribution was generally similar for the preterm and CLD/CHD cohorts, however there were also higher percentage of the following PT's in the nirsevimab treatment group: otitis media (2.5% (10) vs. 1.0% (2)) and nasal congestion (7.4% (30) vs. 5.3% (11)). In the CLD/CHD cohort there were also higher percentages of the following PT's in the nirsevimab group: teething (6.3% (13) vs. 3.1% (3)), rhinitis (11.5% (24) vs. 7.1% (7)), gastroenteritis (2.9% (6) vs. 1% (1), roseola (2.4% vs. 1.0%), rhinorrhoea (3.4% vs. 1.0%) and eczema (3.4% vs. 1%).

Overall, in the nirsevimab group there were more events with higher intensity by the SOC Infections and infestations; Grade 3 (3.3% (20) vs. 2.3% (7)), more Grade 4 (0.3% (2) vs. 0%), and more Grade 5 (0.5% (3) vs. 0.3% (1)). The same trend was seen in the preterm and the CLD/CHD cohorts.

Overall, in the MEDLEY study (including preterm and CLD/CHD cohorts), IP-related AEs were few and balanced and fewer for nirsevimab (1.6% and 2.0%), with a little more subject by the PT agitation (0.5% (3) vs. 0%). Adverse by time relative to dosing (1, 3, 7, 14 days post first dose) pyrexia was reported up to 14 days post dose in the nirsevimab group (1 subject within day 1, 3 and 7 and 4 subjects within day 14, 0 reports in the palivizumab group).

Overall, in the MEDLEY study (including by preterm and CLD/ CHD cohorts), numerical imbalances for AE's were generally balanced and small (including SAEs, severity). AESIs based on selected MedDRA PT codes were more common in the nirsevimab group, most markedly in the CLD/CHD cohort.

Subpopulations: < 29 wGA, CLD, and CHD

Overall, for < 29 wGA, CLD, and CHD subpopulations, the number of subjects with ≥ 1 event through at least 150 days post first dose were generally balanced between the two treatment groups (nirsevimab and palivizumab) with slightly more events in the nirsevimab group for the CHD cohort. There were overall more subjects in all three subpopulations that had ≥1 event of ≥Grade 3 in the nirsevimab group (see below). Subjects with any AE with the outcome death occurred only in the CHD cohort (nirsevimab 4.3% (3) vs. 3.0% (1) palivizumab. There were higher percentages of subjects with ≥1 AESI based on selected MedDRA codes in the nirsevimab group across all subpopulations (< 29 wGA: 18.0 % vs. 13.2%, CLD: 16.3% vs. 8.8% and CHD: 38.6% vs. 33.3%).

Table 32 Overall Summary of Treatment-emergent Adverse Events for <29 wGA, CLD, and CHD Subpopulations Through at Least 150 Days Post First Dose (RSV Season 1) in MEDLEY, As-treated Population

Subjects [a] with	Number (%) of subjects					
	< 29 wGA		CLD		CHD	
	Palivizumab (N=68)	Nirsevimab (N=128)	Palivizumab (N=68)	Nirsevimab (N=147)	Palivizumab (N=33)	Nirsevimab (N=70)
≥ 1 event	50 (73.5)	93 (72.7)	45 (66.2)	94 (63.9)	28 (84.8)	60 (85.7)
Occurring ≤ 1 day post any dose	5 (7.4)	5 (3.9)	3 (4.4)	5 (3.4)	1 (3.0)	5 (7.1)
Occurring ≤ 3 days post any dose	10 (14.7)	20 (15.6)	5 (7.4)	15 (10.2)	6 (18.2)	13 (18.6)
Occurring ≤ 7 days post any dose	23 (33.8)	31 (24.2)	18 (26.5)	30 (20.4)	11 (33.3)	22 (31.4)
Occurring ≤ 14 days post any dose	36 (52.9)	52 (40.6)	31 (45.6)	53 (36.1)	20 (60.6)	35 (50.0)
≥ 1 IP-related event	2 (2.9)	3 (2.3)	1 (1.5)	3 (2.0)	1 (3.0)	2 (2.9)
≥ 1 event of ≥ Grade 3 [b]	5 (7.4)	12 (9.4)	4 (5.9)	12 (8.2)	9 (27.3)	20 (28.6)
Occurring ≤ 1 day post any dose	0	1 (0.8)	0	1 (0.7)	0	0
Occurring ≤ 3 days post any dose	1 (1.5)	1 (0.8)	0	1 (0.7)	2 (6.1)	1 (1.4)
Occurring ≤ 7 days post any dose	1 (1.5)	2 (1.6)	0	3 (2.0)	2 (6.1)	2 (2.9)
Occurring ≤ 14 days post any dose	3 (4.4)	4 (3.1)	2 (2.9)	6 (4.1)	5 (15.2)	7 (10.0)
≥ 1 IP-related event of ≥ Grade 3 [b]	0	0	0	0	0	0
Any AE with outcome death	0	0	0	0	1 (3.0)	3 (4.3)
≥ 1 serious [c] event	9 (13.2)	17 (13.3)	10 (14.7)	18 (12.2)	10 (30.3)	24 (34.3)
≥ 1 serious [c] or ≥ Grade 3 [b] event	9 (13.2)	9 (14.8)	10 (14.7)	21 (14.3)	11 (33.3)	27 (38.6)
≥ 1 IP-related serious [c] event	0	0	0	0	0	0
≥ 1 AESI based on investigator assessments	0	0	0	0	0	1 (1.4)
≥ 1 AESI based on selected MedDRA PT codes	9 (13.2)	23 (18.0)	6 (8.8)	24 (16.3)	6 (18.2)	27 (38.6)
≥ 1 IP-related AESI based on selected MedDRA PT codes	0	1 (0.8)	0	1 (0.7)	0	1 (1.4)
≥ 1 IP-related skin reaction	1 (1.5)	1 (0.8)	1 (1.5)	1 (0.7)	0	1 (1.4)
≥ 1 NOCD	0	1 (0.8)	0	1 (0.7)	0	0
≥ 1 IP-related NOCD	0	0	0	0	0	0
≥ 1 event related to COVID-19	0	0	0	1 (0.7)	1 (3.0)	1 (1.4)

Overall, AE's By SOC and PT were generally balanced between nirsevimab and palivizumab treatment groups across the subpopulations, however more predominant in the CHD subpopulation (< 29 wGA: 72.7% (93)) vs. 73.5% (50), CLD: 63.9% (94) vs. 66.2% (45), and CHD: 85.7% (60) vs. 84.8% (28)) (Table 16). In the CHD subpopulations, there were higher percentages of AE's by the SOCs: Blood and lymphatic system disorders (8.6% vs. 3.0%), eye disorders (2.9% vs. 0%), Gastrointestinal disorders (37.1 vs. 33.3), immune system disorders (7.1% vs. 3.0%), Infections and infestations in the nirsevimab treatment group subpopulations (61.4% vs. 57.6%), Injury, poisoning and procedural complications (11.4% vs. 9.1%), investigations (15.7% vs. 12.1%), metabolism and nutrition disorders (11.4% vs. 3.0%), nervous system disorders (7.1% vs. 3.0%), skin and subcutaneous tissue disorders (38.6% vs. 21.2%), surgical and medical procedures (5.7% vs. 0%).

Adverse events by intensity (Grade 3 or more) were generally more common in the nirsevimab treatment group and for both treatment groups most predominantly in the CHD subpopulation; (Grade 3; < 29 wGA: 9.4% (12) vs. 7.4% (5), CLD: 8.2% (12) vs. 5.9% (4), and CHD: 21.4% (15) vs. 18.2% (6). Grade 4 and Grade 5 events only occurred in the CHD cohort and There were more Grade 5 in the nirsevimab group (4.3% (3) vs. 3.0% (1)). By subpopulations, also, there were a trend towards more events (with higher intensity by the SOC Infections and infestations in the nirsevimab treatment group (< 29 wGA; Grade 3: 7.0% vs. 2.9%, CLD: Grade 3: 4.8% vs. 2.9%, and CHD: Grade 3: 8.6% vs. 6.1%, Grade 4: 1.4% vs. 0 %, Grade 5: 1.4% vs. 3%).

Overall IP-related AEs occurred infrequently with small numerical imbalances between the nirsevimab and palivizumab groups. The PT rash occurred only in the nirsevimab treatment group in all

subpopulations (< 29 wGA: 0.8% (1) vs. 0%, CLD: 0.7% (1) vs. 0%, and CHD: 1.4% (1) vs. 0%), however numbers are low.

For AEs up to 14 days post first dose, in the preterm cohort, there were all over fewer in the nirsevimab group that reported at least one AE. In the CLD cohort more subjects in the nirsevimab group reported at least one AE within the first 3 days post dose (within 1 day: 2.0% (3) vs. 1.5% (1), within 3 days: 4.8% (7) vs. 1.5% (1)) compared to palivizumab. In the CHD there was no clear trend of AEs by time relative to dosing.

All-together, by < 29 wGA, CLD, and CHD subpopulations, AEs were generally balanced between nirsevimab and palivizumab treatment groups across the subpopulations, however imbalances were markedly more predominant in the CHD subpopulation.

2.6.8.5. Serious adverse event/deaths/other significant events

Serious Adverse Events

In the MELODY/Study 3 (All) Safety Pool there were overall more SAEs in the placebo group compared to nirsevimab (12.1% vs. 9.0%). By SOC there were slight numerical imbalances with more SAEs in the nirsevimab treatment group in the category Congenital, familial ang genetic disorders (0.2% (n=3) vs. 0%), ear and labyrinth disorders (1 vs. 0 subjects), general disorders and administration site conditions (0.6% (n=11) vs. 0.1% (n=1), metabolism and nutrition disorders (0.3% (n=5) vs. 0.1% (n=1), respiratory, thoracic and mediastinal disorders (0.4% (n=7) vs. 0.2% (n=2). By PT, SAEs were most commonly for nirsevimab (vs placebo) bronchiolitis (1.6% vs 3.4%), LRTI (0.9% vs 1.3%), pneumonia (0.9% vs 1.3%), gastroenteritis (0.8% vs 0.4%), and bronchitis (0.7% vs 1.2%). None of the SAEs was considered related to IP by the investigator. All-over in MELODY/Study 3 (All) Safety Pool the numbers of SAEs are small, including by PT and no meaningful trends were observed.

In the MEDLEY study there were slightly more SAEs in the nirsevimab group compared to palivizumab in the overall population (11.1% vs 10.2%), including in the preterm cohort (6.9% vs. 5.3%). In the CLD/CHD cohort SAEs were overall more frequent, and slightly more in the palivizumab group (20.4% vs. 19.2%). Generally, numbers were small, but of note, there was a higher frequency of SAEs in the nirsevimab group in the SOC of Infections and infestations (7.2% and 4.3%) including in the preterm and CLD/CHD cohort. By PT, SAE's more frequent in the nirsevimab group were most commonly bronchiolitis (1.8% (11) vs. 1.0% (3)) and gastroenteritis (0.8% (5) vs. 0.3% (1)). Also, here none of the SAEs was considered by the investigator to be IP-related.

In the < 29 wGA, CLD, and CHD Subpopulations, the frequency of SAEs was generally similar between the nirsevimab and palivizumab groups in each subpopulation, but overall, markedly higher for the CHD subgroup; < 29 wGA: (13.3% (17) vs. 13.2% (9)), CLD: (12.2% (18) vs. 14.7% (10)), and CHD: 34.3% (24) vs. 30.3% (10)). There was overall a higher frequency by the SOC Infections and infestations in the nirsevimab treatment group compared to palivizumab: (< 29 wGA: 10.2% vs. 5.9%, CLD: 9.5% vs. 7.4%, CHD: 17.1% vs. 9.1%). In the nirsevimab CHD treated subgroup, particularly SAEs by the SOCs: Infections and infestations, Cardiac disorders, and Congenital, familial and genetic disorders were more frequent compared to Palivizumab. None of the SAEs was considered by the investigator to be IP-related.

