swissmedic

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Swiss Public Assessment Report

Beyfortus

International non-proprietary name: nirsevimab
Pharmaceutical form: solution for injection in pre-filled syringe
Dosage strength(s): 100 mg/1 mL, 50 mg/0.5 mL
Route(s) of administration: intramuscular use
Marketing authorisation holder: Sanofi-Aventis (Suisse) SA
Marketing authorisation no.: 69039
Decision and decision date: approved on 22 December 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHD	Congenital heart disease
CI	Confidence interval
CL	Clearance
CLD	Chronic lung disease
C_{max}	Maximum observed plasma/serum concentration of drug
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
EC90	90% effective concentration
EMA	European Medicines Agency
ERA	Environmental risk assessment
Fc	Fragment crystallisable
FDA	Food and Drug Administration (USA)
GA	Gestational age
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IM	Intramuscular
INN	International non-proprietary name
IP	Investigational product
ITT	Intention-to-treat
LoQ	List of Questions
LRTI	Lower respiratory tract infection
MA	Medically attended
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NIRS	Nirsevimab
NO(A)EL	No observed (adverse) effect level
PALI	Palivizumab
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PFS	Pre-filled syringe
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)

PT	Preferred term
RMP	Risk management plan
RRR	Relative risk reduction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SOC	System Organ Class
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
URTI	Upper respiratory tract infection
WCB	Working cell bank
wGA	Weeks gestational age
YTE	Triple amino acid substitution

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for nirsevimab in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease.

2.2.2 Approved indication

Beyfortus is indicated for the prevention of lower respiratory tract disease caused by the respiratory syncytial virus (RSV) in:

i. neonates and infants entering or during their first RSV season.
ii. toddlers up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season (see *"Warnings and precautions", "Clinical efficacy" and "Pharmacokinetics"*).

Beyfortus should be used in accordance with available official recommendations.

2.2.3 Requested dosage

Neonates and infants: first RSV season
Single IM dose of 50 mg or 100 mg depending on body weight (< 5 kg or ≥ 5 kg).

Toddlers who remain vulnerable to severe RSV disease: second RSV season
The recommended dose is a single dose of 200 mg given as two intramuscular injections (2 x 100 mg).

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 November 2022
Formal control completed	17 November 2022
List of Questions (LoQ)	24 March 2023
Response to LoQ	22 June 2023
Preliminary decision	20 September 2023
Response to preliminary decision	17 November 2023
Final decision	22 December 2023
Decision	approval

3 Medical context

The human respiratory syncytial virus (RSV) causes acute respiratory tract disease in persons of all ages and is the most common cause of acute lower respiratory tract infection (LRTI) in young children. Almost all children are infected by 2 years of age, and reinfection is common. Young children, particularly infants below 6 months, and adults over 65 years of age are the most affected by RSV-associated severe disease.
RSV bronchiolitis is the most common lower respiratory tract infection in infants and leads to the hospitalisation of 1-2% of the annual birth cohort as a result of respiratory insufficiency and/or inadequate fluid intake.

RSV infection is usually a self-limited process that results in no apparent long-term pulmonary sequelae. However, in infancy it has been associated with recurrent wheezing in some patients and with persistent decreased pulmonary function and chronic obstructive pulmonary disease in adulthood. Although mortality rates in healthy infants with RSV pneumonia are less than 0.5%, they can reach up to 60% in untreated immunocompromised children.[1]
Paediatric patients at risk for severe lower respiratory tract disease include infants younger than 6 months of age, infants and children with chronic lung disease or congenital heart disease, preterm infants born before 35 weeks gestation, and immunocompromised patients.
RSV typically causes seasonal outbreaks throughout the world. In the Northern Hemisphere, these usually occur from October/November to April/May, with a peak in January or February. Disruption of the typical seasonal pattern of RSV may result in off-season outbreaks. During the coronavirus disease 2019 (COVID-19) pandemic, mitigation measures (e.g. mask wearing, physical distancing, school closures) were associated with marked reductions in non-COVID-19 respiratory infections in children, including RSV, during the winter season.

Therapy for RSV LRTI is primarily supportive. Supportive care includes frequent monitoring of clinical status and provision of fluid and respiratory support as necessary.
Standard strategies to reduce the risk of a viral infection include hand hygiene, avoiding contact, and minimising passive smoking.
Vaccines for the elderly have been recently approved by the EMA and FDA, and the recombinant bivalent prefusion F protein vaccine is also indicated for maternal immunisation to prevent infant RSV disease.
Immune prophylaxis with palivizumab, a humanised monoclonal antibody against the RSV F glycoprotein, is available. It decreases the risk of hospitalisation due to severe RSV disease among preterm infants and those with chronic lung disease and haemodynamically significant congenital heart disease. It needs to be administered monthly throughout the RSV season (5 times from the onset of the season).
Nirsevimab is a recombinant neutralising human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) to the prefusion conformation of the RSV fusion (F) protein. It has been engineered with a triple amino acid substitution (YTE) in the fragment crystallisable (Fc) region to extend serum half-life.

[1] Asner, Sandra MD*; Stephens, Derek MSc†; Pedulla, Paul BFc*; Richardson, Susan E. MD, FRCPC‡§; Robinson, Joan MD, FRCPC¶; Allen, Upton MBBS, MSc, FRCPC*. Risk Factors and Outcomes for Respiratory Syncytial Virus–related Infections in Immunocompromised Children. The Pediatric Infectious Disease Journal 32(10):p 1073-1076, October 2013. | DOI: 10.1097/INF.0b013e31829dff4d

4 Quality aspects

4.1 Drug substance

Nirsevimab is a recombinant neutralising human immunoglobulin G1 kappa (IgG1κ) long-acting monoclonal antibody to the prefusion conformation of the respiratory syncytial virus (RSV) fusion protein. Nirsevimab is a glycoprotein (molecular weight approx. 150 kDa, including glycosylation) composed of 2 identical heavy chains and 2 identical light chains covalently linked with inter-chain disulphide bonds.

Nirsevimab is produced in CHO-K1 Chinese hamster ovary cells. A two-tiered cell banking system of master cell bank and working cell bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The cell culture fluid is harvested, and purification is performed with a series of chromatography, ultrafiltration/diafiltration, viral inactivation, and viral filtration steps.

The cell culture and purification processes for nirsevimab drug substance are both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for the drug substance, including changes to the manufacturing site and production scale. However, comparability studies, including batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the nirsevimab drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, clinical experience, batch analysis, and stability data, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of nirsevimab drug substance were provided. All specific analytical methods are described and adequately validated.

No significant changes were observed during storage of nirsevimab drug substance under the proposed storage conditions.

4.2 Drug product

Nirsevimab drug product is a sterile, preservative-free, liquid dosage form intended for intramuscular injection. It is supplied as a single-dose pre-filled syringe (PFS) in two presentations: 50 mg or 100 mg of nirsevimab per pre-filled syringe. The 50 mg presentation has a 0.5 mL label-claim volume, the 100 mg presentation has a 1.0 mL label-claim volume.
The drug product is aseptically filled into a 1mL long Luer Lock glass syringe and stoppered with an elastomeric plunger stopper.
All excipients (L-histidine, L-histidine hydrochloride monohydrate, L-arginine hydrochloride, sucrose, polysorbate 80, water for injection) are of compendial grade and commonly used for the formulation of biopharmaceuticals. None of the excipients are of animal or human origin.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.

Compatibility studies were conducted to establish the in-use stability of diluted drug product with the intended materials and conditions of use.

The drug product manufacturing process consists of bioburden-reduction filtration of the formulated drug substance, sterile filtration and aseptic filling, stoppering, visual inspection, labelling, assembly, and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including development batches, clinical batches, and process validation batches, were provided. Batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are validated.

The pre-filled syringe sub-assembly (PFS-SA) primary container closure consists of 2 components: a 1 mL long glass Luer-Lock syringe and an elastomeric plunger stopper coated with a fluoropolymer film on the drug product contact surface. 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 materials of the type I glass syringe barrel and the plunger stopper meet compendial requirements.

The nirsevimab drug product is stored at 2°C to 8°C. The stability data support a shelf life of 24 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

Regarding the marketing authorisation application for Beyfortus (nirsevimab), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment report (EMA/CHMP/647783/2022) that was provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Beyfortus in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered to be sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

Based on the ERA, the risk to the environment is low.

6 Clinical aspects

6.1 Clinical pharmacology

Bioanalytical methods: Validated bioanalytical methods were used for the determination of nirsevimab in serum and for the assessment of immunogenicity, which were in agreement with the current regulatory requirements. The assays performed adequately during bioanalysis of subject samples.

Biopharmaceutics: The MELODY, Study 3, MEDLEY, and MUSIC clinical studies were performed with the same liquid formulation as the commercial formulation, with the exception that the presentation was a glass vial. While the commercial prefilled syringe (PFS) was not used in clinical studies, analytical comparability studies demonstrated that the PFS (commercial presentation) is comparable to the vial (registration clinical study material).

ADME

Absorption

Following intramuscular administration, the maximum concentration was reached within 6 days (range 1 to 28 days) and the estimated absolute bioavailability was 85% based on population PK analyses.

Distribution

Based on population PK analyses, the estimated central and peripheral volumes of distribution of nirsevimab were 249 mL and 241 mL, respectively, for an infant weighing 5 kg. The volume of distribution increases with increasing body weight.

Metabolism

Nirsevimab is a human IgG1κ monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and is not metabolised by hepatic enzymes.

Elimination

As a typical monoclonal antibody, nirsevimab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance at the doses tested clinically. The estimated clearance of nirsevimab was 3.38 mL/day for an infant weighing 5 kg and the terminal half-life was approximately 69 days.

Dose proportionality

The pharmacokinetics of nirsevimab were dose-proportional in infants and adults following administration of clinically relevant intramuscular doses over a dose range of 25 mg to 300 mg

Special populations

Renal impairment

As a typical IgG monoclonal antibody, nirsevimab is not cleared renally due to its large molecular weight; a change in renal function is not expected to influence nirsevimab clearance. However, an increase in nirsevimab clearance was noted in 1 paediatric patient with nephrotic syndrome.