All-over in the MEDLEY study percentages of SAEs were balanced between nirsevimab and palivizumab, however more frequent in the CLD/CHD cohort and by subgroup SAEs were also markedly higher for the CHD subgroup, which can be explained by underlying complex medical conditions in these cohorts.

Overall, there was a higher percentage of SAEs the SOC infections and infestations in the nirsevimab group.

Deaths

Listing of deaths reported in Nirsevimab studies is given below:

Table 33 Listing of Deaths Reported in Nirsevimab Studies

Treatment Group Study	Study Day of Death	Cause of Death[a]	Preferred Term (Day since AE onset)	Relationship to IP
Placebo				
Study 3	343	Pericardial effusion that led to death	Pericardial effusion (1)	Not-related
Study 3	26	Nosocomial pneumonia, *E.coli meningitis*	Pneumonia (2)	Not-related
Study 3	109	Pneumonia complicated by left-sided empyema	Pneumonia (1)	Not-related
Nirsevimab				
Study 3	123	Unknown	Death (1)	Not-related
Study 3	97	Pulmonary vein stenosis	Pulmonary vein stenosis (24)	Not-related
MELODY	143	Diarrhoea	Gastroenteritis (1)	Not-related
MELODY	338	Acute gastroenteritis	Gastroenteritis (3)	Not-related
MELODY	140	Unknown	Death (0)	Not-related
MEDLEY (pre-term Cohort)	162	Severe COVID-19	COVID-19 (14)	Not-related
MEDLEY (pre-term Cohort)	52	Atrophy-caused acute bronchiolitis, which led to acute cardiovascular failure, and respiratory failure leading to death	Bronchiolitis (38)	Not-related
MEDLEY (pre-term Cohort)	19	Sudden death due to bronchopneumonia	Pneumonia (1)	Not-related
MEDLEY (pre-term Cohort)	66	Cardiogenic shock	Cardiogenic shock (2)	Not-related
MEDLEY (pre-term Cohort)	19	The cause of death is congestive heart failure, pulmonary atresia	Cardiac failure congestive (1)	Not-related
Palivizumab				
MEDLEY (CLD/CHD Cohort)	155	Respiratory insufficiency due to bronchiolitis	Bronchiolitis (8)	Not-related

[a] Cause of death as reported by the investigator. For further details, see full narratives in Section 14.4, MELODY iCSR, Module 5.3.5.1; Section 14.3.3, Study 3 CSR, Module 5.3.5.1; Section 14.4, MEDLEY iCSR, Module 5.3.5.1.
Note: no deaths occurred in Study 1 and study 2.
AE= adverse event; CHD congenital heart disease; CLD= chronic lung disease; COVID-19= coronavirus disease-2019; IP = investigational product.
Source: Table 56 , MELODY iCSR, Module 5.3.5.1; Table 46; Study 3 CSR, Module 5.3.5.1; Table 62, MEDLEY iCSR, Module 5.3.5.1.

In the MELODY/Study 3 (All) Safety Pool, overall, the percentage of deaths up to 360 days post dose in the two treatment arms (nirsevimab 0.3% (n=5) vs. placebo 0.3% (n=3)) was identical (study days of death were 26-343). In the MEDLEY study, there were 6 deaths and more deaths reported through at least 150 days post dose in the nirsevimab treated group (nirsevimab 0.8% (n=5) vs. 0.3% (1) in the

palivizumab group) (study days of deaths 19-338 days). None of the deaths was considered related to IP by the investigator.

Three deaths occurred within 3 weeks; In study 3: one death after 26 days (nosocomial pneumonia, e. coli meningitis), In the MEDLEY study (CLD/CHD cohort) two deaths after 19 days (pneumonia in an infant with medical history of atrial septal defect, coarctation of the aorta, and patent ductus arteriosus and one heart failure in an infant with medical history of cerebral ischemia, wound infection fungal, and congenital pneumonia and ongoing medical history included congenital pulmonary valve atresia with VSD, congenital arterial malformation, congenital pulmonary artery anomaly, cardiovascular insufficiency, and hypoxia. Congestive). Two deaths had an unknown cause, one in Study 3 (day 123) and one in the MELODY study (day 140). No concomitant medications were reported prior to study enrolment, besides a hepatitis B vaccine on day of birth. The subject died at home of unknown causes. An autopsy was not performed. An undiagnosed chronic condition given a history of failure to thrive, recent hospitalisation, recurrent vomiting, recurrent hypoglycaemia, and anaemia prior to death was suspected by the investigator. Two additional deaths occurred after day 360.

Other significant events

Skin Reactions and Skin Hypersensitivity Reactions

All-over, in the MELODY/Study 3 (All) Safety Pool the distribution of any skin reaction was balanced between nirsevimab and placebo treatment groups (30.3% (592/1955) vs. 30.4% (295/970), with generalised skin reactions slightly higher in the nirsevimab treatment group (15.4% (301/1955) vs. 14.3% (139/970)) and more skin reactions accompanied by any systemic symptoms (9.7% vs. 8.8%). Also, there were a little higher percentage of subjects in the nirsevimab group that had been exposed to vaccines within 14 days of onset of skin reaction. In the nirsevimab treatment group there were higher percentages of the following (>0.5% difference): skin reactions that were erythematous (15.5% vs. 14.3%) and the locations of the skin reaction were: head (7.1% vs. 5.1%), face (17.4% vs. 15.5%), arms (11.5% vs. 9.4%), hands (6.0% vs. 4.8%), legs (11.0% vs. 10.0%), Buttocks/groin (3.1% vs. 2.1%).

In the MEDLEY study there were a higher percentage of any skin reaction in the nirsevimab treatment group compared to palivizumab (18.4% (113/614) compared to 15.1% (46/304)), which included both generalised (8.1% vs. 5.9%) and symmetrical (7.8% vs. 6.6%) skin distribution. Skin reactions were mainly erythematous (8.8% vs. 8.2%) and maculo-papular (5.4% vs. 3.9%). There were also more skin reactions that were accompanied by systemic symptoms (5.0% vs. 3.3%), mainly fever (4.9% vs. 3.3%).

Generally, in the MELODY/Study 3 (All Safety Pool), numerical imbalances between nirsevimab and placebo treatment groups were small, with no meaningful trends. In the MEDLEY study there were more skin reactions in the nirsevimab treatment group.

New Onset Chronic Diseases

An NOCD was defined as a newly diagnosed medical condition of chronic, ongoing nature observed after receipt of the IP and assessed as medically significant by the investigator.

Table 34 Treatment-Emergent New Onset Chronic Disease by System Organ Class and Preferred Term Through 360 Days Post Dose (MELODY/Study 3 [All] Safety Pool)

System Organ Class Preferred Term (MedDRA version 23.1)	Number (%) of Subjects [a]		
	Placebo (N=970)	Nirsevimab (N=1955)	Total (N=2925)
Total number of TEAEs	6	5	11
Subjects with any TEAE	6 (0.6)	5 (0.3)	11 (0.4)
Endocrine disorders	**2 (0.2)**	**0**	**2 (< 0.1)**
Hypothyroidism	2 (0.2)	0	2 (< 0.1)
General disorders and administration site conditions	**0**	**1 (< 0.1)**	**1 (< 0.1)**
PFAPA syndrome	0	1 (< 0.1)	1 (< 0.1)
Respiratory, thoracic and mediastinal disorders	**4 (0.4)**	**4 (0.2)**	**8 (0.3)**
Asthma	2 (0.2)	3 (0.2)	5 (0.2)
Wheezing	0	1 (< 0.1)	1 (< 0.1)
Bronchitis chronic	1 (0.1)	0	1 (< 0.1)
Childhood asthma	1 (0.1)	0	1 (< 0.1)

Table 35 Treatment-Emergent New Onset Chronic Disease by System Organ Class and Preferred Term though 360 Days Post Dose (MELODY/Study 3 [Proposed Dose] Safety Pool)

System Organ Class Preferred Term (MedDRA version 23.1)	Number (%) of Subjects [a]		
	Placebo (N=779)	Nirsevimab (N=1559)	Total (N=2338)
Total number of TEAEs	4	1	5
Subjects with any TEAE	4 (0.5)	1 (< 0.1)	5 (0.2)
Endocrine disorders	**2 (0.3)**	**0**	**2 (< 0.1)**
Hypothyroidism	2 (0.3)	0	2 (< 0.1)
General disorders and administration site conditions	**0**	**1 (< 0.1)**	**1 (< 0.1)**
PFAPA syndrome	0	1 (< 0.1)	1 (< 0.1)
Respiratory, thoracic and mediastinal disorders	**2 (0.3)**	**0**	**2 (< 0.1)**
Bronchitis chronic	1 (0.1)	0	1 (< 0.1)
Childhood asthma	1 (0.1)	0	1 (< 0.1)

Overall, the percentage of NOCDs was low in the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool, occurring in 0.3% (5) and (< 0.1% (1)) respectively in the nirsevimab group and (0.5% (4)) and 6 (0.6% (6)) subjects in the placebo group. In the MEDLEY study NOCDs occurred more frequent in the nirsevimab group (0.3% vs. 0 %). All together NOCD were very infrequent and in no cases where they considered to be related to IP by the investigator.

Adverse Events of Special Interest by Investigator Assessment

In the MELODY/Study 3 (All) Safety Pool, AESIs (by SOC and PT) based on investigator assessments were infrequent, but comparable between nirsevimab and placebo treatment groups (0.3% (6) vs. 0.3% (3)). Most common was rash in both groups (0.2%). All events were assessed as Grade 1 in severity with the exception of one event of rash in the nirsevimab group from the MELODY study reported as a Grade 3 severity (day 6 post dose, 20 days duration) but was deemed late for the expected onset of an immediate hypersensitivity reaction. There were no events of immune complex disease reported. Also, in the MELODY/Study 3 (Proposed Dose) Safety Pool, AESI's by investigator assessment was low but comparable (0.2% (3)) subjects in the nirsevimab group vs. 0% in the placebo group. In the MEDLEY study there was an overall higher percentage of AESI's in the nirsevimab treatment group (0.3% (2) vs. 0) including in the preterm cohort (0.2% (1) vs. 0) and in the CLD/CHD cohort (0.5% (1) vs. 0%).

All-over numbers are low for AESI's by investigator assessment, and there is no convincing trend towards more AESI's of skin hypersensitivity reactions in nirsevimab treated subject

Adverse Events of Special Interest by MedDRA Preferred Term

In the MELODY/Study 3 (All) Safety Pool, AESI's by PT was generally balanced between the treatment groups (25.7% in nirsevimab vs. 26.2% in placebo, with slight numerical imbalances, but no clinically meaningful trends, including for Hypersensitivity events including anaphylactic reactions (25.1% vs. 25.9%). For thrombocytopenia however, there was a slightly higher percentage in the nirsevimab group, though numbers were small (1.0% vs. 0.5%). The trend was the same for the MELODY/Study 3 (Proposed Dose) Safety Pool.

In the MEDLEY study AESIs were overall balanced between nirsevimab and palivizumab groups (17.6% vs. 14.1%), but higher in the nirsevimab group for hypersensitivity, including anaphylaxis (16.9% vs. 13.8%) for thrombocytopenia (0.8% vs. 0.3%). In the preterm cohort there was 1 case of thrombocytopenia (0.2% vs. 0% in placebo). In the CLD/CHD cohort the percentage of total numbers of AESI's was double compared to palivizumab (22.6% vs. 11.2%), including for hypersensitivity (including anaphylaxis) (21.2% vs. 10.2%) and thrombocytopenia (1.9% vs. 1.0%).

2.6.8.6. Laboratory findings

Overall, laboratory data was sparse. In the MELODY study, laboratory data was collected on 49 subjects (32 in the nirsevimab group and 17 in the placebo group) where haematology, hepatic, and renal chemistry parameters were registered. Shifts ≥ 2 toxicity grades in haematology parameters were reported for 1 subject in the nirsevimab group (and 0 subjects in the placebo group) and no worsening for platelets specifically, bearing in mind that thrombocytopenia was included as a potential risk due to post-approval reports of severe thrombocytopenia in use of Synagis, a mAb with a similar mechanism of action as nirsevimab. Grade ≥ 3 toxicity for bilirubin was overall balanced in both nirsevimab and placebo groups (18.8% vs. 17.6%) and shifts ≥ 2 toxicity grades were evenly distributed between treatment groups. Also, no Grade ≥ 3 toxicity or shifts of ≥ 2 grades in toxicity were reported liver transaminases, and no creatinine values of Grade ≥ 3 toxicity reported.