Hepatic impairment

As IgG monoclonal antibodies are not primarily cleared via the hepatic pathway, a change in hepatic function is not expected to influence nirsevimab clearance. However, in clinical studies an increase in nirsevimab clearance was observed in some paediatric patients with chronic liver disease, which can be accompanied by a loss of protein.

Race

Based on population PK analyses, race had no clinically relevant effect.

Interactions

No interaction studies have been performed. Monoclonal antibodies do not typically have significant interaction potential as they do not directly affect cytochrome P450 enzymes and are not substrates of hepatic or renal transporters.

Extrapolation of efficacy

The PK-based extrapolation of efficacy to higher-risk populations in MEDLEY and MUSIC entering their first RSV season and vulnerable to severe RSV disease entering their second season is based on the following assumptions:

- Comparable viral aetiology between the paediatric populations healthy preterm and term infants, and the higher-risk populations.
- No expected difference in the mechanism of action based on subgroup (age or medical condition) since nirsevimab acts by binding a protein on the causative pathogen (RSV) and does not bind any endogenous targets in animals or humans.
- Similar expected exposure-response relationship between nirsevimab serum concentration and RSV neutralising ability across all subgroups. Similar expected safety across subgroups since nirsevimab does not bind to any internal targets.

The exposure metric $AUC_{baseline\ CL}$ with a value of 12.8 day*mg/mL was established in early studies as the target PK parameter to be used for the efficacy extrapolation for the MEDLEY and MUSIC studies. Efficacy was considered to be demonstrated if serum nirsevimab exposures in MEDLEY and MUSIC were at or above this target exposure metric in >80% of the study population throughout a 5-month period.

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%)

Source: MEDI8897-MALRTI-ER-22Sep2021.Rmd
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

The target threshold of more than 80% of the study subject population with a $AUC_{baseline\ CL}$ value at or above the value of 12.8 day*mg/mL was met.

Extrapolation results for paediatric subjects in MUSIC by season – full data set

	Season 1 (N = 46)	Season 2 (N = 50)	Total (N = 96)
$AUC_{baseline\ CL} \geq$ Target	33 (71.7%)	39 (78.0%)	72 (75.0%)
$AUC_{baseline\ CL} <$ Target	13 (28.3%)	11 (22.0%)	24 (25.0%)

Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)

For the full data set, the target threshold of more than 80% of the study subject population with a $AUC_{baseline\ CL}$ value at or above the value of 12.8 day*mg/mL was not met.

Notably, several subjects were identified with unexpectedly low nirsevimab concentrations. presumably due to protein-losing conditions (such as nephrotic syndrome or protein-losing enteropathy) in some cases, which may have caused a more rapid decline of nirsevimab concentrations due to an increase in nirsevimab clearance. Excluding these subjects, the following results are obtained:

Extrapolation results for paediatric subjects in MUSIC by season – excluding outliers

	Season 1 (N = 41)	Season 2 (N = 41)	Total (N = 82)
$AUC_{baseline\ CL} \geq$ Target	33 (80.5%)	38 (92.7%)	71 (86.6%)
$AUC_{baseline\ CL} <$ Target	8 (19.5%)	3 (7.3%)	11 (13.4%)

Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)

When excluding outliers, the target threshold of more than 80% of the study subject population with a $AUC_{baseline\ CL}$ value at or above the value of 12.8 day*mg/mL was met.

6.2 Dose finding and dose recommendation

In non-clinical efficacy studies, nirsevimab serum concentrations of 6.8 µg/mL (EC90) were shown to result in a 3-log decrease in RSV titres in cotton rat lungs.
PopPK modelling using healthy adult and preterm infant data predicted that a single fixed 50 mg intramuscular (IM) dose will sustain serum concentrations above the target level of 6.8 µg/mL in the majority of infants over the entire RSV season. This dose was used and shown to be efficacious in the Phase 2b Study 3 in preterm infants (29 to < 35 weeks gestational age (GA)) in their first RSV season. Model-based analyses of the Phase 2b clinical PK and efficacy data identified a projected serum $AUC_{baseline\ CL}$ of 12.8 day*mg/mL as the protective exposure threshold.
Although the fixed 50 mg dose resulted in clinically efficacious exposures for 97% of infants weighing < 5 kg in Study 3, this dose was suboptimal for infants weighing ≥ 5 kg in this study. To optimise the exposure, (i.e. to achieve exposures above the serum Q1 efficacy target) in infants weighing ≥ 5 kg, a double dose of 100 mg was proposed and used in the subsequent studies.
Nirsevimab exposures in MELODY (primary cohort) were above the target in > 95% of infants in both weight groups (i.e., < 5 kg and ≥ 5 kg), with similar exposures in infants with or without medically attended RSV-confirmed LRTI (MA RSV LRTI).

A single fixed 200 mg dose of nirsevimab was proposed for subjects entering their second RSV season based on the expected body weight range (8-15 kg). The dosing regimen was predicted to result in at least 80% of the population achieving exposures above the target exposure.
Day 151 nirsevimab serum concentrations were all above the non-clinical EC_{90} threshold of 6.8 µg/mL in MELODY and MEDLEY and were similar across the 2 studies and across sub-groups for Season 1 data. For Season 2 data (subjects receiving 200 mg), serum levels were elevated; in view of the simulation results these elevated levels would still be considered safe.

The above described approach and the doses used in the phase 3 studies are acceptable. The pivotal and supportive clinical studies used the proposed doses, with the exception of Study 3, in which infants with a body weight over 5 kg received 50 mg (half of the proposed dose, as described above).

6.3 Efficacy

Two pivotal studies (Study 3, MELODY) and 2 further supportive studies (MEDLEY, MUSIC) with descriptive efficacy results were submitted in support of this application. MEDLEY provided exploratory efficacy results and PK data to support extrapolation of efficacy results from the pivotal studies to infants eligible for palivizumab. MUSIC was conducted in immunosuppressed subjects.

The design of the pivotal studies Study 3 and MELODY was similar. Pooled secondary efficacy endpoint analysis was pre-specified and the results are described with the results of the MELODY study.

Study 3 (D5290C00003) was a Phase 2b, multicentre, randomised, double-blind, placebo-controlled single-dose study conducted between 2016 and 2018.
The primary objective of the study was to assess the efficacy of nirsevimab in healthy preterm infants entering their first RSV season for the reduction of medically attended LRTI due to reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed RSV compared to placebo. Protocol-defined criteria for LRTI and MA LRTI can be found in the attached information for healthcare professionals.
As a secondary objective, reduction of hospitalisations due to RT-PCR-confirmed RSV compared to placebo was evaluated. Further secondary objectives assessed safety, PK, and immunogenicity, while healthcare utilisation and caregiver burden were estimated as exploratory objectives.
Healthy infants born between 29 weeks 0 days and 34 weeks 6 days gestational age (GA) were included in the study. The enrolled preterm infants were not eligible for palivizumab; thus the placebo control was acceptable.
Subjects were randomised 2:1 to receive a 50 mg intramuscular (IM) dose of nirsevimab or placebo. Notably, this is half of the proposed dose for infants with a bodyweight ≥5kg. The placebo was commercially available saline.
A total of 1453 preterm infants born ≥ 29 to < 35 weeks gestational age (wGA) were randomised (ITT population) to nirsevimab (N = 969) or placebo (N = 484). Overall, the majority of subjects were White (72.2%) and not Hispanic or Latino (78.2%), and more than half of the subjects were male (52.4%). Mean wGA at birth was 32.7 weeks, 35.2% of subjects were born at ≥ 29 to ≤ 32 wGA, and 64.8% of subjects were born at > 32 wGA. The median weight at Day 1 was 4.4 kg. The infant with the lowest weight in the nirsevimab groups was 1.6 kg. A total of 59.5% (59.1% in the nirsevimab arm and 60.3% in the placebo arm) of subjects weighed < 5 kg at the time of dosing.
The mean age at randomisation was 3.29 months with min. 0.1 month, and max. 11.9 months. Subjects were recruited in both hemispheres; Northern Hemisphere: 68.0% and Southern Hemisphere: 32.0%. A total of 94.1% of subjects completed the study.
Baseline characteristics were well balanced between the groups regarding race, sex, age, weight/birth weight, gestational age, and also regarding whether it was a multiple birth/or not.
The primary endpoint was met by 2.6% (225/969) of the subjects in the nirsevimab group and 9.5% (46/484) of the subjects in the placebo group, resulting in a relative risk reduction (RRR) in the incidence of medically attended RSV-confirmed LRTI (MA RSV LRTI) through to 150 days post-dose of 70.1% (95% CI: 52.3%, 81.2%, p < 0.0001). The absolute risk reduction was 6.9% (95% CI 4.1, 9.7).
Subgroup analyses of the primary efficacy endpoint (incidence of medically attended RSV-confirmed LRTI through to 150 days post dose) mostly showed consistent results for hemisphere, age at randomisation, weight at birth, weight at Day 1, gestational age, and siblings enrolled in the study. However, a lower RRR was observed in males compared to females: 62.3% (95% CI 29.4%, 79.8%) and 82.1% (95% CI 62.0%, 91.5%), respectively. Additionally, in the subgroup of age over 6 months at randomisation and in infants with a birthweight over 2.5 kg the confidence intervals (CIs) were wide

and included 0 or even exceeded 0. In both groups the number of patients and thus the number of events were low, which could account for the above findings.
Further, in the predefined subgroup of infants weighing ≥ 5 kg at Day 1, a lower efficacy of 58.5% (22.7%, 77.7%) was observed. Additional PK exposure-efficacy analyses showed that an increased dose of 100 mg in infants ≥ 5 kg would result in similar exposures to exposures following administration of 50 mg in participants weighing <5kg with a predicted improvement in efficacy. (See also section 6.2. Dose Finding)
An important secondary efficacy endpoint was the incidence of RSV-confirmed LRTI hospitalisation, as the aim of prophylaxis is to prevent severe RSV LRTI. The rate of hospitalisations in the nirsevimab group was lower than in the placebo group, with an incidence of 0.8% (8/969) in the nirsevimab and 4.1% (20/484) in the placebo group. RRR in the incidence of RSV-confirmed LRTI hospitalisations through to 150 days post-dose was 78.4% (95% CI: 51.9%, 90.3%) when compared to placebo (p = 0.0002). Due to the low baseline hospitalisation incidence rates, the effect is considered modest, although the impact of nirsevimab is clinically meaningful.
For a tabular presentation of the primary endpoint- and the secondary endpoint-results, please refer to the attached information for healthcare professionals (Table 2 and Table 3).
MELODY (D5290C00004) is an ongoing Phase 3, multicentre, randomised, double-blind, placebo-controlled, single-dose study to determine if nirsevimab will prevent medically attended RSV-confirmed lower respiratory tract infection (MA RSV LRTI) in late preterm and term infants born ≥ 35 weeks 0 days GA entering their first RSV season.
MELODY had a similar design to Study 3, with the exception that it enrolled term/late preterm infants born ≥ 35 weeks 0 days GA, and the proposed dose was used for all subjects.
Primary and secondary efficacy endpoints were also the same as for Study 3, using the same case definitions.
Enrolment into MELODY was paused due to the impact of the COVID-19 pandemic. The study plan was changed via a protocol amendment to mitigate the largely reduced circulation of RSV due to the pandemic-related measures. In agreement with regulatory authorities, the analysis of the primary endpoint was based on the sample size randomised to that point, which meant half of the initially planned sample size. These 1490 subjects were designated as the ‘primary cohort’. The statistical power for the primary efficacy endpoint was maintained (above 90%). However, the statistical power for the secondary efficacy endpoint, MA RSV LRTI with hospitalisation, was reduced. Notably, sample size calculation for the secondary efficacy endpoint was not in place.
A further protocol amendment allowed completion of the initial sample size in the safety cohort.

In total, 1490 subjects were randomised in the primary cohort (994 to nirsevimab; 496 to placebo), with 1478 (99.2%) subjects being dosed and the majority of subjects completing the Day 151 efficacy follow-up (98.3% nirsevimab; 98.4% placebo).
The demographic and key baseline characteristics were similar between the nirsevimab and placebo groups. Overall, 53.5% of subjects were White, 89.8% were not Hispanic or Latino, and 51.6% were male. The median age at randomisation was 2.60 months (range: 0.03 to 11.10 months). Most subjects had a birth weight of > 2.5 kg (85.4% in the nirsevimab group; 82.3% in the placebo group) and were term infants with a gestational age ≥ 37 weeks (86.7% in the nirsevimab group; 84.6% in the placebo group). No infants below 1.8 kg on Day 1 were enrolled in the study.
Three subjects in the nirsevimab group (0.3%) and none in the placebo group had Down syndrome. One subject in the placebo group (0.2%) and none in the nirsevimab group had cystic fibrosis.

Based on the primary analysis of the incidence of MA RSV LRTI, a single IM dose of nirsevimab demonstrated efficacy with an RRR of 74.5% (95% CI: 49.6%, 87.1%) through to 150 days post-dose when compared with placebo (p < 0.0001) in healthy infants born ≥ 35 weeks 0 days GA.
Markedly lower baseline incidence rates of MA RSV LRTI could be observed than in Study 3, most likely due to the pandemic restrictions: 1.2% (12/994) in the nirsevimab group and 5% (25/496) in the placebo group. Absolute risk reduction was 3.8% (95%CI 1.8, 5.9). The incidence of MA RSV LRTI was lower in the nirsevimab group compared to the placebo group, both in the inpatient setting (0.6% vs 1.6%) and the outpatient setting (0.6% vs 3.4%).
Supplementary analyses of the incidence of MA RSV LRTI through to 150 days post-dose in the primary cohort using different methods for imputation of missing data and additional sensitivity

analyses exploring the impact of COVID-19 disruptions demonstrated consistent results with the primary analysis.
Subgroup analyses for the primary endpoint of the incidence of MA RSV LRTI through to Day 150 post-dose in the ITT1 population by sex and age at onset showed generally consistent results. The exception was the slightly higher rate of MA RSV LRTI between 3-6 months of age in the nirsevimab arm in the subgroup of infants younger than 3 months at randomisation (incidence rates were 1.4% in the nirsevimab group versus 1.1% in the placebo group). Also, relatively low point estimates were seen in subgroups with lower weight at birth (≤ 2.5 kg), lower weight on Day 1 (< 5 kg), younger age at randomisation (≤ 3 months), and siblings enrolled in study (yes); however, the number of events were small (with wide overlapping CIs for the RRRs).
The key secondary endpoint, MA RSV hospitalisation through to 150 days post-dose, was not significant (RRR 62.1%; 95% CI -8.6% to 86.8%; p = 0.0708). Only in the pre-specified pooled secondary analysis of MELODY (primary cohort) and Study 3 using a multiplicity-protected hierarchical testing did nirsevimab reduce the incidence of MA RSV LRTI with hospitalisation through to 150 days post-dose versus placebo (RRR of 73.5%, 95% CI: 50.2%, 85.9%; p < 0.0001).

Based on the results of both pivotal studies, nirsevimab was clinically active against both the RSV A and RSV B subtypes.

MEDLEY (D5290C00005) is an ongoing double-blind, Phase 2/3 study to evaluate the safety and PK of nirsevimab in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2). Efficacy was assessed descriptively.
The study has 2 cohorts: (1) the preterm cohort enrolled preterm infants ≤ 35 wGA without chronic lung disease (CLD)/congenital heart disease (CHD), and (2) the CLD/CHD cohort enrolled infants with CLD of prematurity or haemodynamically significant CHD: i.e. infants who had uncorrected, partially corrected, or medically treated CHD or CLD warranting therapeutic intervention within 6 months.
Baseline characteristics of the study population are presented in the attached information for healthcare professionals.
After completion of Season 1, subjects in the CLD/CHD cohort progressed into the Season 2 phase of the study. Subjects who had received nirsevimab in Season 1 received a second dose of nirsevimab in Season 2 (NIRS/NIRS group). Subjects who received palivizumab in Season 1 were randomised 1:1 to receive a dose of nirsevimab (PALI/NIRS group) or a course of palivizumab in Season 2 (PALI/PALI group).
The incidence of MA RSV LRTI through to 150 days post-first dose in Season 1 was balanced and low: 0.6% (4 of 616 subjects) in the nirsevimab group compared with 1.0% (3 of 309 subjects) in the palivizumab group. Similarly, low rates were reported across the preterm cohort (0.5% each) and CLD/CHD cohort (1.0% vs 2.0% nirsevimab and palivizumab, respectively). For the overall population and preterm and CLD/CHD cohorts, 95% CIs were generated by treatment group and were largely overlapping. No MA RSV LRTI cases were observed in the second season; thus no clinical efficacy data for the second RSV season are available for the CHD/CLD risk groups.

MUSIC (D5290C00008) is a completed Phase 2, open-label, uncontrolled, single-dose study in immunocompromised infants and toddlers ≤ 24 months of age.
The study had 2 treatment groups: (1) children in the first year of life (first RSV season) (N = 46) and (2) children in the second year of life (second RSV season) (N = 54). All subjects received the approved dose. MUSIC included subjects with at least 1 of the following conditions: immunodeficiency (combined, antibody, or other aetiology) (28); systemic high-dose corticosteroid therapy (17); organ or bone marrow transplantation (12); receiving immunosuppressive chemotherapy (9); other immunosuppressive therapy (9); and HIV infection (1).
The primary objective of the study was to evaluate the safety, tolerability, and PK of nirsevimab when administered to immunocompromised children ≤ 24 months of age. In the MUSIC study none of the medically attended lower respiratory tract infection met the criteria of a protocol defined MA RSV LRTI.

Efficacy for the MEDLEY and MUSIC populations was extrapolated from the efficacy observed in Study3/MELODY based on PK bridging. For details see section 6.1. Clinical Pharmacology.
The final results of the MUSIC study raise some concerns as the predefined threshold to extrapolate the efficacy in immunocompromised patients was not met when using the full data set. This might result in a reduced efficacy or/and a shorter duration of protection compared to the efficacy observed in Study3/MELODY. This can however be accepted, as the serum nirsevimab concentration at Day151 vs MELODY was mostly comparable and the uncertainty on the exact efficacy and duration of protection is included in the information for healthcare professionals.
When outliers with a rapid decline in nirsevimab concentrations were excluded, the threshold was met.

6.4 Safety

Safety data were available from 3680 subjects dosed with nirsevimab, including 3284 subjects receiving the proposed dose.
Safety was assessed in 2 double-blind, placebo-controlled clinical studies (Study 3 and MELODY) in late preterm and term infants. The MEDLEY study provided information on the safety profile of nirsevimab in very and extremely preterm infants and infants with CHD/CLD compared to palivizumab, while the MUSIC study provided information on the safety of immunocompromised subjects.

Based on the pooled safety analysis of the MELODY and Study 3 proposed dose populations, the types and frequencies of AEs were generally balanced between the nirsevimab and placebo groups through to 360 days post-dose and within immediate post-dose timepoints.
Baseline characteristics were similar between the nirsevimab and placebo groups as detailed in the Efficacy section. Medical history findings were consistent with the common conditions for this population of term and preterm infants in the first year of life and were generally balanced between the nirsevimab and placebo treatment groups.

Overall, 84.0% of subjects in the nirsevimab group and 82.6% of subjects in the placebo group had at least 1 AE. The majority of AEs were mild or moderate in severity. The percentage of subjects was similar in the nirsevimab and placebo groups for AEs of ≥ Grade 3 severity (4.0% and 6.3%, respectively) and SAEs (7.6% and 10.5%, respectively).
During the 7-day post dosing period, the percentage of subjects with AEs associated with reactogenicity measures of injection site reaction or pyrexia was low in both groups (< 1%).