In the MEDLEY study, clinical data included data on 33 Japanese subjects (24 in the nirsevimab group and 9 in the palivizumab group). one subject in the nirsevimab group had a Grade 3 haemoglobin toxicity which also represented a 2-grade shift from baseline, reported as an AE of iron deficiency anaemia (Grade 2 nonserious), onset Day 160, and treated with iron supplementation with resolution of anaemia after a duration of 170 days For bilirubin, Grade ≥ 3 toxicity was higher in the palivizumab group (77.8% [7/9] vs. 50.0% [12/24], including fewer Grade 3 (20.8%) and 4 (29.2%) bilirubin toxicity compared to Palivizumab (grade 3: 22.2%, Grade 4: 55.6%. Two subjects (10.5%) in the nirsevimab group (preterm cohort) had ≥ 2 grade worsening in bilirubin vs. 0 subjects in the palivizumab group. Both subjects had a reported ongoing medical history of jaundice and shifts from Grade 0 (at baseline) to 4. Otherwise no clinically meaningful trends were reported.

Laboratory AEs were reported by SOCs for the MELODY/Study 3 (All) Safety Pool and MEDLEY study. Numbers were generally low and balanced between treatment groups. Overall, there were two reports of acute kidney injury in the nirsevimab treatment groups, one in the MELODY/Study 3 (All) Safety Pool and one in the MEDLEY Study. In both cases there were concurrent severe infection. Both events were considered unrelated to IP by the investigator: Subject 1 had an acute kidney injury (bilateral pneumonia and nosocomial sepsis concurrently) Grade 3 nonserious with onset Day 87, with bilateral pulmonary vein stenosis Day 97 with cardiac failure and cardiac arrest preceding the acute kidney injury. The outcome was fatal. Subject 2 (CHD/CLD cohort) had a reported medical history of Down syndrome, atrio-ventricular septal defect, and subclinical hypothyroidism. A Grade 2 nonserious AE of acute kidney injury was reported on Day 54 concurrently with a Grade 4 SAE of septic shock during a hospitalisation for cardiac failure complicated by nosocomial pneumonia and sepsis. The subject died of cardiogenic shock on Day 66.

Vital signs

According to the CSRs of Study 3 MEDLEY and MELODY vital signs ((temperature, blood pressure, respiratory rate, and heart rate measurements) were collected at screening/day of dosing and during follow-up period.

2.6.8.7. Safety in special populations

1) Effect of Age

All together 358 subjects received nirsevimab in MELODY/Study 3 (All) Safety Pool (out of 533 subjects that were included in the subgroup analyses for neonates (< 28 Days at Randomisation)). All nirsevimab-exposed neonates received the proposed dose. Overall, the distribution of AEs was comparable between the two treatment groups, but slightly more subjects in the nirsevimab group reported at least one serious AE (14.5% vs. 12.0%) and at least one serious and/or ≥ Grade 3 severity event (15.1% vs. 12.6%). Also, there was a higher percentage of subjects in the nirsevimab group reporting at least one AESI based on investigators assessment (0.6% (n=2) vs. 0%). For age of randomisation (≤ 3.0 Months, > 3.0 to ≤ 6.0 Months, and> 6.0 Months) there were no apparent discrepancies with regards to distribution of AE's.

In the MEDLEY study, the distribution of AEs was generally balanced between the treatment arms for the subgroups of ages ≤ 3-months and > 3.0 to ≤ 6.0 Months. However, there was a higher percentage AEs in subjects in the > 6-month age subgroup in the nirsevimab treatment arm (68.7% (46/103) vs. 58.3 (21/36). There was also a higher percentage of ≥1 serious or ≥Grade 3 event (9.0% (6/67) vs. 2.8% (1/36) and 7.5% (5/67) in the nirsevimab group that had ≥ AESI based on selected MedDRA codes. There were 9.0% (6/67) vs. 0% that had ≥ 1 event related to COVID-19.

2) Effect of Body Weight

Infants < 2.5 kg on Day 1 had the highest nirsevimab exposures based on mg/kg body weight. In the MELODY/Study 3 (All) Safety pool study, the distribution of AE's was generally balanced between the treatment groups, apart from 2 IP-related events in the nirsevimab group (1.0%: decreased appetite and petechiae vs. 0/90 in the placebo group. In the MEDLEY study, even though there were fewer subjects reporting more than one AE in the nirsevimab group (64.4% vs. 73.3%, there were a higher percentage of subjects that reported ≥ 1 event of ≥Grade 3: 13.6% (8/89) compared to 0% in the Palivizumab group, and more SAEs were reported; 18.6% (11/59) in the nirsevimab group vs. 10.0% (3/30) in the Palivizumab group. Also, one death occurred in the < 2.5 kg on Day 1 subgroup in the nirsevimab group (PT: bronchiolitis).

In the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool, subjects who had weight on Day 1 < 5 kg, AEs were overall comparable in both treatment groups in < 5 kg and ≥ 5 kg on Day 1 weight groups. Grade 3 events were slightly higher in the placebo group (weight < 5 kg: 12.3% in the nirsevimab group vs. 17.2% in placebo, weight ≥ 5 kg: 7.8% in the nirsevimab group vs. 9.8 in placebo) In the nirsevimab group, subjects who had weight on Day 1 < 5 kg, there was a slightly higher percentage of subjects with an AESI based on investigators assessment: 0.3% (n=3) vs 0% in the placebo group and in subjects who had weight on Day 1 ≥ 5 kg there were two grade 5 severity AE' s (death).

In the MEDLEY study in infants, weight group ≥2.5 kg to < 5 kg the distribution was overall balanced, however a higher percentage in the nirsevimab group reported ≥ AESI based on selected MedDRA PT codes (19.9% in the nirsevimab group vs. 11.8% in the palivizumab group). In the weight group ≥ 5 kg more in the nirsevimab group reported ≥ AE (68.0% vs. 62.3%). Also, more in the nirsevimab group compared to palivizumab reported ≥ 1 event of ≥Grade 3: 6.3 (17/269) % vs. 3.8% (5/130), and SAEs: 10.0% (27/269) vs. 5.4% (7/130).

Subjects who Received Replacement Dose Following Bypass Surgery

In the MEDLEY study subjects 8 in the nirsevimab group., and 7 subjects in palivizumab group received a replacement dose In RSV Season 1 following bypass surgery. No AESIs or skin hypersensitivity reactions were reported.

Nirsevimab and Vaccines

No safety concerns were anticipated for with regards to paediatric vaccination schemes and passive immunization with nirsevimab. The safety of 6 prespecified vaccine groups (tuberculosis vaccine; influenza vaccine; measles/mumps/rubella/varicella vaccine; rotavirus vaccine; polyvalent DPT-containing vaccine, pneumococcal vaccine) when co-administered within ± 7 or ± 14 days of nirsevimab/placebo was however evaluated in the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool. Overall few subjects received a vaccination concomitantly to nirsevimab or placebo (5.9% vs. 6.0% ± 7 days of IP dosing and 20.8% vs. 22.0% within ± 14 days of IP dosing), most commonly polyvalent DPT-containing vaccine, pneumococcal vaccine, and rotavirus vaccine.

Table 36 Vaccine Exposure (MELODY/Study 3 [All] Safety Pool)

Time of dosing	Vaccine Class	Placebo (N=970)	Nirsevimab (N=1955)	Total (N=2925)
Within (±) 7 days of dosing	**Subjects with at least one dose[a], n (%)**			
	Any	58 (6.0)	115 (5.9)	173 (5.9)
	Influenza vaccine	3 (0.3)	9 (0.5)	12 (0.4)
	Measles/Mumps/Rubella/Varicella vaccine	3 (0.3)	4 (0.2)	7 (0.2)
	Pneumococcal vaccines	32 (3.3)	70 (3.6)	102 (3.5)
	Polyvalent DPT-containing vaccine (with or without polio, Hep B, Men A, Men C, Hib)	42 (4.3)	87 (4.5)	129 (4.4)
	Rotavirus vaccine	27 (2.8)	60 (3.1)	87 (3.0)
	Tuberculosis vaccine	7 (0.7)	13 (0.7)	20 (0.7)
	Number of doses received, n			
	Any	115	247	362
	Influenza vaccine	3	9	12
	Measles/Mumps/Rubella/Varicella vaccine	3	4	7
	Pneumococcal vaccine	32	70	102
	Polyvalent DPT-containing vaccine (with or without polio, Hep B, Men A, Men C, Hib)	43	91	134
	Rotavirus vaccine	27	60	87
	Tuberculosis vaccine	7	13	20
Within (±) 14 days of dosing	**Subjects with at least one dose[a], n (%)**			
	Any	213 (22.0)	407 (20.8)	620 (21.2)
	Influenza vaccine	12 (1.2)	26 (1.3)	38 (1.3)
	Measles/Mumps/Rubella/Varicella vaccine	10 (1.0)	12 (0.6)	22 (0.8)
	Pneumococcal vaccine	130 (13.4)	249 (12.7)	379 (13.0)
	Polyvalent DPT-containing vaccine (with or without polio, Hep B, Men A, Men C, Hib)	151 (15.6)	297 (15.2)	448 (15.3)
	Rotavirus vaccine	108 (11.1)	220 (11.3)	328 (11.2)
	Tuberculosis vaccine	30 (3.1)	69 (3.5)	99 (3.4)
	Number of doses received, n			
	Any	446	881	1327
	Influenza vaccine	12	26	38
	Measles/Mumps/Rubella/Varicella	10	12	22
	Pneumococcal vaccine	130	251	381
	Polyvalent DPT-containing vaccine (with or without polio, Hep B, Men A, Men C, Hib)	156	303	459
	Rotavirus vaccine	108	220	328
	Tuberculosis vaccine	30	69	99

[a] Subjects with more than one dose were counted once in each of those categories.

DPT = diphtheria, pertussis and tetanus; Hep B = hepatitis B; Hib = haemophilus influenzae type b; Men A = meningococcal A; Men C = meningococcal C.

Source: Table 1.3.2.9.1, ISA, Module 5.3.5.3.

In the MELODY/Study 3 (All) Safety Pool, there were higher percentages of subjects in the nirsevimab group vs. the placebo group that developed URTI (by PT) in proximity to IP dosing: Vaccination within 7 days before or after dosing, AE within 7 days Rotavirus vaccination: 3.3% (2/60) vs. 0% ; vaccination within 14 days before or after IP dosing, AE within 7 days Polyvalent DPT-containing vaccination: 4.7% (14/297) vs. 3.3% (5/151), pneumococcal vaccination: 4.0% (10/249) vs. 2.3% (3/130), Rotavirus vaccination: 4.1% (9/220) vs. 1.9% (2/108); vaccination within 7 days before or

after IP dosing, AE within 28 days: polyvalent DPT-containing vaccination: 20.7% (18/87) vs. 11.9% (5/42), Pneumococcal vaccination: 21.4% (15/70) vs. 9.4% (3/32), Rotavirus vaccination: 16.7% (10/60) vs. 0%, Tuberculosis vaccination: 28.6% (2/7) vs. 0% ; vaccination within 14 days before or after IP dosing, AE within 28 days: polyvalent DPT-containing vaccination: 23.6% (70/297) vs. 19.2% (29/151), pneumococcal vaccination: 22.9% (57/249) vs. 13.1% (17/130), Rotavirus vaccination: 21.4% (47/220) vs. 10.2% (11/108), Influenza vaccine: 19.2% (5/26) vs. 16.7% (2/12).

Use in Pregnancy and Lactation

Not applicable as Nirsevimab is intended for use in infants.