Overall, the percentages of subjects with:

- investigational product (IP)-related AEs (1.3% and 1.4%)
- investigator-assessed adverse event of special interest AESIs (0.2% and 0%),
- IP-related skin reactions (0.6% and 0.3%)
- new onset chronic diseases, NOCDs (0.1% and 0.3%)

were low and generally comparable between the nirsevimab and placebo groups, respectively.

In the MELODY/Study 3 proposed dose pool, the frequency of SAEs was slightly lower in the nirsevimab group compared with the placebo group (7.6% and 10.5%, respectively).
Deaths were reported for 6 subjects [0.2%] in the nirsevimab group and 3 subjects [0.2%] in the placebo group. The cause of death was unknown for 2 patients: 1 in Study 3 (Day 123) and 1 in the MELODY study (Day 140). It can be agreed that the other deaths were not treatment related.

Safety results from the ongoing MEDLEY study in 2 cohorts of preterm (≤35 wGA) and term CHD/CLD infants were provided in an interim clinical study report (CSR).
The demographic and baseline characteristics of the study population were generally balanced between the nirsevimab and palivizumab groups in the overall population and across the preterm and CLD/CHD cohorts in Season 1. Overall, the majority of subjects were White (79% [732/925 subjects]) and preterm (85% [787/925 subjects] < 35 wGA), with a median age at randomisation of 3.5 months

(range: 0.1 to 12.3 months). Twelve subjects (9/616 nirsevimab, 3/309 palivizumab) had Down syndrome and 2/616 subjects in the nirsevimab arm had cystic fibrosis.
The enrolled subject with the lowest gestational age had wGA 22 (in the CLD/CHD cohort), and the lowest weight at Day 1 was 1.8 kg in the nirsevimab (and 1.7 in the palivizumab) arm in both the preterm and CLD/CHD cohorts. No infants with a wGA lower than 22 weeks were enrolled in the study. Thus, no clinical data for extreme low bodyweight infants are available. Infants with low birthweight were enrolled (mean 1.74 kg - min 0.4 kg); however, they were not dosed after/close to birth. The youngest infant enrolled in the study was 0.07 months old (= 2 days).
In the MEDLEY study through to 360 days post-first dose in Season 1, the incidence of:

- at least one AE,
- IP-related AEs,
- AE ≥ Grade 3 events,
- SAEs and/or ≥ Grade 3 events,
- AESIs,
- IP-related AESIs based on selected MedDRA preferred terms (PTs),
- IP-related skin reactions

were generally balanced between the nirsevimab and palivizumab groups.
Through to at least 150 days post-first IP dose in Season 2, the frequency of AEs was 70.0%, 72.5%, and 69.0%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively. Adverse events were most frequently reported (≥ 20% of subjects in any treatment group) in the SOCs of infections and infestations (57.8%, 62.5%, and 57.1%), gastrointestinal disorders (17.8%, 22.5%, and 26.2%), and general disorders and administration site conditions (12.2%, 20.0%, and 11.9%) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively. No clinically relevant imbalances were observed among the treatment groups at the PT level. The most common AEs by PT (> 10% of subjects in any treatment group) were upper respiratory tract infection (25.0%, 17.5%, and 16.7%), nasopharyngitis (12.2%, 15.0%, and 21.4%), pyrexia (11.7%, 20.0%, and 11.9%), rhinitis (12.2%, 10.0%, and 14.3%), and diarrhoea (5.0%, 5.0%, and 11.9%) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively.

In the MEDLEY overall population, in Season 1 the frequency of SAEs was similar between the nirsevimab and palivizumab groups (13.0% vs 12.5%). SAEs were most frequently reported in the SOC of infections and infestations (8.3% vs 6.6%). The most common SAEs reported for nirsevimab (vs palivizumab) were bronchiolitis (12 vs 4 subjects), gastroenteritis (6 vs 1 subjects), bronchitis (5 vs 2 subjects), pneumonia (5 vs 1 subjects), respiratory syncytial virus bronchiolitis (4 vs 2 subjects), COVID-19, and viral upper respiratory tract infection (3 vs 1 subjects each).
The incidence of SAEs was generally balanced in the nirsevimab group vs the palivizumab group in the preterm (8.6% vs 6.3%) and CLD/CHD (21.6% vs 25.5%) cohorts. The frequency of events was higher in the CLD/CHD cohort than the preterm cohort. This difference is due to a notably higher event rate in the infections and infestations SOC in the CLD/CHD cohort compared with the preterm cohort.
In Season 2 the incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (9.4% vs 10.0% vs 0%, respectively); however, this was not observed within all analysed time points through to 30 days post -first dose.
Serious AEs were most frequently reported (> 2% of subjects in any treatment group) in the SOCs of infections and infestations (7.2% vs 10.0% vs 0%) and nervous system disorders (0% vs 2.5% vs 0%). The most common SAEs (≥ 2 subjects in any treatment group) reported were viral bronchitis (3 vs 0 vs 0 subjects), COVID-19 (2 vs 0 vs 0 subjects), gastroenteritis (2 vs 0 vs 0 subjects), lower respiratory tract infection (2 vs 1 vs 0 subjects), and upper respiratory tract infection (2 vs 0 vs 0 subjects).
None of the SAEs were considered by the investigator to be IP-related (for both seasons). In MEDLEY study, deaths were reported for 5 subjects (0.8%) in the nirsevimab group and 1 subject (0.3%) in the palivizumab group. In the nirsevimab group, 2 deaths in the preterm cohort (bronchiolitis and COVID-19) and 3 in the CLD/CHD cohort (congestive heart failure, cardiogenic shock, and pneumonia) were reported. In the palivizumab arm, 1 (0.3%) fatal event of bronchiolitis occurred in the CLD/CHD cohort. None of the deaths were reported as being IP-related, which can be supported based on the narratives. In the cases of the 2 deaths related to bronchiolitis (1 in the nirsevimab and 1

in the palivizumab group), an RSV aetiology could not be ruled out based on the available information.

In the MUSIC study no new safety concerns were observed in the 100 immunosuppressed subjects ≤ 24 months. In the final CSR of MUSIC, 3 deaths (0.03%) were reported (LRTI, septic shock, and tumour haemorrhage): 2 patients in Season 1 and 1 patient in Season 2, on Day 68, Day 124, and Day 340 after nirsevimab administration, respectively. These events were not considered to be treatment-related.

Overall, 14 deaths (0.37%) were observed in the nirsevimab group in all studies submitted. In the control arms (placebo, palivizumab, and no control arm in MUSIC study) the rate of death was 0.22% (4 deaths). Thus, even if considering the 2:1 randomisation in Study 3 and MELODY, an imbalance regarding deaths could be observed. None of the deaths was considered to be treatment-related by the investigator. However, the causes of death for 1 death in the nirsevimab arm of Study 3 and 1 death in the MEDLEY study were reported as unknown. Additionally an RSV aetiology could not be excluded for one death in the nirsevimab group of MEDLEY based on the available information.

Across all studies, the AESIs hypersensitivity (including anaphylaxis reaction), immune complex disease, and thrombocytopenia based on investigator assessment were reported in very few subjects. None were reported as an SAE, and none of the subjects had any post-baseline ADA detected with samples available for analysis. No cases of anaphylaxis, serious allergic reaction, thrombocytopenia, or immune complex disease were attributed to nirsevimab or placebo by investigator assessment. Hypersensitivity AESIs attributed to nirsevimab were limited to non-serious skin hypersensitivity reactions (mostly of mild to moderate intensity) and occurred in a small percentage of subjects.
The risk of hypersensitivity (including anaphylaxis) is an associated risk with the use of monoclonal antibodies. This is properly described in the information for healthcare professionals.

In the placebo-controlled studies, the AESIs based on selected MedDRA PT were reported in a similar percentage of subjects in each treatment group (23.0% and 22.6%, respectively); those considered IP-related were low and comparable between the nirsevimab and placebo groups (0.5% and 0.2%, respectively).
In MEDLEY Season 1 a numerically higher incidence of AESIs based on selected MedDRA PTs was observed in the nirsevimab group compared with the palivizumab group (23.6% vs 15.3%) in the CLD/CHD cohort, driven by events in the hypersensitivity category. Notably, there was no difference between nirsevimab and comparator groups through to any of the relevant time points close to IP dosing (within 1, 3, 7, 14, or 30 days post-dose [first IP dose for MEDLEY]), inclusive of expected timeframe for immediate hypersensitivity in both the MELODY (all subjects)/Study 3 (proposed dose) safety pool and MEDLEY RSV Season 1.
In MEDLEY RSV Season 2, the percentage of subjects with MedDRA PT-compatible AESIs was comparable across all 3 treatment groups.
In MUSIC, a single MedDRA-compatible AESI of immune complex disease event was reported as a worsening of underlying juvenile idiopathic arthritis (present at baseline) in a subject dosed in the second year of life with negative post-baseline ADA through to 150 days post-dose. Other immune complex diseases were not reported in any of the studies.

There were no discontinuations in any of the studies due to an adverse event in dosed subjects.

The percentage of subjects with any AEs was similar between the nirsevimab and placebo groups for each of the intrinsic factor subgroups (age, weight, gender, and race).

The safety profile of all subgroups evaluated based on intrinsic factors was similar to the overall study populations with no clinically meaningful differences observed in the frequency or pattern of AEs between the nirsevimab and comparator groups.

The available clinical data did not support the (theoretical) risk of an antibody-dependent enhancement of RSV disease. No increased severity of disease for infants administered nirsevimab compared to infants administered placebo was observed.

There were no safety data in infants with a wGA lower than 22 weeks and with a body weight below 1.6 kg. Furthermore, no safety/efficacy or PK data in infants with a body weight below 1 kg were available.

6.5 Final clinical benefit-risk assessment

The human respiratory syncytial virus (RSV) causes acute respiratory tract disease in persons of all ages and is the most common cause of acute lower respiratory tract infection in young children. RSV bronchiolitis is the most common lower respiratory tract infection in infants and leads to the hospitalisation of 1-2% of the annual birth cohort as a result of respiratory insufficiency and/or inadequate fluid intake. RSV typically causes seasonal outbreaks throughout the world. In Europe, these usually occur from October/November to April/May, with a peak in January or February.

Patients at risk for severe lower respiratory tract disease include: infants younger than 6 months; particularly those who are born during the first half of the RSV season; those attending daycare; those with older siblings (who may have asymptomatic RSV infection); infants and children with underlying lung disease, such as chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis) or congenital heart disease; infants born before 35 weeks gestation; patients with Down syndrome; and immunocompromised patients.

Currently, treatment options for RSV disease are mostly supportive. Several vaccines (including maternal vaccination) and monoclonal antibodies are under development for prevention.
During the review, 2 vaccines against RSV were approved by the FDA and EMA for the elderly over 60 years of age, 1 of which was also approved for the passive protection of newborns/infants up-to 6 months through maternal immunisation.
In Switzerland, a monoclonal antibody, palivizumab, with monthly dosing is available for use in high-risk infants to prevent severe RSV infection.

Nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that binds to an epitope within antigenic site Ø on the prefusion confirmation of the RSV fusion (F) protein. It locks the RSV F protein in the prefusion conformation, neutralises the virus, blocks viral entry into the host cell, and blocks cell-to-cell fusion. The antibody has been engineered with a triple amino acid substitution, M252Y/S254T/T256E (YTE) in the fragment crystallisable (Fc) region to prolong the serum half-life. Due to the long-serum half-life of nirsevimab a single dose administration to cover an RSV season is considered an advantage compared to palivizumab.

Efficacy was demonstrated in two well-designed and conducted placebo-controlled studies in healthy preterm (Study 3) and mostly healthy late preterm and term infants (MELODY) in their first RSV season. Nirsevimab as prophylaxis resulted in a statistically significant reduction of 70.1% in medically attended RSV-confirmed LRTI in Study 3. With a reduction of 74.5% in MA RSV LRTI, a similar benefit of nirsevimab was also observed in MELODY.
A statistically significant reduction in the incidence of RSV LRTI hospitalisation was also demonstrated in Study 3, however this was not statistically significant in MELODY most likely due to reduced RSV circulation attributed to the COVID-19 pandemic restrictions.
A prespecified pooled secondary analysis of MELODY and Study 3 demonstrated a significant reduction in the incidence of RSV LRTI hospitalization.

Clinical data confirmed that nirsevimab was active against both RSV subtypes (A and B).

Descriptive efficacy data in infants at high risk of RSV LRTI were available from the palivizumab controlled MEDLEY study in very extremely/preterm and term CHD/CLD infants. A similar incidence of MA RSV LRTI and RSV LRTI hospitalization was observed in the nirsevimab arm compared to the palivizumab arm in season 1.However, statistically solid, confirmatory efficacy data are not available for high-risk subjects.
Efficacy was extrapolated from Study3/MELODY to the MEDLEY and MUSIC populations based on PK bridging. Efficacy was considered to be demonstrated if the proposed doses resulted in serum nirsevimab exposures at or above the predicted efficacious target in > 80% of the MEDLEY and MUSIC population and if Day 151 nirsevimab serum concentrations were comparable to concentrations from MELODY. The extrapolation is justified based on the mode of action of nirsevimab (binding to RSV, preventing viral cell-entry), which is independent of age or medical condition, and comparable viral aetiology; therefore, a similar exposure-response relationship across all populations can be expected. It can be agreed that in general, for monoclonal antibodies the serum concentrations are considered as a surrogate for the likelihood of a clinical benefit.

Due to the lack of specific efficacy data in populations at high risk of severe RSV LRT disease (particularly immunocompromised infants), a more conservative criterion closer to 100% might be more appropriate to ensure adequate protection based on extrapolation.
The predefined criterion was hardly met in infants with CHD in MEDLEY Season 1 (80.3%). In immunocompromised patients in the MUSIC study the threshold was not met in any of the seasons (Season 1: 71.7% and Season 2: 78.0%) using the full data set. When outliers with rapid decline of the nirsevimab concentrations, presumably due to protein-loss conditions in some cases, were excluded, the threshold was met.
Based on the totality of the data, considering that the serum nirsevimab concentration at Day151 in MEDLEY and MUSIC vs MELODY were mostly comparable, with higher concentrations in Season 2, a clinically relevant beneficial effect of nirsevimab is still expected in immunocompromised subjects. However, in some patients the protection might be lower and shorter in duration compared to the efficacy seen in Study 3/MELODY. This can be accepted as protection against an MA RSV LRTI is considered important for this vulnerable population and the safety profile is well characterised and acceptable. The uncertainties on the nirsevimab concentrations including the rapid decline in serum concentrations and the potential reduced protection in some patients are presented in the information for healthcare professionals.

The potential need for nirsevimab is acknowledged in infants with a body weight below 1 kg; however, efficacy, safety, and PK data were not available in this population. No infants below 1.6 kg were enrolled in the clinical studies. The dosing between 1-1.6 kgs is based on extrapolation, and higher exposures are anticipated below 1 kg. The, use of nirsevimab for these infants should therefore be carefully considered as indicated in the information for healthcare professionals.

The safety findings based on the pivotal studies in mostly healthy term and preterm subjects born after 29 week 0 days GA entering their first RSV season were generally mild and in line with what is expected following the administration of a monoclonal antibody with an external target, as injection site reactions, fever, allergic reactions including skin rash.
The supportive studies MEDLEY and MUSIC provided additional information in high-risk subjects entering their first and second RSV season.

A total of 14 fatal events (0.37%) were reported in the submitted clinical studies in the nirsevimab arm, while in the control arms (placebo, palivizumab, no control arm in MUSIC) a total of 4 cases (0.22%) were reported. This results in an imbalance even if the 2:1 randomisation used in Study 3, MELODY, and MEDLEY is taken into account. None of the deaths in the nirsevimab groups was considered drug-related by the investigator, which can be supported. None were known or reported to have been caused by RSV; however, in 1 fatal case in MEDLEY the RSV aetiology could not be excluded, and the causes of 2 deaths – 1 in Study 3 (on study day 123) and 1 in MELODY (Day 140) – were reported as unknown.

In the MEDLEY study the incidence of SAEs was slightly higher in the nirsevimab group vs the palivizumab group in the preterm (8.6% vs 6.3%) and generally balanced in the CLD/CHD (21.6% vs 25.5%) cohort. The frequency of events was higher in the CLD/CHD cohort than the preterm cohort. This difference is likely due to a notably higher event rate in the infections and infestations SOC in the CLD/CHD cohort compared with the preterm cohort.
In Season 2 the incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (9.4% vs 10.0% vs 0%, respectively). However, this was not observed within all analysed time points through to 30 days post-first dose.
There were no safety data in infants with a wGA lower than 22 weeks, with a body weight below 1.6 kg, and no efficacy or PK data in infants with a body weight below 1 kg available.
The information for healthcare professionals adequately reflects the safety findings observed in the clinical studies and the lack of data for certain groups.

In summary, nirsevimab in the proposed dose effectively prevented MA RSV LRTI and hospitalisation during the first RSV season (5 months) in healthy preterm (wGA29+0) and term infants.
Confirmatory efficacy data for high-risk patients for the first and second RSV season were not available, but a beneficial effect of nirsevimab can be expected based on the comparable exposures following administration of nirsevimab at the proposed dose in healthy infants and high-risk infants. This is further strengthened by the exploratory efficacy results in high-risk infants.
The safety profile of nirsevimab was generally in line with the safety findings of other monoclonal antibodies with external target and is acceptable, even though an imbalance in the reported deaths between the nirsevimab and placebo/palivizumab groups was observed, although none of the deaths were treatment-related.
The benefit-risk balance of Beyfortus in the proposed dose for newborns and infants in their first RSV season and toddlers up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season is considered positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Beyfortus was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Beyfortus®

Composition

Active substances

Nirsevimab

Excipients

Histidinum, histidini hydrochloridum, arginini hydrochloridum, saccharum, polysorbatum 80, aqua ad iniectabilia.

Pharmaceutical form and active substance quantity per unit

Beyfortus 50 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 50 mg of nirsevimab in 0.5 mL (100 mg/mL).
Beyfortus 100 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 100 mg of nirsevimab in 1 mL (100 mg/mL).

Clear to opalescent, colourless to yellow, pH 6.0 solution.
Nirsevimab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Indications/Uses

Beyfortus is indicated for the prevention of lower respiratory tract disease caused by Respiratory Syncytial Virus (RSV) in:

i. Neonates and infants entering or during their first RSV season.
ii. Toddlers up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season (see *«Warnings and precautions», «Clinical efficacy» and «Pharmacokinetics»*).

Beyfortus should be used in accordance with available official recommendations.

Dosage/Administration

Posology

Neonates and infants: first RSV season

The recommended dose is an intramuscularly administered single dose of 50 mg for infants with body weight <5 kg and a single dose of 100 mg for infants with body weight ≥5 kg.

Beyfortus should be used from birth in neonates/infants born during the RSV season or entering the RSV season.
In infants born outside the RSV season, Beyfortus should be used once before the start of the RSV season, taking into consideration the duration of protection ensured by Beyfortus (see *«Clinical efficacy»*).

Toddlers who remain vulnerable to severe RSV disease: second RSV season
The recommended dose is a single dose of 200 mg given as two intramuscular injections (2 x 100 mg).

Infants/toddlers undergoing cardiac surgery with cardiopulmonary bypass
For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels.
First RSV season

- If cardiac surgery with cardiopulmonary bypass is performed within 90 days after the first dose of Beyfortus, the additional dose should be 50 mg or 100 mg, based on body weight.
- If more than 90 days have elapsed between the first dose and the bypass surgery, the additional dose can be a single dose of 50 mg regardless of body weight.