Overdose

Only one case of overdose was reported from the clinical trials (MEDLEY) where an infant accidently received double the dose according to weight the infant weighed 4.97 kg (100 mg IM instead of 50 mg IM). No related AE's were reported. It is acknowledged that the treatment is symptomatic in case of overdose. The applicant has no anticipation of drug abuse, withdrawal and rebound effects or effects on mental ability which is agreed.

2.6.8.8. Immunological events

Antibody-dependent Enhancement

No safety concern for development of antibody dependent enhancement (ADE) after nirsevimab was disclosed through non-clinical studies (incl. RSV challenge study in a cotton rat model of RSV infection), however as the rats were mature, and exposed to RSV infection at times of maximal circulating nirsevimab concentrations, the translability of the finding to highly immature infants is unknown**.**

In the pivotal studies, infants with prior RSV or RSV infection, receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination and children with any history of LRTI or active LRTI prior to, or at the time of, randomisation were excluded from the pivotal studies. No cases of ADE have been reported in the safety data, however in the MELODY/Study 3 (All) Safety Pool, generally, numbers of AE's of grade 3 or higher severity by SOC and PT through 360 days post dose are low.

Immunogenicity and Safety

Overall, the percentages of subjects that were ADA-positive in the 3 pivotal safety studies were low (ADA positivity was defined as a titre of $\geq$ 50 for nirsevimab). In the MELODY/Study 3 (All) Safety Pool, 5.9% (110/1880) of subjects in the nirsevimab group and 2.3% (22/942) of subjects in the placebo group were ADA positive to nirsevimab post baseline through day 361. In the MEDLEY study, numbers were small: 2.1% (12/581) subjects in the nirsevimab group and 5.2% (15/286) in the palivizumab group were ADA-positive (90% of subjects had samples available for ADA assessment at Day 151 and 38% of subjects had available samples at Day 361).

Overall, no safety concerns related to ADA were raised from safety data from the MELODY/Study 3 (All) Safety Pool or MEDLEY study (including the preterm and CLH/CHD cohorts). No related immunogenicity (IP-related AE, investigator-assessed skin hypersensitivity reaction, or AESI) was observed in ADA-positive subjects, including no immune complex diseases.

2.6.8.9. Safety related to drug-drug interactions and other interactions

Due to the mode of action of nirsevimab, no altered PK/PD relevant to safety is expected from drug-interactions. Increased adverse events of URTI was observed with nirsevimab vaccine co-administration compared with placebo vaccine co-administration.

2.6.8.10. Discontinuation due to adverse events

Discontinuations of trial product were not evaluated in Study 3 and in the MELODY study, as subjects only received a single dose. This is considered acceptable. In the MEDLEY study one subject (0.2%), a 5.2-month-old male infant in the nirsevimab group discontinued the trial permanently on Day 91 of RSV season 1 due to a Grade 1 rash assessed as a skin hypersensitivity event (AESI) after receiving a placebo dose and was resolved the same day. The infant had mistakenly received nirsevimab on Day 31 of RSV Season 1 and had no detectable ADA to nirsevimab post-baseline. Overall, 8.1% (n=50) of subjects in the MEDLEY study discontinued due to various reasons (death (n=5), lost to follow-up (n=6), withdrawal of consent (n=24), Covid-pandemic (n=11), other (n=3). In the Palivizumab treatment group, 7.1% (n=22) discontinued, hereof none due to adverse events. The number of discontinuations in the MEDLEY study were low.

2.6.8.11. Post marketing experience

None available.

2.6.9. Discussion on clinical safety

Methods

The preliminary safety evaluation was based on safety data from three pivotal studies (**Study 3**, **MELODY** and **MEDLEY**) on the use of nirsevimab (50 mg or 100 mg single IM dose) in 2569 infants in their first RSV season. The three studies included very and moderately preterm infants born ≥ 29 to < 35 wGA, term and late preterm infants born ≥ 35 wGA, and infants at higher risk for severe RSV, including preterm infants born < 35 wGA and infants with CLD/CHD. Supportive safety data from Study 1 and Study 2 was also submitted.

Safety data in term and preterm infants born ≥ 29 wGA with a safety follow-up of 360 days post dose from MELODY and study 3 were analysed in 2 pools:

The **MELODY/study 3 (All) safety pool** included pooled data of all dosed participants from Study 3 and the MELODY primary cohort ((N = 2925 dosed with either nirsevimab [n = 1955] or placebo [n = 970]) and a subpopulation

The **MELODY/Study 3 (proposed dose) safety pool** that include pooled data of subjects receiving the proposed dose (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg at the time of dosing). In study 3 those weighing < 5 kg at the time of dosing and the MELODY primary cohort (N = 2338 dosed with either nirsevimab [n = 1559] or placebo [n = 779]).

The MELODY/Study 3 (All) Safety Pool was used to evaluate the AE profile, ADRs, and potential risks comprising the largest pool of placebo-controlled data for nirsevimab, which is acceptable for this safety evaluation.

Data from the palivizumab-controlled **MEDLEY study** in infants at higher risk for severe RSV disease (including subpopulations of extremely preterm infants born < 29 wGA and infants with CLD or CHD) through at least 150 days post dose was evaluated separately due to differences in study design, which is acceptable. Overall the safety evaluation was appropriately standardised across the studies and adverse events coded using the MedDRA version 23.1, evaluations including treatment-emergent AEs, SAEs, discontinuations, NOCDs, AESIs, and skin reactions.

Dispositions, baseline demographics and characteristics of the enrolled subjects were considered acceptable for all 3 studies.

Exposure

In the MELODY/Study 3 (All) Safety Pool subjects received a single dose of nirsevimab (n=1955) or placebo (n=970). In the nirsevimab group, 70.4% (1377) received a 50 mg dose and 29.6% (578)

received a 100 mg dose. In study 3 there were to subjects that incorrectly received nirsevimab and is included in the safety analysis. In the MELODY/Study 3 (Proposed Dose) Safety Pool group, 62.9% (981) in the nirsevimab group received 50 mg and 37.1% (578) received 100 mg. In the MEDLEY study, a total of 918 subjects (nirsevimab (n=614) and palivizumab (n=304) were dosed. Almost 90% of subjects received all 5 planned doses (nirsevimab:100.0% received at least one active dose; palivizumab: 90.1% received at least 5 active doses). All-over the exposure data was considered appropriate.

Subjects from the MELODY/Study 3 (all) Safety pool was followed for 360 days and an additional follow-up is ongoing. The Primary analysis was complete when subjects in the MELODY primary cohort had been followed up through DAY 361. Subjects in the MEDLEY study were followed through DAY 150 post dose (1st RSV season) and an additional follow up is ongoing. The Primary analysis was complete when all subjects completed follow-up through DAY 151.

Adverse events

In the **MELODY/Study 3 (All) Safety Pool**, overall, the safety profile was acceptable with no safety concerns. Common AE's through 360 days post dose, were similar between the nirsevimab and placebo treatment group. Numerical imbalances with regards to AEs within the first 1,3- or 14-days post dose and severity of AE's were small and not of concern.

In the MELODY/Study 3 (All Safety Pool) the frequency of AE's by SOC in the nirsevimab was generally balanced and similar to the placebo group. AE's commonly reported by SOC (> 25% of subjects in the nirsevimab group and the placebo group) were Infections and infestations (75.1% and 77.5%); Skin and subcutaneous tissue disorders (29.6% and 29.2%); Gastrointestinal disorders (28.3% and 29.2%). AE's by PT most commonly in the nirsevimab groups were; (> 10% of subjects) respiratory tract infection (41.7% vs. 39.7%) and gastroenteritis (10.8% vs. 9.1%). AE's of grade 3 or higher severity by SOC and PT through 360 days post dose were overall similar or less in the nirsevimab group compared to placebo. In the nirsevimab group there was a higher frequency of viral pneumonia (0.4% vs. 0.1%).. in all cases of viral pneumonia (8 subjects in the nirsevimab group) RSV as the causative pathogen was excluded based on central or local RSV test. Grade 4 and 5 events were few and generally reported in one subject each in both treatment groups. Grade 4 and 5 AEs when categorised by PTs in both treatment groups were reported in one subject each, apart from death (2 subjects in the nirsevimab group) and gastroenteritis (2 subjects in the nirsevimab group). Two Grade 4 AE's in two subjects were resolved; congestive heart failure on day 30 and cardiopulmonary arrest on Day 64, both could be explained by their medical history. The frequency of participants with any IP-related AE through 360 days post dose was lower in the nirsevimab group (1.6% vs. 1.8%), mostly Grade 1-2 in severity and most commonly a reflection of mild reactogenicity. The frequency of participants with AE's by SOC and PT in 2 or more subjects by time relative to dosing within 1, 3, 7, and 14 days post dose were overall balanced between the nirsevimab and placebo groups. There was however a trend of mild but slightly enhanced reactogenicity in the nirsevimab treated group compared to placebo within one day post dose, though they occurred infrequently: pyrexia 0.2% vs. 0.1%) and injection site reactions 0.4% vs.0%. In **MELODY/Study 3 (Proposed Dose) Safety Pool**, the overall the distribution of AE's resembled the MELODY/Study (ALL) Safety Pool and was balanced between the nirsevimab and placebo treatment groups.

In the **MEDLEY study** (including preterm and CLD /CHD cohorts), the distribution ≥1 AE through at least Day 151 (up to 14 days post dose) was balanced between nirsevimab and palivizumab treatment groups. Overall, however with a little higher percentage of ≥1 Grade 3 (or higher) AE's in the nirsevimab group (7.2% vs. 6.6%, preterm: 3.4% vs. 3.4%, CLD/CHD: 14.4% vs. 13.3%), AEs were overall balanced between the treatment groups. The pattern of distribution was generally similar for the preterm and CLD/CHD cohorts. Overall, in the nirsevimab group there were more events with higher intensity by the SOC Infections and infestations; Grade 3 (3.3% vs. 2.3%), more Grade 4 (0.3% vs. 0%), and more Grade 5 (0.5% vs. 0.3%) events. The same trend was seen in the preterm and the CLD/CHD subpopulations. Overall (including preterm and CLD/CHD cohorts), IP-related AEs were few and balanced with generally lower percentages for nirsevimab. For adverse events by time relative to dosing (1, 3, 7, 14 days post first dose) pyrexia was reported up to 14 days post dose in the

nirsevimab group (1 subject within day 1, 3 and 7 and 4 subjects within day 14, 0 reports in the palivizumab group).

Overall, for < 29 wGA, CLD, and CHD subpopulations, AE's were generally balanced between nirsevimab and palivizumab treatment groups across the subpopulations, however numerical imbalances were markedly more predominant in the CHD subpopulation. AE's by SOC and PT were frequent and generally also balanced between nirsevimab and palivizumab treatment groups across the subpopulations (< 29 wGA: 72.7% vs. 73.5%, CLD: 63.9% vs. 66.2%, and CHD: 85.7% vs. 84.8%). In the CHD subpopulations, there were higher percentages of AE's by the SOCs in the nirsevimab treatment group: Blood and lymphatic system disorders (8.6% vs. 3.0%), eye disorders (2.9% vs. 0%), Gastrointestinal disorders (37.1 vs. 33.3), immune system disorders (7.1% vs. 3.0%), Infections and infestations subpopulations (61.4% vs. 57.6%), Injury, poisoning and procedural complications (11.4% vs. 9.1%), investigations (15.7% vs. 12.1%), metabolism and nutrition disorders (11.4% vs. 3.0%), nervous system disorders (7.1% vs. 3.0%), skin and subcutaneous tissue disorders (38.6% vs. 21.2%), surgical and medical procedures (5.7% vs. 0%). It is acknowledged that overall, in the CHD subpopulation in the MEDLEY study the percentage of subjects with any AE was similar in the nirsevimab (85.7%) and palivizumab (84.8%) groups. Also, it is noted that the 95% CIs for the proportions of adverse events by SOC are wide and overlapping and generally similar between the treatment groups. Moreover, there was a higher incidence of cardiac failure reported in the medical history in the nirsevimab group (18.6% vs. 9.1%) compared to palivizumab group, indicative of more severe disease in the nirsevimab group at baseline.
Some of the numerical differences, can arguable be attributed to incidental events, with no convincing trend suggestive of a safety signal that could potentially be an issue of concern.