Second RSV season

- If cardiac surgery with cardiopulmonary bypass is performed within 90 days after the use of Beyfortus, the additional dose should be 200 mg.
- If more than 90 days have elapsed between the use of Beyfortus and the bypass surgery, the additional dose can be a single dose of 100 mg.

Dosing in infants with a body weight from 1.0 kg to <1.6 kg is based on extrapolation, no clinical data are available. Exposure in infants <1 kg is anticipated to yield higher exposures than in those weighing more.
The benefits and risks of nirsevimab use in infants <1 kg should be carefully considered.
There are limited data available in extremely preterm infants (Gestational Age [GA] <29 weeks) less than 8 weeks of age. There is no clinical data available in infants with a postmenstrual age (gestational age at birth plus chronological age) of less than 32 weeks.
The safety and efficacy of nirsevimab in children aged 2 to 18 years have not been established. There are no data available.

Method of administration

Beyfortus should only be administered as an intramuscular (IM) injection by a healthcare professional, preferably in the anterolateral aspect of the thigh.

The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. If two injections are required, different injection sites should be used. For instructions on use, handling and disposal (see section «*Instructions for handling*»).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Contraindications

Individuals with a history of severe hypersensitivity reactions, including anaphylaxis, to the active substance or to any of the excipients (see section «Composition»).

Warnings and precautions

Hypersensitivity including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with other monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration, and initiate appropriate treatment with appropriate medicinal products and/or supportive therapy.

Use in individuals with clinically significant bleeding disorders

As with any other IM injections, Beyfortus should be given with caution to infants/toddlers with thrombocytopenia, any coagulation disorder or to individuals on anticoagulation therapy.

Use in immunocompromised infants/toddlers

In a clinical study in immunocompromised patients, a rapid drop in nirsevimab concentration was observed in 14% of the subjects compared to the rest of the study participants.

In these patients, the protection provided by Beyfortus may be lower or of shorter duration (see «Properties/Effects» and «Pharmacokinetics»).

Beyfortus cannot protect everyone who receives this monoclonal antibody from lower respiratory tract disease caused by respiratory syncytial virus.

Interactions

No interaction studies have been conducted. Monoclonal antibodies do not typically have significant interaction potential, as they do not directly affect cytochrome P450 enzymes and are not substrates of hepatic or renal transporters.
Nirsevimab mediated interactions are unlikely as the target of nirsevimab is an exogenous virus.

Nirsevimab does not interfere with RSV diagnostic assays using reverse transcriptase polymerase chain reaction (RT PCR) or rapid antigen detection that employ commercially available antibodies targeting antigenic site I, II, or IV on the RSV fusion (F) protein.

Concomitant administration with vaccines
Since nirsevimab is a monoclonal antibody, a passive immunisation specific for RSV, it is not expected to interfere with the active immune response to co-administered vaccines.

There is limited experience of co-administration with vaccines. In clinical trials, when nirsevimab was given with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone.

Nirsevimab should not be mixed with any vaccine in the same syringe or vial (see section «*Incompatibilities*»). When administered concomitantly with injectable vaccines, they should be given with separate syringes and at different injection sites.

Pregnancy, lactation

Not applicable.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

Summary of the safety profile
In MELODY, Study 3 (D5290C00003), MEDLEY and MUSIC, overall, 3229 neonates and infants including extremely preterm infants (GA < 29 weeks), infants with preterm chronic lung disease (CLD) and hemodynamically relevant congenital heart disease (CHD), and immunocompromised infants in their first RSV season received either 50 mg nirsevimab (if <5 kg body weight at the time of administration) or 100 mg nirsevimab (if ≥5 kg body weight at the time of administration). Additionally, in MEDLEY and MUSIC 274 toddlers up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season received 200mg of nirsevimab, including 180 children who

received a second dose of nirsevimab (MEDLEY) and 94 children who received a first dose of nirsevimab (MUSIC) in season 2. See «*Clinical Efficacy*».

Tabulated list of adverse reactions

Table 1 shows the adverse reactions of the pooled analysis of studies D5290C00003 and MELODY (all subjects).

The adverse reactions reported during clinical trials should be arranged according to MedDRA system organ classes (SOC). Within each SOC, the preferred terms are arranged by decreasing frequency and then by decreasing severity. The information on the frequency of the occurrence of side effects is defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/ 1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Skin and subcutaneous tissue disorders	Rash[1]	Uncommon
General disorders and administration site conditions	Injection site reaction[2]	Uncommon
	Pyrexia[3]	Uncommon

[1] Rash was defined by the following grouped preferred terms: rash, rash maculopapular, rash macular, occurring within 14 days post dose.
[2] Injection site reaction was defined by the following grouped preferred terms: injection site reaction, injection site pain, injection site induration, injection site oedema, injection site swelling, occurring within 7 days post dose.
[3] Pyrexia occurring within 7 days post dose.

Infants and children vulnerable to severe RSV disease

Safety was evaluated in MEDLEY in 918 infants at higher risk for severe RSV disease, including 196 extremely preterm infants (GA <29 weeks) and 306 infants with CLD, or CHD entering their first RSV season, who received nirsevimab (614) or palivizumab (304). The safety profile of nirsevimab in infants who received nirsevimab in their first RSV season was comparable to the palivizumab comparator and consistent with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY).

Safety was evaluated in the ongoing study MEDLEY in 220 children with CLD or CHD who received nirsevimab or palivizumab in their first RSV season and went on to receive nirsevimab entering their second RSV season. The safety profile of nirsevimab in children who received nirsevimab in their first and second RSV season (180) was comparable to that in children who received palivizumab in their first RSV season and then nirsevimab in their second RSV season (40). The safety profile of

nirsevimab in these children from both study arms was consistent with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY) and comparable to that in children who received palivizumab for their first and second RSV season.

Safety was also evaluated in MUSIC, an open label, uncontrolled, single dose trial in 100 immunocompromised infants and children ≤24 months, who received nirsevimab in their first or second RSV season. This included subjects with at least one of the following conditions: immunodeficiency (combined, antibody, or other etiology) (33); systemic high-dose corticosteroid therapy (29); receiving immunosuppressive chemotherapy (20); organ or bone marrow transplantation (16); other immunosuppressive therapy (15), and HIV infection (8). The safety profile of nirsevimab was consistent with that expected for a population of immunocompromised children and with the safety profile of nirsevimab in term and preterm infants GA ≥29 weeks (D5290C00003 and MELODY).

Immunogenicity

As with all therapeutic proteins, there is the possibility of immunogenicity. The detection of antibody development is highly dependent on the sensitivity and specificity of the used test. Additionally, the observed incidence of antibodies (including neutralizing antibodies) in a test can be influenced by several factors, e.g., the test methodology, sample handling, timepoint of sampling, concomitant medications and an underlying disease. For these reasons, a comparison of the incidence of antibodies against nirsevimab in the studies described below with the incidence of antibodies in other studies or against other drugs may be misleading.

In studies D5290C00003 and MELODY anti-drug antibodies (ADA) against nirsevimab were detected in 148/2493 (5.9%) of infants who received nirsevimab at the recommended dosing regimen during the 361 days post dosing period, and 110/148 (74.3%) of ADA-positive infants had anti-drug antibodies (ADA) against the YTE domain. In MELODY 26/121 (21.5%) of ADA-positive infants tested positive for nirsevimab neutralizing antibodies.

In MEDLEY, ADA were detected in 32/587 (5.5%) of infants who received a single dose of nirsevimab in their first RSV season during the 361 days post dosing period. Of the 32 ADA-positive infants 2 (6.3%) had nirsevimab neutralising ADA and 29 (90.6%) tested positive for ADA against the YTE domain. Of 180 infants who received nirsevimab in two consecutive RSV seasons, 8 infants (4.4%) and 13 infants (7.2%) became ADA positive for the first time in the first and second RSV season, respectively. Of the 13 ADA-positive infants in the second RSV season, 8 (61.5%) had anti-YTE-ADA and one infant (7.7%) had nirsevimab neutralising ADA.

For subjects receiving nirsevimab in their first or second RSV season in MUSIC, anti-nirsevimab antibodies were detected in 11/97 (11.3%) of children during the 361 days post dosing period. Of the 11 ADA-positive infants, one (9.1%) had neutralising ADA and all were positive for ADA against the YTE domain.

The development of ADA against nirsevimab appears to have no clinically relevant effect on its clearance (up to 5 months), efficacy or safety. Subjects who developed ADA had reduced nirsevimab concentrations at day 361 compared to subjects who received nirsevimab and were ADA-negative.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is very limited experience of overdose with nirsevimab.
There is no specific treatment for an overdose with nirsevimab. In the event of an overdose, the individual should be monitored for the occurrence of adverse reactions and provided with symptomatic treatment as appropriate.

Properties/Effects

ATC code

J06BD08

Mechanism of action

Nirsevimab is a recombinant, neutralising, human, long-acting monoclonal immunoglobulin-G1-kappa ($IgG1_K$) antibody to the prefusion conformation of the fusion protein of respiratory syncytial virus (RSV-F protein) which has been modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life. Nirsevimab binds to a highly conserved epitope at antigenic binding site Ø of the prefusion protein with dissociation constants K_D = 0.12 nM and K_D = 1.22 nM for subtypes RSV-A and RSV-B, respectively. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

Pharmacodynamics

Antiviral activity
The neutralisation activity of nirsevimab against RSV was measured in cell culture in a dose-response model using cultured Hep-2 cells. Nirsevimab neutralised RSV-A and RSV-B isolates with median EC_{50} 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), respectively. The clinical RSV isolates (70 RSV-A and 49 RSV-B) were collected between 2003 and 2017 from subjects across the United States, Australia, Netherlands, Italy, China and Israel and encoded the most common RSV-F sequence polymorphisms found among circulating strains. Nirsevimab demonstrated in vitro binding to immobilised human Fcγ receptors (FcγRI, FcγRIIA, FcγRIIB, and FcγRIII) and equivalent neutralising activity compared to parental monoclonal

antibodies, IG7 and IG7-TM (Fc region modified to reduce Fc receptor binding and effector function). In an animal model with RSV-infected cotton rats, IG7 and IG7-TM exhibited comparable dose-dependent reduction in RSV replication in the lungs and nasal turbinates, strongly suggesting that protection from RSV infection is dependent on nirsevimab neutralisation activity rather than Fc-mediated effector function.

Antiviral resistance

In cell culture

Escape variants were selected following three passages in cell culture of RSV-A2 and RSV-B9320 strains in the presence of nirsevimab. Recombinant RSV-A variants that showed reduced susceptibility to nirsevimab included those with identified substitutions N67I:N208Y (103-fold as compared to reference). Recombinant RSV-B variants that showed reduced susceptibility to nirsevimab included those with identified substitutions N208D (>90,000 fold), N208S (>24,000 fold), K68N:N201S (>13,000 fold), or K68N:N208S (>90,000 fold). All resistance associated substitutions identified among neutralisation escape variants were located in the nirsevimab binding site (amino acids 62-69 and 196-212) and were shown to reduce binding affinity to RSV fusion protein.

In clinical trials

In MELODY, MEDLEY and MUSIC no known resistance-associated substitutions were identified at ≥25% frequency at any sampling time points. Phenotypic testing of novel substitutions is still ongoing.
In D5290C00003 (where subjects received a single dose of 50 mg Beyfortus), 2 of 40 subjects with RSV infections corresponding to any case definition had a variant containing nirsevimab resistance-associated substitutions. The two subjects received less than the recommended nirsevimab dose and had RSV-B variants harboring I64T+K68E+I206M+Q209R co-occurring substitutions or an N208S substitution. I64T, K68E, and N208S substitutions individually have reduced susceptibility to nirsevimab (fold changes: >496, >283, and >387, respectively). In the placebo group, no subject had an RSV isolate that contained nirsevimab resistance-associated substitutions.
In MELODY, an RSV-B variant harboring binding site substitution L204S (no phenotypic data) concurrent with I206M+Q209R+S211N substitutions (<5-fold change) was detected at ≥25% frequency in one subject who received Beyfortus through day 150. An RSV-B variant present at <25% frequency with I64T+K68E substitutions (>280-fold change) was detected in one subject that received Beyfortus through day 150.
Nirsevimab retains its activity against recombinant RSV harbouring palivizumab resistance-associated substitutions identified in molecular epidemiology studies and in neutralisation escape variants of palivizumab. It is possible that variantsresistant to nirsevimab could have cross-resistance to other monoclonal antibodies targeting the F protein of RSV.

Pharmacokinetic/ pharmacodynamic relationship(s)
In D5290C00003 and MELODY (primary cohort) a positive correlation was observed between a serum AUC (based on clearance at baseline) above 12.8 mg*day/mL and a lower incidence of MA RSV LRTI. The recommended dosing regimen consisting of a 50 mg or 100 mg IM dose for infants in their first RSV season and a 200 mg IM dose for children entering their second RSV season was selected on the basis of these results.

Clinical efficacy
The efficacy and safety of Beyfortus were evaluated in two randomised, double-blind, placebo controlled multicentre trials (D5290C00003 and MELODY) for the prevention of RSV-LRTI in term and preterm infants (GA ≥29 weeks) entering their first RSV season. Safety and pharmacokinetics (PK) of Beyfortus were also evaluated in a randomised, double-blind, palivizumab-controlled multicentre trial (MEDLEY) in infants at higher risk for severe RSV disease, including extremely preterm infants (GA <29 weeks) and infants with CLD of prematurity, or haemodynamically significant CHD, entering their first RSV season, and children with CLD or CHD entering their second RSV season.
Safety and PK of Beyfortus were also evaluated in an open-label, uncontrolled, single dose, multicentre trial (MUSIC) in immunocompromised children ≤24 months of age.

Efficacy against MA RSV LRTI, MA RSV LRTI hospitalisation, and very severe MA RSV LRTI in term and preterm infants (D5290C00003 and MELODY)- first RSV season
D5290C00003 randomised a total of 1,453 very and moderately preterm infants (GA ≥29 to <35 weeks) entering their first RSV season (2:1) to receive a single IM dose of 50 mg Beyfortus or placebo. At the timepoint of randomisation, 20.3% were GA ≥29 to <32 weeks; 79.7% were GA ≥32 to <35 weeks; 52.4% were male; 72.2% were of Caucasian origin; 17.6% were of African origin; 1.0% were of Asian origin; and 59.5% weighed <5 kg. The median age was 2.80 months (range: 0.1 to 11.9 months); 17.3% were ≤1.0 month; 53.2% were ≤3.0 months; 32.6% were >3.0 to ≤6.0 months, and 14.2% were >6.0 months of age.

MELODY (primary cohort) randomised a total of 1,490 term and late preterm infants (GA ≥35 weeks) entering their first RSV season at a ratio of 2:1 to receive a single IM dose of Beyfortus (50 mg Beyfortus if <5 kg body weight or 100 mg Beyfortus if ≥5 kg body weight at the time of dosing) or placebo. At the timepoint of randomisation, 14.0% were GA ≥35 to <37 weeks; 86.0% were GA ≥37 weeks; 51.6% were male; 53.5% were of Caucasian origin; 28.4% were of African origin; 3.6% were of Asian origin; and 40.0% weighed <5 kg. The median age was 2.60 months (range: 0.03 to 11.10 months); 24.5% were ≤1.0 month; 57.9% were ≤3.0 months; 32.1% were >3.0 to ≤6.0 months, and 10.0% were >6.0 months of age.

Infants/toddlers with a history of chronic lung disease/bronchopulmonary dysplasia or a congenital heart defect (apart from infants/toddlers with uncomplicated congenital heart defect) were excluded from the study.
Demographic and baseline characteristics were comparable between the Beyfortus and placebo group in both trials.

The primary endpoint for D5290C00003 and MELODY (primary cohort) was the incidence of medically attended lower respiratory tract infections (inclusive of hospitalisation) caused by RT PCR confirmed RSV (MA RSV LRTI) and characterised predominantly as bronchiolitis or pneumonia, through 150 days after dosing. Signs of LRTI were defined by having one of the following findings at physical examination indicating lower respiratory tract involvement (e.g., rhonchi, rales, crackles, or wheeze); and at least one sign of clinical severity (increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, retractions, grunting, or dehydration due to respiratory distress).
Beyfortus demonstrated efficacy in both individual trials in term and preterm infants (GA ≥29 weeks) entering their first RSV season (Table 2).

Table 2: Efficacy in term and preterm infants against MA RSV LRTI through 150 days post dose, D5290C00003 and MELODY (Primary cohort)

Group	Treatment	N	Incidence % (n)	Absolute risk reduction % (95% CI)	Efficacy[a] (95% CI) [a]
Very and moderately preterm infants GA ≥29 to <35 weeks; D5290C00003	Beyfortus	969	2.6 (25)	6.9 (4.1, 9,7)	70.1% (52.3, 81.2) p<0.0001
	Placebo	484	9.5 (46)	-	
Term and late preterm infants GA ≥35 weeks; MELODY (Primary cohort)	Beyfortus	994	1.2 (12)	3.8 (1.8, 5.9)	74.5% (49.6, 87.1) p<0.0001
	Placebo	496	5.0 (25)		

[a] Based on relative risk reduction versus placebo. Prespecified multiplicity controlled.

Subgroup analyses of the primary efficacy endpoint by gestational age, gender, race and region showed results were consistent with the overall population.

The incidence of hospitalisation in infants with MA RSV LRTI was evaluated. RSV hospitalisation was defined as hospitalisation for LRTI with a positive RSV test or worsening of respiratory status and positive RSV test in an already hospitalised patient. Very severe MA RSV LRTI was defined as MA RSV LRTI with hospitalisation and requirement for supplemental oxygen or intravenous (IV) fluids.

The efficacy of Beyfortus in D5290C00003 and MELODY (primary cohort) in term and preterm infants (GA ≥29 weeks) entering their first RSV season against MA RSV LRTI with hospitalisation is shown in Table 3.

Table 3: Efficacy in term and preterm infants against MA RSV LRTI with hospitalisation through 150 days post dose, D5290C00003 and MELODY (Primary cohort).

Group	Treatment	N	Incidence % (n)	Absolute risk reduction % (95% CI)	Efficacy[a] (95% CI)
Efficacy in infants against MA RSV LRTI with hospitalisation through 150 days post dose					
Very and moderately preterm infants GA ≥29 to <35 weeks; D5290C00003	Beyfortus	969	0.8 (8)	3.3 (1.4, 5.2)	78.4% (51.9, 90.3)[b]
	Placebo	484	4.1 (20)	-	
Term and late preterm infants GA ≥35 weeks; MELODY (Primary cohort)	Beyfortus	994	0.6 (6)	1.0 (-0.2, 2.2)	62.1% (-8.6, 86.8)
	Placebo	496	1.6 (8)	-	

[a] Based on relative risk reduction versus placebo.
[b] Prespecified multiplicity controlled; p-value <0.001.

Efficacy against MA RSV LRTI in infants and children vulnerable to severe RSV disease (MEDLEY and MUSIC) (established by extrapolation, see «Pharmacokinetics*»)*

MEDLEY randomised a total of 925 infants at higher risk for severe RSV disease including infants with CLD or CHD and preterm infants GA <35 weeks, entering their first RSV season. Infants received a single IM dose (2:1) of Beyfortus (50 mg Beyfortus if <5 kg body weight or 100 mg Beyfortus if ≥5 kg body weight at the time of dosing), followed by 4 once monthly IM doses of placebo, or 5 once monthly IM doses of 15 mg/kg palivizumab. At the timepoint of randomisation, 21.6% were GA <29 weeks; 21.5% were GA ≥29 to <32 weeks; 41.9% were GA ≥32 to <35 weeks; 14.9% were GA ≥35 weeks. Of these infants 23.5% had CLD; 11.2% had CHD; 53.5% were male; 79.2% were of Caucasian origin; 9.5% were of African origin; 5.4% were of Asian origin; and 56.5% weighed <5 kg. The median age was 3.46 months (range: 0.07 to 12.25 months); 11,4% were ≤1.0 month; 45.2% were ≤3.0 months; 33.6% were >3.0 months to ≤6.0 months, and 21.2% were >6.0 months of age.