Subjects with more than one AESI occurred more commonly in the nirsevimab group across all subpopulations. Adverse events by intensity (Grade 3 or more) were generally more common in the nirsevimab treatment group and for both treatment groups most predominantly in the CHD subpopulation. Overall, in the MEDLEY study (also by < 29 wGA, CLD, and CHD subpopulations), there is a trend of slightly more events with higher intensity by the SOC Infections and infestations in the nirsevimab treatment group.

A review of ≥Grade 3 events in SOC Infections and infestations in 25 subjects the nirsevimab treatment group was carried out. None of the events were assessed related to nirsevimab. The cases included 7 subjects in CLD subpopulation, 8 subjects in CHD subpopulation, 10 subjects in the Preterm cohort (24 - 36 weeks at gestation), 9 subjects in the < 29 wGA subpopulation (6 subjects in CLD subpopulation, 3 subjects in the Preterm Cohort with gestational age < 29 weeks). All cases occurred at between > 14 days – 260 days post nirsevimab administration.

It is acknowledged and agreed that the slightly more events with higher intensity by the SOC Infections and infestations in the nirsevimab treatment group can to some extent be explained by the underlying medical conditions and that the higher incidence of congestive heart failure at baseline in the CHD subpopulation may have contributed to the higher frequency of infections.

However, it is noted that in the < 29 wGA group 3,9% out of 7% of Grade 3 cases were the PT bronchiolitis (1.5% in the Palivizumab) group. The same was not observed in the CLD/CHD groups, however no obvious causative role of nirsevimab can be determined in this regard. No changes are required for the proposed SmPC

Serious adverse events, deaths, and other significant events

Deaths

In the MELODY/Study 3 (All) Safety Pool, overall the percentage of deaths up to 360 days post dose in the two treatment arms (nirsevimab 0.3% (n=5) vs. placebo 0.3% (n=3)) was identical (study days of death were 26-343). In the MEDLEY study, there were 6 deaths and more deaths reported through at least 150 days post dose in the nirsevimab treated group (nirsevimab 0.8% (n=5) vs. 0.3% (1) in the palivizumab group) (study days of deaths 19-338 days). None of the deaths was considered related to

IP by the investigator. Three deaths occurred within 3 weeks; In study 3: one death after 26 days, In the MEDLEY study (CLD/CHD cohort) two deaths after 19 days. Two deaths had an unknown cause, one in Study 3 (day 123) and one in the MELODY study (day 140). None of the events were likely related to nirsevimab exposure**.** Overall no safety concerns are raised from the deaths reported in this infant population. There was no suspected causality to the IP exposure and in most cases, there were complex medical conditions prior to death. It is unclear whether the overall rates of fatal events are similar to the background death rate expected in this population. A literature review of expected background incidences was provided in order to clarify whether the observed deaths reflect the expected background incidences in the respective populations, including those subjects with pulmonal affections/ pneumonia in the CLD/CHD cohort. Out of 2569 subjects dosed with nirsevimab in the pivotal studies, 10 deaths occurred through Day 361 compared with 4 deaths in the comparator arms. Of note, there was a 2:1 randomisation in all three pivotal trials. All the deaths reported in the studies were considered as not related to study treatment by the investigator. Some of the deaths occurred in countries where the neonatal mortality is relatively higher compared to other countries that were included in the pivotal studies. Causes of death were also considered to be related to e.g. frequent causes of death in those countries, e.g. gastroenteritis and diarrhoea. Hence, there is no concern that nirsevimab is associated with an increased mortality rate.

Serious Adverse Events

In the MELODY/Study 3 (All) Safety Pool there were overall more SAEs in the placebo group compared to nirsevimab (placebo 12.1% vs. nirsevimab 9.0%). By SOC there were slight numerical imbalances with more SAEs in the nirsevimab treatment group in the category Congenital, familial ang genetic disorders (0.2% vs. 0%), ear and labyrinth disorders (1 vs. 0 subjects), general disorders and administration site conditions (0.6% vs. 0.1%), metabolism and nutrition disorders (0.3 vs. 0.1%), respiratory, thoracic and mediastinal disorders (0.4% vs. 0.2%). By PT, SAEs were most commonly for nirsevimab (vs placebo) bronchiolitis (1.6% vs 3.4%), LRTI (0.9% vs 1.3%), pneumonia (0.9% vs 1.3%), gastroenteritis (0.8% vs 0.4%), and bronchitis (0.7% vs 1.2%). None of the SAEs was considered related to IP by the investigator. No meaningful trends of concern for serious adverse events were observed.

In the MEDLEY study there were overall slightly more SAEs in the nirsevimab group compared to palivizumab (11.1% vs 10.2%), including in the preterm cohort (6.9% vs. 5.3%). In the CLD/CHD cohort SAEs were more frequent, and slightly more in the palivizumab group (20.4% vs. 19.2%). Generally, percentages of SAEs were balanced between nirsevimab and palivizumab, however more frequent in the CLD/CHD cohort and by subpopulations (< 29 wGA, CLD, and CHD). SAEs were also markedly higher for the CHD subgroup (< 29 wGA: 13.3% vs. 13.2%, CLD: 12.2% vs. 14.7%, and CHD: 34.3% vs. 30.3%, which can be explained by underlying complex medical conditions in these cohorts. Overall there was a higher percentage of SAEs in the SOC infections and infestations in the nirsevimab group (overall 7.2% and 4.3%, subpopulations < 29 wGA: 10.2% vs. 5.9%, CLD: 9.5% vs. 7.4%, CHD: 17.1% vs. 9.1%). . None of the SAEs was considered by the investigator to be IP-related. It is acknowledged that in the MELODY/Study 3 (All) Safety Pool, the most frequent SAEs occurred in the SOC of Infections and infestations, with a lower incidence in the nirsevimab group compared to placebo group (6.9% vs. 10.1%) while in MEDLEY the incidence of SAEs in the SOC of Infections and infestations was higher in the nirsevimab group compared with palivizumab for the overall population (7.2% vs. 4.3%). The incidence of SAEs in this SOC was higher in the CLD/CHD cohort than in the preterm cohort, which can arguably be ascribed to more severe disease baseline in the nirsevimab treatment group. This was also reflected in the review of 30 SAE's for SOC Infections and infestations for subjects in MEDLEY in the nirsevimab group who experienced ≥ Grade 3 events in the (see assessment of responses to Q124). No specific safety concerns with regards to added risk of infections in nirsevimab use is raised.

Other significant events

- *Skin Reactions and Skin Hypersensitivity Reactions*

All-over, in the MELODY/Study 3 (All) Safety Pool the distribution of any skin reaction was balanced between nirsevimab and placebo treatment groups (30.3% vs. 30.4%), with generalised skin reactions

slightly higher in the nirsevimab treatment group (15.4% vs. 14.3%) and more skin reactions accompanied by any systemic symptoms (9.7% vs. 8.8%). Also, there were a little higher percentage of subjects in the nirsevimab group that had been exposed to vaccines within 14 days of onset of skin reaction. It is acknowledged that the percentage of subjects with generalized skin reaction is a by-subject analysis over the entire 360-day post dose reporting period and also that a subject may have had multiple skin reactions. The between-group differences are small for each location (≤ 2.1%), and are not clinically meaningful.

In the MEDLEY study there were also higher percentage of any skin reaction in the nirsevimab treatment group compared to palivizumab (18.4% compared to 15.1%), which included both generalised (8.1% vs. 5.9%) and symmetrical (7.8% vs. 6.6%) skin distribution. There were also more skin reactions that were accompanied by systemic symptoms (5.0% vs. 3.3%), mainly fever (4.9% vs. 3.3%).

Generally, in the MELODY/Study 3 (All Safety Pool), numerical imbalances between nirsevimab and placebo treatment groups were small, with no convincing clinically meaningful trends. In the MEDLEY study there were more skin reactions in the nirsevimab treatment group. It is acknowledged that CIs across the subpopulations and subject cohorts were wide and overlapping. Also, that the numerical difference in the overall population could indeed be driven by the CHD subpopulation where 32.9% vs. 18.2% reported any skin reaction through at least 150 days post first dose in the nirsevimab group compared to the palivizumab group. Hence, the difference between treatment groups could very well be driven by rash, which was more frequently reported in the nirsevimab group (11.4% vs. 6.1%) and which has been proposed to be included as an ADR occurring within 14 days in section 4.8 in the SmPC.

- *New Onset Chronic Diseases*

All together NOCD were very infrequent and in no cases where they considered to be related to IP by the investigator. No concerns of safety were raised with regards to NOCDs.

Adverse Events of Special Interest

Based on the properties of nirsevimab as monoclonal antibody, the following adverse events were considered of special interest (AESIs): hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia.

In the MELODY/Study 3 (All) Safety Pool and MELODY/Study 3 (Proposed Dose) Safety Pool, AESIs (by SOC and PT) based on investigator assessments were infrequent, but comparable between nirsevimab and placebo treatment groups (0.3% vs. 0.3% and 0.2% vs. 0%, respectively). Rash was most frequent in both groups (0.2%), hereof one Grade 3 event in the nirsevimab treatment group (MELODY study, day 6 post dose, 20 days duration). There were no events of immune complex disease reported. In the MEDLEY study there was an overall higher percentage of AESI's based on investigator assessments in the nirsevimab treatment group (0.3% (2) vs. 0) including in the preterm cohort (0.2% (1) vs. 0) and in the CLD/CHD cohort (0.5% (1) vs. 0%). All-over numbers are low for AESI's by investigator assessment, and there is no convincing trend towards more AESI's of skin hypersensitivity reactions in nirsevimab treated subject, and no concern of such are raised. In the MELODY/Study 3 (All) Safety Pool, AESI's by PT was generally balanced between the treatment groups (25.7% in nirsevimab vs. 26.2% in placebo, with slight numerical imbalances, but no clinically meaningful trends, including for Hypersensitivity events including anaphylactic reactions (25.1% vs. 25.9%). For thrombocytopenia however, there was a slightly higher percentage in the nirsevimab group, though numbers were small (1.0% vs. 0.5%). The trend was the same for the MELODY/Study 3 (Proposed Dose) Safety Pool. In the MEDLEY study AESIs were overall balanced between nirsevimab and palivizumab groups (17.6% vs. 14.1%), but higher in the nirsevimab group for hypersensitivity, including anaphylaxis (16.9% vs. 13.8%), for thrombocytopenia (0.8% vs. 0.3%). In the preterm cohort there was 1 case of thrombocytopenia (0.2% vs. 0% in placebo). In the CLD/CHD cohort the percentage of total numbers of AESI's was double compared to palivizumab (22.6% vs. 11.2%), including for hypersensitivity (including anaphylaxis) (21.2% vs. 10.2%) and thrombocytopenia (1.9% vs. 1.0%). No SAEs of anaphylaxis attributable to nirsevimab were reported. Across the 3 studies, 25

cases of AESI thrombocytopenia (by SOC) in 24 subjects were reported in the nirsevimab treatment group. All cases were of Grade 1 og 2 severity, non-serious and only one event of petechiae was considered related to nirsevimab by the investigator. The cases included 12 events of contusion reported, 2 events of thrombocytopenia with alternate explanations (Heparin induced thrombocytopenia and Thrombocytopenia secondary to nosocomial sepsis), 2 events of hematoma related to trauma or concomitant medication, 6 events of epistaxis, 2 events of petechiae. Based on the review of cases of the AESI thrombocytopenia (by SOC) in the nirsevimab treatment group, no inclusion of thrombocytopenia to the SmPC is currently warranted.