Children at higher risk with CLD or CHD ≤24 months of age continued in the trial for a second RSV season. Subjects who received Beyfortus during their first RSV season received a second single dose of 200 mg Beyfortus entering their second RSV season (180) followed by 4 once monthly IM doses of placebo. Subjects who received palivizumab during their first RSV season were re-randomised 1:1 to

either the Beyfortus or the palivizumab group entering their second RSV season. Subjects in the Beyfortus group (40) received a single dose of 200 mg followed by 4 once monthly IM doses of placebo. Subjects in the palivizumab group (42) received 5 once monthly IM doses of 15 mg/kg palivizumab. Of these children 72.1% had CLD and 30.9% had CHD; 57.6% were male; 85.9% were of Caucasian origin; 4.6% were of African origin; 5.7% were of Asian origin; and 2.3% weighed <7 kg. Demographic and baseline characteristics were comparable between the Beyfortus/Beyfortus, palivizumab/Beyfortus and palivizumab/palivizumab groups.

The efficacy of Beyfortus in infants at higher risk for severe RSV disease, including extremely preterm infants (GA <29 weeks) and infants with CLD or CHD, and in children with CLD or CHD ≤24 months of age entering their second RSV season is established by extrapolation from the efficacy of Beyfortus in D5290C00003 and in MELODY based on PK exposure (see section “Pharmacokinetics”). In MEDLEY, the incidence of MA RSV LRTI was from the first RSV-Season through 150 days post dose was 0.6% (4/616) in the Beyfortus group and 1.0% (3/309) in the palivizumab group. There were no cases of MA RSV LRTI with Beyfortus or palivizumab through 150 days after dosing in the second RSV season.

In MUSIC, the efficacy in 100 immunocompromised infants and children ≤24 months who received the recommended dose of Beyfortus is established by extrapolation from the efficacy of Beyfortus in D5290C00003 and in MELODY based on PK exposure (see sections “Warnings and Precautions” and “Pharmacokinetics”). This included subjects with at least one of the following conditions: immunodeficiency (combined, antibody, or other etiology) (33); systemic high-dose corticosteroid therapy (29); receiving immunosuppressive chemotherapy (20); organ or bone marrow transplantation (16); other immunosuppressive therapy (15), and HIV infection (8).

Duration of protection

Based on clinical and PK data, the duration of protection afforded by nirsevimab is at least 5 months.

Pharmacokinetics

The PK properties of nirsevimab are based on data from individual studies and population PK analyses. The PK of nirsevimab were dose-proportional in children and adults following administration of clinically relevant IM doses over a dose range of 25 mg to 300 mg.

Absorption

The estimated absorption half-life following IM administration was 1.7 days, and the estimated absolute bioavailability was 85% based on population PK analysis. The median time to maximum concentration was 6 days (range: 1 to 28 days).

Distribution

Based on population PK analysis, the estimated central and peripheral volume of distribution of nirsevimab were 249 mL and 241 mL, respectively, for an infant weighing 5 kg. The volume of distribution increases with increasing body weight.

Metabolism

Nirsevimab is a human IgG1κ monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and not metabolised by hepatic enzymes.

Elimination

As a typical monoclonal antibody, nirsevimab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance at the clinically tested doses.
Based on population PK analysis, the estimated clearance of nirsevimab was 3.42 mL/day for an infant weighing 5 kg and the terminal half-life was approximately 71 days.

Kinetics in specific patient groups

Race
Based on population PK analysis there was no clinically relevant effect of race on the PK of nirsevimab.

Renal impairment
As a typical IgG monoclonal antibody, nirsevimab is not cleared renally due to its large molecular weight; therefore, change in renal function is not expected to influence nirsevimab clearance. However, in one subject with nephrotic syndrome, an increased clearance of nirsevimab was observed in clinical trials.

Hepatic impairment
IgG monoclonal antibodies are not primarily cleared via the hepatic pathway. However, in some subjects with chronic liver disease, which may be associated with protein loss, an increased clearance of nirsevimab was observed in clinical trials.

Infants and children vulnerable to servere RSV disease
There was no significant influence of CLD or CHD on the PK of nirsevimab based on population PK analysis. Serum concentrations at day 151 in MEDLEY were comparable to those in MELODY.
In infants born extremely preterm (GA <29 weeks) entering their first RSV season and children with CLD or CHD entering their first or second RSV season (MEDLEY), the pre-defined acceptance criteria for extrapolation were met; >80% of infants/children achieved nirsevimab exposures associated with RSV protection following a single dose.

Serum exposures in children with immunodeficiency (MUSIC) were comparable to those in healthy infants in MELODY.
In MUSIC, 71.7% (33/46) of immunocompromised infants/toddlers entering their first RSV season and 78.0% (39/50) entering their second RSV season achieved nirsevimab exposures associated with RSV protection. In 14 subjects (14), a rapid drop in serum nirsevimab concentration through day 151 was observed. The sharp drop in serum nirsevimab concentration may be related to a protein loss condition (see “Warnings and Precautions”).

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and tissue cross-reactivity studies on human tissues, including juvenile, neonatal and foetal tissues. Since Nirsevimab is a monoclonal antibody, no studies on genotoxicity, carcinogenicity and reproductive toxicity were conducted.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date «EXP» indicated on the package.
Beyfortus may be kept at room temperature (20°C-25°C) for a maximum of 8 hours. After removal from the refrigerator, Beyfortus must be used within 8 hours or discarded.

Special precautions for storage

Store in a refrigerator (2°C-8°C). For storage after removal from refrigeration, (see section «*Shelf life*»).
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not freeze, shake or expose to heat.
Keep out of reach of children.

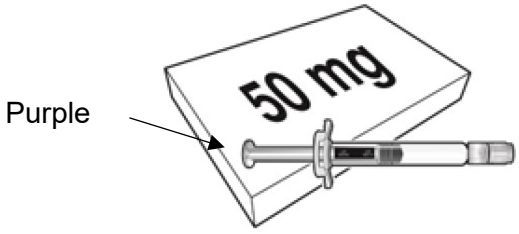
Instructions for handling

Each Beyfortus pre-filled syringe is for single use only.
Visually inspect Beyfortus for particulate matter and discolouration prior to administration. Beyfortus is a clear to opalescent, colourless to yellow solution. Do not inject Beyfortus if the liquid is cloudy, discoloured, or it contains large particles or foreign particulate matter.
Do not use if the Beyfortus pre-filled syringe has been dropped or damaged, the security seal on the carton has been broken or the expiry date („EXP”) has passed.

Instructions for administration

Beyfortus is available in a 50 mg and a 100 mg pre-filled syringe. Check the labels on the Beyfortus carton and pre-filled syringe to make sure you have selected the correct pre-filled syringe with 50 mg or 100 mg as required.

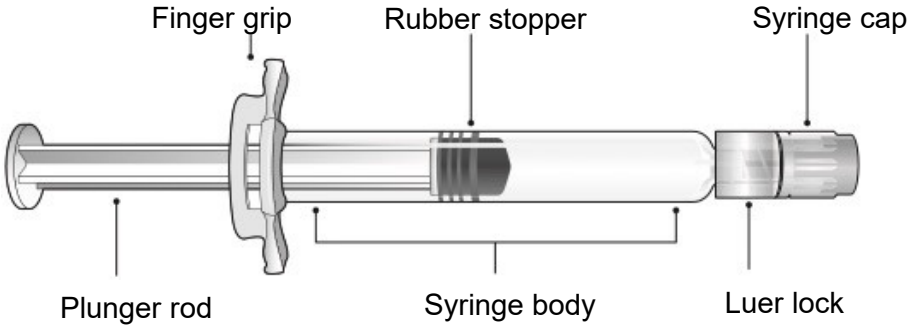
Beyfortus 50 mg (50 mg/0.5 mL) pre-filled syringe with a purple plunger rod.



Beyfortus 100 mg (100 mg/1 mL) pre-filled syringe with a light blue plunger rod.

Refer to Figure 1 for pre-filled syringe components.

Figure 1: Luer lock syringe components



Step 1: Holding the Luer lock in one hand (avoid holding the plunger rod or syringe body), unscrew the syringe cap by twisting it counter clockwise with the other hand.

Step 2: Attach a Luer lock needle to the pre-filled syringe by gently twisting the needle clockwise onto the pre-filled syringe until slight resistance is felt.

Step 3: Hold the syringe body with one hand and carefully pull the needle cover straight off with the other hand. Do not hold the plunger rod while removing the needle cover or the rubber stopper may move. Do not touch the needle or let it touch any surface. Do not recap the needle or detach it from the syringe.

Step 4: Administer the entire contents of the Beyfortus pre-filled syringe as an intramuscular injection, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve.

Step 5: Dispose of the used syringe immediately, together with the needle, in a sharp's disposal container or in accordance with local requirements.

If two injections are required, repeat steps 1-5 in a different injection site.

Authorisation number

69039

Packs

Silicone pre-filled syringe made of type 1 glass with Luer Lock and a FluroTec coated plunger stopper.
Each pre-filled syringe contains 0.5 mL or 1 mL solution.
• 1 pre-filled syringe without needle.
• 1 pre-filled syringe packaged with two separate needles of different sizes. All needles are sterile and for single-use only.

Marketing authorisation holder

sanofi-aventis (suisse) sa, 1214 Vernier

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