Laboratory findings (and vital signs)

Overall laboratory data was sparse and included a total of 82 subjects (**MELODY study**: 49 subjects (32 nirsevimab/17 placebo), **MEDLEY study**: 33 Japanese subjects (24 nirsevimab/9 palivizumab)). Overall, no safety concerns were raised with regards to haematological, hepatic or renal toxicity grade shifts. Shifts ≥ 2 toxicity grades in haematology parameters were reported for 1 subject in the nirsevimab group (and 0 subjects in the placebo group) and no worsening for platelets specifically, bearing in mind that thrombocytopenia was included as a potential risk due to post-approval reports of severe thrombocytopenia in use of Synagis. Laboratory related AE's were reported by SOCs for the **MELODY/Study 3 (All) Safety Pool** and **MEDLEY study**. Numbers were generally low and balanced between treatment groups. Overall, no safety concerns were raised for laboratory-related AEs within Blood and lymphatic system disorders, Hepatobiliary disorders, Investigations or Renal and urinary disorders. Across the studies (Study 3, MEDLEY and MELODY), vital signs ((temperature, blood pressure, respiratory rate, and heart rate measurements) were collected at screening/day of dosing and during follow-up period. No differences were observed between treatment groups. Abnormal physical examination findings were recorded as an AE and no other observations related to safety were reported across the 3 studies.

Safety in special populations

- *Effect of Age*

All together 533 subjects were included in the subgroup analyses, hereof 358 subjects received nirsevimab in **MELODY/Study 3 (All) Safety Pool.** For age at randomisation (⩽ 3.0 Months, > 3.0 to ⩽ 6.0 Months, and> 6.0 Months) there were no apparent discrepancies with regards to distribution of AE's. . Overall, through 150 days post first dose, the incidences of AEs, ≥ Grade 3 AEs, and SAEs were numerically lower in nirsevimab group than the palivizumab group in neonates (< 28 Days at Randomisation), besides from subjects with at least one AESI based on selected MedDRA PT where the frequency was higher in the Nirsevimab treatment group compared to Palivizumab (28.3% (13/46) vs. 17.2% (5/29)). Furthermore, **no IP-related events** were reported in either treatment group for AEs, ≥ Grade 3 AEs, SAEs, AESI based on MedDRA PT, and skin reactions. No safety concerns are raised. In the **MEDLEY study**, the distribution of AE' s was generally balanced between the treatment arms for the subgroups of ages ⩽ 3-months and > 3.0 to ⩽ 6.0 Months. Overall, in the **MEDLEY study** there is a trend for more adverse events in neonates > 6-months in the nirsevimab treatment arm (68.7% vs. 58.3). In the CLD subpopulation, for the nirsevimab treatment group there is only a higher frequency of subjects with at least one adverse event in the ≤ 3.0 months age group (67.6% vs. 50%). In the CHD subpopulation, for the nirsevimab treatment group there is only a higher frequency of subjects with at least one adverse event in the > 3.0 to ≤ 6.0 months age group (85.2% vs. 63.6%). No clinically meaningful explanation can be concluded from this observation. Also, for severity there were higher percentage of ⩾1 serious or ⩾Grade 3 event (9.0% vs. 2.8%) for nirsevimab. There were 9.0% vs. 0% that had ⩾ 1 event related to COVID-19. In the MELODY study, COVID-19 related events in both treatment groups were all nonserious grade 1-2 severity events with onset ranging from Day 218 to Day 353. In the MEDLEY study, COVID-19 related events included some of greater severity (one Grade 3, one Grade 4 and one Grade 5) and with onset of events ranged from Day 66 to Day 357. It is

acknowledged that the MEDLEY study population had underlying comorbidities which could explain the higher severity grades.

As the latency of onset of COVID-19 related events in MELODY and MEDLEY was well after dosing of nirsevimab with the earliest onset in the nirsevimab group on Day 218 and Day 66, respectively, no interference of nirsevimab administration with COVID-19 infection was reported.

. An additional review of cases suggestive of reactogenicity (within 1 day, within 3 days and within 7 days for age groups ≤ 3-months and > 3.0 to ≤ 6.0 months) did not suggest any anticipation of more serious events in infants> 6-month.

- *Effect of Body Weight*

Infants < 2.5 kg on Day 1 had the highest nirsevimab exposures based on mg/kg body weight. In the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool, subjects who had weight on Day 1 < 5 kg, had AE's (including by severity) that were overall comparable in both treatment groups in < 5 kg and ⩾ 5 kg on Day 1 weight groups. In the nirsevimab group, subjects who had weight on Day 1 < 5 kg, there was a slightly higher percentage of subjects with an AESI based on investigators assessment: 0.3% vs 0% in the placebo group. In the MEDLEY study in infants, weight group ⩾2.5 kg to < 5 kg the distribution was overall balanced, however a higher percentage in the nirsevimab group reported ⩾ AESI (19.9% vs. 11.8%). In the weight group ⩾ 5 kg, more in the nirsevimab group reported ⩾ AE (68.0% vs. 62.3%). Also, more in the nirsevimab group compared to palivizumab reported ⩾ 1 event of ⩾Grade 3: 6.3 % vs. 3.8%, and SAEs: 10.0% vs. 5.4%. All-over there is a trend towards enhanced severity of AE's in infants < 2.5 kg on Day 1. It is noted that in the MEDLEY study, (subjects < 2.5 kg on Day 1 (N = 89; Nirsevimab N =59, Palivizumab N=30)), the incidence of enhanced severity AEs (≥ 1 serious or ≥ Grade 3 severity event) was 18.6% (n= 11) in the nirsevimab group, compared to 10% (3 subjects) in the palivizumab group. Among the 11 subjects in the nirsevimab group, 16 events were serious or ≥ Grade 3 severity and of these 10/16 events were associated with infections and the remaining 6/16 events included exacerbation of underlying medical condition etc. From the cases described, no dose-dependent toxicity is suspected.

Nirsevimab and Vaccines

The safety of 6 prespecified vaccine groups when co-administered within ± 7 or ± 14 days of nirsevimab/placebo was evaluated in the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool. The single most frequently reported AEs in the nirsevimab group compared to placebo (within 7- and 28-days post vaccination) for subjects who received a vaccine within 7 or 14 days of dosing were pyrexia and URTI. Overall few subjects received a vaccination concomitantly to nirsevimab or placebo (5.9% vs. 6.0% ± 7 days of IP dosing and 20.8% vs. 22.0% within ± 14 days of IP dosing), most commonly polyvalent DPT-containing vaccine, pneumococcal vaccine, and rotavirus vaccine.

In the MELODY/Study 3 (All) Safety Pool, there were higher percentages of subjects in the nirsevimab group vs. the placebo group that developed URTI (by PT) in timely association to IP dosing. A grading of severity for all AE's was carried out according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events, including in subjects that experienced URTI. A summary provided of URTI by severity post co-administration of any vaccine for the MELODY/Study 3 (All) Safety Pool, show an overall similar frequency of URTI onset within 28 days post vaccine administration (9.6% (11/115) in the nirsevimab treatment group compared to (10.3% (6/58) in the placebo group (vaccine received within 7 and 14 days of IP dosing)). There were no URTI events of ≥ Grade 3 severity in either of the treatment groups. It is reassuring that there are no events of Grade 3 severity

Numerical imbalances with higher frequencies were observed specifically for co-administration with rota-virus vaccine, polyvalent diphtheria-poliomyelitis-tetanus containing vaccine and pneumococcal vaccine. For the rota-virus vaccine, the frequency of URTI onset within 28 days post vaccine administration was 11.7% in the nirsevimab group compared to 3.7% in the placebo group. For

polyvalent diphtheria-poliomyelitis-tetanus vaccine the frequency of URTI onset within 28 days post vaccine administration was 12.6% in the nirsevimab group compared to 2.4% in the placebo group. For pneumococcal vaccine the frequency of URTI onset within 28 days post vaccine administration was 11.4% in the nirsevimab group compared to 3.1% in the placebo group.

Immunological events

No safety concern for development of antibody dependent enhancement (ADE) after nirsevimab was disclosed through non-clinical studies and in the pivotal studies. Infants with prior RSV or RSV infection, receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination and children with any history of LRTI or active LRTI prior to, or at the time of, randomisation were excluded from the pivotal studies. No cases suggestive of ADE have been reported in the safety data. It is acknowledged that the risk of developing ADE in infants treated with nirsevimab is considered to be low based on preclinical and clinical evidence, and biological plausibility. The applicant does not find additional pharmacovigilance activities beyond routine pharmacovigilance warranted, as they are not expected to yield additional information beyond what has been provided, especially given the Day 361 to 511 follow-up data. Also, the applicant is of the opinion that ADE should not be considered an important potential risk based on theoretical considerations. This is considered acceptable.
Overall, the percentages of subjects that were ADA-positive in the 3 pivotal safety studies were low and no safety concerns related to ADA were raised and no related immunogenicity (IP-related AE, investigator-assessed skin hypersensitivity reaction, or AESI) was observed in ADA-positive subjects, including no immune complex diseases.

Safety related to drug/drug Interactions

Due to the mode of action of nirsevimab, no altered PK/PD relevant to safety is expected from drug-interactions.

Discontinuation due to adverse events

Discontinuations were not evaluated in Study 3 and in the MELODY study, as subjects only received a single dose, which was acceptable. In the MEDLEY study, the number of discontinuations were low and overall acceptable. Only one subject (0.2%) in the nirsevimab group discontinued permanently. In the Palivizumab treatment group, 7.1% (n=22) discontinued, none attributed to adverse events. Overall, 8.1% (n=50) of subjects in the MEDLEY study discontinued due to various reasons (death (n=5), lost to follow-up (n=6), withdrawal of consent (n=24), Covid-pandemic (n=11), other (n=3, one subject with hepatomegaly and jaundice discontinued due to ethical considerations in a vulnerable population, another subject was unable to come to the study site. A third subject was early terminated due to wrong cohort assignment (CLD/CHD instead of Preterm cohort) but was reallocated to the Preterm Cohort with a data change form.)

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of nirsevimab is adequately characterised and is acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 37 Summary of safety concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	Long term safety

2.7.2. Pharmacovigilance plan

Table 38 Ongoing and planned additional pharmacovigilance activities

Study [Status]	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates for EMA**
Category 1 - Not applicable				
Category 2 – Not applicable				
Category 3 - Required additional pharmacovigilance activities				
A Phase 3 Randomized, Double- blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants (MELODY). **Study Code:**-D5290C00004. **Status:** Ongoing	To evaluate safety and efficacy of MEDI8897.	Long term safety	Final report	Q4 2023
A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY). **Study Code:**-D5290C00005. **Status:** Ongoing	To evaluate safety and tolerability of MEDI8897 compared to palivizumab.	Long term safety	Final report	Q4 2023

2.7.3. Risk minimisation measures

Table 39 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term Safety	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: MELODY (D5290C00004) MEDLEY (D5290C00005)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will use the EBD to determine the forthcoming Data Lock Points.

2.8.3. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.4. Labelling exemptions

Not applicable.

2.8.5. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Beyfortus (nirsevimab) is included in the

additional monitoring list as it contains a new active substance which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is:

Beyfortus is indicated to immunise infants from birth entering their first Respiratory Syncytial Virus (RSV) season for the prevention of RSV lower respiratory tract disease.

The aim of the therapy is to reduce the risk of RSV infection and hospitalisation of RSV infection.

The primary endpoint in the pivotal trials were medically attended RSV lower respiratory tract infection. Secondary endpoint was hospitalisation, and one of the exploratory endpoints was severe RSV determined by hospitalisation AND requirement of oxygen supplement or intra venous fluid.

3.1.2. Available therapies and unmet medical need

The only approved treatment for severe RSV disease is ribavirin for inhalation, licensed in several EU countries, the United Kingdom, and the USA.

The only currently approved prophylaxis for RSV is palivizumab (Synagis; USA approval 1998, EU approval 1999), licensed only for infants who are at the highest risk for severe RSV disease (ie, preterm infants born at $\leq$ 35 wGA under 6 months of age at the start of the RSV season, children < 2 years of age with CLD of prematurity or hemodynamically significant CHD). With a half-life of approximately 1 month, palivizumab must be administered monthly (IM injection) throughout the RSV season. The burden of monthly healthcare visits during the season can be a barrier to compliance, diminishing the benefits of palivizumab (Wong et al 2018). National recommendations for use are more restrictive. As palivizumab is indicated only for use in the relatively small population of higher-risk infants, its effect on limiting the total disease burden of RSV infection is limited.

3.1.3. Main clinical studies

Three clinical studies have been conducted in three different populations to support the MAA.

MELODY (phase 3) and Study 3 (phase 2b) are of similar design (2:1 randomised double-blind placebo-controlled trials). Both studies included subjects entering their first RSV season. MELODY (n=1490) included subjects with a gestational age from week 35, and Study 3 (n=1453) included subjects with a gestational age from week 29+0 to week 35.

Additionally, a phase II/III study (MEDLEY) included preterm infants born < 35 wGA (without CLD or CHD) and term and preterm infants with CLD or CHD. This study provided data to the extrapolation of efficacy.

3.2. Favourable effects

The primary endpoint (MA RSV LRTI) during 150 days post dose, was statistically significant in MELODY and Study 3. As such, the relative risk reduction was 74.5% (95% CI: 49.6%, 87.1%) in MELODY (GA >35+0 weeks) and 70.1% (95% CI: 52.3%, 81.2%) in Study 3 (GA 29+0 to 35 weeks). This was based on an event rate of 12/994 in the nirsevimab group and 25/496 in the placebo group in MELODY, and 25/969 in the nirsevimab group and 46/484 in the placebo group in Study 3.

In the cohort of preterm children with GA < 35 weeks in MEDLEY, the event rates were similar with nirsevimab and palivizumab (0.5% in both groups), and numerically lower for nirsevimab than palivizumab in high-risk infants with CLD or CHD (1.0% and 2.0%).

For the secondary endpoint (MA RSV LRTI and hospitalisation), the difference between treatment arms was not statistically significant in MELODY but was lower for nirsevimab than placebo in Study 3. In MEDLEY, the event rate was lower for nirsevimab than palivizumab in subjects with CLD/CHD. For the exploratory endpoint (severe RSV), defined as hospitalisation and requirement of oxygen supplementation or intra venous fluid, the results in MELODY were not statistically significant, whereas a statistically significant difference in Study 3 was observed. As such in MELODY, 5/994 subjects (0.5%) in nirsevimab and 7/496 subjects (1.4%) in placebo met the endpoint with a relative risk reduction of 64.2% (-12.1%;88.6%) with nirsevimab compared to placebo. In Study 3, the estimate was numerically higher, and 4/969 subjects (0.4%) and 16/484 subjects (3.3%) met the endpoint, and the relative risk reduction was 87.5% (62.9%;95.8%).

PK matching has been established between MEDLEY and MELODY.

3.3. Uncertainties and limitations about favourable effects

Across the three studies, the minimum gestational age was 22 weeks, and the minimum bodyweight at dosing was 1.6 kg and minimum age at dosing was 0.03 months (~1 day).

Across the 3 studies, 41 extremely preterm infants (≤29 weeks gestational age) received nirsevimab within the first 3 months of life. Only 1 subject (29 weeks gestational age) received nirsevimab below 1 month of age, 12 subjects between 1 and 2 months of age and none of the children with GA of 24-25 weeks received nirsevimab below 3 months chronological age. As discussed in the pharmacology section the minimum postmenstrual age at dosing was 7.4 months. Data is therefore limited in extremely preterm children (gestational age ≤29 weeks) exposed to nirsevimab during the first 2 months of life, which is reflected in the SmPC.

It is understood that the complete possible weight range for the target population might not be covered in clinical trials. However, it might be unreasonable to excluded children in the extreme low weight band from therapy. Based on modelling, the Applicant has proposed that the dose in children from 1 kg – 5 kg should be 50 mg. Due to the mechanism of action; the efficacy is considered similar in children with a bodyweight below 1 kg. In the SmPC it is stated that no data in children below 1 kg exists and that the dosing is based on modelling in children with a bodyweight from 1.0-1.6 kg, and the lack of data is therefore sufficiently reflected in the SmPC.

3.4. Unfavourable effects

Safety was characterised from three pivotal studies (**Study 3**, **MELODY** and **MEDLEY**) on the use of nirsevimab (50 mg or 100 mg single IM dose) in 2569 infants in their first RSV season. As no non-clinical studies raised concern of safety concerns related to nirsevimab, the potential risks were based on the pharmacological class effect of immunoglobulins (including mAbs) and thus included focus on

adverse events as immediate hypersensitivity (including anaphylaxis) and immune complex disease as AESI's. This also included thrombocytopenia as such events were reported in post-approval use of SYNAGIS® (palivizumab).

In the MELODY/Study 3 (All Safety Pool) the frequency of AE's by SOC and PT in the nirsevimab was generally balanced and similar to the placebo group. AE's by PT most commonly in the nirsevimab groups were; (> 10% of subjects) respiratory tract infection (41.7% vs. 39.7%) and gastroenteritis (10.8% vs. 9.1%). In the nirsevimab group there was a higher frequency of viral pneumonia (0.4% vs. 0.1%). in all cases of viral pneumonia (8 subjects in the nirsevimab group) RSV as the causative pathogen was excluded based on central or local RSV test. AE's of grade 3 or higher severity through 360 days post dose were also overall similar or less in the nirsevimab group compared to placebo, and grade 4 and 5 events were few and generally reported in one subject each in both treatment groups (nirsevimab group: death: 2 subjects and gastroenteritis: 2 subjects). The frequency of participants with any IP-related AE through 360 days post dose was lower in the nirsevimab group (1.6% vs. 1.8%), mostly Grade 1-2 in severity and most commonly a reflection of mild reactogenicity. There was however a trend of mild but slightly enhanced reactogenicity in the nirsevimab treated group compared to placebo within one day post dose, though they occurred infrequently. In MELODY/Study 3 (Proposed Dose) Safety Pool, the overall distribution of AE's resembled the MELODY/Study (ALL) Safety Pool and was balanced between the nirsevimab and placebo treatment groups. In the MEDLEY study (including preterm and CLD /CHD cohorts), the distribution ≥1 AE through at least Day 151 (up to 14 days post dose) was balanced between nirsevimab and palivizumab treatment groups, however with a little higher percentage of ≥1 Grade 3 (or higher) AE's in the nirsevimab group. Overall, in the nirsevimab group there were more events with higher intensity by the SOC Infections and infestations; For adverse events by time relative to dosing (1, 3, 7, 14 days post first dose) pyrexia was reported up to 14 days post dose in the nirsevimab group with 0 reports in the palivizumab group).

Overall, for < 29 wGA, CLD, and CHD subpopulations, AE's were frequent but generally balanced between nirsevimab and palivizumab treatment groups across the subpopulations, however numerical imbalances were markedly more predominant in the CHD subpopulation in the nirsevimab treatment group. Adverse events by intensity (Grade 3 or more) were generally more common in the nirsevimab treatment group and for both treatment groups most predominantly in the CHD subpopulation.

In the MELODY/Study 3 (All) Safety Pool, the overall percentage of **deaths** was the same in the two treatment arms (nirsevimab 0.3% (n=5) vs. placebo 0.3% (n=3)). In the MEDLEY study, there were more deaths in the nirsevimab treated group (0.8% (n=5) vs. 0.3% (n=1)). None of the deaths was considered related to IP by the investigator and in most cases, there were complex medical conditions prior to death.

There were overall more **SAEs** in the placebo group compared to nirsevimab in the **MELODY/Study 3 (All) Safety Pool** (placebo 12.1% vs. nirsevimab 9.0%), most commonly reported for the nirsevimab (vs placebo) were bronchiolitis, LRTI, pneumonia, gastroenteritis, and bronchitis. None of the SAEs was considered related to IP by the investigator. In the **MEDLEY study** there were overall slightly more SAEs in the nirsevimab group compared to palivizumab (11.1% vs 10.2%), including in the preterm cohort (6.9% vs. 5.3%). In the CLD/CHD cohort SAEs were more frequent, and slightly more in the palivizumab group (20.4% vs. 19.2%). Generally, percentages of SAEs were balanced between nirsevimab and palivizumab, however more frequent in the CLD/CHD cohort and by subpopulations (< 29 wGA, CLD, and CHD). SAEs were also markedly higher for the CHD subgroup. Overall, there was a higher percentage of SAEs in the SOC infections and infestations in the nirsevimab group (overall 7.2% vs. 4.3%; subpopulations < 29 wGA: 10.2% vs. 5.9%, CLD: 9.5% vs. 7.4%, CHD: 17.1% vs. 9.1%). None of the SAEs was considered by the investigator to be IP-related.

Skin reactions in the MELODY/Study 3 (All) Safety Pool was generally balanced between nirsevimab and placebo treatment groups (30.3% vs. 30.4%). Also, there were a little higher percentage of subjects in the nirsevimab group that had been exposed to vaccines within 14 days of onset of skin reaction. In the MEDLEY study there were also higher percentage of any skin reaction in the nirsevimab treatment group compared to palivizumab (18.4% compared to 15.1%).

AESI's (hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopenia) based on investigator assessments were infrequent in MELODY/Study 3 (All) Safety Pool and MELODY/Study 3 (Proposed Dose) Safety Pool, and comparable between nirsevimab and placebo treatment groups. There were no events of immune complex disease reported. In the MELODY/Study 3 (All) Safety Pool, there was a slightly higher percentage of thrombocytopenia (AESI's by PT) in the nirsevimab group (1.0% vs. 0.5%). In the MEDLEY study AESIs were overall balanced between nirsevimab and palivizumab groups, but higher in the nirsevimab group for hypersensitivity, including anaphylaxis (16.9% vs. 13.8%) and for thrombocytopenia (0.8% vs. 0.3%). In the preterm cohort there was 1 case of thrombocytopenia in the nirsevimab group. In the CLD/CHD cohort the percentage of total numbers of AESI's was double compared to palivizumab (22.6% vs. 11.2%), including for hypersensitivity (including anaphylaxis) (21.2% vs. 10.2%) and thrombocytopenia (1.9% vs. 1.0%). In the MEDLEY study there was an overall higher percentage of AESI's based on investigator assessments in the nirsevimab treatment group (0.3% (2) vs. 0) including in the preterm cohort and in the CLD/CHD cohort.

3.5. Uncertainties and limitations about unfavourable effects

Safety in special populations

Regarding the **effect of age;** in the MELODY/Study 3 (All) Safety Pool, for age at randomisation (≤ 3.0 Months, > 3.0 to ≤ 6.0 Months, and> 6.0 Months) there were no apparent discrepancies with regards to distribution of AE's. In the MEDLEY study, the distribution of AE's was generally balanced between the treatment arms for the subgroups of ages ≤ 3-months and > 3.0 to ≤ 6.0 Months. Overall, in the MEDLEY study there is a trend for more adverse events in neonates > 6-months in the nirsevimab treatment arm. Also, for severity there were higher percentage of ≥1 serious or ≥Grade 3 event for nirsevimab. There were more subjects in the nirsevimab group that had ≥ 1 event related to COVID-19. As the latency of onset of COVID-19 related events in MELODY and MEDLEY was well after dosing of nirsevimab with the earliest onset in the nirsevimab group on Day 218 and Day 66, respectively, no interference of nirsevimab administration with COVID-19 infection was reported. A review of cases suggestive of reactogenicity did not suggest any anticipation of more serious adverse events in infants> 6-month even though infants> 6-month age subgroup that has a more developed immune system and thus potential for reactogenicity.

Regarding the **effect of weight**; infants < 2.5 kg on Day 1 had the highest nirsevimab exposures based on mg/kg body weight. All-over there is a trend towards enhanced severity of AE's in infants < 2.5 kg on Day 1 and it is unclear whether this could reflect a potential toxicity due to higher nirsevimab exposure. However, in the MEDLEY study, among the 11 subjects in the nirsevimab group experiencing enhanced severity AE's, 16 events were serious or ≥ Grade 3 severity and of these 10/16 events were associated with infections and the remaining 6/16 events included exacerbation of underlying medical condition etc. From the cases described, no dose-dependent toxicity is suspected.

In the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool, subjects who had weight on Day 1 < 5 kg, had AE's (including by severity) that were overall comparable in both treatment groups for < 5 kg and ⩾ 5 kg on Day 1 weight groups. In the MEDLEY study in infants, weight group ⩾2.5 kg to < 5 kg the distribution was overall balanced, however a higher percentage in the nirsevimab group reported ⩾ AESI. In the weight group ⩾ 5 kg, more in the

nirsevimab group reported ⩾ AE. Also, more in the nirsevimab group compared to palivizumab reported ⩾ 1 event of ⩾Grade 3. From a review of data and numerical differences, some can arguable be attributed to incidental events, with no convincing trend suggestive of a safety signal that could potentially be an issue of concern was observed.

Regarding **nirsevimab and vaccine-co administration**, the safety of 6 prespecified vaccine groups when co-administered within ± 7 or ± 14 days of nirsevimab/placebo was evaluated in the MELODY/Study 3 (All) Safety Pool and the MELODY/Study 3 (Proposed Dose) Safety Pool. Overall few subjects received a vaccination concomitantly to nirsevimab or placebo (5.9% vs. 6.0% ± 7 days of IP dosing and 20.8% vs. 22.0% within ± 14 days of IP dosing. In the MELODY/Study 3 (All) Safety Pool, there were higher percentages of subjects in the nirsevimab group vs. the placebo group that developed URTI (by PT) in timely association to IP dosing. There were no URTI events of ≥ Grade 3 severity in either of the treatment groups.

Immunological events

No safety concern for development of **ADE** after nirsevimab was disclosed through non-clinical studies (incl. RSV challenge study in a cotton rat model of RSV infection) and no cases of suggestive ADE have been reported in the safety data. The risk of developing ADE in infants treated with nirsevimab is considered to be low based on preclinical and clinical evidence, and biological plausibility. No additional pharmacovigilance activities beyond routine pharmacovigilance are warranted, as they are not expected to yield additional information beyond what has been provided, especially given the Day 361 to 511 follow-up data. ADE is not considered an important potential risk based on theoretical considerations.

As nirsevimab appears to compete with human polyclonal antibodies for binding to neutralizing epitopes in the F protein (Ngwuta 2015), there is a potential risk that masking of epitope site Ø/zero might impact subsequent natural anti-RSV immune responses in nirsevimab-treated infants (Zhu 2017). It is acknowledged that there were no signs of this in cotton rats, but as the animals were mature, and exposed to RSV infection at times of maximal circulating nirsevimab concentrations, the transferability of the finding to highly immature infants are unknown (report ID8897-0032). Measures for follow up on infants treated with nirsevimab to monitor their immunity towards RSV should be included in the RMP.

Laboratory findings

Overall laboratory data was sparse and included only a total of 82 subjects in all three studies (MELODY study (32 nirsevimab/17 placebo), MEDLEY study (24 nirsevimab/9 palivizumab)). Overall, no safety concerns were raised with regards to haematological, hepatic or renal toxicity grade shifts (or laboratory related AE's). Given that cases of thrombocytopenia were reported post-approval for Synagis, thrombocytopenia should be included in the safety specifications as an important potential risk for nirsevimab.

3.6. Effects Table

Table 40. Effects Table for Beyfortus; Indicated to immunise infants from birth entering their first Respiratory Syncytial Virus (RSV) season for the prevention of RSV lower respiratory tract disease.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			Nirsevimab	**Placebo**		
MA RSV LRTI	MA RSV LRTI through 150 days post-dose	Ev/N; RRR (95% CI)	12/994 74.5% (49.6;87.1)	25/496	**SoE**: Primary endpoint. Central RT-PCR verified + PE findings required. Symptoms evaluated through RSV season **Unc**: Severity of disease not evaluated.	*MELODY* Infants born ≥35 wGA
			25/969 70.1% (52.3, 81.2)	46/484		*Study 3 (all included subjects):* Infants born ≥29 to <35 wGA
MA RSV LRTI with hospitalisation	MA RSV LRTI with hospitalisation through 150 days post dose	Ev/N; RRR (95% CI)	6/994 62.1% (-8.6, 86.8)	8/496	**SoE:** Key secondary endpoint **Unc**: hospitalisation prone to external factors	*MELODY* Infants born ≥35 wGA
			8/969 78.4% (51.9, 90.3)	20/484		*Study 3 (all included subjects):* Infants born ≥29 to <35 wGA
MA RSV LRTI (very severe)	MA RSV LRTI with hospitalisation through 150 days post-dose req suppl 0_2 or IV fluids	Ev/N; RRR (95% CI)	5/994 64.2 (-12.1;88.6)	7/496	**SoE**: More objective measure for severe disease **Unc**: Exploratory endpoint, not multiplicity controlled	*MELODY* Infants born ≥35 wGA
			4/969 87.5% (62.9, 95.8)	16/484		*Study 3 (all included subjects):* Infants born ≥29 to <35 wGA
			Nirsevimab	**Palivizumab**		
MA RSV LRTI	MA RSV LRTI through 150 days post-dose	Ev/N IR (95% CI)	4/616 (0.18;1.65)	3/309 (0.20;2.81)	**Unc**: Exploratory analysis. Not multiplicity controlled. Efficacy based on extrapolation from MELODY. **SoE**: Overall population	MEDLEY
			2/407) (0.06;1,76)	1/208 (0.01; 2.65)	Preterm	
			2/209 (0.12;3.41)	2/101 (0.24;6.97)	CLD/CHD	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			Nirsevimab (N=1955)	**Placebo** (N=970)		
TEAEs	Treatment emergent adverse events	%	86.8	86.8	Healthy infants.	MELODY/Study 3 (all) safety pool: term and preterm infants born ≥29 wGA
SAEs	Serious adverse events		9	12.1		
AESIs	Adverse events of special interest		25.7	26.2		
Related AESI			0.6	0.4		
Related TEAEs			1.6	1.8		
Related skin reaction			0.7	0.6		
Deaths		N (%)	5 (0.3)	3 (0.3)		
			Nirsevimab	**Palivizumab**		
TEAEs	Treatment emergent adverse events	%	Preterm (<35 wGA w/o CLD/CHD)[a] (N=406): 66.0	Preterm (<35 wGA w/o CLD/CHD)[a] (N=206): 65.0	CLD/CHD: infants with chronic lung disease and congenital heart disease	MEDLEY Primary analysis RSV season 1
			CLD/CHD[b] (N=208): 71.2	CLD/CHD[b] (N=98): 73.5		
SAEs	Serious adverse events		6.9 [a]	5.3 [a]		
			19.2 [b]	20.4 [b]		
AESIs	Adverse events of special interest		15.0 [a]	15.5 [a]		
			22.6[b]	11.2[b]		
Related AESI			0.2 [a]	0.5 [a]		
			0.5[b]	0[b]		
Related AE			1.5 [a]	1.9 [a]		
			1.9[b]	2.0[b]		
Related skin reaction			0.2 [a]	0.5 [a]		
			0.5[b]	1.0[b]		
Deaths		N (%)	2 (0.5) [a]	0 [a]		
			3 (1.4) [b]	1 (1.0) [b]		

Abbreviations: MA RSV LRTI: medically attended RSV lower respiratory tract infection; RRR: relative risk reduction; AESI: adverse events of special interest: hypersensitivity (including anaphylaxis),

immune complex disease, and thrombocytopenia. CLD: chronic lung disease; CHD: congenital heart disease. [a] Preterm (<35 wGA without CLD/CHD) [b] Chronic lung disease/congenital heart disease.
Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In term and preterm infants (GA>week 29), there was a clinically relevant effect on MA RSV LRTI. Furthermore, in preterm infants (GA between week 29 and 35), a clinically relevant effect on severe RSV defined as RSV hospitalisation and requirement of oxygen supplementation or intravenous fluid was shown. In infants with GA > 35 weeks the effect was not statistically significant, but the estimate pointed in the same direction, and the lack of statistical significance is considered due to the low event rate. No clinical data exist on children with a bodyweight below 1.6 kg, however based on modelling and extrapolation of efficacy and safety, the drug is considered suitable for this subgroup. Exposure in infants <1kg is although anticipated to yield higher exposures than in those weighing more, and the benefits and risks of nirsevimab use in infants <1kg should be carefully considered.

In high-risk infants (preterm or term/preterm with CLD/CHD) the effect was numerically similar between nirsevimab and palivizumab.

The safety profile of nirsevimab is overall considered acceptable based on the data provided from the pivotal safety studies; Study 3, MELODY and MEDLEY. Generally, the safety profile was expected to share pharmacological class effect of immunoglobulins (including mAbs) and thus included focus on adverse events as immediate hypersensitivity (including anaphylaxis) and immune complex disease as adverse events of special interest (AESI's). This also included thrombocytopenia as such events were reported in post-approval use of Synagis (palivizumab).

In the MELODY/Study 3 (All Safety Pool) and MELODY/Study 3 (Proposed Dose) Safety Pool the safety profile was overall balanced between nirsevimab and placebo treatment group and considered acceptable. In the MEDLEY study (including preterm and CLD /CHD cohorts), AE's were overall balanced between nirsevimab and palivizumab treatment groups, however with slightly more Grade 3 or higher severity AE's, SAEs, deaths (none considered related), AESI's and skin reactions in the nirsevimab group. The higher rates of adverse events were mainly driven by events in the CLD/CHD cohorts, most notably the CHD subpopulation. Across subpopulations (< 29 wGA, CLD, and CHD), AE's were frequent but generally balanced between nirsevimab and palivizumab treatment groups, however numerical imbalances were markedly more predominant in the CHD subpopulation in the nirsevimab treatment group. Some of the numerical differences, can arguable be attributed to incidental events, but no convincing trend suggestive of a safety signal that could potentially be an issue of concern was observed.

Adverse events by intensity (Grade 3 or more) were generally more common in the nirsevimab treatment group and for both treatment groups most predominantly in the CHD subpopulation. SAEs were balanced between nirsevimab and palivizumab, also more frequent in the CLD/CHD cohort and by subpopulations (< 29 wGA, CLD, and CHD), but markedly higher for the CHD subgroup. Overall, there was a higher percentage of SAEs in the SOC infections and infestations in the nirsevimab group. The incidence of SAEs in this SOC was higher in the CLD/CHD cohort than in the preterm cohort, which can arguably be ascribed to more severe disease baseline in the nirsevimab treatment group. No specific safety concerns with regards to added risk of infections in nirsevimab use is raised. In the CLD/CHD cohort the percentage of total numbers of AESI's was double compared to palivizumab, including for

hypersensitivity and thrombocytopenia, also most likely due to more severe disease baseline in the nirsevimab treatment group.

Regarding the **effect of age** in the MEDLEY study there is a trend for more adverse events in neonates > 6-months in the nirsevimab treatment arm. Also, there were more subjects in the nirsevimab group that had ≥ 1 AE related to COVID-19. As the latency of onset of COVID-19 related events in MELODY and MEDLEY was well after dosing of nirsevimab with the earliest onset in the nirsevimab group on Day 218 and Day 66, respectively, no interference of nirsevimab administration with COVID-19 infection was reported. A review of cases suggestive of reactogenicity did not suggest any anticipation of more serious adverse events in infants> 6-month even though infants> 6-month age subgroup has a more developed immune system and thus potential for reactogenicity.

Regarding the **effect of weight**; infants < 2.5 kg on Day 1 had the highest nirsevimab exposures based on mg/kg body weight. All-over there is a trend towards enhanced severity of AE's in infants < 2.5 kg on Day 1 but from the cases described, no dose-dependent toxicity is suspected.

Regarding **nirsevimab and vaccine-co administration**, overall few subjects received a vaccination concomitantly to nirsevimab or placebo. In the MELODY/Study 3 (All) Safety Pool, there were higher percentages of subjects in the nirsevimab group vs. the placebo group that developed URTI (by PT) in timely association to IP dosing.

3.7.2. Balance of benefits and risks

The provided data on nirsevimab has overall shown a beneficial effect on medically attended RSV LTRI and on severe RSV. The safety profile of nirsevimab is overall acceptable and in line with an expected safety profile according to the pharmacological class effect.

3.8. Conclusions

The overall benefit/risk balance of Beyfortus is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Beyfortus is favourable in the following indication(s):

"Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

Beyfortus should be used in accordance with official recommendations."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable

- **Obligation to conduct post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that nirsevimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0296/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.